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(56) Related Art
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(54) Title: ANTI-ANGPTL8 ANTIBODIES AND USES THEREOF

(57) Abstract: The present invention provides antibodies that bind to ANGPTL8 and methods of using the same. According to certain embodiments, the antibodies of the invention bind human ANGPTL8 with high affinity. The antibodies of the invention may be fully human antibodies. The antibodies of the invention are useful for the treatment of various diseases or disorders characterized in part by elevated blood triglyceride levels.

WO 2017/027316 A1

ANTI-ANGPTL8 ANTIBODIES AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to antibodies, and antigen-binding fragments thereof, which specifically bind angiopoietin-like protein (ANGPTL) 8, compositions comprising these antibodies and methods of use thereof.

BACKGROUND

[0002] ANGPTL8 (alternatively called TD26, RIFL, Lipasin, C19orf80 and Betatrophin) is a newly recognized ANGPTL family member that has been implicated in both triglyceride (TG) and glucose metabolism. It is a circulating protein that is expressed primarily in liver and adipose tissue. Unlike ANGPTL3 and ANGPTL4, ANGPTL8 lacks a fibrinogen like domain at the C-terminus, but contains an N-terminal coiled-coil domain, much like other ANGPTL family members. Phylogenetic analysis reveals that ANGPTL8 shares common ancestors with ANGPTL3 and ANGPTL4 (Fu, Z. *et. al.*, (2013), Biochem. Biophys. Res. Commun. 430:1126-1131).

[0003] Hepatic overexpression of ANGPTL8 is associated with hypertriglyceridemia, whereas inactivation of *Angptl8* causes a reduction in plasma TG levels (Quagliarini, F. *et. al.* (2012), Proc. Natl. Acad. Sci. USA 109(48):19751-19756; Wang, Y. *et. al.* (2013), Proc. Natl. Acad. Sci. USA 110:16109-16114). Despite the consensus that ANGPTL8 is involved in lipid regulation, the mechanism responsible for this process is still under debate. One proposed mechanism is that ANGPTL8 inhibits lipoprotein lipase (LPL) activity, resulting in reduced triglyceride hydrolysis and clearance (Zhang, R. *et.al.,* (2012), Biochem. Biophys. Res. Commun. 424:786-792).

[0004] ANGPTL8 has also been reported to play a role in beta cell proliferation and beta cell mass in mice, where insulin resistance was induced by an insulin receptor antagonist, S961 (Yi, P. *et. al.* (2013), Cell 153:747-758). However, subsequent studies revealed that ANGPTL8 is not required for beta cell function, or the beta cell growth response to insulin resistance. Furthermore, overexpression of ANGPTL8 does not increase beta cell area or improve glycemic control (Gusarova, V. *et. al.* (2014) Cell 159:691-696).

[0005] Since hepatic overexpression of ANGPTL8 is associated with hypertriglyceridemia and since inactivation of *Angptl8* results in a reduction in plasma triglyceride levels, an inhibitor or antagonist of ANGPTL8 may prove effective in treating a disease characterized in part by elevated levels of triglycerides, such as, but not limited to, hypertriglyceridemia.

[0006] Zhang reported that a monoclonal antibody to lipasin, when injected intraperitoneally to wildtype mice, decreased serum triglyceride levels (Zhang, R. (2015), Endocrine Society's 97th Annual Meeting, Presentation No. OR13-6, March 5-8, San Diego, CA). However, no fully human antibodies specific for ANGPTL8 have been described to date that may be used in a

clinical setting to treat diseases, or conditions characterized by elevated levels of triglycerides, including hypertriglyceridemia.

[0007] Accordingly, there is a need in the art for novel antagonists of ANGPTL8, such as the antibodies described herein, for treating patients suffering from hypertriglyceridemia and other disorders or conditions associated with elevated triglyceride and lipid levels.

[0007a] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

BRIEF SUMMARY OF THE INVENTION

[0008] Advantageously, the present invention may provide antibodies and antigen-binding fragments thereof that bind to angiopoietin-like protein 8 (ANGPTL8). One aspect of the disclosure provides human antibodies and antigen-binding fragments thereof that bind to/interact with ANGPTL8, whereby such binding and/or interaction results in the lowering of triglyceride levels in a mammal.

[0009] Accordingly, in a first aspect, the disclosure provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that specifically bind, neutralize, inhibit, block, abrogate, reduce, or interfere with, at least one activity of ANGTPL8, in particular, human ANGPTL8 (See amino acids 22-198 of GenBank accession number NP_061157.3 and amino acids 1-177 of SEQ ID NO:340). The activity of ANGPTL8 that can be neutralized, inhibited, blocked, abrogated, reduced or interfered with, by an antibody or antigen-binding fragment thereof of the disclosure, includes, but is not limited to, inhibition of LPL activity, or lowering of triglyceride levels *in vivo* and the like.

[0009a] In one aspect, there is provided an anti-angiopoietin-like protein 8 (ANGPTL8) antibody or antigen-binding fragment thereof, which comprises a HCVR/LCVR sequence pair of SEQ ID NOs: 162/170.

[0010] In one embodiment, the disclosure provides a monoclonal antibody or antigen-binding fragment thereof that specifically binds to ANGPTL8 and neutralizes, or inhibits at least one activity associated with ANGPTL8, wherein the antibody or antigen-binding fragment thereof exhibits one or more of the following characteristics:

a) is a fully human monoclonal antibody;

b) binds specifically to a linear epitope in the N-terminal region of human ANGPTL8 as defined by SEQ ID NO: 337;

c) does not bind to a linear epitope in the N-terminal region of human ANGPTL8 as defined by SEQ ID NO: 337;

d) does not bind to the N-terminal coiled-coil region of human ANGPTL3 peptide of SEQ ID NO: 338, or to the N-terminal coiled-coil region of human ANGPTL4 peptide of SEQ ID NO:

339;

e) binds human ANGPTL8 at 25°C with a K_D of less than about 150pM and binds monkey ANGPTL8 at 25°C with a K_D of less than about 90pM as measured by surface plasmon resonance;

f) lowers triglyceride levels in a mammal by about 68% (maximum) when administered subcutaneously at a dose of about 10 mg/kg;

g) lowers triglyceride levels in a mammal for a period ranging from about 7 days to 21 days, when administered subcutaneously at doses ranging from about 5 mg/kg to about 25 mg/kg;

h) comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 266, 274, 282, 290, 298, 306, 314 and 330;

i) comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, and 322; or

j) cross-competes with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0011] In one embodiment, an antibody or antigen-binding fragment thereof of the present disclosure can neutralize, inhibit, block, abrogate, reduce or interfere with, an activity of hANGPTL8 by binding to an epitope of hANGPTL8 that is directly involved in the targeted activity of hANGPTL8 (*e.g.* the LPL inhibitory activity of ANGPTL8).

[0012] In another embodiment, an antibody or antigen-binding fragment thereof of the disclosure can neutralize, inhibit, block, abrogate, reduce or interfere with, an activity of hANGPTL8 by binding to an epitope of hANGPTL8 that is not directly involved in the targeted activity of hANGPTL8, but the antibody or fragment binding thereto may either by steric overlap or by allosteric effects at sites different from the antibody-antigen contact surface inhibit, block, abrogate, reduce or interfere with, the targeted activity of hANGPTL8.

[0013] In another embodiment, an antibody or fragment thereof of the disclosure binds to an epitope of hANGPTL8 that is not directly involved in the targeted activity (*e.g.*, inhibiting LPL activity, and the like) of hANGPTL8 (*i.e.*, a non-blocking antibody), but the antibody or fragment thereof results in lowering of triglyceride levels *in vivo*, compared to the lowering of triglyceride levels in the absence of the antibody or fragment thereof.

[0014] In one embodiment, the disclosure features an isolated anti-hANGPTL8 antibody or antigen-binding fragment thereof that binds to an epitope situated within the N-terminal region at residues 1-39 of SEQ ID NO: 340 (shown also as SEQ ID NO: 337).

[0015] In another embodiment, the disclosure provides an isolated antibody or antigen-binding

fragment of an antibody that binds to an epitope situated within the N-terminal region of human ANGPTL8 at residues 1-39 of SEQ ID NO: 340 (shown also as SEQ ID NO: 337), but does not bind to the N-terminal coiled-coil region of hANGPTL3 (SEQ ID NO:338), or to the N-terminal coiled-coil region of hANGPTL4 (SEQ ID NO:339).

[0016] In one embodiment, the disclosure features an isolated anti-hANGPTL8 antibody or antigen-binding fragment thereof that binds to an epitope situated outside of the region of human ANGPTL8 defined by amino acid residues 1-39 of SEQ ID NO: 340 (shown also as SEQ ID NO: 337), i.e. amino acid residues 40-177 of SEQ ID NO: 340), and neutralizes, inhibits, abrogates, reduces or interferes with, at least one activity of hANGPTL8.

[0017] In one embodiment, the disclosure features an isolated anti-hANGPTL8 antibody or antigen-binding fragment thereof that binds to human ANGPTL8 (amino acid residues 1-177 of SEQ ID NO: 340; See also amino acid residues 22-198 of GenBank accession number NP_061157.3), but does not cross react with a related protein, such as human ANGPTL3 (amino acid sequence of SEQ ID NO: 342, encoded by the nucleic acid sequence shown in SEQ ID NO: 343), or human ANGPTL4 (amino acid sequence of SEQ ID NO: 344, encoded by the nucleic acid sequence shown in SEQ ID NO:345).

[0018] The antibodies of the disclosure can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, e.g., to increase persistence in the host or to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933). In certain embodiments, the antibodies may be bispecific.

[0019] Exemplary anti-ANGPTL8 antibodies of the present disclosure are listed in Tables 1 and 2 herein. Table 1 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of exemplary anti-ANGPTL8 antibodies. Table 2 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary anti-ANGPTL8 antibodies.

[0020] The present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0021] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0022] The present disclosure also provides antibodies, or antigen-binding fragments thereof,

comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1.

[0023] In one embodiment, the disclosure provides an isolated antibody or antigen-binding fragment thereof that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, wherein the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/250, 266/250, 274/250, 282/250, 290/250, 306/250, 314/322, and 330/322.

[0024] In one embodiment, the disclosure provides an isolated antibody or antigen-binding fragment thereof that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, wherein the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 66/74, 162/170, 194/202 and 314/322.

[0025] In one embodiment, the disclosure provides an isolated antibody or antigen-binding fragment thereof that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, wherein the antibody or antigen-binding fragment comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 162/170.

[0026] In one embodiment, the disclosure provides an isolated antibody or antigen-binding fragment thereof that binds to and/or inhibits at least one activity associated with ANGPTL8, wherein the antibody or antigen-binding fragment comprises: (a) three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences as set forth in Table 1; and (b) three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences as set forth in Table 1.

[0027] In one embodiment, the disclosure provides an isolated antibody or antigen-binding fragment thereof that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, wherein the antibody or antigen-binding fragment comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 268, 276, 284, 292, 300, 308, 316 and 332;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 270, 278, 286, 294, 302, 310, 318, and 334;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 272, 280, 288, 296, 304, 312, 320 and 336;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252 and 324;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, and 326; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256 and 328.

[0028] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0029] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0030] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0031] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0032] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0033] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0034] The present disclosure also provides antibodies, or antigen-binding fragments thereof,

comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino acid sequences listed in Table 1. According to certain embodiments, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-ANGPTL8 antibodies listed in Table 1. In certain embodiments, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 72/80 (*e.g.*, H4H15321P), 168/176 (*e.g.*, H4H15341P), 200/208 (*e.g.,* H4H15345P), and 320/328 (*e.g.,* H4H15367P2). In one embodiment, the HCDR3/LCDR3 amino acid sequence pair is SEQ ID NO: 168/176 (*e.g.*, H4H15341P).

[0035] The present disclosure also provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-ANGPTL8 antibodies listed in Table 1. In certain embodiments, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is selected from the group consisting of SEQ ID NOs: 68-70-72-76-78-80 (*e.g.*, H4H15321P); 164-166-168-172-174-176 (*e.g.,* H4H15341P); 196-198-200-204-206-208 (*e.g.*, H4H15345P); 316-318-320-324-326-328 (*e.g.*, H4H15367P2). In one embodiment, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is SEQ ID NOs: 164-166-168-172-174-176 (*e.g.,* H4H15341P).

[0036] In a related embodiment, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-ANGPTL8 antibodies listed in Table 1. For example, the present disclosure includes antibodies, or antigen-binding fragments thereof, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 66/74 *(e.g.,* H4H15321P), 162/170 (*e.g.*, H4H15341P); 194/202 (*e.g.*, H4H15345P); 314/322 (*e.g.,* H415367P2). Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for

identifying CDR sequences within an antibody.

[0037] The present disclosure includes anti-ANGPTL8 antibodies having a modified glycosylation pattern. In some embodiments, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al*. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0038] The present disclosure also provides for antibodies and antigen-binding fragments thereof that compete for specific binding to ANGPTL8 with a reference antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

[0039] In one embodiment, the disclosure provides an isolated monoclonal antibody or antigen-binding fragment thereof that competes for binding to ANGPTL8 with a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/250, 266/250, 274/250, 282/250, 290/250, 306/250, 314/322, and 330/322.

[0040] The present disclosure also provides antibodies and antigen-binding fragments thereof that bind the same epitope on ANGPTL8 as a reference antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

[0041] In one embodiment, the disclosure provides an isolated monoclonal antibody or antigen-binding fragment thereof that binds to the same epitope on ANGPTL8 as a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/250, 266/250, 274/250, 282/250, 290/250, 306/250, 314/322, and 330/322.

[0042] In one embodiment, the isolated antibody that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, is a recombinantly produced human monoclonal antibody.

[0043] In one embodiment, the isolated antibody that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, is a recombinantly produced human monoclonal antibody having a HCVR and/or an LCVR sequence selected from the amino acid sequences found in Table 1.

[0044] In one embodiment, the isolated antibody that binds specifically to and/or inhibits at

least one activity associated with ANGPTL8, is a recombinantly produced human monoclonal antibody having a HCVR /LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/250, 266/250, 274/250, 282/250, 290/250, 306/250, 314/322, and 330/322.

[0045] In one embodiment, the disclosure provides a fully human monoclonal antibody or antigen-binding fragment thereof that neutralizes ANGPTL8 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 266, 274, 282, 290, 298, 306, 314 and 330; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, and 322; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 272, 280, 288, 296, 304, 312, 320 and 336, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256 and 328, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 268, 276, 284, 292, 300, 308, 316 and 332, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 270, 278, 286, 294, 302, 310, 318, and 334, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252 and 324, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, and 326, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds specifically to the N-terminal region of human ANGPTL8 defined by SEQ ID NO: 337; vi) does not bind specifically to the N-terminal region of human ANGPTL8 defined by SEQ ID NO: 337; vii) does not bind to the N-terminal coiled-coil region of human ANGPTL3 peptide of SEQ ID NO: 338, or to the N-

terminal coiled-coil region of human ANGPTL4 peptide of SEQ ID NO: 339; viii) binds human ANGPTL8 at 25°C with a K_D of less than about 150pM and binds monkey ANGPTL8 at 25°C with a K_D of less than about 90pM as measured by surface plasmon resonance; ix) lowers triglyceride levels in a mammal by about 68% (maximum) when administered subcutaneously at a dose of about 10 mg/kg; x) lowers triglyceride levels in a mammal for a period ranging from about 7 days to 21 days, when administered subcutaneously at doses ranging from about 5 mg/kg to about 25 mg/kg; xi) cross-competes with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0046] In a second aspect, the present disclosure also provides nucleic acid molecules encoding anti-ANGPTL8 antibodies or portions thereof. For example, the present disclosure provides nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0047] The present disclosure also provides nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0048] The present disclosure also provides nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0049] The present disclosure also provides nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0050] The present disclosure also provides nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0051] The present disclosure also provides nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0052] The present disclosure also provides nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0053] The present disclosure also provides nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1. In certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0054] The present disclosure also provides nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-ANGPTL8 antibodies listed in Table 1.

[0055] The present disclosure also provides nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary anti-ANGPTL8 antibodies listed in Table 1.

[0056] The present disclosure also provides nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain embodiments according to this aspect of the disclosure, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-ANGPTL8 antibody listed in Table 1.

[0057] The present disclosure also provides recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-ANGPTL8

antibody. For example, the present disclosure includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 1. Also included within the scope of the present disclosure are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[0058] In one embodiment, the isolated antibody that binds specifically to and/or inhibits at least one activity associated with ANGPTL8, is a recombinantly produced human monoclonal antibody having a HCVR and/or a LCVR encoded by a nucleic acid sequence selected from the nucleic acid sequences found in Table 2.

[0059] In one embodiment, the disclosure provides an isolated nucleic acid molecule encoding an antibody or fragment thereof that binds specifically to human ANGPTL8, wherein the antibody or an antigen binding fragment thereof comprises (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having an amino acid sequence as set forth in Table 1; and (b) the CDRs of a light chain variable region (LCVR) having an amino acid sequence as set forth in Table 1.

[0060] In one embodiment, the disclosure provides an isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof that binds specifically to human ANGPTL8, wherein the antibody or antigen-binding fragment comprises an HCVR selected from the group consisting of an amino acid sequence as set forth in Table 1 and a LCVR selected from the group consisting of an amino acid sequence as set forth in Table 1.

[0061] In a third aspect, the disclosure provides a pharmaceutical composition comprising a recombinant human monoclonal antibody or antigen-binding fragment thereof, which specifically binds ANGPTL8 and a pharmaceutically acceptable carrier.

[0062] In one embodiment, the disclosure provide a pharmaceutical composition comprising at least one antibody specific for human ANGPTL8 selected from an antibody or an antigen-binding fragment thereof of any of the anti-ANGPTL8 antibodies found in Table 1 and a pharmaceutically acceptable carrier or diluent.

[0063] In a related aspect, the disclosure features a composition, which is a combination of an anti-ANGPTL8 antibody and a second therapeutic agent. In one embodiment, the second therapeutic agent is any agent that is advantageously combined with an anti-ANGPTL8 antibody.

[0064] In one embodiment, the second therapeutic agent may be an agent capable of lowering triglycerides or reducing at least one symptom in a patient suffering from a disease or condition characterized by high triglyceride levels, such as hypertriglyceridemia.

[0065] In certain embodiments, the second therapeutic agent may be an agent that helps to

counteract or reduce any possible side effect(s) associated with the antibody or antigen-binding fragment of an antibody of the disclosure, if such side effect(s) should occur.

[0066] The second therapeutic agent may be a small molecule drug, a protein/polypeptide, an antibody, a nucleic acid molecule, such as an anti-sense molecule, or a siRNA. The second therapeutic agent may be synthetic or naturally derived.

[0067] It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present disclosure can be employed in other combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (*e.g.,* control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

[0068] In a related embodiment, the disclosure features a composition, which is a combination of an antibody or antigen-binding fragment thereof of the disclosure, and a second therapeutic agent, such as (1) 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, such as cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, and the like; (2) inhibitors of cholesterol uptake and/or bile acid re-absorption; (3) niacin, which increases lipoprotein catabolism; (4) fibrates or amphipathic carboxylic acids, which reduce TG level, low-density lipoprotein (LDL) level and improve high-density lipoprotein (HDL) levels; and (5) activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol, or fixed combinations such as ezetimibe plus simvastatin; a statin with a bile resin (*e.g.*, cholestyramine, colestipol, colesevelam), a fixed combination of niacin plus a statin (*e.g.*, niacin with lovastatin); or with other lipid lowering agents such as omega-3-fatty acid ethyl esters (for example, omacor).

[0069] Furthermore, the second therapeutic agent can be one or more other inhibitors of ANGPTL8 as well as inhibitors of other molecules, such as ANGPTL3, ANGPTL4, ANGPTL5, ANGPTL6, apolipoprotein C-III (APOC3) and proprotein convertase subtilisin/kexin type 9 (PCSK9), which are involved in lipid metabolism, in particular, cholesterol and/or triglyceride homeostasis. Inhibitors of these molecules include small molecules, antisense molecules and antibodies that specifically bind to these molecules and block their activity.

[0070] In one embodiment, if the anti-ANGPTL8 antibodies of the disclosure are used to treat a disease such as diabetes (*e.g.,* type 2 diabetes), then these antibodies may be used in

combination with one or more of the following treatments for diabetes that are currently available. These include the following: insulin, an insulin analog (see below), a biguanide (metformin), a sulfonylurea (e.g. glyburide, glipizide), a PPAR gamma agonist (e.g. pioglitazone, rosiglitazone), an alpha glucosidase inhibitor (e.g. acarbose, voglibose), a glucagon-like peptide 1 (GLP-1) agonist (e.g., BYETTA® (exenatide), TRULICITY™(dulaglutide), VICTOZA® (liraglutide), Lyxumia® (lixisenatide), Tanzeum™ (albiglutide)), a dipeptidyl peptidase IV (DPP-4) inhibitor (e.g. saxagliptin (ONGLYZA®), sitaliptin (JANUVIA®), and vildagliptin (GALVUS®), a sodium-glucose co-transporter 2 (SGLT2) inhibitor (e.g., INVOKANA™ (canagliflozin), FORXIGA® (dapagliflozin), empagliflozin, ipragliflozin, tofogliflozin), SYMLIN® (pramlintide), a glucagon receptor antagonist (as described in, for example, US8545847), and a glucagon antagonist.

[0071] In certain related embodiments, the composition may include a second agent selected from the group consisting of non-sulfonylurea secretagogues, insulin analogs, including fast acting (*e.g.,* Lispro, Aspart, Glulisine) and long acting (*e.g.* Detemir insulin, Degludec insulin, or Glargine insulin, exendin-4 polypeptides, beta 3 adrenoceptor agonists, inhibitors of cholesterol uptake and/or bile acid re-absorption, LDL-cholesterol antagonists, cholesteryl ester transfer protein antagonists (*e.g.* torcetrapib, anacetrapib, dalcetrapib, or evacetrapib), endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, amylin mimetics or agonists, cannabinoid receptor antagonists, glucagon-like peptide-1 receptor agonists, melanocortins, melanin-concentrating hormone receptor agonists, SNRIs, a fibroblast growth factor 21 (FGF21) mimetic (See, for example, US20110002845 and US20080261236), a fibroblast growth factor receptor 1c (FGFR1c) agonist (See, for example, US20110150901), an inhibitor of advanced glycation end product formation, such as, but not limited to, aminoguanidine, and protein tyrosine phosphatase inhibitors.

[0072] In related embodiments, the second therapeutic agent may be one or more other therapeutic agents, such as analgesics, anti-inflammatory agents, including non-steroidal anti-inflammatory drugs (NSAIDS), such as Cox-2 inhibitors, and the like, so as to ameliorate and/or reduce the symptoms accompanying the underlying condition, if needed.

[0073] In a fourth aspect, the disclosure provides a method for neutralizing, inhibiting, blocking, abrogating, reducing or interfering with, at least one activity associated with ANGPTL8 in a patient in need thereof, the method comprising administering any one or more of the antibodies of the disclosure, as found in Table 1, or a pharmaceutical composition comprising any one or more of these antibodies to a patient in need thereof, wherein at least one activity associated with ANGPTL8 is reduced or diminished.

[0074] In one embodiment, the disclosure provides a therapeutic method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising one or more anti-hANGPTL8 antibodies or antigen-binding fragments

thereof of the disclosure and, optionally one or more additional therapeutic agents as described above.

[0075] In a fifth aspect, the disclosure provides a method for treating a disease or condition associated in part with elevated expression and/or activity of ANGPTL8, the method comprising administering an ANGPTL8 inhibitor/antagonist, wherein the ANGPTL8 inhibitor/antagonist is an antibody or an antigen-binding fragment thereof specific for ANGPTL8. In one embodiment, the antibody or an antigen-binding fragment thereof specific for ANGPTL8 comprises an HCVR selected from the group consisting of an amino acid sequence from Table 1 and a LCVR selected from the group consisting of an amino acid sequence from Table 1.

[0076] In one embodiment, the disease or disorder treatable by the methods of the disclosure is any disease or condition which is improved, ameliorated, inhibited or prevented, or at least one symptom associated with the disease is reduced in severity or frequency of occurrence, compared to that without anti-hANGPTL8 antibody treatment (*e.g.*, ANGPTL8-mediated diseases or disorders), by removing, inhibiting, reducing, or otherwise interfering with, ANGPTL8 activity. Examples of diseases or disorders treatable by the methods of the disclosure include, but are not limited to, those involving lipid metabolism, such as hyperlipidemia, hyperlipoproteinemia and dyslipidemia, including atherogenic dyslipidemia, diabetic dyslipidemia, hypertriglyceridemia, including severe hypertriglyceridemia with TG > 1000 mg/dL and associated acute pancreatitis, hypercholesterolemia, chylomicronemia, mixed dyslipidemia (obesity, metabolic syndrome, diabetes, etc.), lipodystrophy, lipoatrophy, and the like, which are caused by, for example, decreased LPL activity and/or LPL deficiency, altered ApoC2, ApoE deficiency, increased ApoB, increased production and/or decreased elimination of very low-density lipoprotein (VLDL), certain drug treatment (*e.g.*, glucocorticoid treatment-induced dyslipidemia), any genetic predisposition, diet, life style, and the like.

[0077] The methods of the disclosure can also prevent or treat diseases or disorders associated with or resulting from triglyceridemia, hypertriglyceridemia, hyperlipidemia, hyper-lipoproteinemia, and/or dyslipidemia, including, but not limited to, cardiovascular diseases or disorders, such as atherosclerosis, aneurysm, hypertension, angina, stroke, cerebrovascular diseases, congestive heart failure, coronary artery diseases, myocardial infarction, peripheral vascular diseases, and the like; acute pancreatitis; nonalcoholic steatohepatitis (NASH); blood sugar disorders, such as diabetes; obesity, and the like.

[0078] In one embodiment, at least one antibody of the disclosure, or an antigen-binding fragment thereof, may be used to treat metabolic syndrome associated dyslipidemia, obesity, or for preventing weight gain, or for maintaining a normal weight.

[0079] In one embodiment, the disclosure provides a method for lowering blood triglyceride levels, or for treating a condition or disease associated with, or characterized in part by high blood triglyceride levels, or at least one symptom or complication associated with the condition

or disease, the method comprising administering a pharmaceutical composition comprising one or more antibodies specific for human ANGPTL8 from Table 1, to a patient in need thereof, such that blood triglyceride levels are lowered or that the condition or disease is mediated, or at least one symptom or complication associated with the condition or disease is alleviated or reduced in severity.

[0080] In one embodiment, at least one antibody of the disclosure, or an antigen-binding fragment thereof, may be used alone or in combination with a second or third therapeutic agent to treat hypertriglyceridemia, or at least one symptom associated with hypertriglyceridemia, or may be used to treat a patient at risk for acquiring hypertriglyceridemia, for example, in a patient who has a genetic predisposition for developing hypertriglyceridemia, *e.g.* familial hypertriglyceridemia or familial dysbetalipoproteinemia.

[0081] Other conditions may predispose a patient to high levels of triglycerides. For example, certain medications such as beta blockers, birth control pills, diuretics, steroids, or the use of tamoxifen may lead to elevated levels of triglycerides and as such, may increase a patient's likelihood of developing conditions, or complications associated with high levels of triglycerides, such as atherosclerosis, stroke, heart attack, and other cardiac conditions.

[0082] In addition, certain other conditions may lead to high levels of triglycerides, including obesity, poorly controlled diabetes, hypothyroidism, kidney disease, or alcohol consumption.

[0083] In one embodiment, the antibodies may be used to prevent the onset of a disease or disorder characterized in part by elevated blood triglyceride levels, or to prevent the likelihood of developing such disease or disorder, or to mitigate the severity of the disease or disorder, or at least one symptom associated with the disease or disorder. It is envisioned that the antibodies of the disclosure may be used alone, or as adjunct therapy with other agents or methods known to be standard care for treating patients suffering from diseases or conditions characterized in part by elevated blood triglyceride levels, such as, but not limited to, hypertriglyceridemia. Such standard therapy may include fluid administration, or administration of any other pharmaceutical agents useful for lowering blood triglycerides, or lipids, or for weight reduction.

[0084] In one embodiment, the use of the antibodies described herein, may be an effective means of achieving normal levels of triglycerides, thereby ameliorating, or preventing one or more symptoms of, or long term complications associated with a disease characterized by high triglyceride levels.

[0085] In one embodiment, the antibodies of the disclosure may be used in the preparation of a medicament for use in treating any disease or disorder characterized in part by elevated levels of triglycerides.

[0086] The antibodies of the disclosure may be used as short-term therapy in an acute setting, or they may be envisioned for long-term use as chronic therapy.

[0087] Other embodiments will become apparent from a review of the ensuing detailed

description.

BRIEF DESCRIPTION OF THE FIGURES

[0088] **Figure 1** shows the mean +/- SEM of serum triglyceride and total cholesterol concentration in humanized ANGPTL8 mice administered a single subcutaneous dose of H4H15341P. Doses administered were 1, 5, 10, or 25 mg/kg on day 0 of the study. Statistical comparison was done by 2-way ANOVA of differences from Control Ab, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

[0089] **Figure 2** shows the levels of circulating anti-human antibody after administration of one subcutaneous dose of H4H15341P at doses of 1, 5, 10, or 25 mg/kg.

[0090] **Figure 3** shows the effect of the H4H15341P mAb on serum lipoprotein lipase (LPL) and hepatic lipase in ANGPTL8 mice compared to control antibody. Statistics were done by unpaired student's t-test; **p<0.01

[0091] **Figure 4** shows the effect of the mAb H4H15341P in a lipid tolerance test in ANGPTL8 mice. Administration of the H4H15341P mAb was assessed for lowering of triglyceride levels after acute fat loading compared to control antibody. Statistics were done by 2-way ANOVA with Bonferroni post-test; ****p<0.0001

DETAILED DESCRIPTION

[0092] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0093] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0094] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All patents, applications and non-patent publications mentioned in this specification are incorporated herein by reference in their entireties.

Definitions

[0095] "Angiopoietin-like protein 8" or, "ANGPTL8," is a member of the angiopoietin family of proteins, and is sometimes referred to as TD26, RIFL, Lipasin, C19orf80 and Betatrophin. "ANGPTL8", as used herein, refers to human ANGPTL8 comprising the amino acid sequence as set forth in amino acid residues 1-177 of SEQ ID NO: 340. The full-length human ANGPTL8 amino acid sequence, including the signal sequence, can also be found in GenBank accession number NP_061157.3, while the full-length nucleic acid sequence encoding human ANGPTL8 can be found in GenBank accession number NM_018687.6. The N-terminal coiled-coil domain of human ANGPTL8 spans amino acid residues 1-39 of SEQ ID NO: 340 and is also depicted as SEQ ID NO: 337. All references to proteins, polypeptides and protein fragments herein are intended to refer to the human version of the respective protein, polypeptide or protein fragment unless explicitly specified as being from a non-human species. Thus, the expression "ANGPTL8" means human ANGPTL8 unless specified as being from a non-human species,

e.g., "mouse ANGPTL8," "monkey ANGPTL8," etc.

[0096] The term “human angiopoietin-like protein 3” or "hANGPTL3", as used herein, refers to ANGPTL3 having the nucleic acid sequence shown in SEQ ID NO:343 and the amino acid sequence of SEQ ID NO:342, or a biologically active fragment thereof. The N-terminal coiled-coil domain of human ANGPTL3 is depicted as SEQ ID NO: 338.

[0097] The term “human angiopoietin-like protein 4” or "hANGPTL4", as used herein, refers to ANGPTL4 having the nucleic acid sequence shown in SEQ ID NO:345 and the amino acid sequence of SEQ ID NO:344, or a biologically active fragment thereof.` The N-terminal coiled-coil domain of human ANGPTL4 is depicted as SEQ ID NO: 339.

[0098] The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety (“immunoconjugate”), such as a second ANGPTL8 antagonist, or any other therapeutic moiety useful for treating a disease or condition caused in part by elevated triglyceride levels.

[0099] As used herein, the expression "anti-ANGPTL8 antibody" includes both monovalent antibodies with a single specificity, as well as bispecific antibodies comprising a first arm that binds ANGPTL8 and a second arm that binds a second (target) antigen, wherein the anti-ANGPTL8 arm comprises any of the HCVR/LCVR or CDR sequences as set forth in Table 1 herein.

[0100] The term "antibody", as used herein, means any antigen-binding molecule or molecular complex comprising at least one complementarity determining region (CDR) that specifically binds to or interacts with a particular antigen (*e.g.*, ANGPTL8). The term "antibody" includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the anti-ANGPTL8 antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0101] The term "antibody", as used herein, also includes antigen-binding fragments of full

antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0102] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0103] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0104] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations

listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[0105] As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (*e.g.*, bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

[0106] The term "human antibody", as used herein, is intended to include non-naturally occurring human antibodies. The term includes antibodies that are recombinantly produced in a non-human mammal, or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject.

[0107] The antibodies of the invention may, in some embodiments, be recombinant human antibodies. The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. In certain embodiments, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0108] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via inter-chain disulfide bonds and a

molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[0109] The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) Molecular Immunology 30:105) to levels typically observed using a human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, C_H2 or C_H3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

[0110] The antibodies of the invention may be isolated antibodies. An "isolated antibody," as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody" for purposes of the present invention. An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0111] The anti-ANGPTL8 antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to sequences available from, for example, public antibody sequence databases. Once obtained, antibodies and antigen-binding fragments that contain one or more mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0112] The present invention also includes anti-ANGPTL8 antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes anti-ANGPTL8 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, *e.g.*, 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences set forth in Table 1 herein.

[0113] A “blocking antibody” or a "neutralizing antibody", as used herein (or an "antibody that

neutralizes ANGPTL8 activity"), is intended to refer to an antibody whose binding to and/or interaction with ANGPTL8 results in inhibition of at least one biological activity of ANGPTL8. For example, an antibody of the invention may inhibit the lipoprotein lipase inhibitory activity of ANGPTL8, or it may lower plasma triglycerides through a mechanism other than through inhibition of the LPL inhibitory activity of ANGPTL8. This inhibition of the biological activity of ANGPTL8 can be assessed by measuring one or more indicators of ANGPTL8 biological activity by one or more of several standard *in vitro* or *in vivo* assays known in the art. An alternate activity is the triglyceride lowering activity associated with an antibody of the invention.

[0114] The term "surface plasmon resonance", or "SPR", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using a BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.), or a MASS-1 system (Sierra Sensors, Hamburg, Germany and Greenville, RI).

[0115] The term "K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0116] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0117] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0118] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A "conservative amino acid

substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. *See, e.g.*, Pearson (1994) Methods Mol. Biol. 24: 307-331, herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443-1445, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0119] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, *e.g.,* GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (*e.g.,* FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, *e.g.,* Altschul *et al.* (1990) J. Mol. Biol. 215: 403 410 and (1997) Nucleic Acids Res. 25:3389 402, each of which is herein incorporated by reference.

[0120] By the phrase “therapeutically effective amount” is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for

example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0121] The term “treating” or “treatment”, as used herein, refers to an approach for obtaining beneficial or desired clinical results. In one embodiment of the invention, a beneficial or desired clinical result includes, but is not limited to, an improvement in blood triglyceride levels, or an improvement in any one or more conditions, diseases, or symptoms associated with, or resulting from, elevated levels of triglycerides, including, but not limited to hypertriglyceridemia, etc.

pH-Dependent Binding

[0122] The present invention includes anti-ANGPTL8 antibodies with pH-dependent binding characteristics. For example, an anti-ANGPTL8 antibody of the present invention may exhibit reduced binding to ANGPTL8 at acidic pH as compared to neutral pH. Alternatively, anti-ANGPTL8 antibodies of the invention may exhibit enhanced binding to ANGPTL8 at acidic pH as compared to neutral pH. The expression "acidic pH" includes pH values less than about 6.2, *e.g.*, about 6.0, 5.95, 5,9, 5.85, 5.8, 5.75, 5.7, 5.65, 5.6, 5.55, 5.5, 5.45, 5.4, 5.35, 5.3, 5.25, 5.2, 5.15, 5.1, 5.05, 5.0, or less. As used herein, the expression "neutral pH" means a pH of about 7.0 to about 7.4. The expression "neutral pH" includes pH values of about 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, and 7.4.

[0123] In certain instances, "reduced binding to ANGPTL8 at acidic pH as compared to neutral pH" is expressed in terms of a ratio of the K_D value of the antibody binding to ANGPTL8 at acidic pH to the K_D value of the antibody binding to ANGPTL8 at neutral pH (or vice versa). For example, an antibody or antigen-binding fragment thereof may be regarded as exhibiting "reduced binding to ANGPTL8 at acidic pH as compared to neutral pH" for purposes of the present invention if the antibody or antigen-binding fragment thereof exhibits an acidic/neutral K_D ratio of about 3.0 or greater. In certain exemplary embodiments, the acidic/neutral K_D ratio for an antibody or antigen-binding fragment of the present invention can be about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 20.0. 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 100.0 or greater.

[0124] Antibodies with pH-dependent binding characteristics may be obtained, *e.g.*, by screening a population of antibodies for reduced (or enhanced) binding to a particular antigen at acidic pH as compared to neutral pH. Additionally, modifications of the antigen-binding domain at the amino acid level may yield antibodies with pH-dependent characteristics. For example, by substituting one or more amino acids of an antigen-binding domain (*e.g.*, within a CDR) with a histidine residue, an antibody with reduced antigen-binding at acidic pH relative to neutral pH may be obtained.

Anti-ANGPTL8 Antibodies Comprising Fc Variants

[0125] According to certain embodiments of the present invention, anti-ANGPTL8 antibodies

are provided comprising an Fc domain comprising one or more mutations, which enhance or diminish antibody binding to the FcRn receptor, *e.g.*, at acidic pH as compared to neutral pH. For example, the present invention includes anti-ANGPTL8 antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.,* in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (*e.g.,* A, W, H, F or Y [N434A, N434W, N434H, N434F or N434Y]); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (*e.g.,* 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (*e.g.,* M428L) and 434S (*e.g.,* N434S) modification; a 428L, 259I (*e.g.,* V259I), and 308F (*e.g.,* V308F) modification; a 433K (*e.g.,* H433K) and a 434 (*e.g.,* 434Y) modification; a 252, 254, and 256 (*e.g.,* 252Y, 254T, and 256E) modification; a 250Q and 428L modification (*e.g.,* T250Q and M428L); and a 307 and/or 308 modification (*e.g.,* 308F or 308P). In yet another embodiment, the modification comprises a 265A (*e.g.*, D265A) and/or a 297A (*e.g.*, N297A) modification.

[0126] For example, the present invention includes anti-ANGPTL8 antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (*e.g.*, T250Q and M248L); 252Y, 254T and 256E (*e.g.*, M252Y, S254T and T256E); 428L and 434S (*e.g.*, M428L and N434S); 257I and 311I (*e.g.*, P257I and Q311I); 257I and 434H (*e.g.*, P257I and N434H); 376V and 434H (*e.g.*, D376V and N434H); 307A, 380A and 434A (*e.g.*, T307A, E380A and N434A); and 433K and 434F (*e.g.*, H433K and N434F). All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present invention.

[0127] The present invention also includes anti-ANGPTL8 antibodies comprising a chimeric heavy chain constant (C_H) region, wherein the chimeric C_H region comprises segments derived from the C_H regions of more than one immunoglobulin isotype. For example, the antibodies of the invention may comprise a chimeric C_H region comprising part or all of a C_H2 domain derived from a human IgG1, human IgG2 or human IgG4 molecule, combined with part or all of a C_H3 domain derived from a human IgG1, human IgG2 or human IgG4 molecule. According to certain embodiments, the antibodies of the invention comprise a chimeric C_H region having a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" amino acid sequence (amino acid residues from positions 216 to 227 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence (amino acid residues from positions 228 to 236 according to EU

numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. According to certain embodiments, the chimeric hinge region comprises amino acid residues derived from a human IgG1 or a human IgG4 upper hinge and amino acid residues derived from a human IgG2 lower hinge. An antibody comprising a chimeric C_H region as described herein may, in certain embodiments, exhibit modified Fc effector functions without adversely affecting the therapeutic or pharmacokinetic properties of the antibody. (*See*, *e.g.*, U.S. Provisional Appl. No. 61/759,578, filed February 1, 2013, the disclosure of which is hereby incorporated by reference in its entirety).

Biological Characteristics of the Antibodies

[0128] The present invention includes antibodies and antigen-binding fragments thereof that bind ANGPTL8 with high affinity. For example, the present invention includes anti-ANGPTL8 antibodies that bind human or monkey ANGPTL8 with a K_D of less than about 150 nM, as measured by surface plasmon resonance (SPR) at 25ºC, or at 37ºC, *e.g.*, using recombinant ANGPTL8 protein with a mouse IgG2a Fc C-terminal fusion, in an assay format as defined in Examples 3 and 4 herein, or a substantially similar assay. According to certain embodiments, anti-ANGPTL8 antibodies are provided that bind human or monkey ANGPTL8 at 25ºC or 37ºC with a K_D of less than about 90 nM, or less than about 50 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM, less than about 900 pM, less than about 500 pM, less than about 300 pM, less than about 150 pM, or less than about 90 pM, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in Examples 3 and 4 herein, or a substantially similar assay.

[0129] The present invention also includes antibodies and antigen-binding fragments thereof that bind the peptide of SEQ ID NO: 337 derived from the N-terminal region of human ANGPTL8 with a dissociative half-life (t½) of greater than about 100 minutes as measured by surface plasmon resonance at 25ºC or 37ºC, *e.g.*, using an assay format as defined in Example 3 herein, or a substantially similar assay. According to certain embodiments, anti-ANGPTL8 antibodies are provided that bind peptides derived from the N-terminal region of human ANGPTL8 at 25ºC with a t½ of greater than or equal to about 110 minutes, greater than about 120 minutes, greater than about 130 minutes, greater than about 200 minutes, greater than about 300 minutes, greater than about 400 minutes, greater than about 500 minutes, or longer, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in Example 3 herein, or a substantially similar assay.

[0130] The present invention also includes antibodies and antigen-binding fragments thereof that lower triglycerides in a mammal by about 20%, or by about 30%, or by about 40%, or by about 50%, or by about 60%, or greater when administered subcutaneously at a dose of about

0.1mg/kg, or about 1mg/kg, or about 10mg/kg, or about 25mg/kg, or about 50mg/kg, or about 100mg/kg. The effect of an antibody of the invention on lowering plasma triglycerides may last from at least 7 days after administration to about 3 weeks, or 4 weeks after administration, or longer.

[0131] An antibody of the invention comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 266, 274, 282, 290, 298, 306, 314 and 330; and

a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, and 322; or may cross-compete with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0132] An antibody of the invention may comprise a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/250, 266/250, 274/250, 282/250, 290/250, 306/250, 314/322, and 330/322.

[0133] An antibody of the invention may comprise:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 268, 276, 284, 292, 300, 308, 316 and 332;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 270, 278, 286, 294, 302, 310, 318, and 334;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 272, 280, 288, 296, 304, 312, 320 and 336;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252 and 324;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, and 326; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256 and 328.

[0134] The antibodies of the present invention may possess one or more of the aforementioned biological characteristics, or any combination thereof. The foregoing list of biological characteristics of the antibodies of the invention is not intended to be exhaustive. Other biological characteristics of the antibodies of the present invention will be evident to a person of ordinary skill in the art from a review of the present disclosure including the working Examples herein.

Epitope Mapping and Related Technologies

[0135] The epitope to which the antibodies of the present invention bind may consist of a single contiguous sequence of 3 or more (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids of an ANGPTL8 protein. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) of ANGPTL8.

[0136] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques include, *e.g.*, routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY), alanine scanning mutational analysis, peptide blots analysis (Reineke, 2004, Methods Mol Biol 248:443-463), and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, Protein Science 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. *See, e.g.*, Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem. 73*:256A-265A.

[0137] The present invention further includes anti-ANGPTL8 antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (*e.g.* antibodies comprising any of the amino acid sequences as set forth in Table 1 herein). Likewise, the present invention also includes anti-ANGPTL8 antibodies that compete for binding to ANGPTL8 with any of the specific exemplary antibodies described herein (*e.g.* antibodies comprising any of the amino acid sequences as set forth in Table 1 herein).

[0138] One can easily determine whether an antibody binds to the same epitope as, or

competes for binding with, a reference anti-ANGPTL8 antibody by using routine methods known in the art and exemplified herein. For example, to determine if a test antibody binds to the same epitope as a reference anti-ANGPTL8 antibody of the invention, the reference antibody is allowed to bind to an ANGPTL8 protein. Next, the ability of a test antibody to bind to the ANGPTL8 molecule is assessed. If the test antibody is able to bind to ANGPTL8 following saturation binding with the reference anti-ANGPTL8 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-ANGPTL8 antibody. On the other hand, if the test antibody is not able to bind to the ANGPTL8 molecule following saturation binding with the reference anti-ANGPTL8 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-ANGPTL8 antibody of the invention. Additional routine experimentation (*e.g.*, peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present invention, two antibodies bind to the same (or overlapping) epitope if, *e.g.*, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990:50:1495-1502). Alternatively, two antibodies are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0139] To determine if an antibody competes for binding (or cross-competes for binding) with a reference anti-ANGPTL8 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a ANGPTL8 protein under saturating conditions followed by assessment of binding of the test antibody to the ANGPTL8 molecule. In a second orientation, the test antibody is allowed to bind to an ANGPTL8 molecule under saturating conditions followed by assessment of binding of the reference antibody to the ANGPTL8 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the ANGPTL8 molecule, then it is concluded that the test antibody and the reference antibody compete for binding to ANGPTL8. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Preparation of Human Antibodies

[0140] The anti-ANGPTL8 antibodies of the present invention can be fully human (non-naturally occurring) antibodies. Methods for generating monoclonal antibodies, including fully human monoclonal antibodies are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human ANGPTL8.

[0141] Using VELOCIMMUNE® technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to an allergen are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[0142] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0143] As described in the experimental section below, the high affinity chimeric antibodies, which are isolated having a human variable region and a mouse constant region, are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are then replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0144] In general, the antibodies of the instant invention possess very high affinities, typically possessing K_D of from about 10^{-12} through about 10^{-9} M, when measured by binding to antigen either immobilized on solid phase or in solution phase.

Bioequivalents

[0145] The anti-ANGPTL8 antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind human ANGPTL8. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the anti-ANGPTL8 antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-ANGPTL8 antibody or antibody fragment that is essentially bioequivalent to an anti-ANGPTL8 antibody or antibody fragment of the invention. Examples of such variant amino acid and DNA sequences are discussed above.

[0146] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, *e.g.*, chronic use, and are considered medically insignificant for the particular drug product studied.

[0147] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0148] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0149] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0150] Bioequivalence may be demonstrated by *in vivo* and *in vitro* methods. Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other

mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0151] Bioequivalent variants of anti-ANGPTL8 antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include anti-ANGPTL8 antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, *e.g.*, mutations which eliminate or remove glycosylation.

Multispecific Antibodies

[0152] The antibodies of the present invention may be monospecific or multispecific (*e.g.*, bispecific). Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., 1991, J. Immunol. 147:60-69; Kufer *et al.*, 2004, Trends Biotechnol. 22:238-244. The anti-ANGPTL8 antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multispecific antibody with a second binding specificity.

[0153] The present invention includes bispecific antibodies wherein one arm of an immunoglobulin binds human ANGPTL8, and the other arm of the immunoglobulin is specific for a second antigen. The ANGPTL8-binding arm can comprise any of the HCVR/LCVR or CDR amino acid sequences as set forth in Table 1 herein.

[0154] An exemplary bispecific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and

V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bispecific antibody format described above are contemplated within the scope of the present invention.

[0155] Other exemplary bispecific formats that can be used in the context of the present invention include, without limitation, *e.g.*, scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (*e.g.*, common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED)body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab^2 bispecific formats (*see*, *e.g.*, Klein *et al.* 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, *e.g.*, wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (*See*, *e.g.*, Kazane *et al.*, *J. Am. Chem. Soc.* [*Epub*: *Dec. 4, 2012*]).

Therapeutic Formulation and Administration

[0156] The invention provides pharmaceutical compositions comprising the anti-ANGPTL8 antibodies or antigen-binding fragments thereof of the present invention. The pharmaceutical compositions of the invention are formulated with suitable carriers, excipients, and other agents that provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™, Life Technologies, Carlsbad, CA), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0157] The dose of antibody administered to a patient may vary depending upon the age and the size of the patient, target disease, conditions, route of administration, and the like. The preferred dose is typically calculated according to body weight or body surface area. In an adult patient, it may be advantageous to intravenously administer the antibody of the present invention normally at a single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering anti-ANGPTL8 antibodies may be determined empirically; for example, patient progress can be monitored by

periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (*e.g.*, Mordenti *et al.*, 1991, *Pharmaceut. Res. 8*:1351).

[0158] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0159] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0160] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (Sanofi-Aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but are not limited to the SOLOSTAR™ pen (Sanofi-Aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand

Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL), to name only a few.

[0161] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0162] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0163] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Immunoconjugates

[0164] The invention encompasses a human anti-ANGPTL8 monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing blood triglyceride or lipid levels. The type of therapeutic moiety that may be conjugated to the anti-ANGPTL8 antibody will take into account the condition to be treated and the desired therapeutic

effect to be achieved. For example, for treating hypertriglyceridemia, or any other condition whereby it is desirable to lower blood triglycerides, and/or to maintain normal blood triglyceride levels, an agent may be conjugated to the ANGPTL8 antibody. Alternatively, if the desired therapeutic effect is to treat the sequelae or symptoms associated with hypertriglyceridemia, or any other condition resulting from high, or uncontrolled blood triglyceride levels, it may be advantageous to conjugate an agent appropriate to treat the sequelae or symptoms of the condition. Examples of suitable agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Therapeutic Uses of the Antibodies

[0165] The present antibodies are useful for lowering blood triglyceride levels, for example, in a patient suffering from hypertriglyceridemia, and also for the treatment of a wide range of conditions and disorders in which inhibiting the activity of ANGPTL8 is beneficial. Thus, the antibodies may find use for example to prevent, treat, or alleviate, diseases or conditions or associated symptoms or sequelae, of the endocrine system, the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, and the gastrointestinal system, while reducing and or eliminating one or more of the unwanted side effects associated with the current treatments.

[0166] For example, the antibodies of the invention may be used to treat a disease or disorder including, but not limited to, those involving lipid metabolism, such as hyperlipidemia, hyperlipoproteinemia and dyslipidemia, including atherogenic dyslipidemia, diabetic dyslipidemia, hypertriglyceridemia, including severe hypertriglyceridemia with TG > 1000 mg/dL and associated acute pancreatitis, hypercholesterolemia, chylomicronemia, mixed dyslipidemia (obesity, metabolic syndrome, diabetes, etc.), lipodystrophy, lipoatrophy, and the like, which are caused by, for example, decreased LPL activity and/or LPL deficiency, altered ApoC2, ApoE deficiency, increased ApoB, increased production and/or decreased elimination of very low-density lipoprotein (VLDL), certain drug treatment (*e.g.*, glucocorticoid treatment-induced dyslipidemia), any genetic predisposition, diet, life style, and the like.

[0167] The methods of the invention can also prevent or treat diseases or disorders associated with or resulting from triglyceridemia, hypertriglyceridemia, hyperlipidemia, hyper-lipoproteinemia, and/or dyslipidemia, including, but not limited to, cardiovascular diseases or disorders, such as atherosclerosis, aneurysm, hypertension, angina, stroke, cerebrovascular diseases, congestive heart failure, coronary artery diseases, myocardial infarction, peripheral vascular diseases, and the like; acute pancreatitis; nonalcoholic steatohepatitis (NASH); blood sugar disorders, such as diabetes (e.g. Type II diabetes); obesity, and the like.

[0168] In one embodiment, at least one antibody of the invention, or an antigen-binding fragment thereof, may be used to treat metabolic syndrome associated dyslipidemia, obesity, or for preventing weight gain, or for maintaining a normal weight.

[0169] In one embodiment, the invention provides a method for lowering blood triglyceride levels, or for treating a condition or disease associated with, or characterized in part by high blood triglyceride levels, or at least one symptom or complication associated with the condition or disease, the method comprising administering a pharmaceutical composition comprising one or more antibodies specific for human ANGPTL8 from Table 1, to a patient in need thereof, such that blood triglyceride levels are lowered or that the condition or disease is mediated, or at least one symptom or complication associated with the condition or disease is alleviated or reduced in severity.

[0170] In one embodiment, at least one antibody of the invention, or an antigen-binding fragment thereof, may be used alone or in combination with a second or third therapeutic agent to treat hypertriglyceridemia, or at least one symptom associated with hypertriglyceridemia, or may be used to treat a patient at risk for acquiring hypertriglyceridemia, for example, in a patient who has a genetic predisposition for developing hypertriglyceridemia, *e.g.* familial hypertriglyceridemia or familial dysbetalipoproteinemia.

[0171] Other conditions may predispose a patient to high levels of triglycerides. For example, certain medications such as beta blockers, birth control pills, diuretics, steroids, or the use of tamoxifen may lead to elevated levels of triglycerides and as such, may increase a patient's likelihood of developing conditions, or complications associated with high levels of triglycerides, such as atherosclerosis, stroke, heart attack, and other cardiac conditions.

[0172] In addition, certain other conditions may lead to high levels of triglycerides, including obesity, poorly controlled diabetes, hypothyroidism, kidney disease, or alcohol consumption.

[0173] In one embodiment, the antibodies may be used to prevent the onset of a disease or disorder characterized in part by elevated blood triglyceride levels, or to prevent the likelihood of developing such disease or disorder, or to mitigate the severity of the disease or disorder, or at least one symptom associated with the disease or disorder. It is envisioned that the antibodies of the invention may be used alone, or as adjunct therapy with other agents or methods known to be standard care for treating patients suffering from diseases or conditions characterized in part by elevated blood triglyceride levels, such as, but not limited to, hypertriglyceridemia. Such standard therapy may include fluid administration, or administration of any other pharmaceutical agents useful for lowering blood triglycerides, or lipids, or for weight reduction.

[0174] In one embodiment, the use of the antibodies described herein, may be an effective means of achieving normal levels of triglycerides, thereby ameliorating, or preventing one or more symptoms of, or long term complications associated with a disease characterized by high triglyceride levels.

[0175] It is envisioned that the antibodies of the invention may be used in an acute setting (for short term use), or for longer term (chronic) use.

Combination Therapies

[0176] Combination therapies may include an anti-ANGPTL8 antibody of the invention and any additional therapeutic agent that may be advantageously combined with an antibody of the invention, or with a biologically active fragment of an antibody of the invention.

[0177] For example, when the antibodies of the invention are contemplated for use in treating a disease or condition characterized in part by elevated triglyceride levels, such as hypertriglyceridemia, a second therapeutic agent may be employed to aid in further lowering of triglyceride levels, or to reduce at least one symptom in a patient suffering from a disease or condition characterized by high blood triglyceride levels. Such a second agent may be selected from, for example, another ANGPTL8 antagonist (*e.g.* another different anti-ANGPTL8 antibody or small molecule inhibitor of ANGPTL8), or may include other therapeutic moieties useful for treating triglyceridemia, or other diseases or conditions associated with, or resulting from elevated blood triglyceride levels, or agents useful for treating any long term complications associated with elevated and/or uncontrolled blood triglyceride levels.

[0178] In related embodiments, the invention features a composition, which is a combination of an antibody or antigen-binding fragment thereof of the invention, and a second therapeutic agent, such as (1) 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, such as cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, and the like; (2) inhibitors of cholesterol uptake and/or bile acid re-absorption; (3) niacin, which increases lipoprotein catabolism; (4) fibrates or amphipathic carboxylic acids, which reduce low-density lipoprotein (LDL) level, improve high-density lipoprotein (HDL) and TG levels, and reduce the number of non-fatal heart attacks; and (5) activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol, or fixed combinations such as ezetimibe plus simvastatin; a statin with a bile resin (*e.g.*, cholestyramine, colestipol, colesevelam), a fixed combination of niacin plus a statin (*e.g.*, niacin with lovastatin); or with other lipid lowering agents such as omega-3-fatty acid ethyl esters (for example, omacor).

[0179] Furthermore, the second therapeutic agent can be one or more other inhibitors/antagonists of glucagon or an inhibitor/antagonist of the glucagon receptor, as well as inhibitors of other molecules, such as other inhibitors of ANGPTL8, as well as inhibitors of other molecules, such as ANGPTL3, ANGPTL4, ANGPTL5, ANGPTL6, apolipoprotein C-III (also referred to as APOC3; see for example, inhibitors of APOC3 described in US8530439, US7750141, US7598227 and volanesorsen, also referred to as ISIS-APOCIIIRx) and proprotein convertase subtilisin/kexin type 9 (PCSK9), which are involved in lipid metabolism, in particular, cholesterol and/or triglyceride homeostasis. Inhibitors of these molecules include small molecules, antisense molecules and antibodies that specifically bind to these molecules and block their activity.

[0180] In one embodiment, if the anti-ANGPTL3 antibodies of the invention are used to treat a disease such as diabetes (*e.g.,* type 2 diabetes), then these antibodies may be used in combination with one or more of the following treatments for diabetes that are currently available. These include the following: insulin, an insulin analog (see below), a biguanide (metformin), a sulfonylurea (e.g. glyburide, glipizide), a PPAR gamma agonist (e.g. pioglitazone, rosiglitazone), an alpha glucosidase inhibitor (e.g. acarbose, voglibose), a glucagon-like peptide 1 (GLP-1) receptor agonist (e.g., BYETTA® (exenatide), TRULICITY™ (dulaglutide), VICTOZA® (liraglutide), LYXUMIA® (lixisenatide), TANZEUM™ (albiglutide), or an analogue of any of the foregoing), a dipeptidyl peptidase IV (DPP-4) inhibitor (e.g. saxagliptin (ONGLYZA®), sitaliptin (JANUVIA®), and vildagliptin (GALVUS®), a sodium-glucose co-transporter 2 (SGLT2) inhibitor (e.g., INVOKANA™ (canagliflozin), FORXIGA® (dapagliflozin), empagliflozin, ipragliflozin, tofogliflozin), (SYMLIN® (pramlintide), a glucagon receptor antagonist (as described in, for example, US8545847), and a glucagon antagonist.

[0181] In certain related embodiments, the composition may include a second agent selected from the group consisting of non-sulfonylurea secretagogues, insulin analogs, including fast acting (*e.g.,* Lispro, Aspart, Glulisine) and long acting (*e.g.* Detemir insulin, Degludec insulin, or Glargine insulin, exendin-4 polypeptides, beta 3 adrenoceptor agonists, inhibitors of cholesterol uptake and/or bile acid re-absorption, LDL-cholesterol antagonists, cholesteryl ester transfer protein antagonists (*e.g.* torcetrapib, anacetrapib, dalcetrapib, or evacetrapib), endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, amylin mimetics or agonists, cannabinoid receptor antagonists, glucagon-like peptide-1 receptor agonists, melanocortins, melanin-concentrating hormone receptor agonists, SNRIs, a fibroblast growth factor 21 (FGF21) mimetic (See, for example, US20110002845 and US20080261236), a fibroblast growth factor receptor 1c (FGFR1c) agonist (See, for example, US20110150901), an inhibitor of advanced glycation end product formation, such as, but not limited to, aminoguanidine, and protein tyrosine phosphatase inhibitors.

[0182] In related embodiments, the second therapeutic agent may be one or more other therapeutic agents, such as analgesics, anti-inflammatory agents, including non-steroidal anti-inflammatory drugs (NSAIDS), such as Cox-2 inhibitors, and the like, so as to ameliorate and/or reduce the symptoms accompanying the underlying condition, if needed.

[0183] The additional therapeutically active component(s) may be administered prior to, concurrent with, or after the administration of the anti-ANGPTL8 antibody of the present invention. For purposes of the present disclosure, such administration regimens are considered the administration of an anti-ANGPTL8 antibody "in combination with" a second therapeutically active component.

Administration Regimens

[0184] According to certain embodiments of the present invention, multiple doses of an anti-ANGPTL8 antibody (or a pharmaceutical composition comprising a combination of an anti-ANGPTL8 antibody and any of the additional therapeutically active agents mentioned herein) may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an anti-ANGPTL8 antibody of the invention. As used herein, "sequentially administering" means that each dose of anti-ANGPTL8 antibody is administered to the subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an anti-ANGPTL8 antibody, followed by one or more secondary doses of the anti-ANGPTL8 antibody, and optionally followed by one or more tertiary doses of the anti-ANGPTL8 antibody.

[0185] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the anti-ANGPTL8 antibody of the invention. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of anti-ANGPTL8 antibody, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of anti-ANGPTL8 antibody contained in the initial, secondary and/or tertiary doses varies from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (*e.g.*, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (*e.g.*, "maintenance doses").

[0186] In certain exemplary embodiments of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (*e.g.*, 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of anti-ANGPTL8 antibody, which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0187] The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an anti-ANGPTL8 antibody. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are

administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient. The administration regimen may be carried out indefinitely over the lifetime of a particular subject, or until such treatment is no longer therapeutically needed or advantageous.

[0188] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks or 1 to 2 months after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 12 weeks after the immediately preceding dose. In certain embodiments of the invention, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

Diagnostic Uses of the Antibodies

[0189] The anti-ANGPTL8 antibodies of the present invention may also be used to detect and/or measure ANGPTL8 in a sample, *e.g.*, for diagnostic purposes. For example, an anti-ANGPTL8 antibody, or fragment thereof, may be used to diagnose a condition or disease characterized by aberrant expression (*e.g.*, over-expression, under-expression, lack of expression, etc.) of ANGPTL8. Exemplary diagnostic assays for ANGPTL8 may comprise, *e.g.*, contacting a sample, obtained from a patient, with an anti-ANGPTL8 antibody of the invention, wherein the anti-ANGPTL8 antibody is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate ANGPTL8 protein from patient samples. Alternatively, an unlabeled anti-ANGPTL8 antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase.

[0190] Specific exemplary assays that can be used to detect or measure ANGPTL8 in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0191] Samples that can be used in ANGPTL8 diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of ANGPTL8 protein, or fragments thereof, under normal or pathological conditions. Generally, levels of ANGPTL8 in a particular sample obtained from a healthy patient (*e.g.*, a

patient not afflicted with a disease or condition associated with abnormal ANGPTL8 levels or activity) will be measured to initially establish a baseline, or standard, level of ANGPTL8. This baseline level of ANGPTL8 can then be compared against the levels of ANGPTL8 measured in samples obtained from individuals suspected of having a ANGPTL8 related disease or condition, or symptoms associated with such disease or condition.

EXAMPLES

[0192] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0193] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0194] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Example 1. Generation of Anti-ANGPTL8 Antibodies

[0195] Anti-ANGPTL8 antibodies were obtained by immunizing a VELOCIMMUNE® mouse (*i.e.*, an engineered mouse comprising DNA encoding human immunoglobulin heavy and kappa light chain variable regions) with an immunogen comprising a recombinant human ANGPTL8 expressed with a C-terminal mouse IgG2a tag (See SEQ ID NO: 340). The antibody immune response was monitored by an ANGPTL8-specific immunoassay. When a desired immune response was achieved, several fully human anti-ANGPTL8 antibodies were generated from antigen-positive B cells as described in US 2007/0280945A1, incorporated by reference herein in its entirety.

[0196] Certain biological properties of the exemplary anti-ANGPTL8 antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2. Heavy and Light Chain Variable Region Amino Acid and Nucleic Acid Sequences

[0197] Table 1 sets forth the amino acid sequence identifiers of the heavy and light chain variable regions and CDRs of selected anti-ANGPTL8 antibodies of the invention. The corresponding nucleic acid sequence identifiers are set forth in Table 2.

Table 1: Amino Acid Sequence Identifiers

	SEQ ID NOs:							
Antibody Designation	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
H4H15314P2	2	4	6	8	10	12	14	16
H4H15316P	18	20	22	24	26	28	30	32
H4H15318P	34	36	38	40	42	44	46	48
H4H15319P	50	52	54	56	58	60	62	64
H4H15321P	66	68	70	72	74	76	78	80
H4H15323P	82	84	86	88	90	92	94	96
H4H15330P	98	100	102	104	106	108	110	112
H4H15331P	114	116	118	120	122	124	126	128
H4H15334P	130	132	134	136	138	140	142	144
H4H15335P	146	148	150	152	154	156	158	160
H4H15341P	162	164	166	168	170	172	174	176
H4H15343P	178	180	182	184	186	188	190	192
H4H15345P	194	196	198	200	202	204	206	208
H4H15346P	210	212	214	216	218	220	222	224
H4H15347P	226	228	230	232	234	236	238	240
H4H15350P2	242	244	246	248	250	252	254	256
H4H15353P2	258	260	262	264	250	252	254	256
H4H15354P2	266	268	270	272	250	252	254	256
H4H15355P2	274	276	278	280	250	252	254	256
H4H15357P2	282	284	286	288	250	252	254	256
H4H15361P2	290	292	294	296	250	252	254	256
H4H15362P2	298	300	302	304	250	252	254	256
H4H15363P2	306	308	310	312	250	252	254	256
H4H15367P2	314	316	318	320	322	324	326	328
H4H15369P2	330	332	334	336	322	324	326	328

Table 2: Nucleic Acid Sequence Identifiers

	SEQ ID NOs:							
Antibody Designation	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
H4H15314P2	1	3	5	7	9	11	13	15
H4H15316P	17	19	21	23	25	27	29	31
H4H15318P	33	35	37	39	41	43	45	47
H4H15319P	49	51	53	55	57	59	61	63
H4H15321P	65	67	69	71	73	75	77	79
H4H15323P	81	83	85	87	89	91	93	95
H4H15330P	97	99	101	103	105	107	109	111
H4H15331P	113	115	117	119	121	123	125	127

H4H15334P	129	131	133	135	137	139	141	143
H4H15335P	145	147	149	151	153	155	157	159
H4H15341P	161	163	165	167	169	171	173	175
H4H15343P	177	179	181	183	185	187	189	191
H4H15345P	193	195	197	199	201	203	205	207
H4H15346P	209	211	213	215	217	219	221	223
H4H15347P	225	227	229	231	233	235	237	239
H4H15350P2	241	243	245	247	249	251	253	255
H4H15353P2	257	259	261	263	249	251	253	255
H4H15354P2	265	267	269	271	249	251	253	255
H4H15355P2	273	275	277	279	249	251	253	255
H4H15357P2	281	283	285	287	249	251	253	255
H4H15361P2	289	291	293	295	249	251	253	255
H4H15362P2	297	299	301	303	249	251	253	255
H4H15363P2	305	307	309	311	249	251	253	255
H4H15367P2	313	315	317	319	321	323	325	327
H4H15369P2	329	331	333	335	321	323	325	327

[0198] Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (*e.g.* "H1H," "H1M," "H2M", "H4H", etc.), followed by a numerical identifier (*e.g.* "15321," "15341," "15350," etc.), followed by a "P" or "N" suffix, as shown in Tables 1 and 2. Thus, according to this nomenclature, an antibody may be referred to herein as, *e.g.*, "H4H15321P", etc. The H4H prefix on the antibody designations used herein indicate the particular Fc region isotype of the antibody. For example, an "H4H" antibody has a human IgG4 Fc, an "H1M" antibody has a mouse IgG1 Fc, and an "H2M" antibody has a mouse IgG2 Fc, (all variable regions are fully human as denoted by the first 'H' in the antibody designation). As will be appreciated by a person of ordinary skill in the art, an antibody having a particular Fc isotype can be converted to an antibody with a different Fc isotype (*e.g.*, an antibody with a mouse IgG1 Fc can be converted to an antibody with a human IgG4, etc.), but in any event, the variable domains (including the CDRs) – which are indicated by the numerical identifiers shown in Tables 1 and 2 – will remain the same, and the binding properties are expected to be identical or substantially similar regardless of the nature of the Fc domain.

Example 3: Surface plasmon resonance (SPR) determination of dissociation rate constants (k_d) for ANGPTL8 antibodies binding to ANGPTL8, ANGPTL3, and ANGPTL4 peptides

[0199] It was previously demonstrated that antibodies binding to the N-terminal coiled-coil region of ANGPTL3 [WO 2012/174178 A1; Lee et al. (2009) JBC, 284:13735-13745] and ANGPTL4 [Desai et al. (2007) PNAS, 104:11766-11771] blocked the LPL inhibitory activity of the ANGPTL proteins. In this experiment, antibodies against ANGPTL8 were tested for binding to a peptide from the N-terminal region of ANGPTL8.

[0200] Dissociation rate constants for ANGPTL8 antibodies binding to human ANGPTL8 peptide (hANGPTL8 peptide, SEQ ID NO: 337) were determined using a real-time surface

plasmon resonance based MASS-1 biosensor platform. The assay utilized a format where ANGPTL8 antibodies were captured on the sensor surface and peptides were injected over the antibody surface. Peptides from the N-terminal coiled-coil region of human ANGPTL3 (hANGPTL3 peptide, SEQ ID NO: 338) and human ANGPTL4 (hANGPTL4 peptide, SEQ ID NO: 339) were also included as controls. Also included was a control antibody (H4H268P from US2011/0159015A1) that binds to the ANGPTL4 peptide and a negative isotype control antibody. All binding studies were performed in 10mM HEPES pH 7.4, 150mM NaCl, 3mM EDTA, and 0.05% v/v Surfactant Tween-20 (HBS-ET running buffer) at 25°C. The HCA sensor surface was derivatized via amine coupling to a monoclonal mouse anti-human Fc antibody (GE, # BR-1008-39), and to this surface was captured approximately 1000RU of each ANGPTL8 antibody or control antibody. Peptide stock solutions were diluted in HBS-ET running buffer to 500nM and injected over the antibody-captured surfaces for 4 minutes at a flow rate of 30µL/minute followed by the dissociation of bound peptide in HBS-ET running buffer for 10 minutes.

[0201] The association phase of peptides binding to captured ANGPTL8 antibodies could not be fit to a 1:1 binding model; therefore, only the dissociation rate constant (k_d) values were calculated by fitting the real-time binding sensorgrams using Scrubber 2.0c curve-fitting software. Dissociative half-lives (t½) were calculated from k_d as:

$$t½\ (min) = \frac{\ln(2)}{60 \times kd}$$

[0202] Binding parameters for the ANGPTL8, ANGPTL3, and ANGPTL4 N-terminal region peptides binding to captured ANGPTL8 antibodies, the control ANGPTL4 antibody, and the isotype control antibody are shown in Tables 3-5.

Results:

[0203] Under these experimental conditions, the maximum non-specific binding signal exhibited by 500nM of hANGPTL8, hANGPTL3, or hANGPTL4 peptides to blank anti-hFc surface was 3 RUs. Hence, binding interactions with signals that were three-fold above the 3 RU non-specific background (i.e., ≥ 9RU) were considered specific binding interactions. Based on this criterion, antibody-peptide binding signals less than 9 RUs were considered non-binding (NB in Table 1).

[0204] From this binding study it was shown that ANGPTL8 antibodies H4H15321P, H4H15367P2, and H4H15345P bind specifically to the N-terminal region ANGPTL8 peptide (SEQ ID NO: 337). None of the ANGPTL8 antibodies bound to the hANGPTL3 (SEQ ID NO: 338) or hANGPTL4 (SEQ ID NO: 339) N-terminal region peptides.

Table 3: Binding of anti-ANGPTL8 monoclonal antibody to hANGPTL8 peptide at 25ºC

mAb Captured	mAb Capture Level (RU)*	500nM hANGPTL8 peptide Bound (RU)	kd (1/s)	t½ (min)
H4H15321P	1101 ± 6.1	61	8.29E-05	139
H4H15367P2	1116 ± 17.4	43	9.82E-05	118
H4H15345P	1096 ± 3.6	37	2.03E-05	570
H4H15361P2	1394 ± 12.3	4	NB	NB
H4H15347P	1554 ± 54.6	0	NB	NB
H4H15318P	1087 ± 31.5	0	NB	NB
H4H15350P2	1298 ± 30.7	0	NB	NB
H4H15363P2	1281 ± 13.7	0	NB	NB
H4H15346P	1277 ± 26.3	0	NB	NB
H4H15334P	1256 ± 5.3	0	NB	NB
H4H15335P	1625 ± 31	0	NB	NB
H4H15343P	1129 ± 19.8	0	NB	NB
H4H15357P2	1159 ± 13.1	0	NB	NB
H4H15353P2	1296 ± 8.5	0	NB	NB
H4H15341P	1023 ± 30.1	0	NB	NB
H4H15369P2	1196 ± 54.2	0	NB	NB
H4H15330P	1168 ± 20.1	0	NB	NB
H4H15362P2	1131 ± 15.5	0	NB	NB
H4H15319P	974 ± 3.5	0	NB	NB
H4H15316P	1107 ± 24.7	0	NB	NB
H4H15323P	1068 ± 16.4	0	NB	NB
H4H15354P2	1297 ± 8.5	0	NB	NB
H4H15355P2	1323 ± 25.4	0	NB	NB
H4H15314P2	1011 ± 3.4	0	NB	NB
H4H15331P	1264 ± 16.8	-1	NB	NB
(α-AngPTL4 Ab)	1281 ± 50.2	0	NB	NB
Negative isotype control Ab	1092 ± 41.5	0	NB	NB
Blank α-hFc Surface	5 ± 0.3	3	NB	NB

* This column displays the average and standard deviation of antibody surface densities used for binding to ANGPTL8.

Table 4: Binding of anti-ANGPTL8 monoclonal antibody to hANGPTL3 shift peptide at 25ºC

mAb Captured	mAb Capture Level (RU)*	500nM hANGPTL3 peptide Bound (RU)	kd (1/s)	t½ (min)
H4H15321P	1101 ± 6.1	0	NB	NB
H4H15367P2	1116 ± 17.4	0	NB	NB

H4H15345P	1096 ± 3.6	0	NB	NB
H4H15361P2	1394 ± 12.3	0	NB	NB
H4H15347P	1554 ± 54.6	-1	NB	NB
H4H15318P	1087 ± 31.5	0	NB	NB
H4H15350P2	1298 ± 30.7	0	NB	NB
H4H15363P2	1281 ± 13.7	0	NB	NB
H4H15346P	1277 ± 26.3	0	NB	NB
H4H15334P	1256 ± 5.3	0	NB	NB
H4H15335P	1625 ± 31	-1	NB	NB
H4H15343P	1129 ± 19.8	0	NB	NB
H4H15357P2	1159 ± 13.1	0	NB	NB
H4H15353P2	1296 ± 8.5	0	NB	NB
H4H15341P	1023 ± 30.1	0	NB	NB
H4H15369P2	1196 ± 54.2	0	NB	NB
H4H15330P	1168 ± 20.1	-1	NB	NB
H4H15362P2	1131 ± 15.5	0	NB	NB
H4H15319P	974 ± 3.5	0	NB	NB
H4H15316P	1107 ± 24.7	0	NB	NB
H4H15323P	1068 ± 16.4	0	NB	NB
H4H15354P2	1297 ± 8.5	0	NB	NB
H4H15355P2	1323 ± 25.4	0	NB	NB
H4H15314P2	1011 ± 3.4	0	NB	NB
H4H15331P	1264 ± 16.8	0	NB	NB
(α-AngPTL4 Ab)	1281 ± 50.2	0	NB	NB
Negative isotype control Ab	1092 ± 41.5	0	NB	NB
Blank α-hFc Surface	5 ± 0.3	0	NB	NB

* This column displays the average and standard deviation of antibody surface densities used for binding to ANGPTL3 peptide.

Table 5: Binding of anti-ANGPTL8 monoclonal antibody to hAngPTL4 peptide at 25ºC

mAb Captured	mAb Capture Level (RU)*	500nM hAngPTL4 peptide Bound (RU)	kd (1/s)	t½ (min)
H4H15321P	1101 ± 6.1	0	NB	NB
H4H15367P2	1116 ± 17.4	0	NB	NB
H4H15345P	1096 ± 3.6	0	NB	NB
H4H15361P2	1394 ± 12.3	0	NB	NB
H4H15347P	1554 ± 54.6	0	NB	NB
H4H15318P	1087 ± 31.5	0	NB	NB
H4H15350P2	1298 ± 30.7	0	NB	NB

H4H15363P2	1281 ± 13.7	0	NB	NB
H4H15346P	1277 ± 26.3	0	NB	NB
H4H15334P	1256 ± 5.3	1	NB	NB
H4H15335P	1625 ± 31	1	NB	NB
H4H15343P	1129 ± 19.8	0	NB	NB
H4H15357P2	1159 ± 13.1	0	NB	NB
H4H15353P2	1296 ± 8.5	0	NB	NB
H4H15341P	1023 ± 30.1	0	NB	NB
H4H15369P2	1196 ± 54.2	0	NB	NB
H4H15330P	1168 ± 20.1	0	NB	NB
H4H15362P2	1131 ± 15.5	0	NB	NB
H4H15319P	974 ± 3.5	0	NB	NB
H4H15316P	1107 ± 24.7	0	NB	NB
H4H15323P	1068 ± 16.4	0	NB	NB
H4H15354P2	1297 ± 8.5	0	NB	NB
H4H15355P2	1323 ± 25.4	0	NB	NB
H4H15314P2	1011 ± 3.4	1	NB	NB
H4H15331P	1264 ± 16.8	0	NB	NB
(α-AngPTL4 Ab)	1281 ± 50.2	23	1.02E-03	11
Negative isotype control Ab	1092 ± 41.5	0	NB	NB
Blank α-hFc Surface	5 ± 0.3	0	NB	NB

* This column displays the average and standard deviation of antibody surface densities used for binding to ANGPTL4 peptide.

Example 4: Determination of kinetic binding parameters for H4H15341P binding to full-length human and monkey ANGPTL8 proteins by surface plasmon resonance (SPR)

[0205] The equilibrium dissociation constant (K_D) for ANGPTL8 antibody H4H15341P binding to full-length human and cynomolgus monkey ANGPTL8 proteins was determined using a real-time surface plasmon resonance-based MASS-1 biosensor platform. For the assay H4H15341P was injected over sensor surfaces onto which human or monkey ANGPTL8 proteins were immobilized. All binding studies were performed in 10mM HEPES pH 7.4, 150mM NaCl, 3mM EDTA, and 0.05% v/v Surfactant Tween-20 (HBS-ET running buffer) at 25°C. The HCA sensor surface was first derivatized by amine coupling goat anti-mouse IgG2a polyclonal antibody (Southern Biotech, # 1080-01) onto which was then captured approximately 30 RU (binding units) of human ANGPTL8 expressed with C-terminal mouse IgG2a Fc tag (hANGPTL8-mFc; SEQ ID NO: 340) or monkey ANGPTL8 expressed with C-terminal mouse IgG2a Fc tag (MfANGPTL8-mFc; SEQ ID NO: 341). Different concentrations of ANGPTL8 mAb were first prepared in HBS-ET running buffer (300nM – 1.23nM; 3-fold serial dilution) and then injected

over the ANGPTL8-mFc captured surfaces for 4 minutes at a flow rate of 30μL/minute followed by the dissociation of bound mAb in HBS-ET running buffer for 10 minutes.

[0206] Kinetic association (k_a) and dissociation (k_d) rate constants were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using Scrubber 2.0c curve-fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives (t½) were calculated from the kinetic rate constants as:

$$K_D\ (M) = \frac{kd}{ka}, \quad \text{and} \quad t½\ (min) = \frac{\ln(2)}{60 \times kd}$$

[0207] Binding kinetic parameters for anti-ANGPTL8 mAb binding to hANGPTL8-mFc and MfANGPTL8-mFc at 25℃ is shown in Table 6.

Results:

[0208] Antibody H4H15341 bound to both human and monkey ANGPTL8 proteins immobilized on the sensor surface and did not exhibit measureable dissociation during the recorded dissociation phase. To obtain an estimate of the binding affinity the dissociation rate constant, k_d, was fixed at the upper detection limit under the experimental conditions, 1.0E-05 1/s. The equilibrium dissociation constant (K_D) values of H4H15341P binding to hANGPTL8-mFc and MfANGPTL8-mFc were estimated to be 117pM and 86pM or lower, respectively.

Table 6: Binding kinetics parameters of H4H15341P binding to hANGPTL8-mFc and MfANGPTL8-mFc at 25℃.

Capture Surface	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
hANGPTL8-mFc	8.50E+04	1.00E-05*	≤ 1.17E-10	≥ 1155
MfANGPTL8-mFc	1.16E+05	1.00E-05*	≤ 8.60E-11	≥ 1155

*No dissociation of anti-ANGPTL8 mAb was observed under the experimental conditions; therefore, the value of k_d was fixed at the upper detection limit of 1.00E-05s^{-1}.

Example 5: Determination of human and monkey ANGPTL8 binding specificity by Bio-Layer Interferometry (BLI)

[0209] Binding of ANGPTL8 antibodies to human and monkey ANGPTL8 proteins was investigated using Bio-layer Interferometry with an Octet HTX biosensor platform (ForteBio, A Division of Pall Life Sciences). All experiments were performed at 25℃ in 10mM HEPES pH 7.4, 150mM NaCl, 0.05% v/v Surfactant Tween-20, and 1mg/ml BSA with the reaction multiwell plate agitated at 1000rpm. Approximately 1.6nm of human ANGPTL8 produced with a C-terminal mouse IgG2a Fc tag (hANGPTL8-mFc; SEQ ID NO: 340) or cynomolgus monkey

ANGPTL8 produced with a C-terminal mouse IgG2a Fc tag (MfANGPTL8-mFc; SEQ ID NO: 341) was captured onto anti-mFc (AMC) Octet biosensors by submerging the sensors into wells containing 10µg/mL of each protein for 4 minutes. Under the same conditions a negative control protein with the same mFc tag (hLDLR-mFc) was also coupled to the AMC sensor. All four sensors, three protein-coupled and one blank, were then submerged into wells containing 100nM of different ANGPTL8 monoclonal antibodies or an isotype control for 4 minutes. Binding signals observed after the 4 minute binding step are tabulated in Table 7.

Results:

[0210] Among 25 ANGPTL8 mAbs tested in this study, 24 antibodies displayed binding signals higher than the maximum binding signals on the irrelevant control sensor tips (0.03 nm; this value was used to calculate binding signals as fold above background). Among the 24 human ANGPTL8 binders, 20 displayed positive binding on the monkey ANGPTL8 protein. The 4 antibodies that did not bind to monkey ANGPTL8 protein also displayed low binding signal on the human ANGPTL8 protein with values between 1-2 fold above the background binding signal. For the 24 antibodies binding to human ANGPTL8 protein, 4 antibodies (H4H15362P2, H4H15321P, H4H15330P, H4H15367P2) showed binding signals of 10-fold above background. Another group of 12 antibodies displayed binding signals between 5-10-fold above background. The remaining antibodies bound the human ANGPTL8 protein with binding signals that were between 1-5-fold above the background level.

Table 7: Binding specificity of 100 nM ANGPTL8 monoclonal antibodies to human and monkey ANGPTL8-mFc captured on Octet biosensors

	mAb Binding Response (nm)			
mAb PID#	**hANGPTL8.mFc Captured Surface**	**MfANGPTL8.mFc Captured Surface**	**Irrelevant control (hLDLR.mFc) Captured Surface**	**Blank AMC Sensor**
H4H15362P2	0.39	0.36	0.03	0.01
H4H15321P	0.36	0.51	0.01	0.00
H4H15330P	0.34	0.39	0.02	0.01
H4H15367P2	0.32	0.33	0.01	0.00
H4H15363P2	0.25	0.26	0.01	0.02
H4H15347P	0.25	0.29	0.01	0.03
H4H15345P	0.25	0.31	0.00	0.01
H4H15319P	0.22	0.26	-0.01	0.00
H4H15361P2	0.20	0.21	0.01	0.02
H4H15318P	0.19	0.20	0.01	0.01

H4H15323P	0.18	0.15	0.00	0.00
H4H15350P2	0.17	0.20	0.00	-0.01
H4H15343P	0.17	0.20	-0.01	0.01
H4H15331P	0.16	0.21	0.01	0.01
H4H15355P2	0.15	0.13	0.02	0.03
H4H15353P2	0.15	0.11	0.02	0.02
H4H15369P2	0.14	0.17	0.00	0.01
H4H15357P2	0.13	0.08	0.01	0.02
H4H15341P	0.12	0.10	0.02	0.03
H4H15346P	0.07	0.01	0.00	-0.01
H4H15335P	0.06	0.04	0.01	0.01
H4H15354P2	0.05	0.03	0.01	0.02
H4H15334P	0.05	0.01	0.00	0.03
H4H15314P2	0.04	0.01	0.01	0.00
H4H15316P	0.03	0.02	0.02	0.02
Negative Isotype control Ab	0.01	0.00	0.01	0.01

Example 6: *In Vivo* Effect of IgG4 Anti-hANGPTL8 Antibodies on circulating tryglyceride levels in humanized ANGPTL8 mice

[0211] The effect of anti-hANGPTL8 antibodies on serum triglyceride (TG) levels was determined in humanized ANGPTL8 mice. Mice were pre-bled 7 days before the experiment and put into groups of five mice each for each antibody tested. Antibodies were administered at 10mg/kg dose (anti-hANGPTL8 and isotype-matched (hIgG4) control with irrelevant specificity) by subcutaneous injection on Day 0 of the study. Mice were bled (nonfasted) at consecutive days after antibody injections and TG levels were determined in the serum by ADVIA® 1800 Serum Chemistry Analyzer (Siemens). Averages were calculated for each of the time points for all tested antibodies. Results, expressed as (mean ± SEM) of serum TG concentration, are shown in Tables 8-13.

Levels of circulating anti-hANGPTL8 (Serum Ab) were also determined using a standard ELISA assay. Briefly, plates were coated with a goat anti-human Fc antibody (Sigma-Aldrich) to capture Serum Ab. Serum was then added to the plates and captured antibodies were detected by chemiluminescence using a horseradish peroxidase (HRP) conjugated goat anti-human IgG antibody (Sigma-Aldrich). Results, expressed as (mean ± SEM) of are shown in Tables 14-19.

Control: Mice that received an isotype-matched Control Ab

Results:

[0212] The effect of 25 mAbs to hANGPTL8 on circulating TG levels were tested in humanized ANGPTL8 mice. Antibody H4H15341P led to significant reduction in circulating TG (up to 68% average) after administration (compared to control mAb).

Table 8. Study 1, serum triglycerides (mg/dL)

Days after injection	Antibody									
	Control		H4H15321P		H4H15331P		H4H15343P		H4H15367P2	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 7	205.4	14.20	203.8	19.68	206.6	16.20	205.2	12.13	203.6	14.21
1	233.6	16.93	239.4	28.61	259.8	35.52	196.8	16.05	222.0	27.41
4	210.4	12.79	233.2	26.19	244.4	33.83	175.2	10.32	234.8	27.28
7	261.0	19.66	235.6	33.82	241.8	55.74	201.8	23.50	203.2	27.79

Table 9. Study 2, serum triglycerides (mg/dL)

Days after injection	Antibody							
	Control		H4H15341P		H4H15319P		H4H15318P	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 7	214.8	20.08	211.4	21.67	213.6	20.50	212.8	20.00
1	255.4	25.18	82.0	3.35	217.4	26.92	235.2	24.62
4	228.6	33.43	93.6	7.69	195.0	29.93	270.6	34.28
7	197.0	21.22	90.8	7.68	235.4	35.70	209.6	31.88
14	223.0	14.98	126.4	21.75	185.2	29.94	166.0	24.58

Table 9 (continued)

Days after injection	Antibody			
	H4H15355P2		H4H15345P	
	Mean	SEM	Mean	SEM
- 7	214.4	19.18	213.0	20.34
1	248.2	45.93	228.8	37.97
4	221.2	30.30	195.80	23.87
7	254.2	37.93	252.60	25.24
14	219.4	36.69	190.60	13.13

Table 10. Study 3, serum triglycerides (mg/dL)

Days after injection	Antibody									
	Control		H4H15350P2		H4H15314P2		H4H15330P		H4H15361P2	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 7	247.8	23.88	242.8	21.60	244.0	26.34	243.2	22.29	242.4	25.29
1	214.6	20.37	206.6	21.60	228.2	35.33	206.6	25.44	215.4	20.20
4	222.4	13.78	198.2	22.61	192.4	17.25	216.6	15.84	200.0	15.89
7	288.8	35.41	274.6	45.48	238.6	21.21	244.4	14.61	247.4	37.93

Table 11. Study 4, serum triglycerides (mg/dL)

Days after injection	Antibody									
	Control		H4H15357P2		H4H15363P2		H4H15347P		H4H15369P	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 7	197.0	18.29	201.6	25.18	201.6	26.15	200.4	24.71	198.8	22.43
1	227.6	46.41	221.6	37.35	189.4	5.963	194.6	28.33	217.0	39.68
6	194.0	18.06	211.2	35.96	190.6	20.21	248.2	16.12	223.0	25.61

Table 12. Study 5, serum triglycerides (mg/dL)

Days after injection	Antibody							
	Control		H4H15353P2		H4H15323P		H4H15362P2	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 7	199.2	26.68	197.4	27.02	199.8	30.33	200.8	27.55
2	217.2	16.09	184.4	28.67	179.8	35.99	166.6	26.76
8	161.8	18.58	185.4	24.78	187.0	38.76	180.2	18.22
14	227.2	33.70	216.4	11.74	212.4	31.29	173.2	17.75

Table 12 (continued)

Days after injection	Antibody			
	H4H15334P		H4H15354P2	
	Mean	SEM	Mean	SEM
- 7	199.8	26.25	200.0	26.33
2	183.0	16.93	169.8	23.14
8	160.0	16.56	162.6	20.50
14	167.6	18.73	197.4	34.20

Table 13. Study 6, serum triglycerides (mg/dL)

Days after injection	Antibody							
	Control		H4H15316P		H4H15335P		H4H15346P	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
- 7	232.0	24.94	232.0	28.26	232.4	23.88	232.8	30.30
2	211.0	23.19	248.2	35.35	203.2	6.785	197.2	20.42
7	256.8	32.02	249.6	35.72	248.0	17.28	234.8	66.74

Table 14. Study 1, Serum Ab (µg/mL)

Days after injection	Antibody									
	Control		H4H15321P		H4H15331P		H4H15343P		H4H15367P2	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	64.1	9.0	76.4	8.6	9.8	2.0	74.4	8.5	113.0	9.6
4	55.8	6.3	66.5	4.6	3.3	0.7	68.3	4.4	101.4	11.3

Table 15. Study 2, Serum Ab (µg/mL)

Days after injection	Antibody							
	Control		H4H15341P		H4H15319P		H4H15318P	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	50.8	3.9	104.0	18.7	81.8	8.2	74.4	8.5
4	51.2	9.5	70.6	23.6	59.1	9.6	68.3	4.4
7	40.9	5.4	50.7	13.3	46.8	8.9	68.3	4.4
14	32.2	3.1	8.2	4.6	24.1	8.7	68.3	4.4

Table 15 (continued)

Days after injection	Antibody			
	H4H15355P2		H4H15345P	
	Mean	SEM	Mean	SEM
1	68.4	3.8	59.3	3.6
4	58.4	3.0	46.3	16.2
7	35.7	6.6	50.1	3.9
14	3.1	0.8	35.9	4.6

Table 16. Study 3, Serum Ab (µg/mL)

Days after injection	Antibody									
	Control		H4H15350P2		H4H15314P2		H4H15330P		H4H15361P2	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	47.3	7.0	57.2	23.4	89.9	13.0	38.3	14.7	50.0	13.6
4	50.6	13.4	66.1	22.6	69.9	12.9	35.4	0.9	57.4	10.1
7	38.8	9.2	39.9	14.7	48.6	17.3	30.0	5.1	38.7	11.1

Table 17. Study 4, Serum Ab (µg/mL)

Days after injection	Antibody									
	Control		H4H15357P2		H4H15363P2		H4H15347P		H4H15369P	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	100.9	100.9	78.4	26.7	93.2	10.1	53.6	7.5	99.7	15.6
6	84.0	84.0	56.9	14.8	62.0	7.6	9.5	2.9	68.0	12.0

Table 18. Study 5, Serum Ab (µg/mL)

Days after injection	Antibody							
	Control		H4H15353P2		H4H15323P		H4H15362P2	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
2	93.7	14.4	63.5	17.6	99.9	34.5	91.0	24.6

8	79.8	8.7	42.8	11.1	50.3	9.7	50.8	10.3
14	55.1	11.4	18.2	14.0	32.3	10.0	29.5	20.9

Table 18 (continued)

Days after injection	Antibody			
	H4H15334P		H4H15354P2	
	Mean	SEM	Mean	SEM
2	64.4	15.0	71.3	7.2
8	38.7	7.1	46.0	15.4
14	8.6	4.6	30.1	26.6

Table 19. Study 6, Serum Ab (µg/mL)

Days after injection	Antibody							
	Control		H4H15316P		H4H15335P		H4H15346P	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
2	87.4	9.2	79.3	18.5	66.9	17.5	61.1	22.8
7	97.4	23.0	77.9	12.8	78.6	16.2	56.7	23.7

Example 7: Dose Response of hANGPTL8 Antibody H4H15341P in humanized ANGPTL8 mice

[0213] The effects of different doses of hANGPTL8 mAb, H4H15341P, on serum triglycerides (TG) were evaluated in humanized ANGPTL8 mice. Mice were pre-bled 7 days before the experiment and put into groups of five mice each for each dose tested. H4H15341P was administered at 1, 5, 10 and 25 mg/kg and isotype-matched (hIgG4) control with irrelevant specificity at 10mg/kg by single-dose subcutaneous injection on Day 0 of the study. Mice were bled (nonfasted) at days 2, 7, 14 and 21 after antibody injection and TG levels were determined in the serum by ADVIA® 1800 Chemistry System (Siemens). Averages were calculated for each time point. Results, expressed as (mean ± SEM) of serum TG concentration, are shown in Figure 1.

[0214] Levels of circulating anti-human antibodies (Serum Ab) were determined using a standard ELISA assay. Briefly, plates were coated with a goat anti-human Fc antibody (Sigma-Aldrich) to capture Serum Ab. Serum was then added to the plates and captured antibodies were detected by chemiluminescence using a horseradish peroxidase (HRP) conjugated goat anti-human IgG antibody (Sigma-Aldrich). Results, expressed as (mean ± SEM) are shown in Figure 2.

Control Ab refers to mice that received an isotype-matched control Ab.

Results:

[0215] The effect of 4 different doses of H4H15341P (anti-hANGPTL8) on circulating TG and cholesterol levels were tested in humanized ANGPTL8 mice. H4H15341P led to dose-dependent sustained significant reduction in serum TG (up to 66% average, compared to control mAb) with 5mg/kg being the lowest efficacious dose. No effect was observed on total cholesterol levels.

Example 8. Evaluation of lipoprotein lipase (LPL) activity after hANGPTL8 mAb treatment in humanized ANGPTL8 mice

[0216] The effect of hANGPTL8 mAb (H4H15341P) administration on LPL activity was evaluated in humanized ANGPTL8 mice. Mice were pre-bled 7 days before the experiment and put into groups of five mice each for each mAb tested. H4H15341P and Control Ab were administered at 10 mg/kg by single-dose subcutaneous injection on Day 0 of the study. On day 4 of the study, mice were dosed with heparin by intravenous injection via tail vein at 250U/kg that releases LPL from vascular endothelial surfaces. Five minutes later mice were bled from the retro-orbital sinus and post-heparin plasma collected and fractionated to separate LPL from hepatic lipase using heparin-Sepharose chromatography. Post-heparin plasma was loaded onto 1.0-ml heparin-Sepharose HiTrap columns (GE Healthcare) controlled by the GE Akta Prime, equilibrated with 0.25 M NaCl, 20% glycerol, 1% BSA, 10 mM sodium phosphate, pH 6.5. The column was washed with 10 ml of the equilibration buffer and eluted with a 30 ml NaCl gradient (0.25–1.5 M in 20% glycerol, 1% BSA, 10 mM sodium phosphate, pH 6.5). Resulting fractions were pooled by hepatic lipase and LPL peaks and the lipase activities were assayed using Invitrogen Enzchek Lipase substrate (cat#E33955). The kinetic reaction was read on Molecular Devices SpectraMax i3 plate reader at 482nm excitation / 518nm emission. Results, expressed as relative fluorescence units (RFU) (mean ± SEM) are shown in Figure 3. Control Ab refers to mice that received an isotype-matched negative control Ab.

Results

[0217] The results showed that administration of H4H15341P (anti-hANGPTL8) to humanized ANGPTL8 mice leads to a significant increase in LPL activity and has no effect on hepatic lipase activity.

Example 9. Lipid Tolerance Test in Humanized ANGPTL8 Mice Treated with hANGPTL8 mAb H4H15341P

[0218] The effect of ANGPTL8 inhibition with the mAb H4H15341P on triglyceride clearance was evaluated by acute fat loading. Humanized ANGPTL8 mice were pre-bled 8 days before the experiment and put into groups of 6 mice each for each mAb tested. H4H15341P and isotype-matched control Ab were administered at 10 mg/kg by single-dose subcutaneous injection on Day 0 of the study. On day 4 of the study mice were fasted for 4 hours following intravenous administration of 20% intralipid (Baxter Healthcare, IL) at 2.5 µl/g body weight. TG

level was evaluated in blood collected from the tail vein at subsequent time points. Results, expressed as (mean ± SEM) of TG concentration are shown in Figure 4. Control Ab refers to mice that received an isotype-matched negative control Ab.

Results

[0219] Administration of H4H15341P (anti-hANGPTL8) to humanized ANGPTL8 mice leads to a significantly lower TG level after acute fat load compared to control antibody. These data suggest that H4H15341P, by blocking ANGPTL8, promotes accelerated TG clearance from the circulation.

Example 10. HiSense Linear Epitope Mapping for Angiopoietin-Like Protein 8

[0220] Pepscan analysis using HiSense linear peptides was employed to establish linear epitopes for antibodies H4H15341P and H4H15367P2. The study was conducted at Pepscan Presto BV, (Zuidersluisweg 2, 8243RC Lelystad, The Netherlands). All Pepscan data is stored in the software package Peplab™, a proprietary database application developed in-house and built on a PostgreSQL storage back-end.

SYNTHESIS OF PEPTIDES

[0221] To reconstruct epitopes of the target molecule, a library of peptides was synthesized. An amino functionalized polypropylene support was obtained by grafting with a proprietary hydrophilic polymer formulation, followed by reaction with t-butyloxycarbonyl-hexamethylenediamine (BocHMDA) using dicyclohexylcarbodiimide (DCC) with Nhydroxybenzotriazole (HOBt) and subsequent cleavage of the Boc-groups using trifluoroacetic acid (TFA). Standard Fmocpeptide synthesis was used to synthesize peptides on the amino-functionalized solid support by custom modified JANUS liquid handling stations (Perkin Elmer).

COUPLING OF ANGIOPOIETIN-LIKE PROTEIN 8 ONTO THE ARRAY

[0222] The target protein was coupled on the mini-card as a positive control. To couple Angiopoietin-like protein 8 (hANGPTL8-mFc) onto the arrays, two cross-linking agents were used - m-maleimidobenzoyl-Nhydroxysuccinimide ester (MBS) and glutaraldehyde (GDA). For MBS 40 µl of hANGPTL8-mFc were mixed with 1 µl of MBS (2 mg/ml), incubated for 45 min at room temperature, and then applied onto the array at positions containing the linker motif CGGCGG (SEQ ID NO:346). For the GDA linking, 0.05% GDA in phosphate buffer (pH 5.0) was applied onto the array, incubated at room temperature for 4 hours, then hANGPTL8-mFc at concentration 5 or 20 µg/ml in phosphate buffer pH 8.0 was added onto the array on positions containing Gly only to allow coupling to the free N terminus.

ELISA SCREENING

[0223] The binding of antibody to each of the synthesized peptides was tested in a

PEPSCAN-based ELISA. The peptide arrays were incubated with primary antibody solution (overnight at 4℃). After washing, the peptide arrays were incubated with a 1/1000 dilution of an appropriate antibody peroxidase conjugate (goat anti-human HRP conjugate, Southern Biotech, catalog no. 2010-05) for one hour at 25℃. After washing, the peroxidase substrate 2,2'-azino-di-3-ethylbenzthiazoline sulfonate (ABTS) and 20 µl/ml of 3 percent H_2O_2 were added. After one hour, the color development was measured. The color development was quantified with a charge coupled device (CCD) - camera and an image processing system.

SCREENING DETAILS

[0224] Antibody binding depends on a combination of factors, including concentration of the antibody and the amounts and nature of competing proteins in the ELISA buffer. Also, the pre-coat conditions (the specific treatment of the peptide arrays prior to incubation with the experimental sample) affect binding. These details are summed up as follows:

Label	Dilution	Sample buffer	Pre-conditioning
H4H15341P	1 µg/ml	100% SQ	100% SQ
H4H15367P2	1 µg/ml	100% SQ	100% SQ
Negative isotype control	1 µg/ml	100% SQ	100% SQ

For the Pepscan Buffer and Preconditioning (SQ), the numbers indicate the relative amount of competing protein (a combination of horse serum and ovalbumin).

DATA PROCESSING

[0225] The values obtained from the CCD camera range from 0 to 3000 mAU, similar to a standard 96-well plate ELISA-reader. The results are quantified and stored into the Peplab database. Occasionally, a well contains an air-bubble resulting in a false-positive value, the cards are manually inspected and any values caused by an air-bubble are scored as 0.

SYNTHESIS QUALITY CONTROL

[0226] To verify the quality of the synthesized peptides, a separate set of positive and negative control peptides was synthesized in parallel. These were screened with antibody 57.9 (Posthumus, *et al.* 1990 *J Virol* 64:3304-3309).

Results

DESIGN OF PEPTIDES

[0227] The following sets of peptides were synthesized on the target sequence:

[0228] Human ANGPTL8, mature sequence, amino acids 22-198 from NP_061157.3

1 APMGGPELAQ HEELTLLFHG TLQLGQALNG VYRTTEGRLT KARNSLGLYG 50

51 RTIELLGQEV SRGRDAAQEL RASLLETQME EDILQLQAEA TAEVLGEVAQ 100

101 AQKVLRDSVQ RLEVQLRSAW LGPAYREFEV LKAHADKQSH ILWALTGHVQ 150

151 RQRREMVAQQ HRLRQIQERL HTAALPA 177 (SEQ ID NO:347)

[0229] The antibodies were tested for binding a series of 15-mer peptides covering the full sequence of ANGPTL8, each peptide offset by one amino acid from the next. Also included were double alanine ("AA") substitutions within the series of tested peptides for finer epitope analysis.

SET 1. Mimic: linear. Type: LIN

Description Peptides of length 15 derived from the target sequence of Angiopoietin-like protein 8 with an offset of one residue.

Sequences (first 10)

APMGGPELAQHEELT (SEQ ID NO: 348)

PMGGPELAQHEELTL (SEQ ID NO: 349)

MGGPELAQHEELTLL (SEQ ID NO: 350)

GGPELAQHEELTLLF (SEQ ID NO: 351)

GPELAQHEELTLLFH (SEQ ID NO: 352)

PELAQHEELTLLFHG (SEQ ID NO: 353)

ELAQHEELTLLFHGT (SEQ ID NO: 354)

LAQHEELTLLFHGTL (SEQ ID NO: 355)

AQHEELTLLFHGTLQ (SEQ ID NO: 356)

QHEELTLLFHGTLQL (SEQ ID NO: 357)

SET 2. Mimic: linear. Type: LIN.AA

Description Peptides of set 1, but with residues on positions 10 and 11 replaced by Ala. When a native Ala would occur on either position, it is replaced by Gly. The order of peptides in this set was randomized. The actual order on the array is shown.

Sequences (first 10)

TAEVLGEVAAGQKVL (SEQ ID NO: 358)

VYRTTEGRLAAARNS (SEQ ID NO: 359)

GVYRTTEGRAAKARN (SEQ ID NO: 360)

VQRLEVQLRAGWLGP (SEQ ID NO: 361)

LTGHVQRQRAAMVAQ (SEQ ID NO: 362)

VLKAHADKQAAILWA (SEQ ID NO: 363)

LRDSVQRLEAALRSA (SEQ ID NO: 364)

RREMVAQQHAARQIQ (SEQ ID NO: 365)

VSRGRDAAQAARASL (SEQ ID NO: 366)

AYREFEVLKGAADKQ (SEQ ID NO: 367)

[0230] The raw ELISA results of the screening were provided and plotted (box plot, data not shown) to depict each dataset and indicate the average ELISA signal, the distribution, and the outliers within each dataset. Depending on experiment conditions (amount of antibody, blocking strength, etc.), different distributions of ELISA data were obtained.

ANTIBODY H4H15367P2

[0231] When tested under high stringency conditions, antibody H4H15367P2 avidly bound only one linear peptide comprised of sequence 1APMGGPELAQHEELT15 (SEQ ID NO: 348). This sample was tested twice under the same conditions and repeatedly yielded the same result. Antibody H4H15367P2 also strongly bound Angiopoietin-like protein 8, which was coupled onto the array as a positive control. Interestingly, somewhat weaker binding was obtained with the target protein coupled using MBS when compared to GDA coupling.

ANTIBODY H4H15341P

[0232] When tested under high stringency conditions, antibody H4H15341P avidly bound a series of linear peptides, which contain common sequence $_{150}$QRQRREMVAQ$_{159}$ (SEQ ID NO: 368). Comparison of intensity profiles recorded on set 1 (native linear epitope mimics) and set 2 (double Ala mutants) indicates that residues R154, E155, and Q159 are essential for antibody binding. Antibody H4H15341P also strongly bound Angiopoietin-like protein 8, which was coupled onto the array as a positive control, regardless of the immobilization.

NEGATIVE ISOTYPE CONTROL

[0233] Negative isotype control did not bind any peptide present on the array. Furthermore, no detectable binding was recorded with Angiopoietin-like protein 8, which was coupled onto the array as a positive control. Negative isotype control was additionally tested with goat anti-human secondary conjugate used in Pepscan ELISA. The antibody can be recognized by this secondary.

Conclusion

[0234] Three antibodies provided for this study were tested on HiSense peptide arrays. It was possible to establish tentative linear epitopes for two antibodies. Despite repeated incubations, antibody Negative isotype control did not bind to the array. Core tentative epitopes identified in this study are listed as follows:

Antibody	Core epitope
H4H15341P	$_{150}$QRQRREMVAQ$_{159}$ (SEQ ID NO: 368)
H4H15367P2	$_{1}$APMGGPELAQHEELT$_{15}$ (SEQ ID NO: 348)
Negative isotype control	-.

[0235] Thus, Antibodies H4H15341P and H4H15367P2 recognize distinct linear sequences within C- and N-termini respectively. The fact that signal obtained for antibody H4H15367P2 with MBS coupling was less than with GDA coupling, together with its localization on the extreme N terminus indicate that the N terminal amine itself may be part of the epitope. Additionally, for antibody H4H15341P double alanine mutants served to pinpoint residues that are critical for binding (residues shaded in light grey, above).

[0236] Antibody H4H15341P targets a C-terminal region of Angiopoietin-like protein 8, while H4H15367P2 targets the very N-terminus. Antibody Negative isotype control did not bind to the array.

[0237] In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

What is claimed is:

1. An anti-angiopoietin-like protein 8 (ANGPTL8) antibody or antigen-binding fragment thereof, which comprises a HCVR/LCVR sequence pair of SEQ ID NOs: 162/170.

2. The antibody of claim 1, which is an IgG1 or IgG4 antibody.

3. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof as defined in claim 1 or 2.

4. A recombinant expression vector comprising a nucleic acid molecule of claim 3 or a host cell comprising the vector.

5. A method of producing an antibody or antigen-binding fragment thereof of claim 1 or 2, comprising culturing the host cell of claim 4 under conditions permitting production of the antibody or fragment and recovering the antibody or fragment so produced.

6. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of claim 1 or 2 and a pharmaceutically acceptable carrier or diluent.

7. A method of treating a condition or disease associated with, or characterized in part by high blood triglyceride levels, or at least one symptom or complication associated with the condition or disease, the method comprising administering the antibody or antigen-binding fragment thereof of claim 1 or 2, or the pharmaceutical composition of claim 6, to a patient in need thereof, such that blood triglyceride levels are lowered or that the condition or disease is mediated, or the at least one symptom or complication associated with the condition or disease is alleviated or reduced in frequency or severity, wherein the condition or disease is selected from the group consisting of hyperlipidemia, hyperlipoproteinemia, dyslipidemia such as atherogenic dyslipidemia, diabetic dyslipidemia, diabetic dyslipidemia or mixed dyslipidemia, hypertriglyceridemia, severe hypertriglyceridemia with TG > 1000 mg/dL and associated acute pancreatitis, hypercholesterolemia, chylomicronemia, obesity, metabolic syndrome, diabetes, lipodystrophy, lipoatrophy resulting from, or caused by altered ApoC2, ApoE deficiency, nonalcoholic steatohepatitis, or glucocorticoid treatment-induced dyslipidemia.

8. Use of the antibody or antigen-binding fragment thereof of claim 1 or 2, or the pharmaceutical composition of claim 6, in the manufacture of a medicament for treating a

condition or disease associated with, or characterized in part by high blood triglyceride levels, or at least one symptom or complication associated with the condition or disease, wherein blood triglyceride levels are lowered or that the condition or disease is mediated, or the at least one symptom or complication associated with the condition or disease is alleviated or reduced in frequency or severity, and wherein the condition or disease is selected from the group consisting of hyperlipidemia, hyperlipoproteinemia, dyslipidemia such as atherogenic dyslipidemia, diabetic dyslipidemia, diabetic dyslipidemia or mixed dyslipidemia, hypertriglyceridemia, severe hypertriglyceridemia with TG > 1000 mg/dL and associated acute pancreatitis, hypercholesterolemia, chylomicronemia, obesity, metabolic syndrome, diabetes, lipodystrophy, lipoatrophy resulting from, or caused by altered ApoC2, ApoE deficiency, nonalcoholic steatohepatitis, or glucocorticoid treatment-induced dyslipidemia.

9. The method of claim 7 or use the of claim 8, wherein the condition or disease is a cardiovascular disease or disorder selected from the group consisting of atherosclerosis, aneurysm, hypertension, angina, stroke, cerebrovascular diseases, congestive heart failure, coronary artery diseases, myocardial infarction, and peripheral vascular diseases.

10. The method of claim 7 or 9 or the use of claim 8 or 9, wherein the antibody or antigen-binding fragment thereof or the pharmaceutical composition or the medicament is to be administered to the patient in combination with a second therapeutic agent.

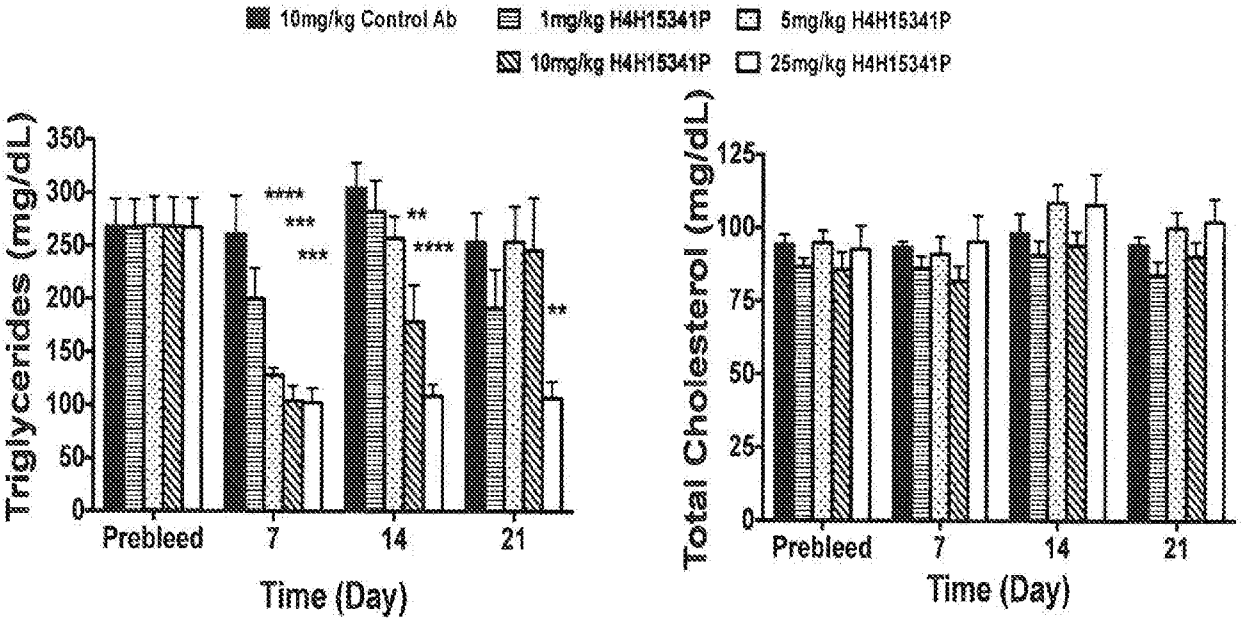
11. The method or use of claim 10, wherein the second therapeutic agent is selected from the group consisting of:

(a) niacin; fibrates 22-hydroxycholesterol; ezetimibe plus simvastatin; a statin with cholestyramine, colestipol or colesevelam; niacin plus a statin such as niacin with lovastatin; omega-3-fatty acid ethyl esters; cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, and pravastatin;

(b) an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to angiopoietin-like protein 3 (ANGPTL3), angiopoietin-like protein 4 (ANGPTL4), angiopoietin-like protein 5 (ANGPTL5), angiopoietin-like protein 6 (ANGPTL6) and human proprotein convertase subtilisin/kexin type 9 (PCSK9); or

(c) insulin, metformin, glyburide, glipizide, pioglitazone, rosiglitazone, acarbose, voglibose, exenatide, dulaglutide, liraglutide, lixisenatide, albiglutide, saxagliptin, sitaliptin, vildagliptin, canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, tofogliflozin, pramlintide, fast acting Lispro, Aspart, Glulisine

and long acting Detemir insulin, Degludec insulin, Glargine insulin, torcetrapib, anacetrapib, dalcetrapib, evacetrapib or aminoguanidine.



*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Figure 1

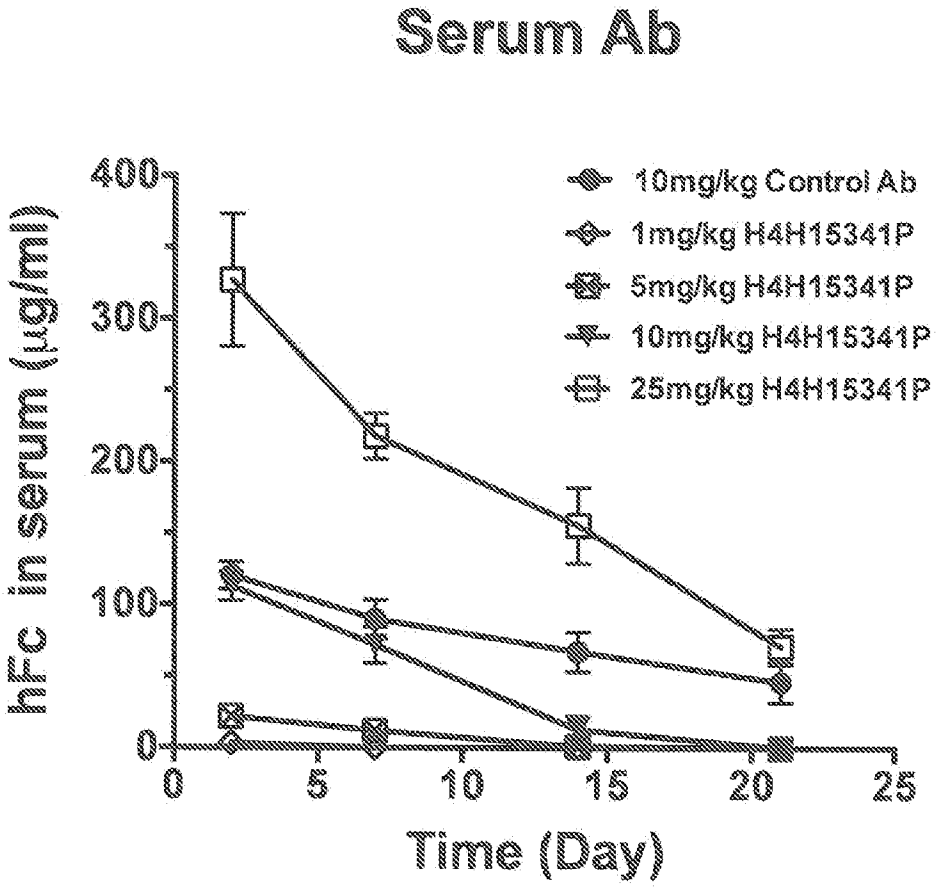
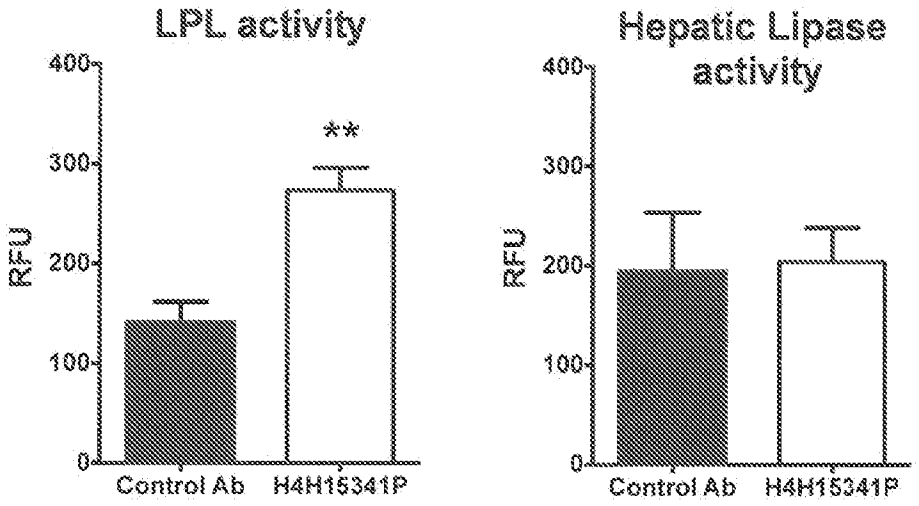

Serum Ab
hFc in serum (µg/ml)
400
300
200
100
0
0
5
10
15
20
25
Time (Day)
10mg/kg Control Ab
1mg/kg H4H15341P
5mg/kg H4H15341P
10mg/kg H4H15341P
25mg/kg H4H15341P

Figure 2



**p<0.01

Figure 3

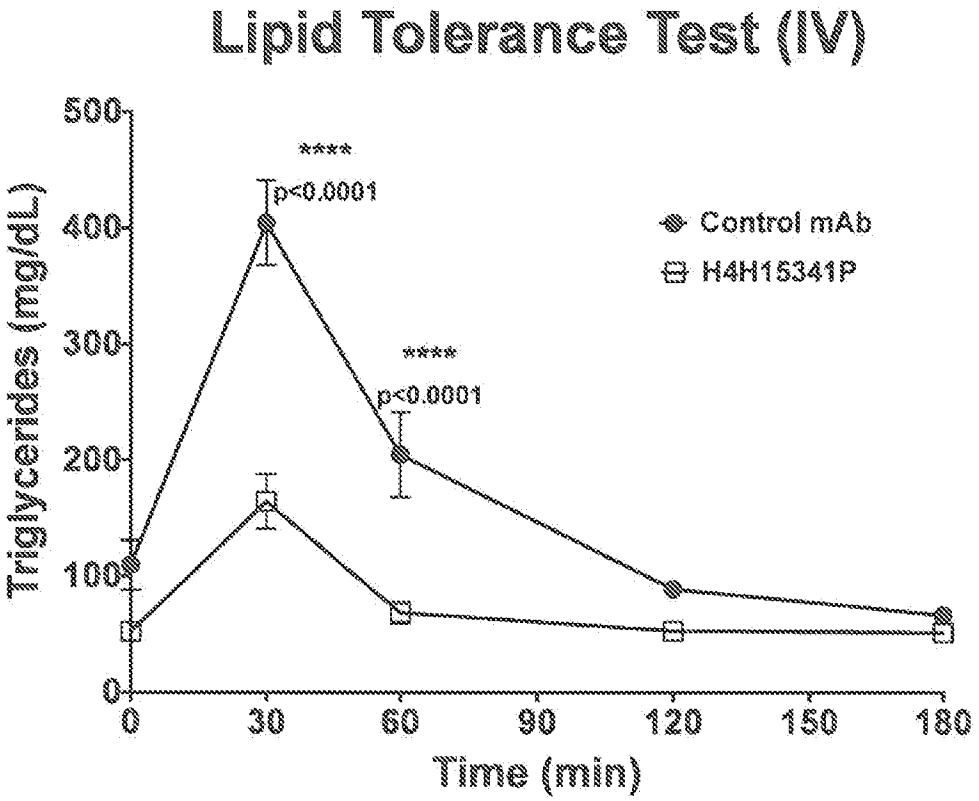

Lipid Tolerance Test (IV)
Triglycerides (mg/dL)
500
400
300
200
100
0
****
p<0.0001
****
p<0.0001
Control mAb
H4H15341P
0
30
60
90
120
150
180
Time (min)

Figure 4

<110> REGENERON PHARMACEUTICALS, INC.

<120> ANTI-ANGPTL8 ANTIBODIES AND USES THEREOF

<130> 0431.21PCT

<140>
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<150> 62/202,366
<151> 2015-08-07

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actggacaag ggcttgagtg gatggggtgg atgaacccta acggtgataa cacaggctat 180

gcacagaagt tccagggcag agtcaccatg accggggaca cctccataag cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagaggga 300

atttgggggt tcgacccctg gggccaggga accctggtca ccgtctcctc a 351

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Gly Asp Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Gly Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Ile Trp Gly Phe Asp Pro Trp Gly Gln Gly Thr Leu
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Val Thr Val Ser Ser
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gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

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20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Phe Tyr Cys Leu Gln His Asn Thr Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

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<210> 14
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<210> 15
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<220>
<221> source
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<210> 16
<211> 9
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<210> 17
<211> 351
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<220>
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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag taaaggctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtac aaaagggccc 300

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Asp Asp Tyr
20 25 30

Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Lys Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Thr Lys Gly Pro Trp Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
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Val Thr Val Ser Ser
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<210> 25
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<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag tataatagtt attcgtacac ttttggccag 300

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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<210> 33
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ccaggcaagg ggctggagtg ggtggcggtc atatcatatg atggaactga taaattctat 180

gcagaccccg tgaagggccg attcattatc tccagagaca attctatgaa cattctgtat 240

ctgcaaatga acagcctgag agctgaagac acggctgtat actattgtgc gaaagatggg 300

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acggtcaccg tctcctca 378

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Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Gly Asn Phe
20 25 30

Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Thr Asp Lys Phe Tyr Ala Asp Pro Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Met Asn Ile Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Glu Met Glu Leu Arg Gly Tyr Tyr Tyr Tyr Tyr Gly
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Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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gggacagccc caaagctcct gatctttgct gcatccagtt tggagagcgg agtcccatca 180

aggttcagcg gcagtggatt tggtacagat ttcactctca ccatcagcag cctacagtct 240

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20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Thr Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Leu Ala Thr Tyr Phe Cys Gln Gln Val His Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 46
Ala Ala Ser
1

<210> 47
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 47
caacaggttc acagtccccc gtacact 27

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 48
Gln Gln Val His Ser Pro Pro Tyr Thr
1 5

<210> 49
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 49
gaggtgcagc tggtggagtc tggaggaggt gtggtacggc cgggggggtc actgagactc 60

tcctgtgctg cctctggatt caccgttgat gattatgaca tgagttgggt ccgccaaact 120

ccaggaaagg ggctggagtg gatctctggc attaattgga atggaggtaa cacaggttat 180

gcagactctg tgaagggccg attcatcatc tccagagaca gcgccaagaa ctccctgttt 240

ctgcaaatga acagtctgag agccgaggac acggccttgt atcactgttg gggagcgatt 300

ggtgcttttg atatttgggg ccaagggaca atggtcaccg tctcttca 348

<210> 50
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 50
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Gly Ile Asn Trp Asn Gly Gly Asn Thr Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Trp Gly Ala Ile Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
100 105 110

Thr Val Ser Ser
115

<210> 51
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 51
ggattcaccg ttgatgatta tgac 24

<210> 52
<211> 8
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 52
Gly Phe Thr Val Asp Asp Tyr Asp
1 5

<210> 53
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 53
attaattgga atggaggtaa caca 24

<210> 54
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 54
Ile Asn Trp Asn Gly Gly Asn Thr
1 5

<210> 55
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 55
tggggagcga ttggtgcttt tgatatt 27

<210> 56
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 56
Trp Gly Ala Ile Gly Ala Phe Asp Ile
1 5

<210> 57
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 57
gatattgtga tgacccagtc tccactctcc tcacctgtca cccttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta cacagtgatg gcggcaccta cttgagttgg 120

cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttt taaccggttc 180

tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgagaatc 240

agtagggtgg aagctgagga tgtcggggtt tattactgca tgcaaacaac acaatttccg 300

ctcactttcg gcggagggac caaggtggag atcaaa 336

<210> 58
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 58
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asp Gly Gly Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Ile Phe Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
85 90 95

Thr Gln Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 59
<211> 33
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 59
caaagcctcg tacacagtga tggcggcacc tac 33

<210> 60
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 60
Gln Ser Leu Val His Ser Asp Gly Gly Thr Tyr
1 5 10

<210> 61
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 61
aagattttt 9

<210> 62
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 62
Lys Ile Phe
1

<210> 63
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 63
atgcaaacaa cacaatttcc gctcact 27

<210> 64
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 64
Met Gln Thr Thr Gln Phe Pro Leu Thr
1 5

<210> 65
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 65
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attactggta gtggtggtag aacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca atgccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaaacttt 300

ccctttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 66
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 66
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Gly Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asn Phe Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 67
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 67
ggattcacct ttagcagcta tgcc 24

<210> 68
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 68
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 69
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 69
attactggta gtggtggtag aaca 24

<210> 70
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 70
Ile Thr Gly Ser Gly Gly Arg Thr
1 5

<210> 71
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 71
gcgaaaaact ttccctttga ctac 24

<210> 72
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 72
Ala Lys Asn Phe Pro Phe Asp Tyr
1 5

<210> 73
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 73
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60

atcaactgcg agtccagcca gagtgtttta tacagctcca acaataagaa ctacttagct 120

tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctacccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

atcagcaccc tgcaggctga ggatgtggca gtttattact gtcagcaata ttatagtact 300

ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

<210> 74
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 74
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Glu Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Thr Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 75
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 75
cagagtgttt tatacagctc caacaataag aactac 36

<210> 76
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 76
Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 77
<211> 9
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 77
tgggcatct 9

<210> 78
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 78
Trp Ala Ser
1

<210> 79
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 79
cagcaatatt atagtactcc gtacact 27

<210> 80
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 80
Gln Gln Tyr Tyr Ser Thr Pro Tyr Thr
1 5

<210> 81
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 81
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttcc agctatgcca tgacctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

acagactccg tgaagggccg gttcaccctc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaatctgac 300

tacagtaaca ccatctactg gtactacggt atggacgtct ggggccaagg gaccacggtc 360

accgtctcct ca 372

<210> 82
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 82

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5				10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20					25				30			
Ala	Met	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Thr	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Leu	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Lys	Ser	Asp	Tyr	Ser	Asn	Thr	Ile	Tyr	Trp	Tyr	Tyr	Gly	Met	Asp
			100					105					110		
Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser				
		115					120								

<210> 83
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 83
ggattcacct tttccagcta tgcc 24

<210> 84

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 84
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 85
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 85
attagtggta gtggtggtag caca 24

<210> 86
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 86
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 87
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 87
gcgaaatctg actacagtaa caccatctac tggtactacg gtatggacgt c 51

<210> 88
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 88

Ala Lys Ser Asp Tyr Ser Asn Thr Ile Tyr Trp Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 89
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 89
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtgggtc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 90
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 90
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 91
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 91
cagagcatta gcagctat 18

<210> 92
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 92
Gln Ser Ile Ser Ser Tyr
1 5

<210> 93
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 93
gctgcatcc 9

<210> 94
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 94
Ala Ala Ser
1

<210> 95
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 95
caacagagtt acagtacccc tcggacg 27

<210> 96
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 96
Gln Gln Ser Tyr Ser Thr Pro Arg Thr
1 5

<210> 97
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 97
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactata tgagctggat ccgccaggct 120

ccagggaagg gactggagtg gatttcacac attagtggta gtggtagaac cacacactac 180

gcagactcta tgaagggccg attcaccatt tccagggaca acgccaagaa ctcactgtat 240

ttgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgt gagagaggga 300

ggttttaact ggaactacga gggtactttt gatatctggg gccaggggac aatggtcacc 360

gtctcttca 369

<210> 98
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 98
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile

35 40 45

Ser His Ile Ser Gly Ser Gly Arg Thr Thr His Tyr Ala Asp Ser Met
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Arg Glu Gly Gly Phe Asn Trp Asn Tyr Glu Gly Thr Phe Asp Ile
100 105 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 99
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 99
ggattcacct tcagtgacta ctat 24

<210> 100
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 100
Gly Phe Thr Phe Ser Asp Tyr Tyr
1 5

<210> 101
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 101
attagtggta gtggtagaac caca 24

<210> 102
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 102
Ile Ser Gly Ser Gly Arg Thr Thr
1 5

<210> 103
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 103
gtgagagagg gaggttttaa ctggaactac gagggtactt ttgatatc 48

<210> 104
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 104
Val Arg Glu Gly Gly Phe Asn Trp Asn Tyr Glu Gly Thr Phe Asp Ile
1 5 10 15

<210> 105
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 105
gatattgtga tgacccagac tccactctct tcacctgtca cccttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctctta cacagtgatc aaaacaccta cttgagttgg 120

cttcaccaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180

tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240

agcagggtgg aagctgagga tgtcgggatt tattactgca tgcaaggtac acaatttccg 300

ctcactttcg gcggagggac caaggtggag atcaaa 336

<210> 106
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 106
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gln Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly
85 90 95

Thr Gln Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 107
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 107
caaagcctct tacacagtga tcaaaacacc tac 33

<210> 108
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 108
Gln Ser Leu Leu His Ser Asp Gln Asn Thr Tyr
1 5 10

<210> 109
<211> 9

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 109
aagatttct 9

<210> 110
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 110
Lys Ile Ser
1

<210> 111
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 111
atgcaaggta cacaatttcc gctcact 27

<210> 112
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 112
Met Gln Gly Thr Gln Phe Pro Leu Thr
1 5

<210> 113
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 113
gaggtgcagc tggtggagtc tgggggggagg cttggtacag gggggggtc cctgagactc 60

tcctgtgaag cctctggatt cacatttagc agctttgcca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaggt cttagtggta gtggtagaag tacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca actccaagaa tagactctat 240

ttgcaaatgg acagcctgag agccgaggac tcggccgtat attattgtgc ggcctacgtg 300

ttacgaattt tggatcggtg gttcgacccc tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 114
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 114

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Arg	Leu	Gly	Thr	Gly	Gly	Gly
1				5				10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Glu	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Phe
			20					25				30			
Ala	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Gly	Leu	Ser	Gly	Ser	Gly	Arg	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Arg	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asp	Ser	Leu	Arg	Ala	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Ala	Tyr	Val	Leu	Arg	Ile	Leu	Asp	Arg	Trp	Phe	Asp	Pro	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
		115					120								

<210> 115
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 115

ggattcacat ttagcagctt tgcc 24

<210> 116
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 116
Gly Phe Thr Phe Ser Ser Phe Ala
1 5

<210> 117
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 117
cttagtggta gtggtagaag taca 24

<210> 118
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 118
Leu Ser Gly Ser Gly Arg Ser Thr
1 5

<210> 119
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 119
gcggcctacg tgttacgaat tttggatcgg tggttcgacc cc 42

<210> 120
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 120
Ala Ala Tyr Val Leu Arg Ile Leu Asp Arg Trp Phe Asp Pro
1 5 10

<210> 121
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 121
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctt cataggactg gatacaacta tttggactgg 120

tacctgcaga agccagggca gtctccacag atcctgatct atttgggttc ttatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaagatc 240

agcagagtgg aggctgaaga tgttggggtt tattactgca tgcaagctct acaaactccg 300

tggacgttcg gccaagggac caaggtggaa atcaaa 336

<210> 122
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 122
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Arg
20 25 30

Thr Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Ile Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105 110

<210> 123
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 123
cagagcctcc ttcataggac tggatacaac tat 33

<210> 124
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 124
Gln Ser Leu Leu His Arg Thr Gly Tyr Asn Tyr
1 5 10

<210> 125
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 125
ttgggttct 9

<210> 126
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 126
Leu Gly Ser
1

<210> 127
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 127
atgcaagctc tacaaactcc gtggacg 27

<210> 128
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 128
Met Gln Ala Leu Gln Thr Pro Trp Thr
1 5

<210> 129
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 129
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcaac agtggtggtt actactggaa ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

ttcaacccgt ccctcaagag tcgagttacc atatcaatag acacgtctaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagag 300

gggatttatg cttttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 130
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 130
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
20 25 30

Gly Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Phe Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Glu Gly Ile Tyr Ala Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 131
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 131
ggtggctcca tcaacagtgg tggttactac 30

<210> 132
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 132
Gly Gly Ser Ile Asn Ser Gly Gly Tyr Tyr
1 5 10

<210> 133
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 133
atctattaca gtgggagcac c 21

<210> 134
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 134
Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> 135
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 135
gcgagagagg ggatttatgc ttttgactac 30

<210> 136
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 136
Ala Arg Glu Gly Ile Tyr Ala Phe Asp Tyr
1 5 10

<210> 137
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 137
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctattct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcggcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacaa cataatagtt acccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 138
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 138
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ser Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Gly Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 139
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 139
cagggcatta gaaatgat 18

<210> 140
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 140
Gln Gly Ile Arg Asn Asp
1 5

<210> 141
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 141
tctgcatcc 9

<210> 142
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 142
Ser Ala Ser
1

<210> 143
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 143
ctacaacata atagttaccc gtggacg 27

<210> 144
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 144
Leu Gln His Asn Ser Tyr Pro Trp Thr
1 5

<210> 145
<211> 378
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 145
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcaat aactatggca tacactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atgaaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgttt attactgtgc gaaagacata 300

cggatagcag ctcgtcggca ctactactac tacggtatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcctca 378

<210> 146
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 146

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5				10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Asn	Tyr
			20					25					30		
Gly	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ala	Val	Ile	Ser	Tyr	Asp	Glu	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Lys	Asp	Ile	Arg	Ile	Ala	Ala	Arg	Arg	His	Tyr	Tyr	Tyr	Tyr	Gly
			100					105					110		
Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser		
		115					120					125			

<210> 147
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 147
ggattcacct tcaataacta tggc 24

<210> 148
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 148
Gly Phe Thr Phe Asn Asn Tyr Gly
1 5

<210> 149
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 149
atatcatatg atgaaagtaa taaa 24

<210> 150
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 150
Ile Ser Tyr Asp Glu Ser Asn Lys
1 5

<210> 151
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 151
gcgaaagaca tacggatagc agctcgtcgg cactactact actacggtat ggacgtc 57

<210> 152
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 152
Ala Lys Asp Ile Arg Ile Ala Ala Arg Arg His Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 153
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 153
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc aggtggttag cctggtatca gcagaaacca 120

gggaaagccc caaagctcct gatctatgct gcatccagtt tggaaagtgg ggtcccagca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctaacagtt tcccaatcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> 154
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 154
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 155
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 155
cagggtatta gcaggtgg 18

<210> 156
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 156
Gln Gly Ile Ser Arg Trp
1 5

<210> 157
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 157
gctgcatcc 9

<210> 158
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 158
Ala Ala Ser
1

<210> 159
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 159
caacaggcta acagtttccc aatcact 27

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 160
Gln Gln Ala Asn Ser Phe Pro Ile Thr
1 5

<210> 161
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 161
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcaat aatcatgaaa tgaattgggt ccgccaggct 120

ccagggaagg gtctggagtg ggtttcatac attagtagta gtggtaatac cgtaacctac 180

gcagactttc tgaagggccg attcaccatc tccagagaca acgccaagaa ctcgctgttt 240

ctgcaaatga acagcctgcg agacgaggac acggctgttt attactgtgc gcgagatcat 300

ttaagtggaa cctccccact ttcttattgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 162
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 162
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn His
20 25 30

Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Tyr Ile Ser Ser Ser Gly Asn Thr Val Thr Tyr Ala Asp Phe Leu
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp His Leu Ser Gly Thr Ser Pro Leu Ser Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 163
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 163
ggattcacct tcaataatca tgaa 24

<210> 164
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 164
Gly Phe Thr Phe Asn Asn His Glu
1 5

<210> 165
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 165
attagtagta gtggtaatac cgta 24

<210> 166
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 166
Ile Ser Ser Ser Gly Asn Thr Val
1 5

<210> 167
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 167
gcgcgagatc atttaagtgg aacctcccca ctttcttat 39

<210> 168
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 168
Ala Arg Asp His Leu Ser Gly Thr Ser Pro Leu Ser Tyr
1 5 10

<210> 169
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 169
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtgggaga cagagtcacc 60

atcacttgcc aggcgagtca ggacattaac aactacttaa attggtttca gcagaaacca 120

gggaaagccc ctaaactcct gatcttcgat gcatccaatt tagaaacagg ggtcccatca 180

aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240

gaagatattg caacatattt ctgtcaacag tatgaaaatc tcccttacac ttttggccag 300

gggaccaagc tggagatcaa a 321

<210> 170
<211> 107

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 170
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Asn Asn Tyr
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Tyr Glu Asn Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 171
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 171
caggacatta acaactac 18

<210> 172
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 172
Gln Asp Ile Asn Asn Tyr
1 5

<210> 173
<211> 9

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 173
gatgcatcc 9

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 174
Asp Ala Ser
1

<210> 175
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 175
caacagtatg aaaatctccc ttacact 27

<210> 176
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 176
Gln Gln Tyr Glu Asn Leu Pro Tyr Thr
1 5

<210> 177
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 177
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatcatatg ctggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acggcctgag agctgaggac acggctgtgt attactgtgc gaaagatccc 300

tacggtgact acgaggggtt tcttgactac tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 178
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 178
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Ala Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Pro Tyr Gly Asp Tyr Glu Gly Val Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 179
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 179

ggattcacct tcagtagcta tggc 24

<210> 180
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 180
Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 181
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 181
atatcatatg ctggaagtaa taaa 24

<210> 182
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 182
Ile Ser Tyr Ala Gly Ser Asn Lys
1 5

<210> 183
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 183
gcgaaagatc cctacggtga ctacgagggg gttcttgact ac 42

<210> 184
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 184
Ala Lys Asp Pro Tyr Gly Asp Tyr Glu Gly Val Leu Asp Tyr
1 5 10

<210> 185
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 185
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctacgat gcttccaatt tggaaacagg ggtcccatca 180

aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240

gaagatattg caacatatta ctgtcagcag tatgatcatc tcccgatcac cttcggccaa 300

gggacacgac tggagattaa a 321

<210> 186
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 186
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp His Leu Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys

100 105

<210> 187
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 187
caggacatta gcaactat 18

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 188
Gln Asp Ile Ser Asn Tyr
1 5

<210> 189
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 189
gatgcttcc 9

<210> 190
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 190
Asp Ala Ser
1

<210> 191
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 191
cagcagtatg atcatctccc gatcacc 27

<210> 192
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 192
Gln Gln Tyr Asp His Leu Pro Ile Thr
1 5

<210> 193
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 193
gaggtgcagc tggtggagtc tgggggaggc ttggttcagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc acctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagtt attagtggta gttttattag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga ccagcctgag agccgaggac acggccgtat attactgtgc gaaaaactcc 300

ccctttgact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 194
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 194
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Ser Gly Ser Phe Ile Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asn Ser Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 195
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 195
ggattcacct ttagcaccta tgcc 24

<210> 196
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 196
Gly Phe Thr Phe Ser Thr Tyr Ala
1 5

<210> 197
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 197
attagtggta gttttattag caca 24

<210> 198
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 198
Ile Ser Gly Ser Phe Ile Ser Thr
1 5

<210> 199
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 199
gcgaaaaact ccccctttga ctac 24

<210> 200
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 200
Ala Lys Asn Ser Pro Phe Asp Tyr
1 5

<210> 201
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 201
gacatcgtga tgacccagtc tccagactcc ctgactgtat ctctgggcga gagggccacc 60

atcaactgca agtccagcca gagtgtttta tacagctcca acaataagaa ctacttagct 120

tggtaccagc agaaaccagg acagcctcct aacctgctca tttactgggc atctacccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatactact 300

ccgtggacgt tcggccgagg gaccaaggtg gagatcaaa 339

<210> 202
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 202
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Thr Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Asn Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Thr Thr Pro Trp Thr Phe Gly Arg Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 203
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 203
cagagtgttt tatacagctc caacaataag aactac 36

<210> 204
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 204
Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 205
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 205
tgggcatct 9

<210> 206
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 206
Trp Ala Ser
1

<210> 207
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 207
cagcaatatt atactactcc gtggacg 27

<210> 208
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 208
Gln Gln Tyr Tyr Thr Thr Pro Trp Thr
1 5

<210> 209
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 209
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc cgggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc aactatgcca tgagctgggt ccgccaggct 120

ccagggaagg gactggagtg ggtctcaact attagtgata ctggtggtag cacatactac 180

gcagactccg tgaagggccg gttcgccctc tccagagaca attccaggaa cacgctgtat 240

ctacaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300

cccccggact actggggaca gggcaccctg gtcaccgtct cctca 345

<210> 210
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 210
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Asp Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ala Leu Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Glu Gly Pro Pro Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 211
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 211

ggattcacct ttagcaacta tgcc 24

<210> 212
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 212
Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 213
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 213
attagtgata ctggtggtag caca 24

<210> 214
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 214
Ile Ser Asp Thr Gly Gly Ser Thr
1 5

<210> 215
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 215
gcgaaagagg ggcccccgga ctac 24

<210> 216
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 216
Ala Lys Glu Gly Pro Pro Asp Tyr
1 5

<210> 217
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 217
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca ggaccagtca gagtgtcagc atctacttag cctggtacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaga gggccactgg catcccagcc 180

aggttcagtg gcagagggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctctcac cttcggccaa 300

gggacacgac tggagattaa a 321

<210> 218
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 218
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Gln Ser Val Ser Ile Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Lys Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Arg Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys

100 105

<210> 219
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 219
cagagtgtca gcatctac 18

<210> 220
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 220
Gln Ser Val Ser Ile Tyr
1 5

<210> 221
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 221
gatgcatcc 9

<210> 222
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 222
Asp Ala Ser
1

<210> 223
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 223
cagcagcgta gcaactggcc tctcacc 27

<210> 224
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 224
Gln Gln Arg Ser Asn Trp Pro Leu Thr
1 5

<210> 225
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 225
gaggtgcagc tggtggagtc tgggggaggc ttggtgcagc cgggggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcaga aactatgcca tgaactgggc ccgccaggct 120

ccagggaagg gactggagtg ggtctcaggt attactggta gtggtggtgc cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaaa attccaagaa cacgctgttt 240

ctgcaaatgg acaccctgag agccgaggac acggccgttt attattgtgc gaaagatcgg 300

aggtatttcc ctacttcggg gggtcctcag tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 226
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 226
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Tyr
20 25 30

Ala Met Asn Trp Ala Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Gly Ile Thr Gly Ser Gly Gly Ala Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asp Thr Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Arg Tyr Phe Pro Thr Ser Gly Gly Pro Gln Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 227
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 227
ggattcacct tcagaaacta tgcc 24

<210> 228
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 228
Gly Phe Thr Phe Arg Asn Tyr Ala
1 5

<210> 229
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 229
attactggta gtggtggtgc caca 24

<210> 230
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 230
Ile Thr Gly Ser Gly Gly Ala Thr
1 5

<210> 231
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 231
gcgaaagatc ggaggtattt ccctacttcg gggggtcctc ag 42

<210> 232
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 232
Ala Lys Asp Arg Arg Tyr Phe Pro Thr Ser Gly Gly Pro Gln
1 5 10

<210> 233
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 233
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtcttctcg gagcctcctg catagttctg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgctct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca catattttac actgaaaatc 240

agcagagtgg acgctgaaga tgttggggtt tattactgca tgcaagctct acaaactccg 300

tggacgttcg gccaagggac caaggtggaa atcaaa 336

<210> 234
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 234
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Arg Ser Leu Leu His Ser
20 25 30

Ser Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Asp Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 235
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 235
cggagcctcc tgcatagttc tggatacaac tat 33

<210> 236
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 236
Arg Ser Leu Leu His Ser Ser Gly Tyr Asn Tyr
1 5 10

<210> 237
<211> 9

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 237
ttgggttct 9

<210> 238
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 238
Leu Gly Ser
1

<210> 239
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 239
atgcaagctc tacaaactcc gtggacg 27

<210> 240
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 240
Met Gln Ala Leu Gln Thr Pro Trp Thr
1 5

<210> 241
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 241
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc cgggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctttagga tgacctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaagcaag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggggg 300

ggtatagcag cttactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 242
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 242
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Arg Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gly Ile Ala Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 243
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 243
ggattcacct ttagtagctt tagg 24

<210> 244
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 244
Gly Phe Thr Phe Ser Ser Phe Arg
1 5

<210> 245
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 245
ataaagcaag atggaagtga gaaa 24

<210> 246
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 246
Ile Lys Gln Asp Gly Ser Glu Lys
1 5

<210> 247
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 247
gcgagagggg ggggtatagc agcttac 27

<210> 248
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 248
Ala Arg Gly Gly Gly Ile Ala Ala Tyr
1 5

<210> 249
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 249
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgtca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300

caagggacac gactggagat taaa 324

<210> 250
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 250
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 251
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 251
cagagcatta gcagctat 18

<210> 252
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 252
Gln Ser Ile Ser Ser Tyr
1 5

<210> 253
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 253
gctgcatcc 9

<210> 254
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 254
Ala Ala Ser
1

<210> 255
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 255
caacagagtt acagtacccc tccgatcacc 30

<210> 256
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 256
Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
1 5 10

<210> 257
<211> 375
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 257
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatcgg 300

ggggaaaacc ggtattacta ctactactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> 258
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 258
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Gly Glu Asn Arg Tyr Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 259
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 259
ggattcacct ttagcagcta tgcc 24

<210> 260
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 260
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 261
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 261
attagtggta gtggtggtag caca 24

<210> 262
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 262
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 263
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 263
gcgaaagatc ggggggaaaa ccggtattac tactactact acggtatgga cgtc 54

<210> 264
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 264
Ala Lys Asp Arg Gly Glu Asn Arg Tyr Tyr Tyr Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 265
<211> 396
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 265
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtacag cctctggatt caccttcaat aactatggca tccactgggt ccgccaggct 120

ccaggcaagg ggctggaatg ggtggcagtt atatcatatg atggaagtaa taaattctat 180

gcagagtccg tgaggggccg attcaccatc tccagagaca attccaggaa cacactgttt 240

ctgcagatga tcagcctgcg aggtgaggac tcggctgttt attactgtgc gaaagatcga 300

ccctattacg atattttgac tgctcattat ccctctgact actacttcta cgctatggac 360

gtctggggcc atgggaccac ggtcaccgtc tcctca 396

<210> 266
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 266
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Asn Asn Tyr
20 25 30

Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Phe Tyr Ala Glu Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Ile Ser Leu Arg Gly Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Pro Tyr Tyr Asp Ile Leu Thr Ala His Tyr Pro Ser
100 105 110

Asp Tyr Tyr Phe Tyr Ala Met Asp Val Trp Gly His Gly Thr Thr Val
115 120 125

Thr Val Ser Ser
130

<210> 267
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 267
ggattcacct tcaataacta tggc 24

<210> 268
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 268
Gly Phe Thr Phe Asn Asn Tyr Gly
1 5

<210> 269
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 269
atatcatatg atggaagtaa taaa 24

<210> 270
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 270
Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 271
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 271
gcgaaagatc gaccctatta cgatattttg actgctcatt atccctctga ctactacttc 60

tacgctatgg acgtc 75

<210> 272
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 272
Ala Lys Asp Arg Pro Tyr Tyr Asp Ile Leu Thr Ala His Tyr Pro Ser
1 5 10 15

Asp Tyr Tyr Phe Tyr Ala Met Asp Val
20 25

<210> 273
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 273
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggctt caccttcact aactatgcca tgcactgggt ccgccaggct 120

ccaggcaagg gactggagtg ggtggcagtt atatcatatg atggaagtca cacatacttt 180

gcagactccg tgaagggccg attcaccatg tccagagaca attccaagaa cacgatatct 240

ctacaaatga acagtctgag acctgaggac acggctgttt atttttgtgc gggaggagga 300

gctactacgt ggttctactt ttacggtttg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> 274
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 274
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser His Thr Tyr Phe Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Ile Ser
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Gly Gly Gly Ala Thr Thr Trp Phe Tyr Phe Tyr Gly Leu Asp Val

100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 275
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 275
ggcttcacct tcactaacta tgcc 24

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 276
Gly Phe Thr Phe Thr Asn Tyr Ala
1 5

<210> 277
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 277
atatcatatg atggaagtca caca 24

<210> 278
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 278
Ile Ser Tyr Asp Gly Ser His Thr
1 5

<210> 279
<211> 48
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 279
gcgggaggag gagctactac gtggttctac ttttacggtt tggacgtc 48

<210> 280
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 280
Ala Gly Gly Gly Ala Thr Thr Trp Phe Tyr Phe Tyr Gly Leu Asp Val
1 5 10 15

<210> 281
<211> 378
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 281
gaggtgcagc tggtggagtc tgggggaggc ttggtaaaac cgggggggtc ccttagactc 60

tcctgtacag cctctggatt cactttcggt aatgcctgga tgagctgggt ccggcaggct 120

ccagggaagg gcctggagtg ggttggcctt attaaaggta aaactgatgg tgggacaaca 180

aactacgctg cacccgtgaa aggcagattc accatctcaa gagatgattc aaaaaacacg 240

ctgtatctgc atttgaacag cctgagaacc gaggacacag ccttgtatta ctgtaccaca 300

gatcaggtgg aactacgaca atactactac tacggtttgg acgtctgggg ccaggggacc 360

acggtcaccg tctcctca 378

<210> 282
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 282
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Gly Asn Ala

20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Leu Ile Lys Gly Lys Thr Asp Gly Gly Thr Thr Asn Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu His Leu Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr
85 90 95

Tyr Cys Thr Thr Asp Gln Val Glu Leu Arg Gln Tyr Tyr Tyr Tyr Gly
100 105 110

Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 283
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 283
ggattcactt tcggtaatgc ctgg 24

<210> 284
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 284
Gly Phe Thr Phe Gly Asn Ala Trp
1 5

<210> 285
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 285
attaaaggta aaactgatgg tgggacaaca 30

<210> 286
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 286
Ile Lys Gly Lys Thr Asp Gly Gly Thr Thr
1 5 10

<210> 287
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 287
accacagatc aggtggaact acgacaatac tactactacg gtttggacgt c 51

<210> 288
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 288
Thr Thr Asp Gln Val Glu Leu Arg Gln Tyr Tyr Tyr Tyr Gly Leu Asp
1 5 10 15

Val

<210> 289
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 289
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc cagggcggtc cctgagactc 60

tcctgtacag cttctggatt cagctttggt gataatgcta tgggctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtaagtttc attagaagga aagcttctgg tgggacaaca 180

gaatacgccg cgtctgtgaa aggcagattc accatctcaa gagatgattc caaaagcatc 240

gcctatctgc aaatgaacag tctgaaaacc gaggacacag gcgtttatta ttgtactaga 300

ggaggagcag tgtacggcta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 290
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 290
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Ser Phe Gly Asp Asn
20 25 30

Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Arg Arg Lys Ala Ser Gly Gly Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Gly Val Tyr
85 90 95

Tyr Cys Thr Arg Gly Gly Ala Val Tyr Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 291
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 291
ggattcagct ttggtgataa tgct 24

<210> 292
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 292
Gly Phe Ser Phe Gly Asp Asn Ala
1 5

<210> 293
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 293
attagaagga aagcttctgg tgggacaaca 30

<210> 294
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 294
Ile Arg Arg Lys Ala Ser Gly Gly Thr Thr
1 5 10

<210> 295
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 295
actagaggag gagcagtgta cggctac 27

<210> 296
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 296
Thr Arg Gly Gly Ala Val Tyr Gly Tyr
1 5

<210> 297
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 297
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagagattgg 300

gtacgatttt tggagtggtt tccccacttt gactactggg gccagggaac cctggtcacc 360

gtctcctca 369

<210> 298
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 298
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Trp Val Arg Phe Leu Glu Trp Phe Pro His Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 299
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 299
ggattcacct tcagtagcta tggc 24

<210> 300
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 300
Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 301
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 301
atatggtatg atggaagtaa taaa 24

<210> 302
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 302
Ile Trp Tyr Asp Gly Ser Asn Lys
1 5

<210> 303
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 303
gcgagagatt gggtacgatt tttggagtgg tttccccact ttgactac 48

<210> 304
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 304
Ala Arg Asp Trp Val Arg Phe Leu Glu Trp Phe Pro His Phe Asp Tyr
1 5 10 15

<210> 305
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 305
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc aactatgcca tgagctgggt ccgccaggtt 120

ccagggaagg ggctggagtg ggtctcaact attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa ctcgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attattgtgc gaaattggtt 300

cggggagtta ttggctggtt cgacccctgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 306
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 306
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Leu Val Arg Gly Val Ile Gly Trp Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 307
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 307
ggattcacct ttagcaacta tgcc 24

<210> 308
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 308
Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 309
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 309
attagtggta gtggtggtag caca 24

<210> 310
<211> 8
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 310
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 311
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 311
gcgaaattgg ttcggggagt tattggctgg ttcgacccc 39

<210> 312
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 312
Ala Lys Leu Val Arg Gly Val Ile Gly Trp Phe Asp Pro
1 5 10

<210> 313
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 313
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cgtgagactc 60

tcctgtggag cgtctggatt cactttcaaa tactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggaatg ggtggcagtc atttggtatg atggaagaaa taaattttat 180

gcagactctg tgaagggccg cttcactatc tccagagaca attccaagaa cacggtgaat 240

ctggaaatga acaacctgag agccgaggac acggctatat attactgtgc gagagatgga 300

ggaacagcgg atggcgacta ttttgactac tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 314
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 314
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Val Arg Leu Ser Cys Gly Ala Ser Gly Phe Thr Phe Lys Tyr Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Arg Asn Lys Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Asn
65 70 75 80

Leu Glu Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Gly Thr Ala Asp Gly Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 315
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 315
ggattcactt tcaaatacta tggc 24

<210> 316
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 316
Gly Phe Thr Phe Lys Tyr Tyr Gly
1 5

<210> 317
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 317
atttggtatg atggaagaaa taaa 24

<210> 318
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 318
Ile Trp Tyr Asp Gly Arg Asn Lys
1 5

<210> 319
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 319
gcgagagatg gaggaacagc ggatggcgac tattttgact ac 42

<210> 320
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 320
Ala Arg Asp Gly Gly Thr Ala Asp Gly Asp Tyr Phe Asp Tyr
1 5 10

<210> 321
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 321
gaaatagttt tgacacagag tcccggcaca ctgtcactct ctcccgggga aagagccacc 60

ttgtcatgta gagcaagtca gtcagtctct agctcttatc tcgcctggta ccagcagaag 120

ccgggacagg cccctagact gctgatctac ggggcaagtt ccagggccac cggaatcccc 180

gaccggttca gtggaagcgg aagcggaacc gattttactt tgacgatttc tagactggag 240

ccagaggatt tcgccgttta ctattgtcaa cagtacggaa gcagcccgtg gacgtttggc 300

cagggcacga aggtagaaat caag 324

<210> 322
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 322
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

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

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 323
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 323
agagcaagtc agtcagtctc tagctcttat ctcgcc 36

<210> 324

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 324
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 325
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 325
ggggcaagtt ccagggccac c 21

<210> 326
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 326
Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 327
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 327
caacagtacg gaagcagccc gtggacg 27

<210> 328
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 328

Gln Gln Tyr Gly Ser Ser Pro Trp Thr
1 5

<210> 329
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 329
gaggtgcagc tggtggagtc tgggggaggt ttggtacagc ctgggggtc cctgagactc 60

tcctgtgtag gcactggatt cacctttagc aactatgcca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaggt attagtggta gaagtagtgg cacattctac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attcccagaa tacgctgtat 240

ctgcaaatga acagcctggg agccgaggac acggccgtat attactgtgc gaaagtttcc 300

cgttataact gggactacgt ccccttgac ttctggggcc agggaaccct ggtcaccgtc 360

tcctca 366

<210> 330
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 330
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Gly Thr Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Arg Ser Ser Gly Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Gly Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Ser Arg Tyr Asn Trp Asp Tyr Val Pro Phe Asp Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 331
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 331
ggattcacct ttagcaacta tgcc 24

<210> 332
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 332
Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 333
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 333
attagtggta gaagtagtgg caca 24

<210> 334
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 334
Ile Ser Gly Arg Ser Ser Gly Thr
1 5

<210> 335
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 335
gcgaaagttt cccgttataa ctgggactac gtccccttg acttc 45

<210> 336
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 336
Ala Lys Val Ser Arg Tyr Asn Trp Asp Tyr Val Pro Phe Asp Phe
1 5 10 15

<210> 337
<211> 39
<212> PRT
<213> Homo sapiens

<220>
<221> source
<223> /note="Human AngPTL8 Naked Peptide: amino acids 22-60"

<300>
<308> /note="GenBank Database: NP_061157.3"

<400> 337
Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu
1 5 10 15

Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala Leu Asn Gly Val Tyr
20 25 30

Arg Thr Thr Glu Gly Arg Leu
35

<210> 338
<211> 26
<212> PRT
<213> Homo sapiens

<220>
<221> source
<223> /note="Human ANGPTL3 Shift Naked Peptide: amino acids 32-57"

<300>
<308> /note="GenBank Database: NP_055310.1"

<400> 338
Glu Pro Lys Ser Arg Phe Ala Met Leu Asp Asp Val Lys Ile Leu Ala
1 5 10 15

Asn Gly Leu Leu Gln Leu Gly His Gly Leu
20 25

<210> 339
<211> 34
<212> PRT
<213> Homo sapiens

<220>
<221> source
<223> /note="Human ANGPTL4 Naked Peptide: amino acids 34-67"

<300>
<308> /note="GenBank Database: NP_001034756.1"

<400> 339
Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu Leu
1 5 10 15

Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser Gln
20 25 30

Leu Cys

<210> 340
<211> 413
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
hANGPTL8-mFc aa 1-177: amino acids 22-198 of NP_061157.3
aa 178-413: GPG linker and mouse IgG2a Fc tag polypeptide"

<300>
<308> /note="GenBank Database: NP_061157.3 (part of full length seq)"

<400> 340
Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu
1 5 10 15

Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala Leu Asn Gly Val Tyr
20 25 30

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

Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu Val Ser Arg Gly Arg
50 55 60

Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu Glu Thr Gln Met Glu
65 70 75 80

Glu Asp Ile Leu Gln Leu Gln Ala Glu Ala Thr Ala Glu Val Leu Gly

85 90 95

Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp Ser Val Gln Arg Leu
100 105 110

Glu Val Gln Leu Arg Ser Ala Trp Leu Gly Pro Ala Tyr Arg Glu Phe
115 120 125

Glu Val Leu Lys Ala His Ala Asp Lys Gln Ser His Ile Leu Trp Ala
130 135 140

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

His Arg Leu Arg Gln Ile Gln Glu Arg Leu His Thr Ala Ala Leu Pro
165 170 175

Ala Gly Pro Gly Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro
180 185 190

Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile
195 200 205

Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile
210 215 220

Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln
225 230 235 240

Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln
245 250 255

Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu
260 265 270

Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys
275 280 285

Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys
290 295 300

Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro
305 310 315 320

Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr
325 330 335

Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys
340 345 350

Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly

355 360 365

Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val
370 375 380

Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn
385 390 395 400

His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
405 410

<210> 341
<211> 410
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic MfAngPTL8-mFc aa 1-177: amino acids 78-254 of XP_005588064.1aa 178-410: mouse IgG2a Fc tag polypeptide"

<300>
<308> /note="GenBank Database: XP_005588064.1 (part of full length seq)"

<400> 341
Ala Pro Val Gly Ser Pro Glu Leu Ala Glu His Glu Glu Leu Thr Leu
1 5 10 15

Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala Leu Asn Gly Val Tyr
20 25 30

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

Tyr Gly Arg Thr Val Glu Leu Leu Gly Gln Glu Val Ser Arg Gly Arg
50 55 60

Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu Glu Thr Gln Met Glu
65 70 75 80

Glu Asp Ile Leu Gln Leu Lys Ala Glu Ala Ile Ala Glu Val Leu Glu
85 90 95

Glu Val Ala Gln Ala Gln Lys Val Leu Gln Asp Ser Val Arg Arg Leu
100 105 110

Glu Val Gln Leu Arg Ser Ala Trp Leu Gly Pro Ala Tyr Gln Glu Phe
115 120 125

Glu Val Leu Lys Ala His Ala Asp Lys Gln Ser His Ile Leu Trp Ala
130 135 140

Leu Thr Gly His Val Gln Arg Gln Arg Arg Glu Met Val Ala Gln Gln

145 150 155 160

His Arg Leu Arg Gln Ile Gln Glu Arg Ile His Lys Ala Ala Leu Pro
165 170 175

Ala Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys
180 185 190

Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro
195 200 205

Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys
210 215 220

Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp
225 230 235 240

Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg
245 250 255

Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln
260 265 270

His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn
275 280 285

Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly
290 295 300

Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu
305 310 315 320

Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met
325 330 335

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

Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe
355 360 365

Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn
370 375 380

Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr
385 390 395 400

Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
405 410

<210> 342

<211> 460
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic hANGPTL3 polypeptide"

<400> 342

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Met Phe Thr Ile Lys Leu Leu Leu Phe Ile Val Pro Leu Val Ile Ser
1               5                  10                  15

Ser Arg Ile Asp Gln Asp Asn Ser Ser Phe Asp Ser Leu Ser Pro Glu
            20                  25                  30

Pro Lys Ser Arg Phe Ala Met Leu Asp Asp Val Lys Ile Leu Ala Asn
        35                  40                  45

Gly Leu Leu Gln Leu Gly His Gly Leu Lys Asp Phe Val His Lys Thr
    50                  55                  60

Lys Gly Gln Ile Asn Asp Ile Phe Gln Lys Leu Asn Ile Phe Asp Gln
65                  70                  75                  80

Ser Phe Tyr Asp Leu Ser Leu Gln Thr Ser Glu Ile Lys Glu Glu Glu
                85                  90                  95

Lys Glu Leu Arg Arg Thr Thr Tyr Lys Leu Gln Val Lys Asn Glu Glu
            100                 105                 110

Val Lys Asn Met Ser Leu Glu Leu Asn Ser Lys Leu Glu Ser Leu Leu
        115                 120                 125

Glu Glu Lys Ile Leu Leu Gln Gln Lys Val Lys Tyr Leu Glu Glu Gln
    130                 135                 140

Leu Thr Asn Leu Ile Gln Asn Gln Pro Glu Thr Pro Glu His Pro Glu
145                 150                 155                 160

Val Thr Ser Leu Lys Thr Phe Val Glu Lys Gln Asp Asn Ser Ile Lys
                165                 170                 175

Asp Leu Leu Gln Thr Val Glu Asp Gln Tyr Lys Gln Leu Asn Gln Gln
            180                 185                 190

His Ser Gln Ile Lys Glu Ile Glu Asn Gln Leu Arg Arg Thr Ser Ile
        195                 200                 205

Gln Glu Pro Thr Glu Ile Ser Leu Ser Ser Lys Pro Arg Ala Pro Arg
    210                 215                 220

Thr Thr Pro Phe Leu Gln Leu Asn Glu Ile Arg Asn Val Lys His Asp
225                 230                 235                 240
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```
Gly Ile Pro Ala Glu Cys Thr Thr Ile Tyr Asn Arg Gly Glu His Thr
                245                 250                 255

Ser Gly Met Tyr Ala Ile Arg Pro Ser Asn Ser Gln Val Phe His Val
            260                 265                 270

Tyr Cys Asp Val Ile Ser Gly Ser Pro Trp Thr Leu Ile Gln His Arg
        275                 280                 285

Ile Asp Gly Ser Gln Asn Phe Asn Glu Thr Trp Glu Asn Tyr Lys Tyr
    290                 295                 300

Gly Phe Gly Arg Leu Asp Gly Glu Phe Trp Leu Gly Leu Glu Lys Ile
305                 310                 315                 320

Tyr Ser Ile Val Lys Gln Ser Asn Tyr Val Leu Arg Ile Glu Leu Glu
                325                 330                 335

Asp Trp Lys Asp Asn Lys His Tyr Ile Glu Tyr Ser Phe Tyr Leu Gly
            340                 345                 350

Asn His Glu Thr Asn Tyr Thr Leu His Leu Val Ala Ile Thr Gly Asn
        355                 360                 365

Val Pro Asn Ala Ile Pro Glu Asn Lys Asp Leu Val Phe Ser Thr Trp
    370                 375                 380

Asp His Lys Ala Lys Gly His Phe Asn Cys Pro Glu Gly Tyr Ser Gly
385                 390                 395                 400

Gly Trp Trp Trp His Asp Glu Cys Gly Glu Asn Asn Leu Asn Gly Lys
                405                 410                 415

Tyr Asn Lys Pro Arg Ala Lys Ser Lys Pro Glu Arg Arg Arg Gly Leu
            420                 425                 430

Ser Trp Lys Ser Gln Asn Gly Arg Leu Tyr Ser Ile Lys Ser Thr Lys
        435                 440                 445

Met Leu Ile His Pro Thr Asp Ser Glu Ser Phe Glu
    450                 455                 460


<210> 343
<211> 1383
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic hANGPTL3
      polynucleotide"
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<400> 343
atgttcacaa ttaagctcct tctttttatt gttcctctag ttatttcctc cagaattgat 60

caagacaatt catcatttga ttctctatct ccagagccaa aatcaagatt tgctatgtta 120

gacgatgtaa aaattttagc caatggcctc cttcagttgg gacatggtct taaagacttt 180

gtccataaga cgaagggcca aattaatgac atatttcaaa aactcaacat atttgatcag 240

tctttttatg atctatcgct gcaaaccagt gaaatcaaag aagaagaaaa ggaactgaga 300

agaactacat ataaactaca agtcaaaaat gaagaggtaa agaatatgtc acttgaactc 360

aactcaaaac ttgaaagcct cctagaagaa aaaattctac ttcaacaaaa agtgaaatat 420

ttagaagagc aactaactaa cttaattcaa aatcaacctg aaactccaga acacccagaa 480

gtaacttcac ttaaaacttt tgtagaaaaa caagataata gcatcaaaga ccttctccag 540

accgtggaag accaatataa acaattaaac caacagcata gtcaaataaa agaaatagaa 600

aatcagctca gaaggactag tattcaagaa cccacagaaa tttctctatc ttccaagcca 660

agagcaccaa gaactactcc ctttcttcag ttgaatgaaa taagaaatgt aaaacatgat 720

ggcattcctg ctgaatgtac caccatttat aacagaggtg aacatacaag tggcatgtat 780

gccatcagac ccagcaactc tcaagttttt catgtctact gtgatgttat atcaggtagt 840

ccatggacat taattcaaca tcgaatagat ggatcacaaa acttcaatga aacgtgggag 900

aactacaaat atggttttgg gaggcttgat ggagaatttt ggttgggcct agagaagata 960

tactccatag tgaagcaatc taattatgtt ttacgaattg agttggaaga ctggaaagac 1020

aacaaacatt atattgaata ttctttttac ttgggaaatc acgaaaccaa ctatacgcta 1080

catctagttg cgattactgg caatgtcccc aatgcaatcc cggaaaacaa agatttggtg 1140

ttttctactt gggatcacaa agcaaaagga cacttcaact gtccagaggg ttattcagga 1200

ggctggtggt ggcatgatga gtgtggagaa aacaacctaa atggtaaata taacaaacca 1260

agagcaaaat ctaagccaga gaggagaaga ggattatctt ggaagtctca aaatggaagg 1320

ttatactcta taaaatcaac caaaatgttg atccatccaa cagattcaga aagctttgaa 1380

tga 1383

<210> 344
<211> 406
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic hANGPTL4
polypeptide"

<400> 344
Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala
1 5 10 15

Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser
20 25 30

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Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu
        35                  40                  45

Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser
    50                  55                  60

Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys
65                  70                  75                  80

Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg
                85                  90                  95

Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln
            100                 105                 110

Asn Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg
        115                 120                 125

His Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe
    130                 135                 140

Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala
145                 150                 155                 160

Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His
                165                 170                 175

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

Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly
        195                 200                 205

Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp
    210                 215                 220

Thr Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro
225                 230                 235                 240

Trp Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp
                245                 250                 255

Leu Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser Arg
            260                 265                 270

Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln
        275                 280                 285

Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu
    290                 295                 300
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Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser
305 310 315 320

Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg
325 330 335

Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly
340 345 350

Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro
355 360 365

Gln Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg
370 375 380

Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met
385 390 395 400

Ala Ala Glu Ala Ala Ser
405

<210> 345
<211> 1221
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic hANGPTL4 polynucleotide"

<400> 345
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ctgagcgctc agggcggacc cgtgcagtcc aagtcgccgc gctttgcgtc ctgggacgag 120

atgaatgtcc tggcgcacgg actcctgcag ctcggccagg ggctgcgcga acacgcggag 180

cgcacccgca gtcagctgag cgcgctggag cggcgcctga gcgcgtgcgg gtccgcctgt 240

cagggaaccg aggggtccac cgacctcccg ttagcccctg agagccgggt ggaccctgag 300

gtccttcaca gcctgcagac acaactcaag gctcagaaca gcaggatcca gcaactcttc 360

cacaaggtgg cccagcagca gcggcacctg gagaagcagc acctgcgaat tcagcatctg 420

caaagccagt ttggcctcct ggaccacaag cacctagacc atgaggtggc caagcctgcc 480

cgaagaaaga ggctgcccga gatggcccag ccagttgacc cggctcacaa tgtcagccgc 540

ctgcaccggc tgcccaggga ttgccaggag ctgttccagg ttggggagag gcagagtgga 600

ctatttgaaa tccagcctca ggggtctccg ccatttttgg tgaactgcaa gatgacctca 660

gatggaggct ggacagtaat tcagaggcgc cacgatggct cagtggactt caaccggccc 720

tgggaagcct acaaggcggg gtttggggat ccccacggcg agttctggct gggtctggag 780

aaggtgcata gcatcacggg ggaccgcaac agccgcctgg ccgtgcagct gcgggactgg 840

gatggcaacg ccgagttgct gcagttctcc gtgcacctgg gtggcgagga cacggcctat 900

agcctgcagc tcactgcacc cgtggccggc cagctgggcg ccaccaccgt cccacccagc 960

ggcctctccg tacccttctc cacttgggac caggatcacg acctccgcag ggacaagaac 1020

tgcgccaaga gcctctctgg aggctggtgg tttggcacct gcagccattc caacctcaac 1080

ggccagtact tccgctccat cccacagcag cggcagaagc ttaagaaggg aatcttctgg 1140

aagacctggc ggggccgcta ctacccgctg caggccacca ccatgttgat ccagcccatg 1200

gcagcagagg cagcctccta g 1221

<210> 346
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 346
Cys Gly Gly Cys Gly Gly
1 5

<210> 347
<211> 177
<212> PRT
<213> Homo sapiens

<400> 347
Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu
1 5 10 15

Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala Leu Asn Gly Val Tyr
20 25 30

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

Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu Val Ser Arg Gly Arg
50 55 60

Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu Glu Thr Gln Met Glu
65 70 75 80

Glu Asp Ile Leu Gln Leu Gln Ala Glu Ala Thr Ala Glu Val Leu Gly
85 90 95

Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp Ser Val Gln Arg Leu
100 105 110

Glu Val Gln Leu Arg Ser Ala Trp Leu Gly Pro Ala Tyr Arg Glu Phe
115 120 125

Glu Val Leu Lys Ala His Ala Asp Lys Gln Ser His Ile Leu Trp Ala
130 135 140

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

His Arg Leu Arg Gln Ile Gln Glu Arg Leu His Thr Ala Ala Leu Pro
165 170 175

Ala

<210> 348
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 348
Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr
1 5 10 15

<210> 349
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 349
Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu
1 5 10 15

<210> 350
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 350
Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu
1 5 10 15

<210> 351
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 351
Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe
1 5 10 15

<210> 352
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 352
Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His
1 5 10 15

<210> 353
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 353
Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly
1 5 10 15

<210> 354
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 354
Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr
1 5 10 15

<210> 355
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 355
Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu
1 5 10 15

<210> 356
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 356
Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln
1 5 10 15

<210> 357
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 357
Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu
1 5 10 15

<210> 358
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 358
Thr Ala Glu Val Leu Gly Glu Val Ala Ala Gly Gln Lys Val Leu
1 5 10 15

<210> 359
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 359
Val Tyr Arg Thr Thr Glu Gly Arg Leu Ala Ala Ala Arg Asn Ser
1 5 10 15

<210> 360
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 360
Gly Val Tyr Arg Thr Thr Glu Gly Arg Ala Ala Lys Ala Arg Asn
1 5 10 15

<210> 361
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 361
Val Gln Arg Leu Glu Val Gln Leu Arg Ala Gly Trp Leu Gly Pro
1 5 10 15

<210> 362
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 362
Leu Thr Gly His Val Gln Arg Gln Arg Ala Ala Met Val Ala Gln
1 5 10 15

<210> 363
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 363
Val Leu Lys Ala His Ala Asp Lys Gln Ala Ala Ile Leu Trp Ala
1 5 10 15

<210> 364
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 364
Leu Arg Asp Ser Val Gln Arg Leu Glu Ala Ala Leu Arg Ser Ala
1 5 10 15

<210> 365

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 365
Arg Arg Glu Met Val Ala Gln Gln His Ala Ala Arg Gln Ile Gln
1 5 10 15

<210> 366
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 366
Val Ser Arg Gly Arg Asp Ala Ala Gln Ala Ala Arg Ala Ser Leu
1 5 10 15

<210> 367
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 367
Ala Tyr Arg Glu Phe Glu Val Leu Lys Gly Ala Ala Asp Lys Gln
1 5 10 15

<210> 368
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 368
Gln Arg Gln Arg Arg Glu Met Val Ala Gln
1 5 10