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(54) **METHODS FOR TREATING
HYPERCHOLESTEROLEMIA AND
REDUCING LDL-C USING ANTIBODIES TO
PCSK9**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

5,260,440 A 11/1993 Hirai
5,273,995 A 12/1993 Roth
(Continued)

FOREIGN PATENT DOCUMENTS

CN 101489565 7/2009
EP 0409281 1/1991
(Continued)

OTHER PUBLICATIONS

Wang et al., (Clin Pharmacology. Sep. 2009.49(9):1012-1024).
(Continued)

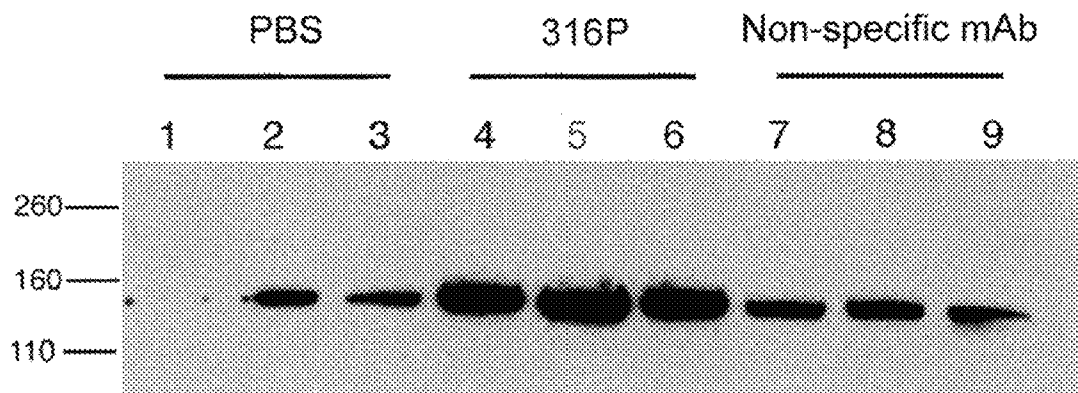
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(57) **ABSTRACT**

The present invention provides methods for treating hyper-
cholesterolemia and reducing LDL-C. The methods of the
present invention comprise administering to a subject in
need thereof a therapeutic composition comprising an anti-
PCSK9 antibody or antigen-binding fragment thereof.

32 Claims, 14 Drawing Sheets



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References Cited

U.S. PATENT DOCUMENTS

5,399,670	A	3/1995	Bhattacharya
5,851,999	A	12/1998	Ullrich
5,939,598	A	8/1999	Kucherlapati
6,011,003	A	1/2000	Charmock-Jones
6,171,586	B1	1/2001	Lam
6,267,958	B1	7/2001	Andya
6,270,993	B1	8/2001	Shibuya
6,596,541	B2	7/2003	Murphy
6,629,949	B1	10/2003	Douglas
6,659,982	B2	12/2003	Douglas
6,875,432	B2	4/2005	Liu
6,946,548	B2	9/2005	Sarkar et al.
7,001,892	B1	2/2006	Chmielewski
7,029,895	B2	4/2006	Glucksmann
7,060,268	B2	6/2006	Andya
7,129,338	B1	10/2006	Ota
7,300,754	B2	11/2007	Fadel
7,482,147	B2	1/2009	Glucksmann
7,572,618	B2	8/2009	Mintier
7,608,693	B2	10/2009	Martin
7,754,208	B2	7/2010	Ledbetter
8,030,457	B2 *	10/2011	Jackson 424/130.1
8,062,640	B2	11/2011	Sleeman
8,080,243	B2	12/2011	Liang
8,092,803	B2	1/2012	Furfine
8,168,762	B2	5/2012	Jackson
8,188,233	B2	5/2012	Condra
8,188,234	B2	5/2012	Condra
8,357,371	B2	1/2013	Sleeman
8,795,669	B2	8/2014	Dix
8,829,165	B2	9/2014	Jackson
9,550,837	B2	1/2017	Sleeman
2003/0092606	A1	5/2003	L'Italien
2003/0113316	A1	6/2003	Kaisheva
2003/0118592	A1	6/2003	Ledbetter
2003/0133939	A1	7/2003	Ledbetter
2004/0101920	A1	5/2004	Radziejewski
2004/0197324	A1	10/2004	Liu
2005/0281831	A1	12/2005	Davis-Smyth
2006/0147945	A1	7/2006	Edmonds
2007/0082345	A1	4/2007	Ota
2007/0224663	A1	9/2007	Rosen
2008/0008697	A1	1/2008	Mintier
2009/0142352	A1	6/2009	Jackson
2009/0232795	A1	9/2009	Condra

2009/0246192	A1	10/2009	Condra
2009/0269350	A1	10/2009	Glucksmann
2009/0318536	A1	12/2009	Freier
2009/0326202	A1	12/2009	Jackson
2010/0040610	A1	2/2010	Sitlani
2010/0040611	A1	2/2010	Sparrow
2010/0041102	A1	2/2010	Sitlani
2010/0068199	A1	3/2010	Liang
2010/0136028	A1	6/2010	Sparrow
2010/0150937	A1	6/2010	Sparrow
2010/0166768	A1	7/2010	Sleeman
2010/0233177	A1	9/2010	Yowe
2011/0027287	A1	2/2011	Jackson
2011/0033465	A1	2/2011	Hedrick
2011/0065902	A1	3/2011	Sleeman
2011/0098450	A1	4/2011	Igawa et al.
2011/0111406	A1	5/2011	Igawa et al.
2011/0142849	A1	6/2011	Rue
2011/0171241	A1	7/2011	Dix
2011/0229489	A1	9/2011	Pons
2011/0256148	A1	10/2011	Sleeman
2012/0014951	A1	1/2012	Liang
2012/0015435	A1	1/2012	Liang
2012/0020975	A1	1/2012	Jackson
2012/0027765	A1	2/2012	Jackson
2012/0076799	A1	3/2012	Sparrow
2012/0077964	A1	3/2012	Sparrow
2012/0082679	A1	4/2012	Sparrow
2012/0082680	A1	4/2012	Sitlani
2012/0093818	A1	4/2012	Jackson
2012/0097565	A1	4/2012	Dix
2012/0195910	A1	8/2012	Wu
2012/0213794	A1	8/2012	Luo
2012/0213797	A1	8/2012	Jackson
2012/0219558	A1	8/2012	Ni
2012/0231005	A1	9/2012	Luo
2012/0251544	A1	10/2012	Jackson
2013/0011866	A1	1/2013	Igawa et al.
2013/0064825	A1	3/2013	Chan
2013/0064834	A1 *	3/2013	Sleeman A61K 39/3955 424/158.1
2013/0085266	A1	4/2013	Sleeman
2013/0243784	A1	9/2013	Swergold
2014/0004122	A1	1/2014	Chan
2014/0030270	A1	1/2014	Clogston
2014/0065649	A1	3/2014	Schaefer
2014/0154262	A1	6/2014	Hanotin
2014/0161821	A1	6/2014	Udata
2014/0178402	A1	6/2014	Hanotin
2014/0356370	A1	12/2014	Swergold
2014/0356371	A1	12/2014	Swergold
2015/0231236	A1	8/2015	Pordy
2016/0152734	A1	6/2016	Udata
2017/0049886	A1	2/2017	Pordy

FOREIGN PATENT DOCUMENTS

EP	0521471	1/1993
EP	1 067 182 A2	1/2001
EP	1 514 933 A1	3/2005
EP	1317537	12/2006
EP	1618212	11/2007
EP	2 703 008	8/2012
EP	2 703 009	8/2012
EP	2 706 070	3/2014
WO	WO 93/00807	1/1993
WO	WO97/35620	10/1997
WO	WO 98/22136	5/1998
WO	WO 99/38495	8/1999
WO	WO 01/57081 A2	8/2001
WO	WO 01/92340	12/2001
WO	WO 2004/055164	7/2004
WO	WO 2004/097947	11/2004
WO	WO 2005/047331	5/2005
WO	WO 2005/103081	11/2005
WO	WO 2007/143315	12/2007
WO	WO 2007/149334	12/2007
WO	WO 2008/054606	5/2008
WO	WO 2008/057457 A2	5/2008

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	WO 2008/057458	A2	5/2008
WO	WO 2008/057459		5/2008
WO	WO 2008/063382	A2	5/2008
WO	WO 2008/073300		6/2008
WO	WO 2008/125623		10/2008
WO	WO 2008/133647	A2	11/2008
WO	WO 2009/026558	A1	2/2009
WO	WO 2009/055783		4/2009
WO	WO 2009/100297		8/2009
WO	WO 2009/100318	A1	8/2009
WO	WO 2010/029513		3/2010
WO	WO2010/077854		7/2010
WO	WO 2010/102241		9/2010
WO	WO 2011/028938		3/2011
WO	WO 2011/039578		4/2011
WO	WO 2011/053759		5/2011
WO	WO 2011/061712		5/2011
WO	WO 2011/072263		6/2011
WO	WO 2011/111007		9/2011
WO	WO 2012/054438		4/2012
WO	WO 2012/064792		5/2012
WO	WO 2012/101251		8/2012
WO	WO 2012/101252		8/2012
WO	WO 2012/101253		8/2012
WO	WO 2012/109530		8/2012
WO	WO 2012/146776		11/2012
WO	WO 2012/154999		11/2012
WO	WO 2013/039958		3/2013
WO	WO 2013/039969		3/2013
WO	WO 2013/158984		10/2013
WO	WO 2013/166448		11/2013
WO	WO 2014/194111		12/2014
WO	WO 2014/197752		12/2014
WO	WO 2015/054619		4/2015
WO	WO 2015/073494		5/2015
WO	WO 2015/123423		8/2015
WO	WO 2015/140079		9/2015
WO	WO 2015/142668		9/2015
WO	WO 2016/011256		1/2016
WO	WO 2016/011260		1/2016

OTHER PUBLICATIONS

Bays H, Farnier M, Gaudet D, Weiss R, Lima Ruiz J, Watts GF, Gouni-Berthold I, Robinson J, Jones P, Severance R, Averna M, Steinhagen-Thiessen E, Colhoun HM, Zhao J, Du Y, Hanotin C, Donahue S. Efficacy and safety of combining alirocumab with atorvastatin or rosuvastatin versus statin intensification or adding ezetimibe in high cardiovascular risk patients: Odyssey Options I and II. *Circulation*. 2014;130:2105-2126.

Bays H; Gaudet D; Weiss R; Lima Ruiz J; Watts GF; Gouni-Berthold I; Robinson J; Zhao J; Hanotin C; Donahue S. PCSK9 Inhibitor Alirocumab as Add-on to Atorvastatin versus Other Lipid Treatment Strategies in Patients at High CVD Risk: Odyssey Options I. *Circulation*. 2014;130:A16194.

Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, Chaudhari U, Colhoun HM. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated daily statin: results from the Odyssey Combo II study; presented at ESC Congress Aug. 31, 2014, abstract not published.

Catapano AL, Papadopoulos N. The safety of therapeutic monoclonal antibodies: implications for cardiovascular disease and targeting the PCSK9 pathway. *Atherosclerosis* 2013;228(1):18-28.

Duff et al. *Biochem Journal*, the Biochemical Society, vol. 419, No. 3, May 1, 2009 pp. 577-584.

Dufour R, Moriarty PM, Genestin E, Sasiela WJ, Du Y, Ferrand A-C; Ginsberg HN. Effect of REGN727/SAR236553 PCSK9 fully human monoclonal antibody in patients with elevated triglycerides/low high-density lipoprotein cholesterol: data from three phase 2 studies. *Circulation* 2012;126:Abstract A16127.

Farnier M, Kastelein JJP, Roth E, Taskinen MR, Ginsberg HN, Colhoun HM, Robinson JG, Merlet L, Brunet A, Pordy R, Baccara-Dinet MT. Relationship between alirocumab, PCSK9 and LDL-C levels: results from the Odyssey Mono Phase 3 trial of alirocumab 75 mg every 2 weeks. *Atherosclerosis*. 2014;235(2):e34-e35. [Abstract MP02E].

Foody J, Khan I, Lewis B. Attainment of low-density lipoprotein cholesterol goals in patients at high cardiovascular risk: results from a managed care population study. *Circulation*. 2013;128:A17254.

Gaudet D, Kereiakes D, McKenney J, Roth E, Hanotin C, Gipe D, Du Y, Ferrand A-C, Ginsberg H, Stein E. Alirocumab, a fully human monoclonal antibody to PCSK9, reduces high plasma Lp(a) concentration: pooled analysis of 352 patients from phase 2. *J Clin Lipidol* 2013;7(3):283-284.

Gaudet D, Kereiakes D, McKenney J, Roth E, Hanotin C, Gipe D, Du Y, Ferrand A-C, Ginsberg H, Stein E. Effect of Alirocumab, a Monoclonal Proprotein Convertase Subtilisin/Kexin 9 Antibody, on Lipoprotein(a) Concentrations (a Pooled Analysis of 150 mg Every 2 Weeks Dosing from Phase 2 Trials). *Am J Cardiol*. 2014;114(5):711-715.

Gaudet D, Kereiakes D, McKenney J, Roth E, Hanotin C, Gipe D, Du Y, Ferrand A-C, Ginsberg H, Stein E. Effect of SAR236553/REGN727 fully human monoclonal anti-protein convertase subtilisin/kexin type 9 antibody on plasma lipoprotein(a) concentrations: pooled analysis from three phase 2 studies (NCT:01266876; 01288469; 01288443). *Circulation* 2012;126:Abstract A14725.

Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Lorenzato C, Pordy R, Baccara-Dinet MT, Stroes E. Odyssey High FH: efficacy and safety of alirocumab in patients with severe heterozygous familial hypercholesterolemia. *Circulation*. 2014;130:2119.

Gusarova V, Howard VG, Okamoto H, Koehler-Stec EM, Papadopoulos N, Murphy AJ, Yancopoulos GD, Stahl N, Sleeman MW. Reduction of LDL cholesterol by a monoclonal antibody to PCSK9 in rodents and nonhuman primates. *Clin Lipidol* 2012;7(6):737-743.

Hochleitner et al., Characterization of a discontinuous epitope of the human immunodeficiency virus-HIV1 core protein p24 by epitope excision and differential chemical modification followed by mass spectrometric peptide mapping analysis; *Protein Science* 2000, 9:487-496. Cambridge University Press.

Hopkins PN, Swergold GD, Mellis S, Bruckert E, Luc G, Mendoza J, Du Y, Krempf M. A randomized placebo-phase clinical trial with the monoclonal antibody alirocumab demonstrates reductions in low-density lipoprotein cholesterol in patients with proprotein convertase subtilisin/kexin type 9 gain-of-function mutations. *Circulation*. 2013;128:A17156.

Hovingh GK, Davidson MH, Kastelein JJ, O'Connor AM. Diagnosis and treatment of familial hypercholesterolaemia. *Eur Heart J* 2013;34(13):962-971.

International Preliminary Report on Patentability dated Jul. 30, 2013 for International application No. PCT/EP12/051321, 7 pages.

International Search Report and Written Opinion dated Aug. 19, 2015 for International application No. PCT/US2015/015633, 23 pages.

International Search Report and Written Opinion mailed Apr. 16, 2015 for International Application No. PCT/US2014/060109 (19 pages).

International Search Report and Written Opinion mailed Feb. 3, 2015 for International Application No. PCT/US2014/065149 (17 pages).

International Search Report and Written Opinion mailed Jun. 12, 2015 for International Application No. PCT/US2015/020564 (20 pages).

International Search Report dated Aug. 2, 2012 for International application No. PCT/EP12/051321, (4 pages).

Jones P, Bays H, Chaudhari U, Pordy R, Lorenzato C, Miller K, Robinson J. Pooled safety and adverse events in nine randomized, placebo-controlled, phase 2 and 3 clinical trials of alirocumab. *J Am Coll Cardiol* 2015;65(10_S):A1363.

(56)

References Cited

OTHER PUBLICATIONS

- Junghans et al.: Anti-Tac-H, a Humanized Antibody to the Interleukin 2 Receptor with New Features for Immunotherapy in Malignant and Immune Disorders; *Cancer Research*, 50. 1495-1502; Mar. 1, 1990.
- Kastelein JJP, Ginsberg HN, Langslet G, Kees Hovingh G, Ceska R, Dufour R, Blom D, Civeira F, Krempf M, Farnier M. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolaemia not adequately controlled with current lipid-lowering therapy: results of Odyssey FH I and FH II studies; presented at ESC Congress Aug. 31, 2014, abstract not published.
- Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, Colhoun HM. Efficacy and safety of alirocumab in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia on maximally tolerated doses of statins: the Odyssey Combo I study. *Circulation*. 2014;130:2119.
- Koren M, Stein E, McKenney JM, Gipe D, Hanotin C, Ferrand A-C, Wu R, Dufour R. Efficacy, safety and tolerability of 150 mg Q2W dose of the anti-PCSK9 mAb, REGN727/SAR236553: data from 3 phase 2 studies. *Eur Heart J* 2012;33(Abtract Supplement);37. Abstract 429.
- Koren MJ, Kereiakes D, Pourfarzib R, Winegar D, Banerjee P, Hamon S, Hanotin C, McKenney JM. Effects of alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, on lipoprotein particle concentrations determined by nuclear magnetic resonance: substudy of a randomized double-blind phase II clinical trial. *J Am Coll Cardiol* 2014;63(12 Suppl 1): A1373.
- Koren MJ, Roth EM, McKenney JM, Gipe D, Hanotin C, Ferrand AC, Wu R, Dufour R. Safety and efficacy of alirocumab 150 mg every 2 weeks, a fully human proprotein convertase subtilisin/kexin type 9 monoclonal antibody: a Phase II pooled analysis. *Postgrad Med* 2015;22:1-8.
- Koren MJ, Stein E, Roth E, McKenney JM, Gipe D, Hanotin C, Ferrand A-C, Wu R, Dufour R. Efficacy, safety and tolerability of alirocumab 150 mg Q2W, a fully human PCSK9 monoclonal antibody: a pooled analysis of 352 patients from phase 2. *J Clin Lipidol* 2013;7(3):279-280.
- Krauss RM, Banerjee P, Hamon S, Hanotin C, Sasiela B, Koren MJ, McKenney JM. Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, and its effects on lipoprotein subfractions determined by ion mobility. *Circulation*. 2014;130:A15525.
- Kühnast S, van der Hoorn JW, Pieterman E, Sasiela WJ, Gusarova V, Peyman A, Schäfer H-L, Schwahn U, Jukema JW, Princen HM. PCSK-9 monoclonal antibody alirocumab dose-dependently decreases atherosclerosis development and enhances the effects of atorvastatin in APOE*3Leiden.CETP mice. *Circulation*. 2013;128:A15823.
- Kühnast S, van der Hoorn JWA, Pieterman EJ, van den Hoek AM, Sasiela WJ, Gusarova V, Peyman A, Schafer H-L, Schwahn U, Jukema JW, Princen HMG. Alirocumab inhibits atherosclerosis, improves the plaque morphology, and enhances the effects of a statin. *J Lipid Res*. 2014;55(10):2103-2112.
- Lambert G, Chatelais M, Petrides F, Passard M, Thedrez A, Rye KA, Schwahn U, Gusarova V, Blom DJ, Sasiela W, Marais AD. Normalization of Low-Density Lipoprotein Receptor Expression in Receptor Defective Homozygous Familial Hypercholesterolemia by Inhibition of PCSK9 With Alirocumab. *J Am Coll Cardiol*. 2014;64(21):2299-2300.
- Lambert G, Sjouke B, Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. *J Lipid Res* 2012;53(12):2515-2524.
- Lunven C, Paehler T, Lewanczyk P, Poitiers F, Brunet A, Rey J, Hanotin C, Sasiela WJ. A randomized study of the relative bioavailability, pharmacodynamics, and safety of alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, after single subcutaneous administration at three different injection sites in healthy subjects. *J Am Coll Cardiol* 2014;63(12 Suppl 1): A1377.
- Lunven C, Paehler T, Poitiers F, Brunet A, Rey J, Hanotin C, Sasiela WJ. A randomized study of the relative pharmacokinetics, pharmacodynamics and safety of alirocumab, a fully human monoclonal antibody to PCSK9, after single subcutaneous administration at three different injection sites in healthy subjects. *Cardiovasc Ther*. Dec. 2014;32(6):297-301.
- McKenney J, Koren M, Kereiakes D, Hanotin C, Ferrand A-C. A randomized, double-blind, placebo-controlled trial of the safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, REGN727/SAR236553, in patients with primary hypercholesterolemia (NCT: 01288443). Presented as a late-breaking oral presentation at the American College of Cardiology (ACC) Annual Scientific Session, Mar. 24-27, 2012, Chicago, Illinois, USA.
- Missouri DU Report, Drug Use Review Newsletter, vol. 8, No. 6, Oct./Nov. 2003 "Statin Therapy" pp. 1-9.
- Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, Gipe D. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: Design and rationale of Odyssey Alternative, a randomized Phase 3 trial. *J Clin Lipidol*. 2014;8(6):554-561.
- Moriarty PM, Lecorps G, Hanotin C, Pordy R, Roth EM. Homogeneity of treatment effect of REGN727/SAR236553, a fully human monoclonal antibody against PCSK9, in lowering LDL-C: data from three phase 2 studies. *Eur Heart J*. 2013;34(Suppl 1):doi:10.1093/eurheartj/ehs307.142.
- Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, BaccaraDinet MT, Zhao J, Pordy R, Gipe R. Odyssey Alternative: Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 monoclonal antibody, alirocumab, versus ezetimibe, in patients with statin intolerance as defined by a placebo run-in and statin rechallenge arm. *Circulation*. 2014;130:2108.
- Pordy R, Lecorps G, Bessac L, Sasiela WJ, Ginsberg H. Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9: therapeutic dosing in phase 3 studies. *J Clin Lipidol* 2013;7(3):279.
- Ramanathan A, Gusarova V, Kyrtasous C. Role of alirocumab (proprotein convertase subtilisin/kexin type 9 antibody) on CD81 levels and hepatitis C virus entry into hepatocytes. *Circulation*. 2013;128:A12052.
- Ray KK, Foody J, Khan I, Lewis BE. Attainment of low-density lipoprotein cholesterol goals in patients at very high cardiovascular risk in the United Kingdom: results from a general practice population study. *Value Health* 2013;16(7):A513.
- Rey J, Poitiers F, Paehler T, Brunet A, Pinquier JL, Hanotin C, Sasiela B. Randomized, partial blind study of the pharmacodynamics, pharmacokinetics and safety of multiple subcutaneous doses of alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, administered every 4 weeks alone or in combination with ezetimibe or fenofibrate in healthy subjects. *J Am Coll Cardiol* 2014;63(12 Suppl 1):A1375.
- Robinson J, Farnier M, Chaudhari U, Sasiela B, Lorenzato C, Miller K, Kastelein JJP. Adverse events in patients with low-density lipoprotein cholesterol levels <25 or <15 mg/dL on at least two consecutive visits in fourteen randomized, controlled, clinical trials of alirocumab. *J Am Coll Cardiol* 2015;65(10_S):A1350.
- Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes E, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor N, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJP. Long-term safety, tolerability and efficacy of alirocumab versus placebo in high cardiovascular risk patients: first results from the Odyssey Long Term study in 2,341 patients. *Circulation*. 2014;130:2120.
- Roth E, Taskinen M-R, Ginsberg HN, Kastelein JJP, Colhoun HM, Robinson JG, Merlet L, Pordy R, Baccara-Dinet MT. A 24-week study of alirocumab monotherapy versus ezetimibe: The first phase 3 data of a proprotein convertase subtilisin/kexin type 9 inhibitor. *J Am Coll Cardiol* 2014;63(12 Suppl 1): A.
- Roth EM, McKenney J, Hanotin C, Asset G, Stein E. The effects of co-administering a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, REGN727/SAR236553, with 10 and 80 mg atorvastatin compared to 80 mg atorvastatin

(56)

References Cited

OTHER PUBLICATIONS

- alone in patients with primary hypercholesterolemia (NCT: 01288469). *J Am Coll Cardiol* 2012;59:E1620.
- Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367(20):1891-1900.
- Roth EM, McKenney JM. Odyssey Mono: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. *Future Cardiol* 2015;11(1):27-37.
- Roth EM, Taskinen M-R, Ginsberg H, Kastelein JJP, Colhoun HM, Robinson JG, Merlet L, Pordy R, Baccara-Dinet MT. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial. *Int J Cardiol*. 2014;176(1):55-61.
- Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby J-F, Tricoci P, White H, Zeiher A, Steg PG. Effect of alirocumab, a monoclonal antibody to pcsk9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the odyssey outcomes trial. *Am Heart J*. 2014;168(5):682-689.e1.
- Steen D, Khan I, Becker L, Gorcyca K, Foody J. Attainment of Lipid Levels in Patients at High Cardiovascular Risk: Results from a U.S. Managed Care Population Study. *Circulation*. 2014;130:A19949.
- Steen D, Khan I, Song X, Sanchez R, Gorcyca K, Hollenbeak CS, Foody J. Cardiovascular Event Rates in a High-Risk Managed Care Population in the United States. *J Am Coll Cardiol* 2015;65(10_S):A1647.
- Stein E, Bergeron J, Gaudet D, Weiss R, Gipe D, Wu R, Dufour R, Pordy R. Safety and efficacy of a monoclonal antibody to PCSK9, REGN727/SAR236553, in statin-treated heterozygous familial hypercholesterolemia patients. Presented as an oral presentation at the 80th European Atherosclerosis Society (EAS) Congress, May 25-28, 2012, Milan, Italy. Abstract 1398.
- Stein EA, Bergeron J, Gaudet D, Weiss R, Dufour R, Du Y, Yang F, Andisik M, Toni A, Pordy R, Gipe D. One year open-label treatment with alirocumab 150 mg every two weeks in heterozygous familial hypercholesterolemic patients. *Lancet* 2012 380:29-36.
- Stroes E, Guyton JR, Farnier M, Rader D, Moriarty PM, Bergeron J, Langslet G, Lepor N, Civeira F, Gaudet D, Watts GF, Manvelian G, Lecorps G, Zhao J, Baccara-Dinet M, Roth EM. Efficacy and safety of different dosing regimens of alirocumab (starting doses of 75 mg every two weeks and 150 mg every four weeks) versus placebo in patients with hypercholesterolemia not treated using statins: the Odyssey Choice II study. *J Am Coll Cardiol* 2015;65(10_S):A1370.
- Sullivan, et al. Effect of a Monoclonal Antibody to PCSK9 on Low-Density Lipoprotein Cholesterol Levels in Statin-Intolerant Patients. *JAMA*. Dec. 19, 2012. vol. 308, No. 23. pp. 2497-2506.
- Swergold G, Biedermann S, Renard R, Du Y, Nadler D, Wu R, Mellis S, Lisbon E. REGN727/SAR236553, a fully-human monoclonal antibody to proprotein convertase subtilisin kexin 9 (PCSK9), decreases ApoB and non-HDL-C when administered intravenously to healthy volunteers. *J Clin Lipidol* 2011;5(3):219.
- Swergold G, Biedermann S, Renard R, Nadler D, Wu R, Lisbon EA, Gutierrez MJ, Mellis S. REGN727/SAR236553, a fully human proprotein convertase subtilisin kexin 9 (PCSK9) monoclonal antibody: effects on safety and lipid and lipoprotein profiles when administered subcutaneously. *J Am Coll Cardiol* 2011;57(14s1):E2023.
- Swergold G, Biedermann S, Renard R, Nadler D, Wu R, Mellis S. Safety, lipid, and lipoprotein effects of REGN727/SAR236553, a fully human proprotein convertase subtilisin kexin 9 (PCSK9) neutralizing monoclonal antibody administered intravenously to healthy volunteers. *Circulation* 2010;122:Abstract A23251.
- Swergold G, Smith W, Mellis S, Logan D, Webb C, Wu R, Du Y, Krans T, Gasparino E, Stein EA. Inhibition of proprotein convertase subtilisin/kexin type 9 with a monoclonal antibody REGN727/SAR236553, effectively reduces low-density-lipoprotein cholesterol, as mono or add-on therapy in heterozygous familial and non-familial hypercholesterolemia. *Circulation* 2011;124:Abstract A16265.
- Teramoto T, Kobayashi M, Uno K, Takagi Y, Matsuoka O, Sugimoto M, Inoue S, Minami F, Baccara-Dinet MT. Efficacy and safety of alirocumab in Japanese patients with hypercholesterolemia on stable statin therapy: first data with the 75 mg every two weeks dose. *Circulation*. 2014;130:A13651.
- Toth PP, Hamon S, Jones SR, Joshi PH, Martin SS, Pordy R, Hanotin C. Alirocumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, reduces cholesterol concentrations of all serum low-density lipoprotein cholesterol fractions. *Circulation*. 2013;128:A17313.
- Toth PP, Hamon S, Jones SR, Martin SS, Joshi PH, Kulkarni K, Banerjee P, Hanotin C. Proprotein convertase subtilisin/kexin 9 monoclonal antibody therapy significantly reduces apolipoprotein CII and CIII levels in serum. *Atherosclerosis*. 2014;235(2):e107-e108. [Abstract 593].
- Van der Hoorn JWA, Kuhnast S, Pieterman E, van der Hoek AM, Sasiela WJ, Gusarova V, Peyman A, Schafer H-L, Schwahn U, Jukema JW, Princen HMG. Alirocumab, a monoclonal antibody to PCSK-9, dose-dependently decreases atherosclerosis, improves plaque stability and shows additive effects with atorvastatin in APOE*3Leiden.CETP mice. *Atherosclerosis*. 2014;235(2):e19. [Abstract WS16].
- Wong ND, Chuang J. Residual Dyslipidemia According to LDL-C, non-HDL-C and Apolipoprotein B by Cardiovascular Risk Category in Statin Treated US Adults. *J Clin Lipidol*. 2014;8:323-324. Presented as a poster presentation at the National Lipid Association Scientific Sessions, May 1-4, 2014, Orlando, Florida, USA.
- Horton, et al. (2007) *Trends Biochem Sci*. 32(2): 71-77, "Molecular biology of PCSK9: its role in LDL metabolism".
- Lopez, Dayami (2008) *Drug News & Perspectives* Abstract 21(6): 323, "Inhibition of PCSK9 as a Novel Strategy for the Treatment of Hypercholesterolemia".
- Park, et al. (2004) *J. Biol. Chem*. 279: 50630-50638, "Post-transcriptional Regulation of Low Density Lipoprotein Receptor Protein by Proprotein Convertase Subtilisin/Kexin Type 9a in Mouse Liver".
- Colhoun, et al., (2014) *BMC Cardiovascular Disorders*, Biomed Central 14(1):121, "Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the Odyssey Combo I and II trials".
- Kastelein et al., (2014) *Cardiovascular Drugs and Therapy* 28(3):281-289, "Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia not Adequately Controlled with Current Lipid-Lowering Therapy: Design and Rationale of the Odyssey FH Studies".
- Robinson et al., (2014) *Clinical Cardiology* 37(10):597-604, "Efficacy and Safety of Alirocumab as Add-on Therapy in High-Cardiovascular-Risk Patients with Hypercholesterolemia Not Adequately Controlled with Atorvastatin (20 or 40 mg) or Rosuvastatin (10 or 20 mg): Design and Rationale of the Odyssey Options Studies".
- International Search Report dated Aug. 19, 2015 for International Application No. PCT/US2015/015633.
- Dube, et al. (2012) *Curr Opin Lipidol* 23(2):133-140, "Lipoprotein(a): more interesting than ever after 50 years".
- Koschinsky and Boffa (2014) *Endocrinology and Metabolism Clinics of North America* 43(4): 949-962, "Lipoprotein(a): An Important Cardiovascular Risk Factor and a Clinical Conundrum".
- Lamon-Fava, et al. (2011) *Journal of Lipid Research* 52:1181-1187 "Lipoprotein(a) levels, apo(a) isoform size, and coronary heart disease risk in the Framingham Offspring Study".
- Third Party Observation for European Patent Application No. 12761864.3 dated Feb. 24, 2016.
- Tsimikas, et al. (2015) *The Lancet* 386(10002):1472-1483, "Anti-sense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study".

(56)

References Cited

OTHER PUBLICATIONS

- Pfizer: 'Safety and Tolerability of Multiple Doses of PF-04950615 (RN316) in Subjects With Hypercholesterolemia.' Nov. 3, 2012, XP002682100. Retrieved from the Internet: clinicaltrials.gov/ct2/show?term=rn316&rank=2.
- Pearson, William R., 'Using the FASTA program to search protein and DNA sequence databases.' *Computer Analysis of Sequence Data*. 1994, pp. 307-331.
- Powell et al., 'Compendium of Excipients for Parenteral Formulations PDA.' *Journal of Pharmaceutical Science and Technology*. 1998, vol. 52, No. 5, pp. 238-311.
- Qui et al., 'Small antibody mimetics comprising two complementarity-determining regions and a framework region for tumor targeting.' *Nature Biotechnology*. 2007, vol. 25, No. 8, pp. 921-929.
- Reddy et al., 'Elimination of Fc receptor-dependent effector functions of a modified IgG4 monoclonal antibody to human CD4.' *The Journal of Immunology*. 2000, vol. 164, No. 4, pp. 1925-1933.
- Reineke, Ulrich, 'Antibody epitope mapping using arrays of synthetic peptides.' *Antibody Engineering*. Humana Press. 2004, pp. 443-463.
- Sefton, Michael V., 'Implantable Pumps.' *Critical Reviews in Biomedical Engineering*. 1986, vol. 14, No. 3, pp. 201-240.
- Seidah et al., 'The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation.' *PNAS*. 2003, 100(3):928-933.
- Shields et al., 'Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human FcγRIII and antibody-dependent cellular toxicity.' *Journal of Biological Chemistry*. 2002, vol. 277, No. 30, pp. 26733-26740.
- Soutar, Anne, 'Unexpected Roles for PCSK9 in Lipid Metabolism.' *Current Opinion in Lipidology*. 2011, vol. 22, pp. 192-196.
- Tiwari et al., 'Statins therapy: a review on conventional and novel formulation approaches.' *Journal of Pharmacy and Pharmacology*. 2011, vol. 63, No. 8, pp. 983-998.
- Tutt et al., 'Trispecific F (ab')₃ derivatives that use cooperative signaling via the TCR/CD3 complex and CD2 to activate and redirect resting cytotoxic T cells.' *The Journal of Immunology*. 1991, vol. 147, No. 1, pp. 60-69.
- Vajdos et al., 'Comprehensive functional maps of the antigen-binding site of an anti-ErbB2 antibody obtained with shotgun scanning mutagenesis.' *Journal of Molecular Biology*. 2002, vol. 320, No. 2, pp. 415-428.
- Ward et al., 'Binding activities of a repertoire of single immunoglobulin variable domains secreted from *Escherichia coli*.' *Nature*. 1989, vol. 341, No. 6242, pp. 544-546.
- Written Opinion of the International Searching Authority for International Application No. PCT/EP2012/051320, Jul. 30, 2013 (16 pages).
- Wu et al., 'Receptor-mediated in vitro gene transformation by a soluble DNA carrier system.' *Journal of Biological Chemistry*. 1987, vol. 262, No. 10, pp. 4429-4432.
- Holliger et al., 'Diabodies: small bivalent and bispecific antibody fragments.' *Proceedings of the National Academy of Sciences*. 1993, vol. 90, No. 14, pp. 6444-6448.
- Huston et al., 'Protein engineering of antibody binding sites: recovery of specific activity in an anti-digoxin single-chain Fv analogue produced in *Escherichia coli*.' *Proceedings of the National Academy of Sciences*. 1988, vol. 85, No. 16, pp. 5879.
- International Search Report for International Application No. PCT/EP2012/051320, Sep. 21, 2012 (9 pages).
- Langer et al., 'New methods of drug delivery.' *Science*. 1990, vol. 249, No. 4976, pp. 1527-1533.
- Langer et al., 'Medical Applications of Controlled Release.' CRC Press, Boca Raton, Florida. 1974, pp. 115-138.
- Leuenberger et al., 'A Multilingual Glossary of Biotechnological Terms.' *Recueil des Travaux Chimiques des Pays Bas*. 1996, vol. 115, No. 7, pp. 382.
- Padlan et al., 'Identification of specificity-determining residues in antibodies.' *The FASEB Journal*. 1995, vol. 9, No. 1, pp. 133-139.
- Almagro et al., 'Humanization of antibodies.' *Frontiers in Bioscience*. 2008, vol. 13, pp. 1619-1633.
- Altschul et al., 'Basic local alignment search tool.' *Journal of Molecular Biology*. 1990, vol. 215, No. 3, pp. 403-410.
- Altschul et al., 'Gapped BLAST and PSI-BLAST: a new generation of protein database search programs.' *Nucleic Acids Research*. 1997, vol. 25, No. 17, pp. 3389-3402.
- Amgen: 'Ascending Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 145 in Subjects With Hyperlipidemia on Stable Doses of a Statin'. May 27, 2010, XP002682099. Retrieved from the Internet: clinicaltrials.gov/ct2/show/nct01133522?term=amg+145&rank=2 Accessed on Aug. 6, 2014.
- Angal et al., 'A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody.' *Molecular Immunology*. 1993, vol. 30, No. 1, pp. 105-108.
- Bird et al., 'Single-chain antigen-binding proteins.' *Science*. 1988, vol. 242, No. 4877, pp. 423-426.
- Heap et al., 'Analysis of a 17-amino acid residue, virus-neutralizing microantibody.' *Journal of General Virology*. 2005, vol. 86, No. 6, pp. 1791-1800.
- Anonymous: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome. Archive from ClinicalTrials.gov for NCT01663402 on Mar. 11, 2014 (3 pages).
- Anonymous: Long-term Safety and Tolerability of Alirocumab SAR236553 (REGN727) in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy: A Randomized, Double-Blind, Placebo-Controlled Study. Archive from ClinicalTrials.gov for NCT01507831 on Jun. 27, 2013 (3 pages).
- Blom, Dirk J. et al.: 'A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia' vol. 370, No. 19, May 8, 2014 pp. 1809-1819.
- Costet. PCSK9 inhibitors as LDL cholesterol-lowering agents: Rationale, concerns and preliminary outcomes. *Drugs of the Future*. May 1, 2012. vol. 37, No. 5, pp. 331-341.
- Gonnet et al.: Exhaustive Matching of the Entire Protein Sequence Database; *Science*; 1992, vol. 256, pp. 1443-1445.
- Gusarova V, Sleeman M, Swergold G, Sasiela B, Stahl N, Yancopoulos G, Murphy A. Fully human antibody that blocks PCSK9 demonstrates reduction in LDL-C preclinically and in early clinical trials. Abstract of oral presentation at the Keystone Symposium on Molecular and Cellular Biology, Mar. 25-30, 2012, Montanana, USA.
- Haddley et al. Alirocumab Anti-Proprotein Convertase 9 (PCSK9) Mab Treatment of Hypercholesterolemia. *Drugs of the Future*; Apr. 1, 2013. vol. 38, No. 4, pp. 215-216.
- Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Avena M, Stroes E, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor N, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJP. Long-term safety, tolerability and efficacy of alirocumab versus placebo in high cardiovascular risk patients: first results from the Odyssey Long Term study in 2,341 patients; presented at ESC Congress Aug. 31, 2014, abstract not published.
- Roth et al. Alirocumab for hyperlipidemia: physiology of PCSK9 inhibition, pharmacodynamics and Phase I and II clinical trial results of a PCSK9 monoclonal antibody. *Future Cardiology*. Mar. 2014; vol. 10, No. 2. pp. 187-197. 183-199.
- Shao W. New Therapies for Lowering LDL-C: Targeting PCSK9. Abstract of oral presentation at the Sino-American Pharmaceutical Professionals Association—2014 Scientific Symposium, Apr. 26, 2014, New Jersey, USA.
- Swergold GD, et al. Identification and characterization of patients with autosomal dominant hypercholesterolemia caused by gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 and comparison with patients with Familial Hypercholesterolemia (FH) and Familial Defective apolipoprotein B (FDB). Abstract of a poster presentation at the American Society of Human Genetics (ASHG), Oct. 22-26, 2013, Boston, USA.

(56)

References Cited

OTHER PUBLICATIONS

- Chinese Patent Application No. 201280015477.6, Office Action dated Dec. 2, 2014 with English summary, 12 pages.
- Chinese Patent Application No. 201280015571.1, Office Action dated Sep. 3, 2014 with English summary, 12 pages.
- European Patent Application No. 12701015.5, Communication pursuant to Article 94(3) EPC dated Apr. 24, 2015, 9 pages.
- European Patent Application No. 12701015.5, Communication pursuant to Article 94(3) EPC dated May 30, 2014, 8 pages.
- European Patent Application No. 12701742.4, Communication pursuant to Article 94(3) EPC dated May 28, 2014, 8 pages.
- Alborn, et al. (2007) *Clinical Chemistry* 53(10):1814-1819, "Serum proprotein convertase subtilisin Kexin type 9 is correlated directly with serum LDL cholesterol".
- Abifade, et al. (2003) *Nature Genetics* 34(2):154-156, "Mutations in PCSK9 cause autosomal dominant hypercholesterolemia".
- Attie and Seidah (2005) *Cell Metabolism* 5:290-292, "Dual regulation of the LDL receptor—Some clarity and new questions".
- Benjannet, et al. (2006) *J. Biological Chemistry* 281(41): 30561-30572, "The Proprotein Convertase (PC) PCSK9 is Inactivated by Furin and/or PC5/6A".
- Foot and Winter (1992) *J. Mol. Biol.* 224:487-499, "Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops".
- Winter and Harris (1993) *Immunology Today* 14(6):243-246, "Humanized Antibodies".
- Chan, et al. (2009) *PNAS* 106(24):9820-9825, "A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates".
- Chaparro-Riggers, et al. (2012) *J. Biological Chemistry* 287(14):11090-11097, "Increasing serum half-life and extending cholesterol lowering in vivo by engineering antibody with pH-sensitive binding to PCSK9".
- Fallon, et al. (2000) *J. Biological Chemistry* 275(10):6790-6797, "Increased endosomal sorting of ligand to recycling enhances potency of an interleukin-2 analog".
- Grozdanov, et al. (2006) *Biochem. Cell. Biol.* 84:80-92, "Expression and localization of PCSK9 in rat hepatic cells".
- Igawa, et al. (2010) *Nature Biotechnology* 28(11):1203-1208, "Antibody recycling by engineered pH-dependent antigen binding improves the duration of antigen neutralization".
- Ito, et al. (1992) *Federation of European Biochemical Societies* 309(1):85-88, "The His-probe method: effects of histidine residues introduced into the complementarity-determining regions of antibodies on antigen-antibody interactions at different pH values".
- Lagace, et al. (2006) *J Clin Invest Am Soc Clin Invest* 116(11):2995-3005, "Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in liver of parabiotic mice".
- Lippi and Guidi (2000) *QJ Med* 93:75-84, "Lipoprotein(a): from ancestral benefit to modern pathogen?".
- Maeda, et al. (2002) *J. Controlled Release* 82:71-82, "pH-dependent receptor/ligand dissociation as a determining factor for intracellular sorting of ligands for epidermal growth factor receptors in rat hepatocytes".
- Maxwell and Breslow (2004) *PNAS* 101(18):7100-7105, "Adenoviral-mediated expression of Pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype".
- McKenney, et al. (2012) *Journal of the American College of Cardiology* 59(25):2335-2353, "Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients With Primary Hypercholesterolemia Receiving Ongoing Stable Atorvastatin Therapy".
- Nakasako, et al. (1999) *J. Mol. Biol.* 291:117-134, "The pH-dependent structural variation of complementarity-determining region H3 in the crystal structures of the Fv fragment from an anti-dansyl monoclonal antibody".
- Naureckiene, et al. (2003) *Archives of Biochemistry and Biophysics* 420:55-67, "Functional characterization of Narc 1, a novel proteinase related to proteinase K".
- Parhofer (2011) *Current Pharmaceutical Design* 17:871-876, "Lipoprotein(a): Medical Treatment Options for an Elusive Molecule".
- Rashid, et al. (2005) *PNAS* 102(15):5374-5379, "Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9".
- Sarkar, et al. (2002) *Nature Biotechnology* 20:908-913, "Rational cytokine design for increased lifetime and enhanced potency using pH-activated histidine switching".
- Seidah, et al. (2003) *PNAS* 100(3):928-933, "The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation".
- Stein, et al. (2012) *New England Journal of Medicine* 366:1108-1118, "Effect of a Monoclonal Antibody to PCSK9 on D Cholesterol".
- Stein, et al. (2012) *The Lancet* 380:29-36, "Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomized controlled trial".
- Watanabe, et al. (2009) *J. Biological Chemistry* 284(18):12373-12383, "Optimizing pH response of affinity between protein G and IgG Fc".
- Annex to Form PCT/ISA/206—Communication Relating to the Results of the Partial International Search for PCT/US2009/068013, mailed Mar. 10, 2010.
- Davidson et al. (2011) *Journal of Clinical Lipidology* 5:338-367, "Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists".
- Rader, et al. (1995) *The Journal of Clinical Investigation*, Inc. 95:1403-1408, "The Low Density Lipoprotein Receptor is Not Required for Normal Catabolism of Lp(a) in Humans".
- Kostner et al. (2013) *European Heart Journal* 34:3268-3276, "When should we measure lipoprotein (a)?"
- Romagnuolo, et al. (2015) *The Journal of Biological Chemistry* 290(18):11649-11662, "Lipoprotein(a) Catabolism is Regulated by Proprotein Convertase Subtilisin/Kexin Type 9 through the Low Density Lipoprotein Receptor".
- Bee, et al. (2009) *Journal of Pharmaceutical Sciences* 98(9): 3290-3301, "Precipitation of a monoclonal antibody by soluble tungsten".
- Breen, et al. (2001) *Pharmaceutical Research* 18(9): 1345-1353, "Effect of moisture on the stability of a lyophilized humanized monoclonal antibody formulation".
- Carpenter, 1997 *Pharm. Res.* 14(8): 969-975, Rational Design of Stable Lyophilized Protein Formulations: Some Practical Advice.
- Daugherty, et al., 2006 *Advanced Drug Delivery Reviews* 58: 686-706, "Formulation and delivery issues for monoclonal antibody therapeutics".
- Katayama, et al. 2004 *J. Pharm. Sci.* 93(10): 2609-2623, "Retrospective statistical analysis of lyophilized Protein Formulations of Progenipietin Using PLS: Determination of the Critical Parameters for Long-Term Storage Stability".
- Lefranc, M.-P., et al., IMGT®, the international ImMunoGeneTics information system®, Nucl. Acids Res, 37, D1006-D1012 (2009).
- Majumdar, et al. (2011) *Journal of Pharmaceutical Sciences* 100(7):2563-2573, "Evaluation of the effect of syringe surfaces on protein formulations".
- Meehan et al., 1996, *J. Controlled Release* 46:107-116, "A microinfusor device for the delivery of therapeutic levels of peptides and macromolecules".
- Robinson, N., 2002, *PNAS*, 99(8):5283-5288 "Protein Deamidation".
- Scaviner, D. et al., 1999 *Exp. Clin. Immunogenet.* 16:234-240 "Protein Displays of the Human Immunoglobulin Heavy, Kappa and Lambda Variable and Joining Regions".
- Varret, et al., 1999 *Am. J. Hum. Genet.* 64: 1378-1387, "A third major locus for autosomal dominant hypercholesterolemia Maps to 1 p. 34.1-p. 32".
- Wang, 1999 *International J. Pharmaceutics* 185(2): 129-188, "Instability, stabilization, and formulation of liquid protein pharmaceuticals".
- Webb, et al. 2002 *J. Pharm. Sci.* 91(2): 543-558, "A new mechanism for decreasing aggregation of Recombinant Human Interferon- γ by

(56)

References Cited**OTHER PUBLICATIONS**

a Surfactant: Slowed Dissolution of Lyophilized Formulations in a Solution Containing 0.03% Polysorbate 20".

Anthem (Sep. 21, 2015) "Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors," Policy No. Drug.00078. American Medical Association. Accessible on the Internet at URL: www.anthem.com/ca/medicalpolicies/policies/mp_pw_c182635.htm. [Last Accessed Apr. 27, 2016].

Defesche et al. (Jun. 2-5, 2013) "Natural history of autosomal dominant hypercholesterolemia caused by gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) (funded by Regeneron/Sanofi)," Abstract of a presentation presented at the 81st European Atherosclerosis Society (EAS) Congress, Jun. 2-5, 2013, Lyon, France.

Hiriyama et al. (Jan. 1, 2014) "Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk—primary results from the phase 2 YUKAWA study," *Circulation Journal*. 78(5):1073-1082.

International Search Report with Written Opinion corresponding to International Patent Application No. PCT/EP2012/051321, mailed Apr. 19, 2012, 10 pages.

International Search Report with Written Opinion corresponding to International Patent Application No. PCT/EP2012/057890, mailed Aug. 28, 2012, 14 pages.

International Search Report with Written Opinion corresponding to International Patent Application No. PCT/US2015/040754, mailed Oct. 14, 2015, 15 pages.

International Search Report with Written Opinion corresponding to International Patent Application No. PCT/US2015/040765, mailed Nov. 26, 2015, 15 pages.

McKenney et al. (Jun. 2-5, 2013) "Dynamics between the monoclonal antibody SAR236553/REGN727, proprotein convertase subtilisin/kexin type 9 (PCSK9) and low-density lipoprotein cholesterol (LDL-C) levels (funding: Regeneron/Sanofi)," Presented as a poster presentation at the 81st European Atherosclerosis Society (EAS) Congress, Jun. 2-5, 2013, Lyon, France.

Schäfer et al. (Mar. 14-16, 2011) "Cholesterol lowering effect of SAR236553/REGN727, a fully human PCSK9 blocking monoclonal antibody in male Syrian hamster," Presented as a poster at the Drugs Affecting Lipid Metabolism (DALM)—XVII International Symposium, Mar. 14-16, 2011, Doha, Qatar.

Jorgensen et al. (2013) *European Heart Journal* 34:1826-1833, "Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as casual risk factors for myocardial infarction".

Kawashiri, et al. (2012) *Circulation* 126(21):13869, "Statin Therapy Improves Fractional Catabolic Rate of LDL without Affecting Impaired VLDL and VLDL Remnant Catabolism in Homozygous FH Patient Due to PCSK9 Gene Mutation: Evidence from Kinetic Study with Stable Isotope".

Toth, et al., (2013) *Circulation* 128(22):17492, "Alirocumab, a Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibody, Reduces Cholesterol Concentrations of Serum Remnant Lipoprotein Fractions, Very Low-Density Lipoproteins and Triglycerides".

Varbo, et al., (2013) *Journal of the American College of Cardiology* 61(4):427-436, "Remnant Cholesterol as a Casual Risk Factor for Ischemic Heart Disease".

Partial International Search Report mailed Nov. 6, 2014 for International Application No. PCT/US2014/040163.

Abifadel, et al., 2012 *Atherosclerosis* 223(2):394-400, "Identification and characterization of new gain-of-function mutations in the PCSK9 gene responsible for autosomal dominant hypercholesterolemia".

Abifadel, et al., 2009 *Human Mutations* 30(4):520-529, "Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease".

Al-Mashhadi et al., 2013 *Science Translation Medicine*, American Association for the Advancement of Science 5(166):44-53, "Ath-

erosclerosis: Familial hypercholesterolemia and atherosclerosis in clones minipigs created by DNA transposition of a human PCSK9 gain-of-function mutant".

Farnier, 2011 *American Journal of Cardiovascular Drugs* 11(3):145-152, "The role of proprotein convertase subtilisin/kexin type 9 in hyperlipidemia: Focus on therapeutic implications".

Fasano, et al., 2008 *NMCD Nutrition Metabolism and Cardiovascular Diseases* 18(1):S46, "45 Activity of Gain-of-Function PCSK9 Mutants on LDLR Correlates with Total-Cholesterol Values in ADH patients".

Hopkins, et al., 2011 *Journal of Clinical Lipidology* 5(3):S9-S17, "Familial Hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia".

Noguchi, et al., 2010 *Atherosclerosis* 210(1):166-172, "The E32K variant of PCSK9 exacerbates the phenotype of familial hypercholesterolemia by increasing PCSK9 function and concentration in the circulation".

Nordestgaard, et al. (2010) *European Heart Journal* 31:2844-2853, "Lipoprotein(s) as cardiovascular risk factor: current status".

Rhoads, et al., 2012 *Clinical Lipidology* 7(6):621-640, "PCSK9 inhibition and LDL cholesterol lowering: The biology of an attractive therapeutic target and critical review of the latest clinical trials".

Stein and Swergold, 2013 *Current Atherosclerosis Reports* 15(31):1-14, "Potential of proprotein Convertase Subtilisin/Kexin Type 9 Based Therapeutics".

Stein, et al., 2012 *Obstetrical and Gynecological Survey* 67(7):413-414, "Effect of a monoclonal antibody to PCSK9 on LDL cholesterol".

Timms, et al., (2004) *Human Genetics* 114(4):349-353, "A mutation in PCSK9 causing autosomal-dominant hypercholesterolemia in a Utah pedigree".

Lose, et al., 2013 *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 33(4):447-460, "Evaluation of Proprotein Convertase Subtilisin/Kexin Type 9: Focus on Potential Clinical and Therapeutic Implications for Low-Density Lipoprotein Cholesterol Lowering".

Amgen (May 27, 2010) Ascending Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 145 in Subjects With Hyperlipidemia on Stable Doses of a Statin; Available website: www.clinicaltrials.gov/ct2/show/study?term=amg+145&rank=2; Last update: Mar. 16, 2012; Accessed on: Aug. 6, 2014.

Anthem.com (Sep. 21, 2015) Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibitors; Available Website: www.anthem.com/ca/medicalpolicies/policies/mp_pw_c182635.htm; Last Update: Aug. 4, 2016; Accessed on: Apr. 27, 2016.

Barbie and Lefranc, 1998 *Exp. Clin. Immunogenet.* 15:171-183, "The Human Immunoglobulin Kappa Variable (IGKV) Genes and Joining (IGKJ) Segments".

Cannon et al. (2015) *Eur Heart J* 36(19):1186-1194 "The Odyssey Combo II Investigators. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the Odyssey Combo III randomized controlled trial".

Cariou et al. (May 23-26, 2015) "Patient and physician perspectives on administration of the PCSK9 monoclonal antibody alirocumab, an injectable medication to lower LDL-C levels," International Symposium on Atherosclerosis. Abstract No. 1039.

clinicaltrials.gov (Feb. 1, 2011) "View of NCT01288443," US National Institutes of Health. [accessible on the internet at: https://clinicaltrials.gov/archive/NCT01288443/2011_02_01].

clinicaltrials.gov (Dec. 23, 2010) "View of NCT01266876," US National Institutes of Health. [accessible on the internet at: https://clinicaltrials.gov/archive/NCT01266876/2010_12_23].

clinicaltrials.gov (First Received: Aug. 8, 2012) "View of NCT01663402," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01663402>].

clinicaltrials.gov (First Received: Jun. 8, 2012) "View of NCT01617655," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01617655?term=NCT01617655&rank=1>].

(56)

References Cited**OTHER PUBLICATIONS**

- clinicaltrials.gov (First Received: Jan. 6, 2012) "View of NCT01507831," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01507831?term=NCT01507831&rank=1>].
- clinicaltrials.gov (First Received: Feb. 1, 2011) "View of NCT01288469," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01288469?term=NCT01288469&rank=1>].
- clinicaltrials.gov (First Received: Oct. 8, 2012) "View of NCT01709500," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01709500?term=NCT01709500&rank=1>].
- clinicaltrials.gov (First Received: Jul. 16, 2012) "View of NCT01644175," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01644175?term=NCT01644175&rank=1>].
- clinicaltrials.gov (First Received: Jul. 16, 2012) "View of NCT01644188," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01644188?term=NCT01644188&rank=1>].
- clinicaltrials.gov (First Received: Jul. 9, 2010) "View of NCT01161082," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01161082?term=NCT01161082&rank=1>].
- clinicaltrials.gov (First Received: Jul. 17, 2012) "View of NCT01644474," US National Institutes of Health. [accessible on the internet at: <https://clinicaltrials.gov/ct2/show/NCT01644474?term=NCT01644474&rank=1>].
- International Search Report and Written Opinion dated Oct. 2, 2014 for corresponding International application No. PCT/US2014/046170.
- International Search Report and Written Opinion from PCT/US2014/040050 19 pages dated Oct. 6, 2014.
- International Search Report with Written Opinion corresponding to International Patent Application No. PCT/EP2015/055369, mailed May 21, 2015, 11 pages.
- International Search Report with Written Opinion corresponding to International Patent Application No. PCT/US2014/041204, mailed Oct. 17, 2014, 14 pages.
- Kereiakes et al. (2015) *Am Heart J* 169(6):906-915 "Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the Odyssey Combo I study".
- Konrad et al. (2011) *Lipids in Health and Disease*. 10(1):38 "Effects of currently prescribed LDL-C-lowering drugs on PCSK9 and implications for the next generation of LDL-C-lowering agents".
- Li et al. (2009) *Recent Patents on DNA and Gene Sequences*. 3(3):201-212 "Recent Patents on PCSK9: A New Target for Treating Hypercholesterolemia".
- McPherson (2013) *Journal of the American College of Cardiology* 61(4):437-439, "Remnant Cholesterol: Non-(HDL-C + LDL-C) as a Coronary Artery Disease Risk Factor".
- Moriarty (2015) 10th International Society for Apheresis Congress XP55317363, Cancun Mexico "PCSK9 Inhibitors and their Effect on Patients who are Statin Intolerant or Receiving Lipoprotein-apheresis".
- Moriarty et al. (2015) *J Clin Lipidol*. 9(6):758-769 "Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin-re-challenge arm: The Odyssey Alternative randomized trial".
- Pfizer (Nov. 3, 2012) Safety and Tolerability of Multiple Doses of PF-04950615 (RN316) In Subjects With Hypercholesterolemia; Available website: www.clinicaltrials.gov/ct2/show/NCT01243151; Last update: Jul. 9, 2012; Accessed on: Feb. 27, 2017.
- Ray (2015) *Clin Lipidol*. 10(1):9-12 "Alirocumab: an investigational treatment for hypercholesterolemia".
- Regeneron/Sanofi (Nov. 5, 2012) IR Conference Call on PCSK9 "SAR236553/REGN727 PCSK9 Antibody for Hypercholesterolemia Phase 3 Odyssey Program Underway"; pp. 1-30; Available website: www.sanofi.com/Images/31341_2012-11-05_PCSK9_call.pdf; Last update: Nov. 5, 2012; Accessed on: Feb. 27, 2017.
- Reyes-Soffer et al. (2015) *Arterioscler Thromb Vasc Biol* 35:A129 "Effects of a proprotein convertase subtilisin/kexin type 9 inhibitor, alirocumab, on lipid and lipoprotein metabolism in normal subjects".
- Robinson et al. (2015) *N Eng J Med* 372:1489-1499 "Odyssey Long Term Investigators. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events".
- Roth et al. (2015) International Symposium on Atherosclerosis, Abstract No. 254 "Phase 3 Randomized Trial Evaluating Alirocumab Every Four Weeks Dosing as Add-on to Statin or as Monotherapy: Odyssey Choice I".
- Roth et al. (2015) *J. Clin. Lipidol*. 37(9):1945-1954 "Patient and physician perspectives on administration of the PCSK9 monoclonal antibody alirocumab, an injectable medication to lower LDL-C levels".
- Sahebkar et al. (2013) *Clinical Therapeutics* 35(8):1082-1098 "New LDL-Cholesterol Lowering Therapies: Pharmacology, Clinical Trials, and Relevance to Acute Coronary Syndromes".
- Stahl (2010) "Early Clinical Development #1 REGN727: anti-PCSK9," Regeneron Pharmaceuticals. Accessible on the Internet at URL: <http://files.shareholder.com/downloads/REGN/0x0x387214/534aaeb6-5e66-4e8f-86a9-0f9cac20d72f/REGN%20Investor%20Day%20Early%20Clinical%20Development1.pdf>.
- Stein et al. (2012) *The Lancet* 380:29-36, "Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomized controlled trial".
- Steinberg et al. (2009) *Proceedings of the National Academy of Sciences USA*. 106(24):9546-9547 "Inhibition of PCSK9: A powerful weapon for achieving ideal LDL cholesterol levels".

* cited by examiner

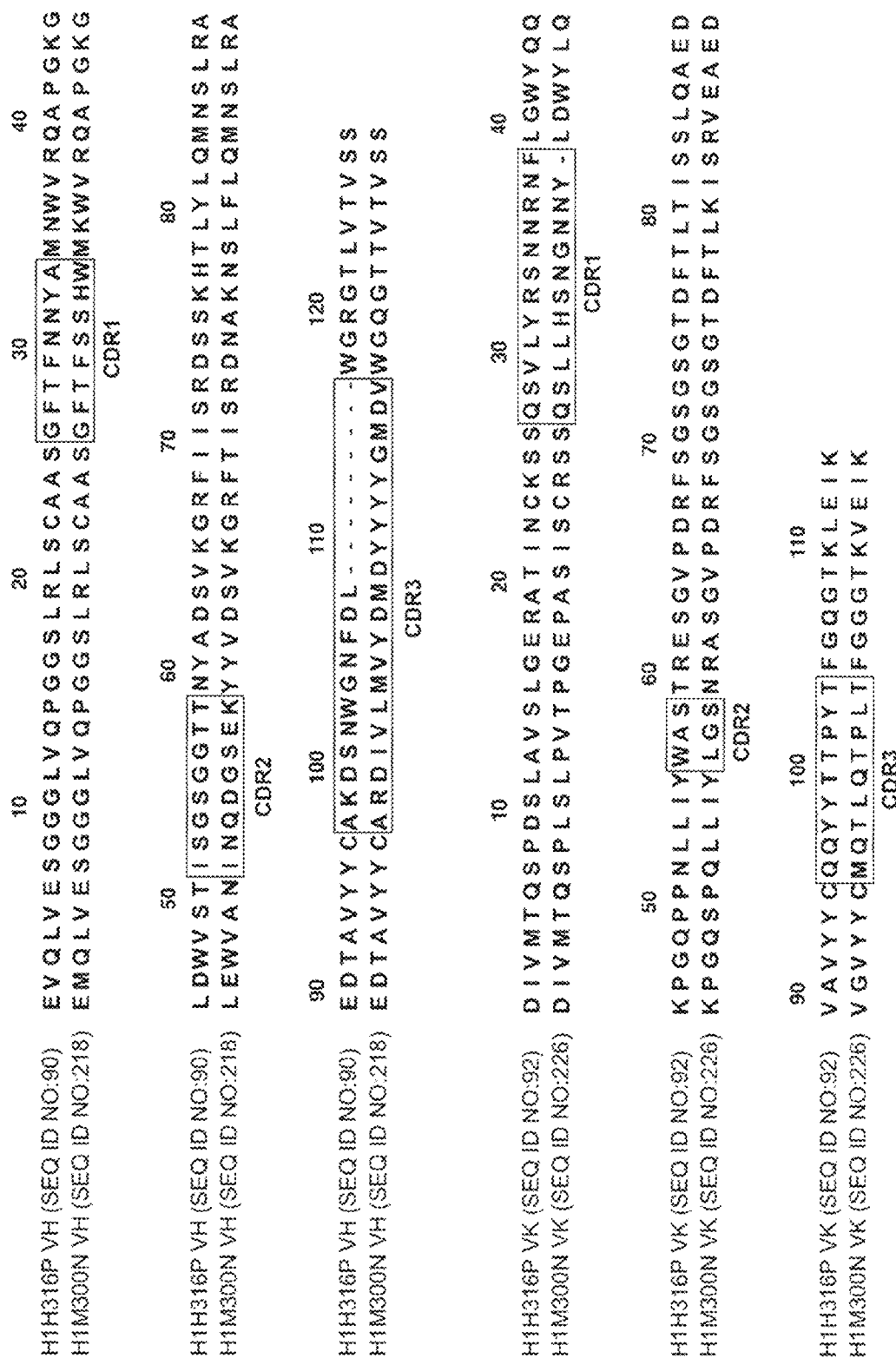


Fig. 1

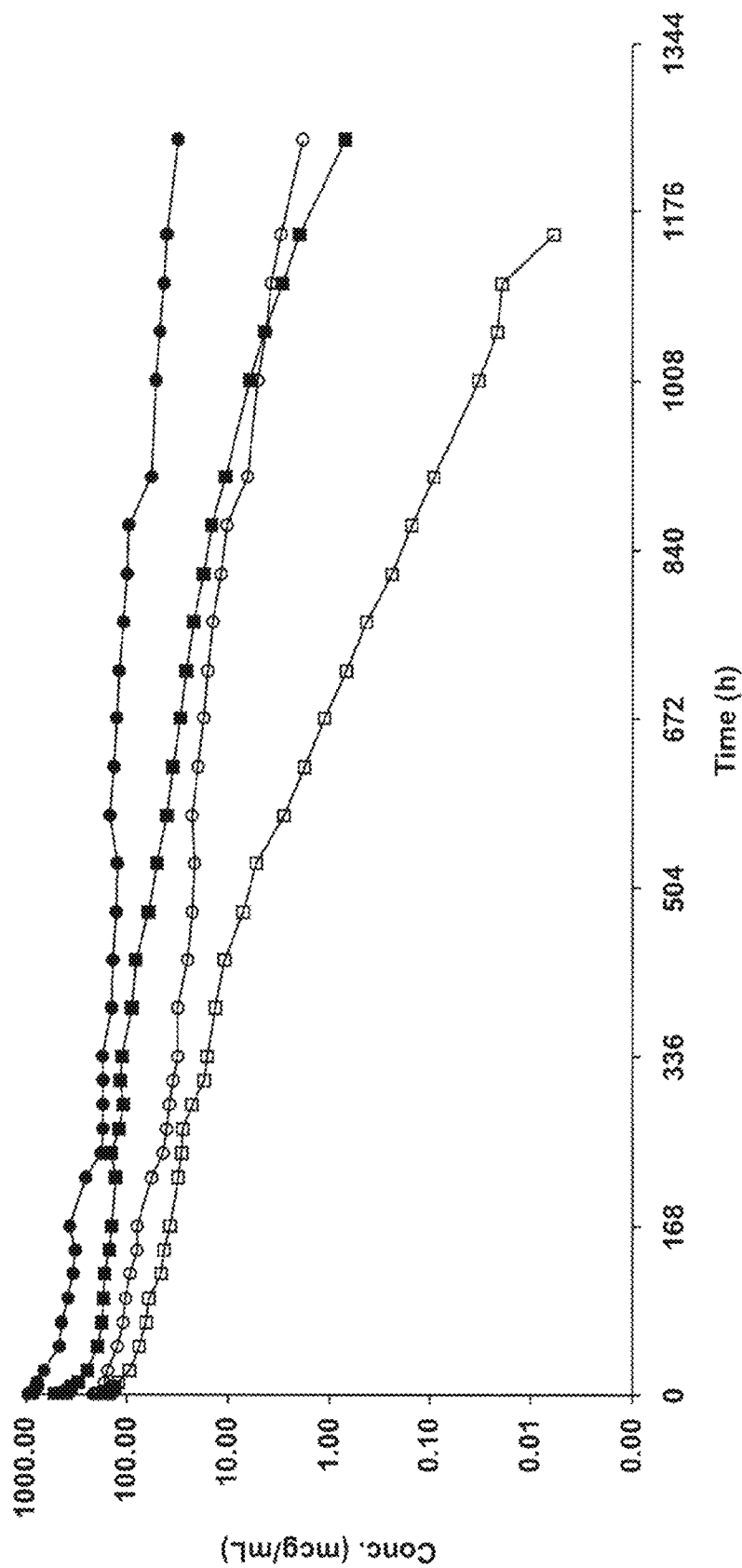


Fig. 2

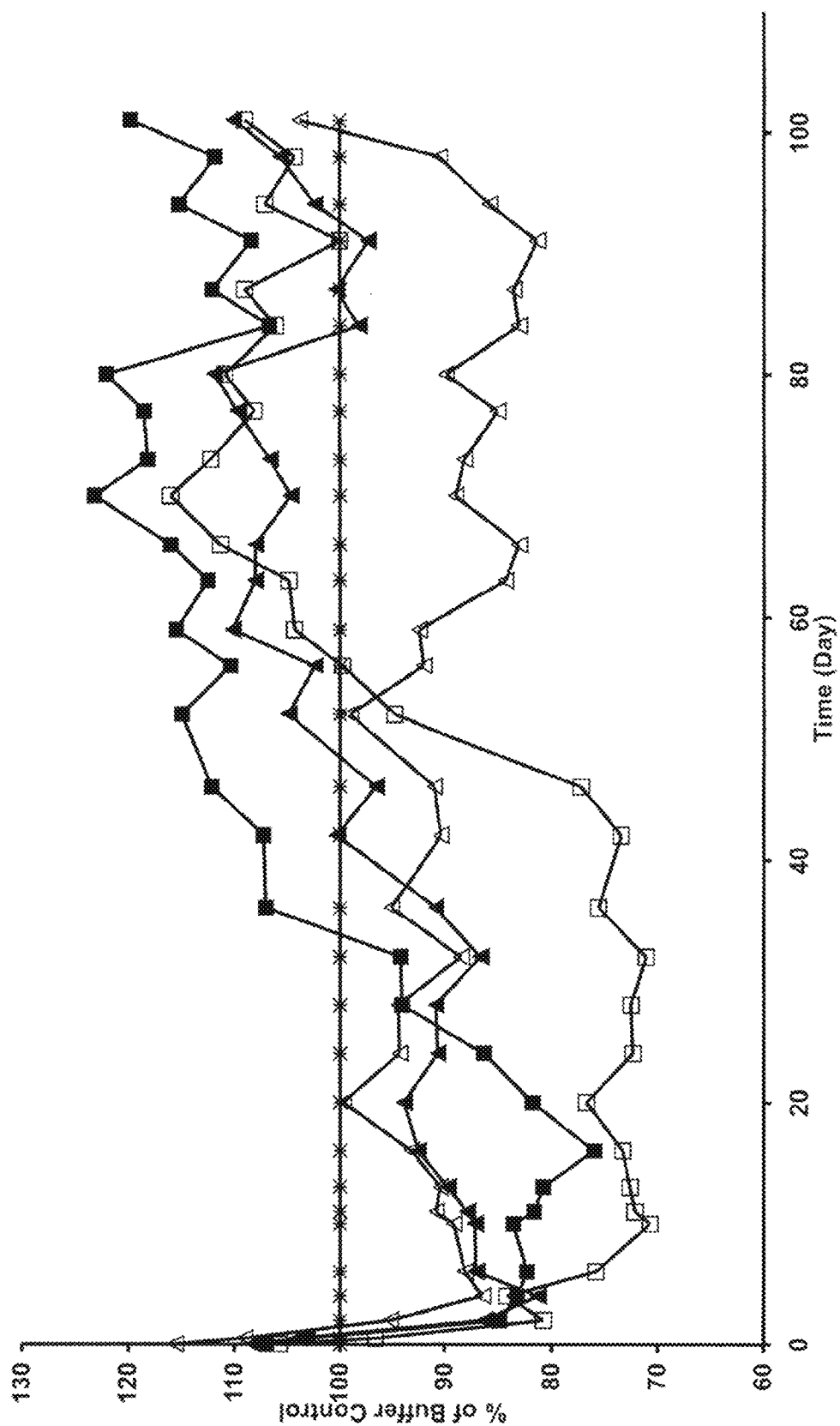


Fig. 3

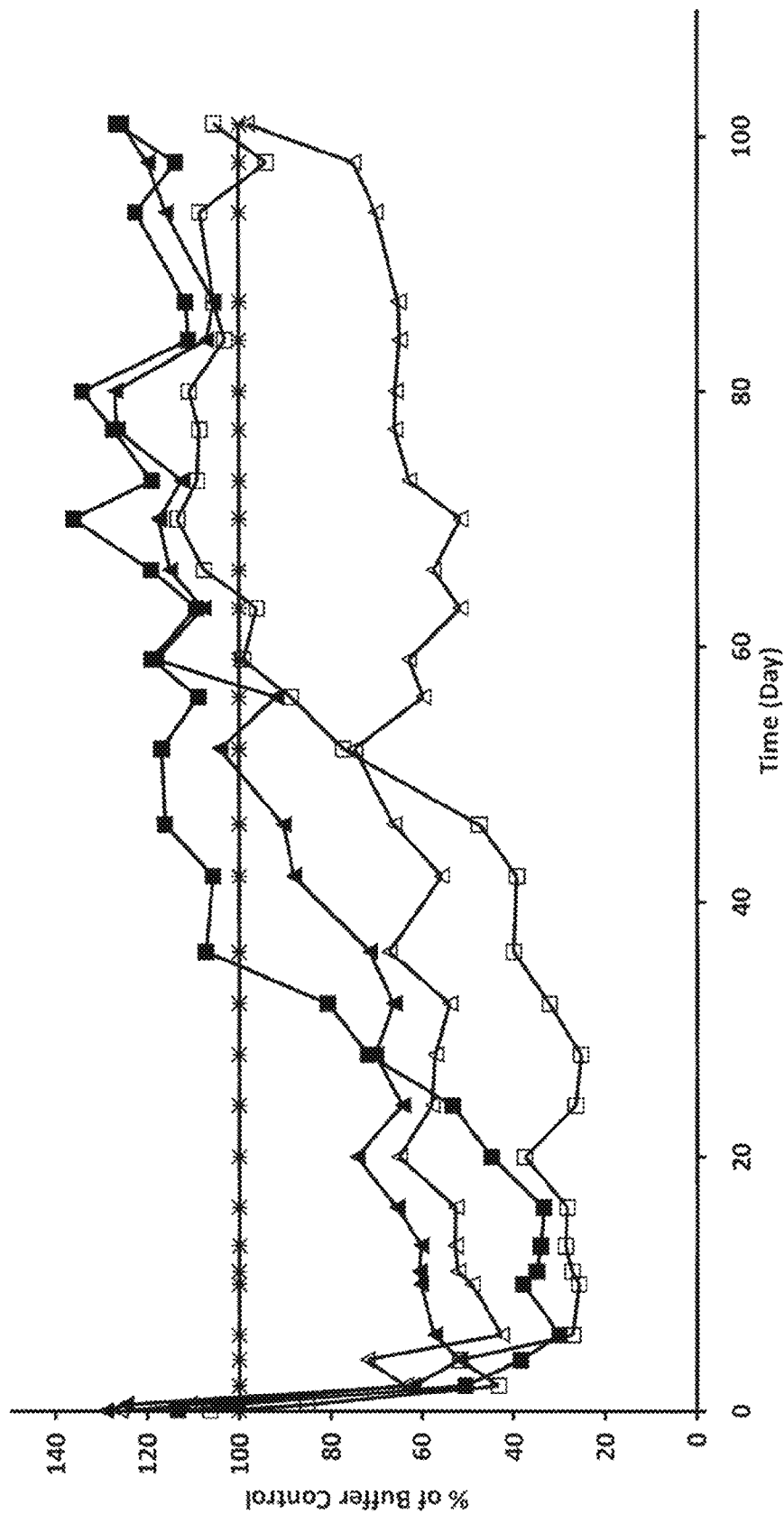


Fig. 4

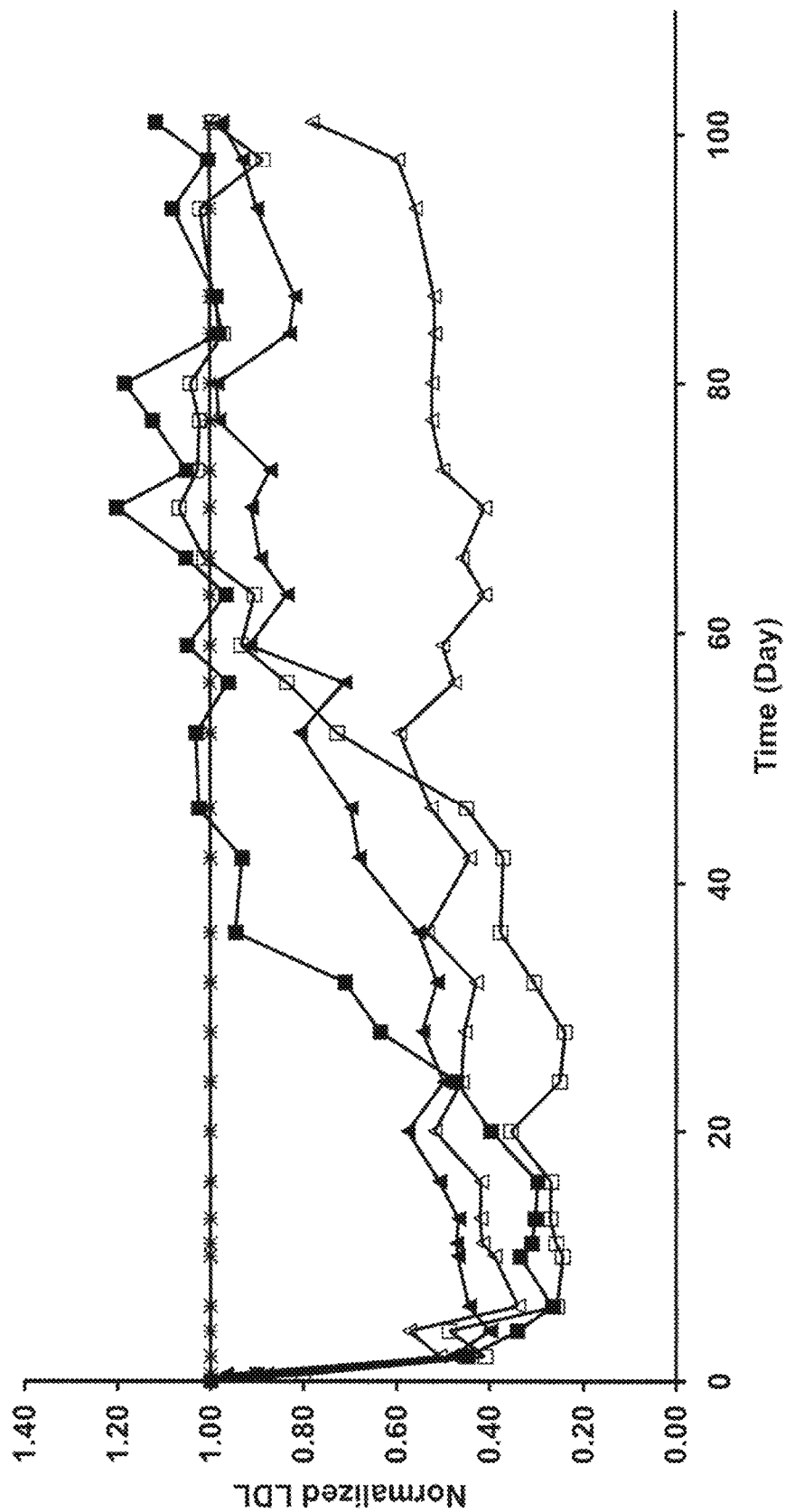


Fig. 5

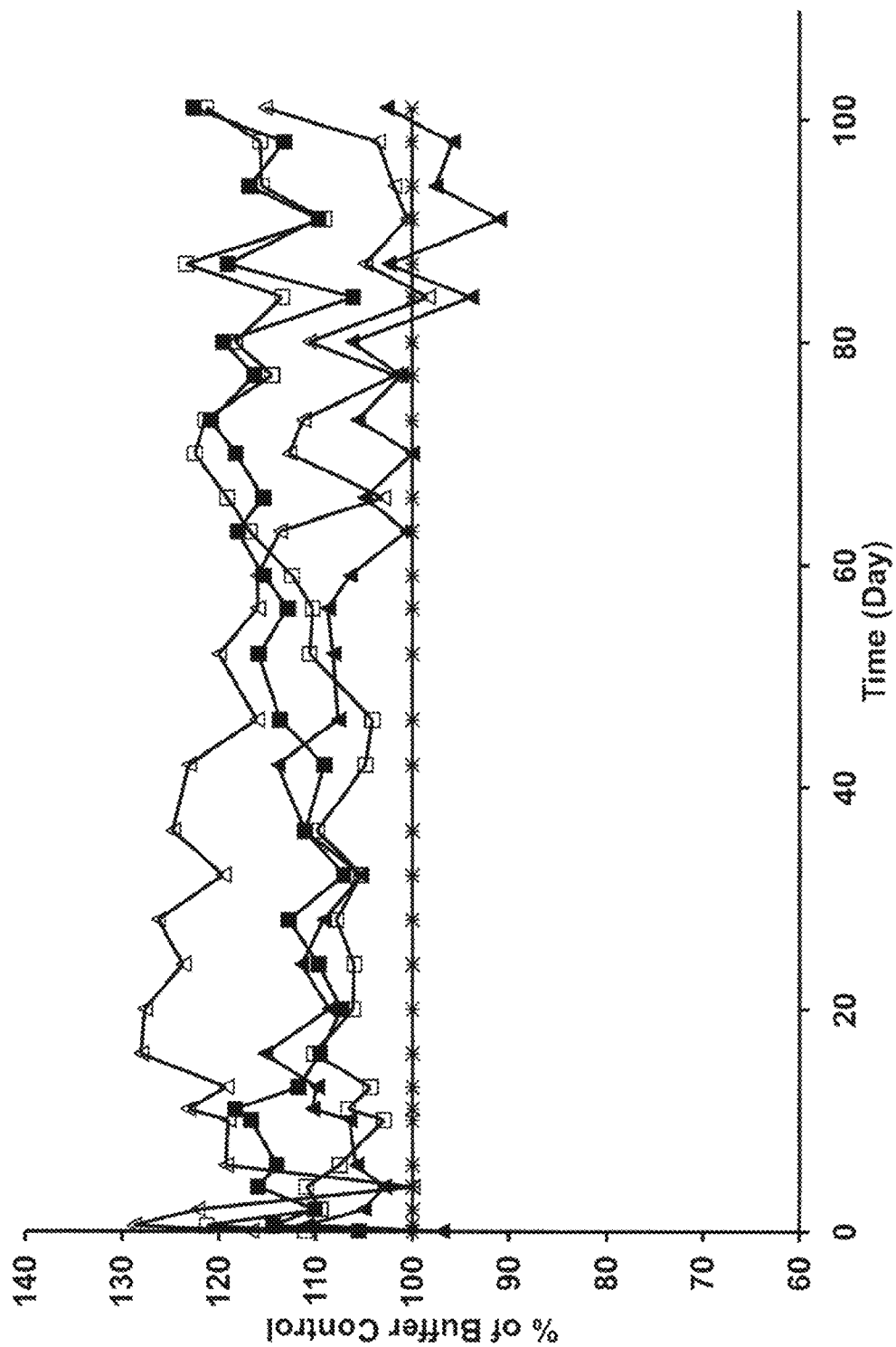


Fig. 6

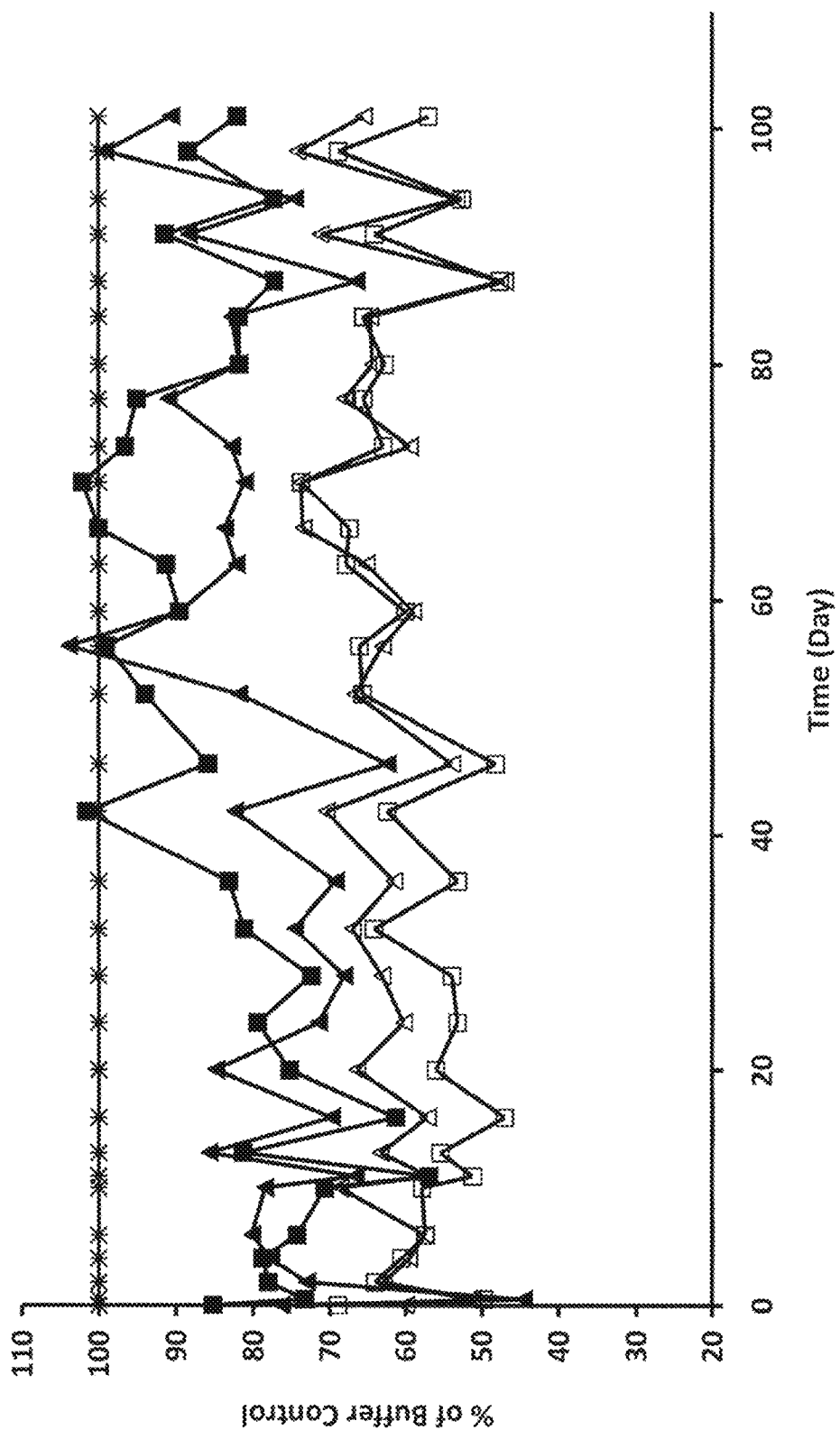


Fig. 7

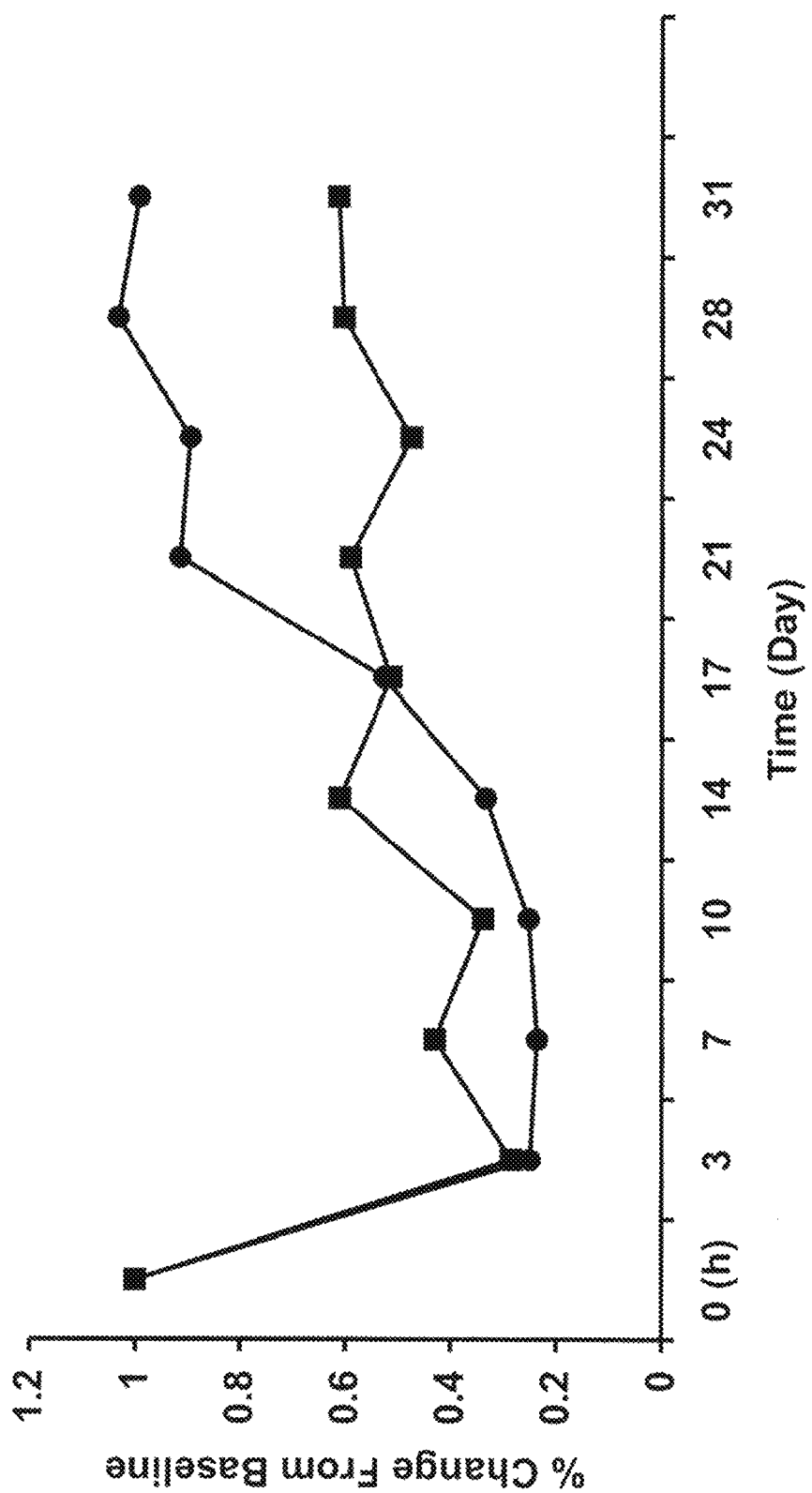


Fig. 8

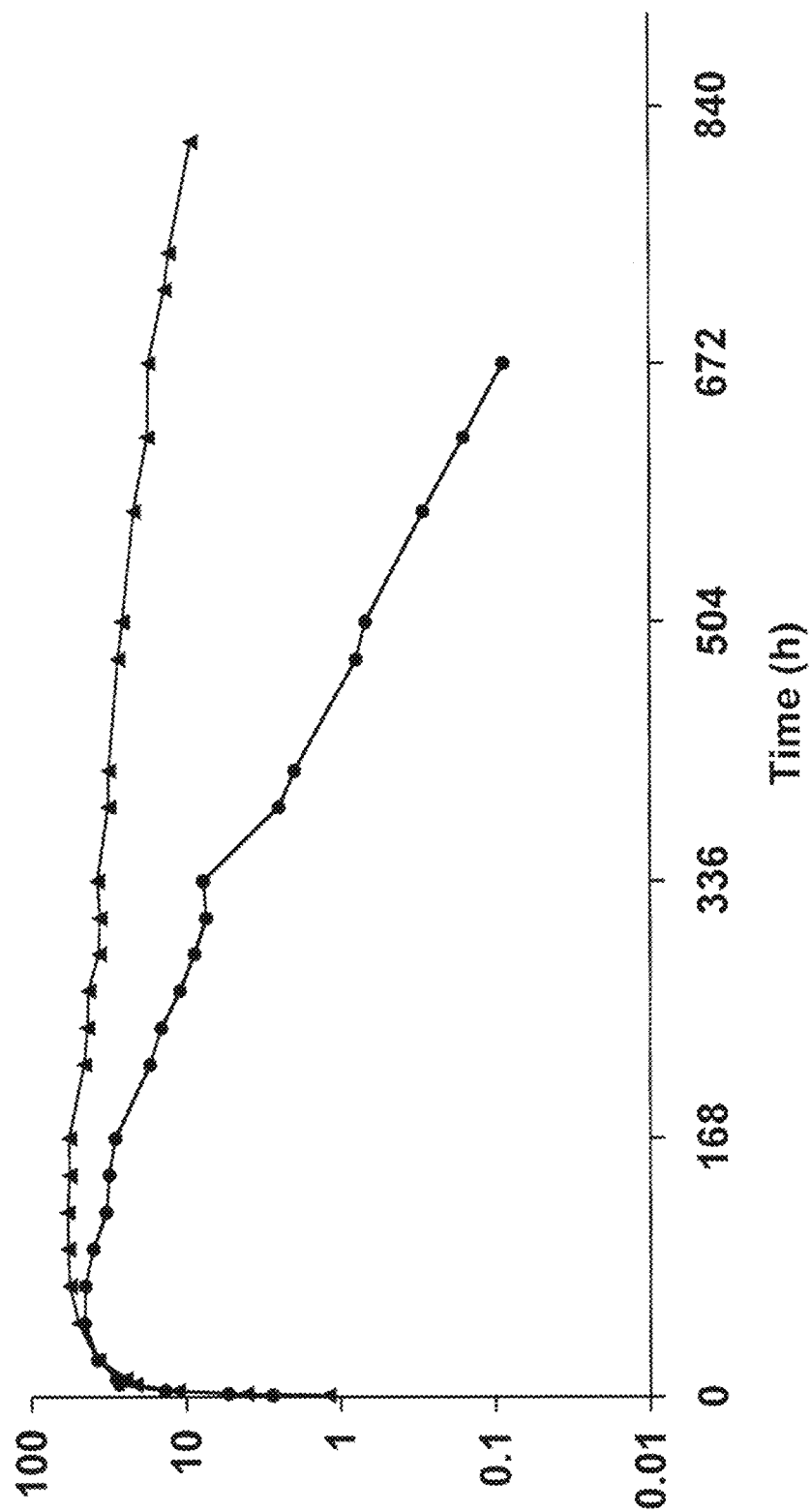


Fig. 9

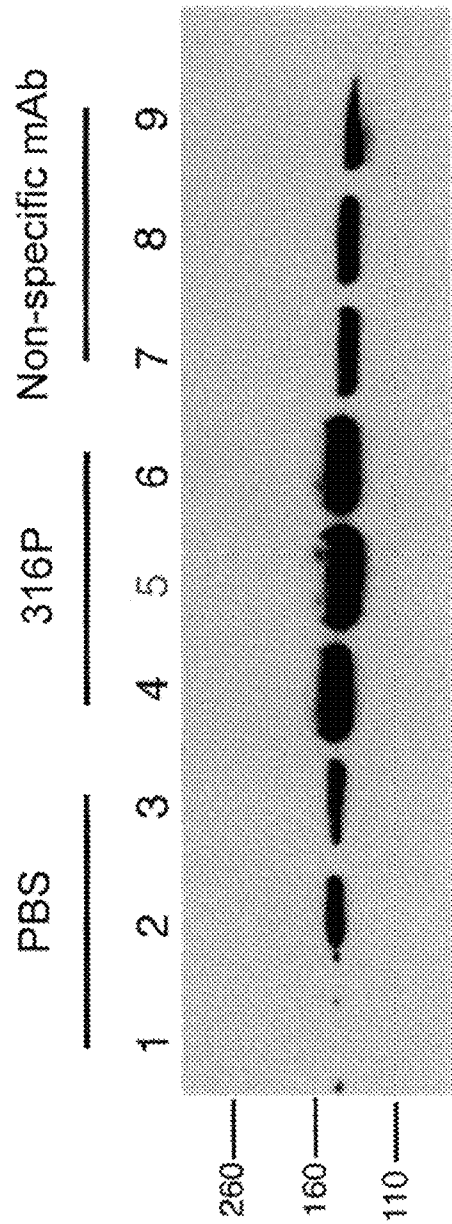


Fig. 10

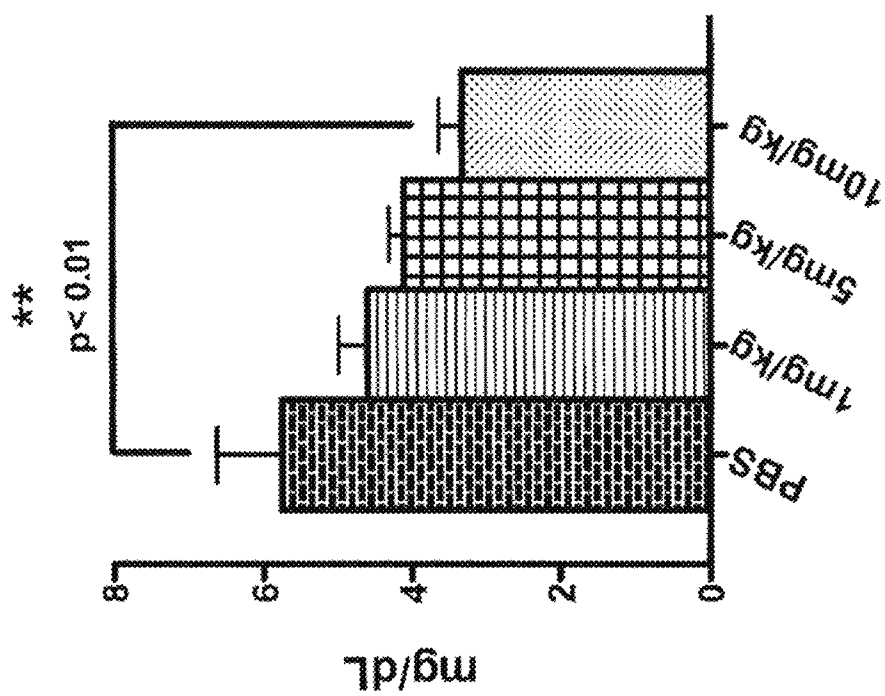


Fig. 11

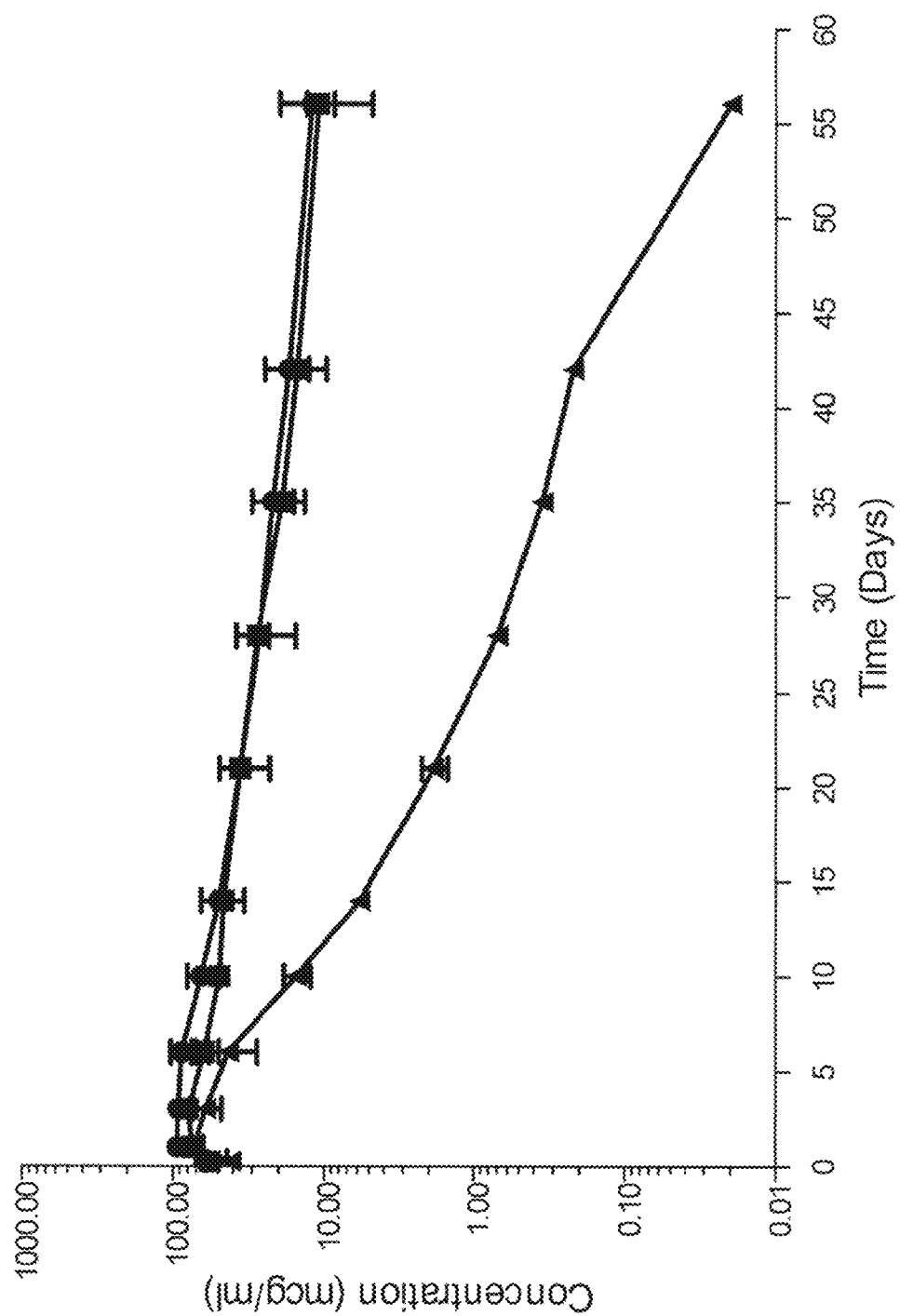


Fig. 12

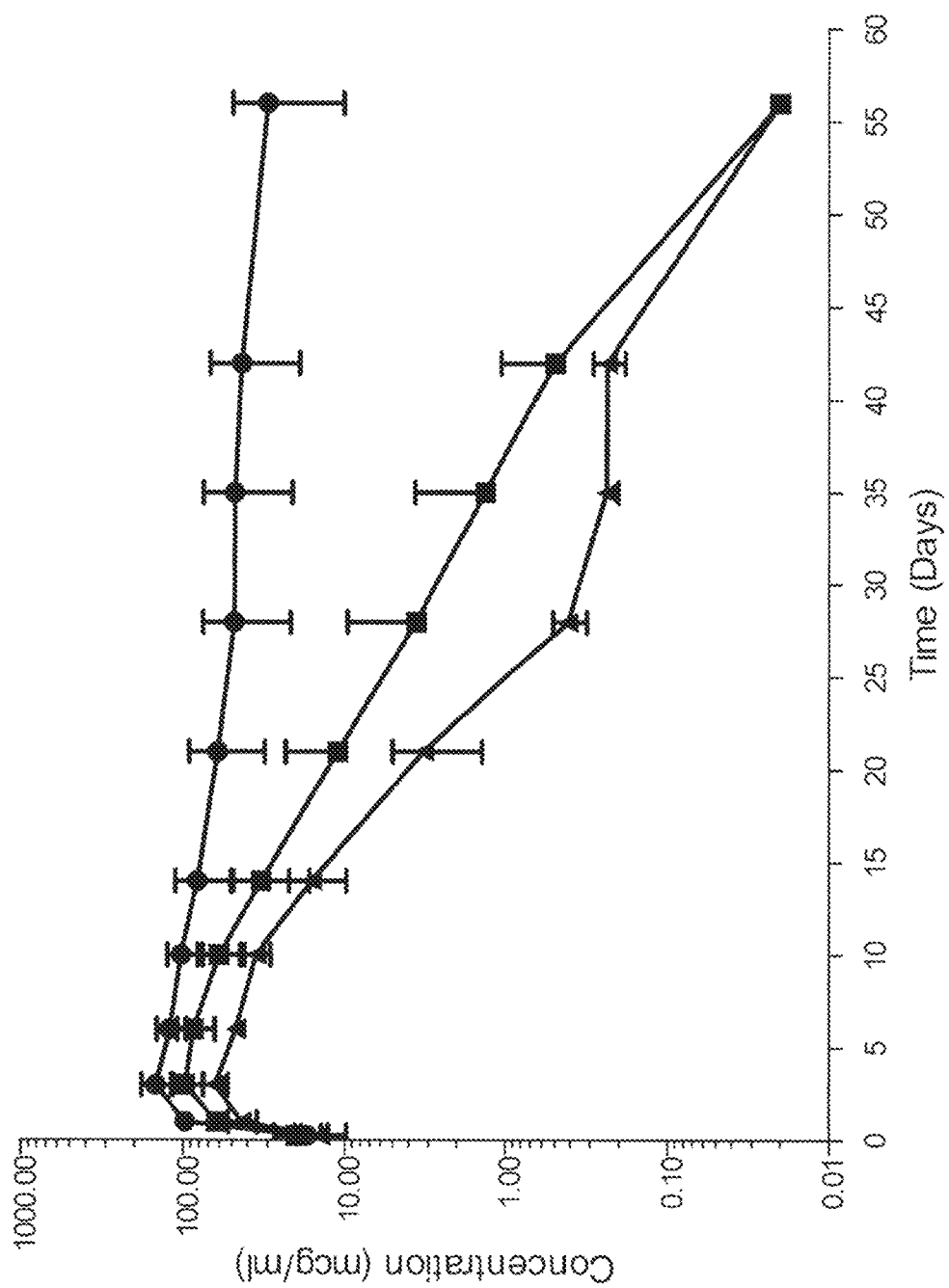


Fig. 13

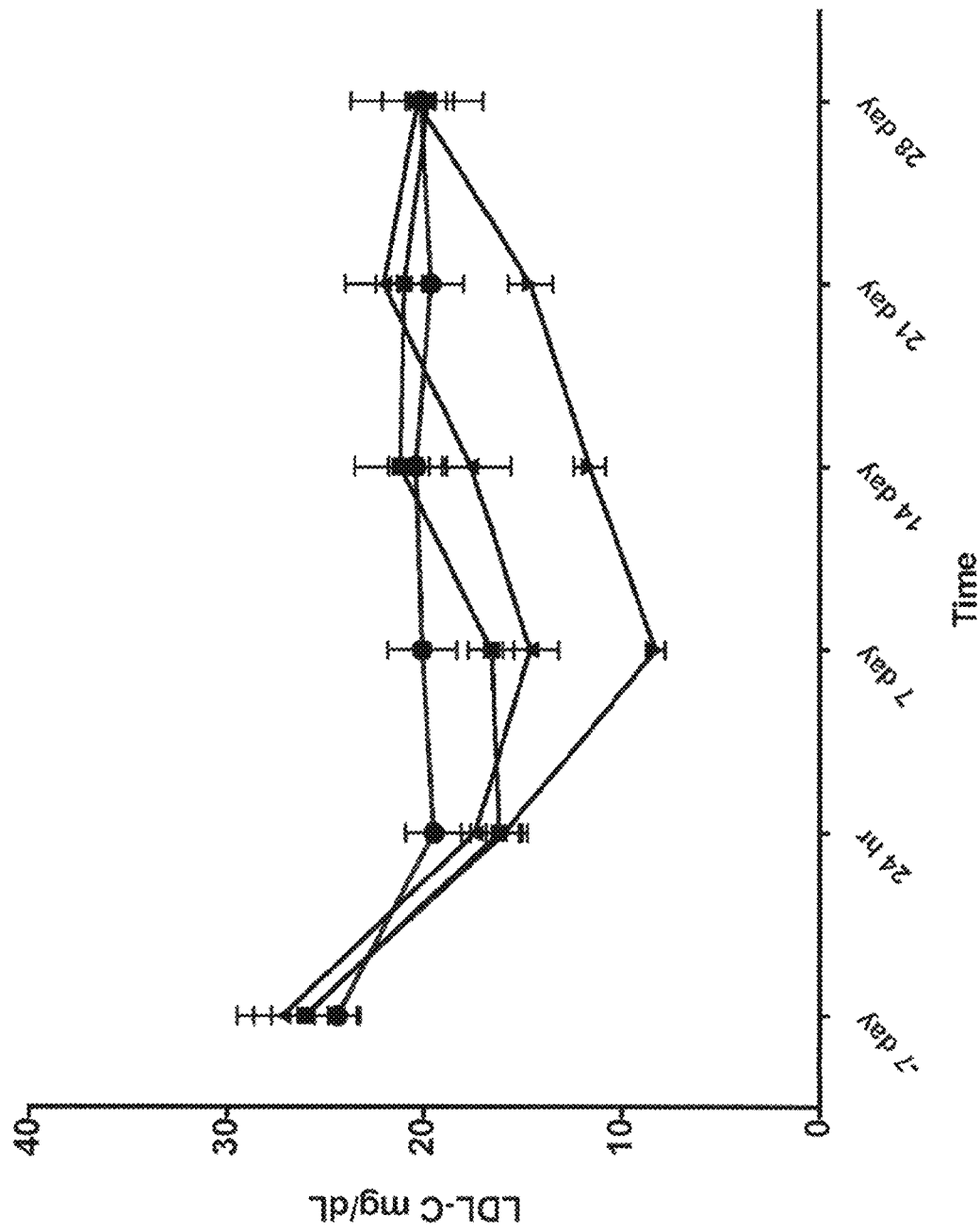


Fig. 14

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METHODS FOR TREATING HYPERCHOLESTEROLEMIA AND REDUCING LDL-C USING ANTIBODIES TO PCSK9

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/672,792, filed on Nov. 9, 2012, which is a continuation-in-part of U.S. application Ser. No. 13/095,234, filed on Apr. 27, 2011, now U.S. Pat. No. 8,357,371, which is a continuation-in-part of U.S. application Ser. No. 12/637,942, filed on Dec. 15, 2009, now U.S. Pat. No. 8,062,640, which claims the benefit under 35 USC §119(e) of U.S. Provisional Patent Appl. Nos. 61/122,482, filed on Dec. 15, 2008; 61/210,566, filed on Mar. 18, 2009; 61/168,753, filed on Apr. 13, 2009; 61/218,136, filed on Jun. 18, 2009; 61/249,135, filed on Oct. 6, 2009; and 61/261,776, filed on Nov. 17, 2009, which applications are herein specifically incorporated by reference in its entirety.

Incorporated by reference herein in its entirety is the Sequence Listing, entitled "7000D1_SeqList-text.txt," which was created on Dec. 4, 2013, size 418 kilobyte.

FIELD OF THE INVENTION

The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind human proprotein convertase subtilisin/kexin type 9 (PCSK9), and therapeutic methods of using those antibodies.

STATEMENT OF RELATED ART

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proprotein convertase belonging to the proteinase K subfamily of the secretory subtilase family. The encoded protein is synthesized as a soluble zymogen that undergoes autocatalytic intramolecular processing in the endoplasmic reticulum. Evidence suggest that PCSK9 increases plasma LDL cholesterol by promoting degradation of the LDL receptor, which mediates LDL endocytosis in the liver, the major route of LDL clearance from circulation. The structure of PCSK9 protein shows that it has a signal sequence, followed by a prodomain, a catalytic domain that contains a conserved triad of residues (D186, H226 and S386), and a C-terminal domain. It is synthesized as a soluble 74-kDa precursor that undergoes autocatalytic cleavage in the ER, generating a 14-kDa prodomain and 60-kDa catalytic fragment. The autocatalytic activity has been shown to be required for secretion. After cleavage the prodomain remains tightly associated with the catalytic domain.

Antibodies to PCSK9 are described in, for example, WO 2008/057457, WO 2008/057458, WO 2008/057459, WO 2008/063382, WO 2008/125623, and US 2008/0008697.

BRIEF SUMMARY OF THE INVENTION

In a first aspect, the invention provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that specifically bind and neutralize human PCSK9 (hPCSK9) activity.

In one embodiment, the invention comprises an antibody or antigen-binding fragment of an antibody that specifically binds hPCSK9 and is characterized by at least one of:

2

(i) capable of reducing serum total cholesterol at least about 25-35% and sustaining the reduction over at least a 24 day period relative to a predose level, preferably the reduction in serum total cholesterol is at least about 30-40%;

(ii) capable of reducing serum LDL cholesterol at least about 65-80% and sustaining the reduction over at least a 24 day period relative to a predose level;

(iii) capable of reducing serum triglyceride at least about 25-40% relative to predose level;

(iv) does not reduce serum HDL cholesterol or reduces serum HDL cholesterol no more than 5% relative to predose level.

In one embodiment, the invention comprises an antibody or antigen-binding fragment of an antibody that specifically binds hPCSK9 and is characterized by at least one of:

(i) capable of reducing serum LDL cholesterol at least about 40-70% and sustaining the reduction over at least a 60 or 90 day period relative to a predose level;

(ii) capable of reducing serum triglyceride at least about 25-40% relative to predose level;

(iii) does not reduce serum HDL cholesterol or reduces serum HDL cholesterol no more than 5% relative to predose level.

In one embodiment, the antibody or antigen-binding fragment is characterized as binding an epitope comprising amino acid residue 238 of hPCSK9 (SEQ ID NO:755). In a more specific embodiment, the antibody or antigen-binding fragment binds an epitope comprising one or more of amino acid residue 238, 153, 159 and 343 of hPCSK9 (SEQ ID NO:755). In a more specific embodiment, the antibody or fragment thereof is characterized as binding an epitope which does not comprise an amino acid residue at position 192, 194, 197 and/or 237 of SEQ ID NO:755.

In one embodiment, the antibody or antigen-binding fragment is characterized as binding an epitope comprising amino acid residue 366 of hPCSK9 (SEQ ID NO:755). In a more specific embodiment, the antibody or antigen-binding fragment binds an epitope comprising one or more of amino acid residue at position 147, 366 and 380 of SEQ ID NO:755. In a more specific embodiment, the antibody or antigen-binding fragment of an antibody is characterized as binding an epitope which does not comprise an amino acid residue at position 215 or 238 of SEQ ID NO:755.

In one embodiment, the antibody or antigen-binding fragment is characterized as exhibiting an enhanced binding affinity (K_D) for hPCSK9 at pH 5.5 relative to the K_D at pH 7.4, as measured by plasmon surface resonance. In a specific embodiment, the antibody or fragment thereof exhibits at least a 20-fold, at least a 40-fold or at least a 50-fold enhanced affinity for PCSK9 at an acidic pH relative to a neutral pH, as measured by surface plasmon resonance.

In one embodiment, the antibody or antigen-binding fragment is characterized as not exhibiting an enhanced binding affinity for PCSK9 at an acidic pH relative to a neutral pH, as measured by surface plasmon resonance. In a specific embodiment, the antibody or fragment thereof exhibits a decreased binding affinity at an acidic pH.

In another embodiment, the antibody or antigen-binding fragment binds human, human GOF mutation D374Y, cynomolgus monkey, rhesus monkey, mouse, rat and hamster PCSK9.

In one embodiment, the antibody or antigen-binding fragment binds human and monkey PCSK9, but does not bind mouse, rat or hamster PCSK9.

The mAbs can be full-length (e.g., an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (e.g., a Fab, F(ab')₂ or scFv fragment), and may be modified

to affect functionality, e.g., to eliminate residual effector functions (Reddy et al. (2000) J. Immunol. 164:1925-1933).

In one embodiment, the invention comprises an antibody or antigen-binding fragment of an antibody comprising a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO:2, 18, 22, 26, 42, 46, 50, 66, 70, 74, 90, 94, 98, 114, 118, 122, 138, 142, 146, 162, 166, 170, 186, 190, 194, 210, 214, 218, 234, 238, 242, 258, 262, 266, 282, 286, 290, 306, 310, 314, 330, 334, 338, 354, 358, 362, 378, 382, 386, 402, 406, 410, 426, 430, 434, 450, 454, 458, 474, 478, 482, 498, 502, 506, 522, 526, 530, 546, 550, 554, 570, 574, 578, 594, 598, 602, 618, 622, 626, 642, 646, 650, 666, 670, 674, 690, 694, 698, 714, 718, 722, 738 and 742, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In one embodiment, the HCVR comprises an amino acid sequence selected from the group consisting of SEQ ID NO:50, 66, 70, 74, 90, 94, 122, 138, 142, 218, 234, 238, 242, 258, 262, 314, 330 and 334. In a more specific embodiment, the HCVR comprises SEQ ID NO:90 or 218.

In one embodiment, the antibody or fragment thereof further comprises a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO:10, 20, 24, 34, 44, 48, 58, 68, 72, 82, 92, 96, 106, 116, 120, 130, 140, 144, 154, 164, 168, 178, 188, 192, 202, 212, 216, 226, 236, 240, 250, 260, 264, 274, 284, 288, 298, 308, 312, 322, 332, 336, 346, 356, 360, 370, 380, 384, 394, 404, 408, 418, 428, 432, 442, 452, 456, 466, 476, 480, 490, 500, 504, 514, 524, 528, 538, 548, 552, 562, 572, 576, 586, 596, 600, 610, 620, 624, 634, 644, 648, 658, 668, 672, 682, 692, 696, 706, 716, 720, 730, 740 and 744, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In one embodiment, the LCVR comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 58, 68, 72, 82, 92, 96, 130, 140, 144, 226, 236, 240, 250, 260, 264, 322, 332 and 336. In a more specific embodiment, the LCVR comprises SEQ ID NO:92 or 226.

In specific embodiments, the antibody or fragment thereof comprises a HCVR and LCVR (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NO: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164, 166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 266/274, 282/284, 286/288, 290/298, 306/308, 310/312, 314/322, 330/332, 334/336, 338/346, 354/356, 358/360, 362/370, 378/380, 382/384, 386/394, 402/404, 406/408, 410/418, 426/428, 430/432, 434/442, 450/452, 454/456, 458/466, 474/476, 478/480, 482/490, 498/500, 502/504, 506/514, 522/524, 526/528, 530/538, 546/548, 550/552, 554/562, 570/572, 574/576, 578/586, 594/596, 598/600, 602/610, 618/620, 622/624, 626/634, 642/644, 646/648, 650/658, 666/668, 670/672, 674/682, 690/692, 694/696, 698/706, 714/716, 718/720, 722/730, 738/740 and 742/744. In one embodiment, the HCVR and LCVR sequence pair comprises one of SEQ ID NO: 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 122/130, 138/140, 142/144, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 314/322, 330/332 and 334/336. In a more specific embodiment, the HCVR/LCVR pair comprises SEQ ID NO:90/92 or 218/226.

In a second aspect, the invention features an antibody or antigen-binding fragment of an antibody comprising a heavy chain CDR3 (HCDR3) domain selected from the group consisting of SEQ ID NO:8, 32, 56, 80, 104, 128, 152, 176, 200, 224, 248, 272, 296, 320, 344, 368, 392, 416, 440, 464,

488, 512, 536, 560, 584, 608, 632, 656, 680, 704 and 728, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain selected from the group consisting of SEQ ID NO:16, 40, 64, 88, 112, 136, 160, 184, 208, 232, 256, 280, 304, 328, 352, 376, 400, 424, 448, 472, 496, 520, 544, 568, 592, 616, 640, 664, 688, 712 and 736, or substantially similar sequences thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In one embodiment, the HCDR3/LCDR3 sequence pair is selected from the group consisting of SEQ ID NO:56/64, 80/88, 128/136, 224/232, 248/256 and 320/328. In a more specific embodiment, the HCDR3/LCDR3 sequence pair comprises SEQ ID NO:80/88 or 224/232.

In a further embodiment, the invention comprising an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) domain selected from the group consisting of SEQ ID NO:4, 28, 52, 76, 100, 124, 148, 172, 196, 220, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460, 484, 508, 532, 556, 580, 604, 628, 652, 676, 700 and 724, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain selected from the group consisting of SEQ ID NO:6, 30, 54, 78, 102, 126, 150, 174, 198, 222, 246, 270, 294, 318, 342, 366, 390, 414, 438, 462, 486, 510, 534, 558, 582, 606, 630, 654, 678, 702 and 726, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain selected from the group consisting of SEQ ID NO:12, 36, 60, 84, 108, 132, 156, 180, 204, 228, 252, 276, 300, 324, 348, 372, 396, 420, 444, 468, 492, 516, 540, 564, 588, 612, 636, 660, 684, 708 and 732, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain selected from the group consisting of SEQ ID NO:14, 38, 62, 86, 110, 134, 158, 182, 206, 230, 254, 278, 302, 326, 350, 374, 398, 422, 446, 470, 494, 518, 542, 566, 590, 614, 638, 662, 686, 710 and 734, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In one embodiment, the heavy and light chain CDR sequences comprise a sequence selected from the group consisting of SEQ ID NO:52, 54, 56, 60, 62, 64; 76, 78, 80, 84, 86, 88; 124, 126, 128, 132, 134, 136; 220, 222, 224, 228, 230, 232; 244, 246, 248, 252, 254, 256; and 316, 318, 320, 324, 326, 328. In more specific embodiments, the CDR sequences comprise SEQ ID NO: 76, 78, 80, 84, 86, 88; or 220, 222, 224, 228, 230, 232.

In a related embodiment, the invention comprises an antibody or antigen-binding fragment of an antibody which specifically binds hPCSK9, wherein the antibody or fragment comprises heavy and light chain CDR domains contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NO: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164, 166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 266/274, 282/284, 286/288, 290/298, 306/308, 310/312, 314/322, 330/332, 334/336, 338/346, 354/356, 358/360, 362/370, 378/380, 382/384, 386/394, 402/404, 406/408, 410/418, 426/428, 430/432, 434/442, 450/452, 454/456, 458/466, 474/476, 478/480, 482/490, 498/500, 502/504, 506/514, 522/524, 526/528, 530/538, 546/548, 550/552, 554/562, 570/572,

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574/576, 578/586, 594/596, 598/600, 602/610, 618/620, 622/624, 626/634, 642/644, 646/648, 650/658, 666/668, 670/672, 674/682, 690/692, 694/696, 698/706, 714/716, 718/720, 722/730, 738/740 and 742/744. In one embodiment, the CDR sequences are contained within HCVR and LCVR selected from the amino acid sequence pairs of SEQ ID NO: 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 122/130, 138/140, 142/144, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 314/322, 330/332 and 334/336. In more specific embodiments, the CDR sequences are comprised within HCVR/LCVR sequences selected from SEQ ID NO: 90/92 or 218/226.

In one embodiment, the invention provides fully human monoclonal antibody or antigen-binding fragment thereof that specifically bind hPCSK9 and neutralize PCSK9 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) capable of reducing serum total cholesterol at least about 25-35% and sustaining the reduction over at least a 24 day period relative to a predose level, preferably the reduction in serum total cholesterol is at least about 30-40%; (ii) capable of reducing serum LDL cholesterol at least about 65-80% and sustaining the reduction over at least a 24 day period relative to a predose level; (iii) capable of reducing serum triglyceride at least about 25-40% relative to predose level; (iv) does not reduce serum HDL cholesterol or reduces serum HDL cholesterol no more than 5% relative to predose level; (v) binds an epitope comprising amino acid residue 238 of hPCSK9 (SEQ ID NO:755); (vi) exhibits an enhanced binding affinity (K_D) for hPCSK9 at pH 5.5 relative to the K_D at pH 7.4, as measured by plasmon surface resonance, wherein the enhanced affinity is at least about a 20- to 50-fold increase in affinity; (vii) binds human, human GOF mutation D374Y, cynomolgus monkey, rhesus monkey, mouse, rat and hamster PCSK9; (viii) comprises heavy and light chain CDR3 sequences comprising SEQ ID NO:80 and 88; and (ix) comprises CDR sequences from SEQ ID NO:90 and 92.

In one embodiment, the invention provides fully human monoclonal antibody or antigen-binding fragment thereof that specifically bind human PCSK9 (hPCSK9) and neutralize PCSK9 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) capable of reducing serum LDL cholesterol at least about 40-70% and sustaining the reduction over at least a 60 or 90 day period relative to a predose level; (ii) capable of reducing serum triglyceride at least about 25-40% relative to predose level; (iii) does not reduce serum HDL cholesterol or reduces serum HDL cholesterol no more than 5% relative to predose level; (iv) binds an epitope comprising amino acid residue 366 of hPCSK9 (SEQ ID NO:755); (v) does not exhibit an enhanced binding affinity for PCSK9 at an acidic pH relative to a neutral pH, as measured by surface plasmon resonance; (vi) binds human and monkey PCSK9, but does not bind mouse, rat or hamster PCSK9; (vii) comprises heavy and light chain CDR3 sequences comprising SEQ ID NO:224 and 232; and (viii) comprises CDR sequences from SEQ ID NO:218 and 226.

In a third aspect, the invention provides nucleic acid molecules encoding anti-PCSK9 antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

6

In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 21, 25, 41, 45, 49, 65, 69, 73, 89, 93, 97, 113, 117, 121, 137, 141, 145, 161, 165, 169, 185, 189, 193, 209, 213, 217, 233, 237, 241, 257, 261, 265, 281, 285, 289, 305, 309, 313, 329, 333, 337, 353, 357, 361, 377, 381, 385, 401, 405, 409, 425, 429, 433, 449, 453, 457, 473, 477, 481, 497, 501, 505, 521, 525, 529, 545, 549, 553, 569, 573, 577, 593, 597, 601, 617, 621, 625, 641, 645, 649, 665, 669, 673, 689, 693, 697, 713, 717, 721, 737 and 741, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 49, 65, 69, 73, 89, 93, 121, 137, 141, 217, 233, 237, 241, 257, 261, 313, 329 and 333. In more specific embodiments, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 89 and 217.

In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 19, 23, 33, 43, 47, 57, 67, 71, 81, 91, 95, 105, 115, 119, 129, 139, 143, 153, 163, 167, 177, 187, 191, 201, 211, 215, 225, 235, 239, 249, 259, 263, 273, 283, 287, 297, 307, 311, 321, 331, 335, 345, 355, 359, 369, 379, 383, 393, 403, 407, 417, 427, 431, 441, 451, 455, 465, 475, 479, 489, 499, 503, 513, 523, 527, 537, 547, 551, 561, 571, 575, 585, 595, 599, 609, 619, 623, 633, 643, 647, 657, 667, 671, 681, 691, 695, 705, 715, 719, 729, 739 and 743, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 57, 67, 71, 81, 91, 95, 129, 139, 143, 225, 235, 239, 249, 259, 263, 321, 331 and 335. In more specific embodiments, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 91 and 225.

In one embodiment, the invention features an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:7, 31, 55, 79, 103, 127, 151, 175, 199, 223, 247, 271, 295, 319, 343, 367, 391, 415, 439, 463, 487, 511, 535, 559, 583, 607, 631, 655, 679, 703 and 727, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 39, 63, 87, 111, 135, 159, 183, 207, 231, 255, 279, 303, 327, 351, 375, 399, 423, 447, 471, 495, 519, 543, 567, 591, 615, 639, 663, 687, 711 and 735, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the HCDR3 and LCDR3 comprise a sequence pair encoded by the nucleic acid sequence of SEQ ID NO: 55/63, 79/87, 127/135, 223/231, 247/255 and 319/327, respectively. In more specific embodiments, the HCDR3 and LCDR3 comprise a sequence pair encoded by the nucleic acid sequence of SEQ ID NO: 79/87 and 223/231.

In a further embodiment, the antibody or fragment thereof further comprises, a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 27, 51, 75, 99, 123, 147, 171, 195, 219, 243, 267, 291, 315, 339, 363, 387, 411, 435, 459, 483, 507, 531, 555, 579, 603, 627, 651, 675, 699 and 723, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a HCDR2 domain

encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 29, 53, 77, 101, 125, 149, 173, 197, 221, 245, 269, 293, 317, 341, 365, 389, 413, 437, 461, 485, 509, 533, 557, 581, 605, 629, 653, 677, 701 and 725, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a LCDRI domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 35, 59, 83, 107, 131, 155, 179, 203, 227, 251, 275, 299, 323, 347, 371, 395, 419, 443, 467, 491, 515, 539, 563, 587, 611, 635, 659, 683, 707 and 731, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDRI domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 37, 61, 85, 109, 133, 157, 181, 205, 229, 253, 277, 301, 325, 349, 373, 397, 421, 445, 469, 493, 517, 541, 565, 589, 613, 637, 661, 685, 709 and 733, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the heavy and light chain CDR sequences are encoded by the nucleic acid sequences of SEQ ID NO: 51, 53, 55, 59, 61, 63, 75, 77, 79, 83, 85, 87, 123, 125, 127, 131, 133, 135, 219, 221, 223, 227, 229, 231, 243, 245, 247, 251, 253, 255; and 315, 317, 319, 323, 325, 327. In more specific embodiments, the heavy and light chain CDR sequences are encoded by the nucleic acid sequences of SEQ ID NO: 75, 77, 79, 83, 85, 87; and 219, 221, 223, 227, 229, 231.

In a fourth aspect, the invention features an isolated antibody or antigen-binding fragment thereof that specifically binds hPCSK9, comprising a HCVR3 and a LCDRI3, wherein HCVR3 comprises an amino acid sequence of the formula $X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-X^{19}-X^{20}$ (SEQ ID NO: 747), wherein X^1 is Ala, X^2 is Arg or Lys, X^3 is Asp, X^4 is Ser or Ile, X^5 is Asn or Val, X^6 is Leu or Trp, X^7 is Gly or Met, X^8 is Asn or Val, X^9 is Phe or Tyr, X^{10} is Asp, X^{11} is Leu or Met, X^{12} is Asp or absent, X^{13} is Tyr or absent, X^{14} is Tyr or absent, X^{15} is Tyr or absent, X^{16} is Tyr or absent, X^{17} is Gly or absent, X^{18} is Met or absent, X^{19} is Asp or absent, and X^{20} is Val or absent; and LCDRI3 comprises an amino acid sequence of the formula $X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8-X^9$ (SEQ ID NO: 750), wherein X^1 is Gln or Met, X^2 is Gln, X^3 is Tyr or Thr, X^4 is Tyr or Leu, X^5 is Thr or Gln, X^6 is Thr, X^7 is Pro, X^8 is Tyr or Leu, and X^9 is Thr.

In a further embodiment, the antibody or fragment thereof further comprise a HCVR1 sequence of the formula $X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8$ (SEQ ID NO: 745), wherein X^1 is Gly, X^2 is Phe, X^3 is Thr, X^4 is Phe, X^5 is Ser or Asn, X^6 is Ser or Asn, X^7 is Tyr or His, and X^8 is Ala or Trp; a HCVR2 sequence of the formula $X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8$ (SEQ ID NO: 746), wherein X^1 is Ile, X^2 is Ser or Asn, X^3 is Gly or Gln, X^4 is Asp or Ser, X^5 is Gly, X^6 is Ser or Gly, X^7 is Thr or Glu, and X^8 is Thr or Lys; a LCDRI1 sequence of the formula $X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}$ (SEQ ID NO: 748) wherein X^1 is Gln, X^2 is Ser, X^3 is Val or Leu, X^4 is Leu, X^5 is His or Tyr, X^6 is Arg or Ser, X^7 is Ser or Asn, X^8 is Asn or Gly, X^9 is Asn, X^{10} is Arg or Asn, X^{11} is Asn or Tyr, and X^{12} is Phe or absent; a LCDRI2 sequence of the formula $X^1-X^2-X^3$ (SEQ ID NO: 749) wherein X^1 is Trp or Leu, X^2 is Ala or Gly, and X^3 is Ser. FIG. 1 shows the sequence alignment of heavy and light chain variable regions for 316P and 300N mAbs.

In a fifth aspect, the invention features a human anti-PCSK9 antibody or antigen-binding fragment of an antibody comprising a heavy chain variable region (HCVR) encoded by nucleotide sequence segments derived from V_H , D_H and

J_H germline sequences, and a light chain variable region (LCVR) encoded by nucleotide sequence segments derived from V_K and J_K germline sequences, wherein the germline sequences are (a) V_H gene segment 3-23, D_H gene segment 7-27, J_H gene segment 2, V_K gene segment 4-1 and J_K gene segment 2; or (b) V_H gene segment 3-7, D_H gene segment 2-8, J_H gene segment 6, V_K gene segment 2-28 and J_K gene segment 4.

In a sixth aspect, the invention features an antibody or antigen-binding fragment thereof that binds to a PCSK9 protein of SEQ ID NO: 755, wherein the binding of the antibody or fragment thereof to a variant PCSK9 protein is less than 50% of the binding between the antibody or fragment thereof and the PCSK9 protein of SEQ ID NO: 755. In specific embodiment, the antibody or fragment thereof binds to the variant PCSK9 protein with a binding affinity (K_D) which is less than about 50%, less than about 60%, less than about 70%, less than about 80%, less than about 90% or less than about 95% compared to the binding to PCSK9 (SEQ ID NO: 755).

In one embodiment, the variant PCSK9 protein comprises at least one mutation at position 238 of SEQ ID NO: 755. In a more specific embodiment, the mutation is D238R. In one embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 90% less relative to the wildtype protein of SEQ ID NO: 755, wherein the variant protein comprises a mutation at residue 238. In one embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 80% less relative to the wildtype protein of SEQ ID NO: 755, wherein the variant protein comprises a mutation at one or more of residue 153, 159, 238 and 343. In a more specific embodiment, the mutation is one of S153R, E159R, D238R and D343R.

In one embodiment, the variant PCSK9 protein comprises at least one mutation at position 366 of SEQ ID NO: 755. In a more specific embodiment, the mutation is E366K. In one embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 95% less relative to the wildtype protein of SEQ ID NO: 755, wherein the variant protein comprises a mutation at residue 366. In one embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 90% less relative to the wildtype protein of SEQ ID NO: 755, wherein the variant protein comprises a mutation at one or more of residue 147, 366 and 380. In a more specific embodiment, the mutation is one of S147F, E366K and V380M. In one embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 80% less relative to the wildtype protein of SEQ ID NO: 755, wherein the variant protein comprises a mutation at one or more of residue 147, 366 and 380. In a more specific embodiment, the mutation is one of S147F, E366K and V380M.

The invention encompasses anti-PCSK9 antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety 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).

In a seventh aspect, the invention features a pharmaceutical composition comprising a recombinant human antibody or fragment thereof which specifically binds hPCSK9 and a pharmaceutically acceptable carrier. In one embodiment, the invention features a composition which is a combination of an antibody or antigen-binding fragment of

an antibody of the invention, and a second therapeutic agent. The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, an agent capable of inducing a cellular depletion of cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase, such as, for example, cerovastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, etc.; capable of inhibiting cholesterol uptake and or bile acid re-absorption; capable of increasing lipoprotein catabolism (such as niacin); and/or activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol.

In an eighth aspect, the invention features methods for inhibiting hPCSK9 activity using the anti-PCSK9 antibody or antigen-binding portion of the antibody of the invention, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the invention. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of PCSK9 activity. Specific populations treatable by the therapeutic methods of the invention include subjects indicated for LDL apheresis, subjects with PCSK9-activating mutations (gain of function mutations, "GOF"), subjects with heterozygous Familial Hypercholesterolemia (heFH); subjects with primary hypercholesterolemia who are statin intolerant or statin uncontrolled; and subjects at risk for developing hypercholesterolemia who may be preventably treated. Other indications include dyslipidemia associated with secondary causes such as Type 2 diabetes mellitus, cholestatic liver diseases (primary biliary cirrhosis), nephrotic syndrome, hypothyroidism, obesity; and the prevention and treatment of atherosclerosis and cardiovascular diseases.

In specific embodiments of the method of the invention, the anti-hPCSK9 antibody or antibody fragment of the invention is useful to reduce elevated total cholesterol, non-HDL cholesterol, LDL cholesterol, and/or apolipoprotein B (apolipoprotein B100).

The antibody or antigen-binding fragment of the invention may be used alone or in combination with a second agent, for example, an HMG-CoA reductase inhibitor and/or other lipid lowering drugs.

Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Sequence comparison tables of heavy chain (A) and light chain (B) variable regions and CDRs of antibodies H1H316P and H1M300N.

FIG. 2. Antibody concentrations in serum over time. 316P 5 mg/kg (□); 300N 5 mg/kg (○); 316P 15 mg/kg (■); 300N 15 mg/kg (●).

FIG. 3. Serum total cholesterol level as a percentage of change over buffer control. Buffer control (*); 316P 5 mg/kg (■); 300N 5 mg/kg (▲); 316P 15 mg/kg (□); 300N 15 mg/kg (Δ).

FIG. 4. Serum LDL cholesterol level as a percentage of change over buffer control: Buffer Control (*); 316P 5 mg/kg (■); 300N 5 mg/kg (▲); 316P 15 mg/kg (□); 300N 15 mg/kg (Δ).

FIG. 5. Serum LDL cholesterol level normalized to buffer control. Buffer control (*); 316P 5 mg/kg (■); 300N 5 mg/kg (▲); 316P 15 mg/kg (□); 300N 15 mg/kg (Δ).

FIG. 6. Serum HDL cholesterol level as a percentage of change over buffer control. Buffer control (*); 316P 5 mg/kg (■); 300N 5 mg/kg (▲); 316P 15 mg/kg (□); 300N 15 mg/kg (Δ).

FIG. 7. Serum triglyceride level expressed as a percentage of change over buffer control. Buffer control (*); 316P 5 mg/kg (■); 300N 5 mg/kg (▲); 316P 15 mg/kg (□); 300N 15 mg/kg (Δ).

FIG. 8. Serum LDL cholesterol level expressed as a percentage of change over baseline following a single dose subcutaneous administration. 316P 5 mg/kg (■); 300N 5 mg/kg (●).

FIG. 9. Antibody concentrations in serum over time following a single dose subcutaneous administration. 316P 5 mg/kg (●); 300N 5 mg/kg (▲).

FIG. 10. Western blot for mouse LDL receptor of total liver homogenates. Samples were taken 24 hours after PBS (lanes 1-3), 5 mg/kg 316P (lanes 4-6), or 5 mg/kg of non-hPCSK9 specific mAb (lanes 7-8) administration and 4 hours after 1.2 mg/kg hPCSK9-mmh (all lanes).

FIG. 11. Effects of 316P on serum LDL cholesterol level in PCSK9^{hu/hu} mice. Buffer control (■); 316P 1 mg/kg (≡); 316P 5 mg/kg (▣); 316P 10 mg/kg (▤).

FIG. 12. Anti-hPCSK9 mAb serum pharmacokinetic profile in C57BL/6 mice. Single dose of Control I mAb (●) at 10 mg/kg; 316P (▲) at 10 mg/kg and 300N (■) at 10 mg/kg.

FIG. 13. Anti-hPCSK9 mAb serum pharmacokinetic profile in hPCSK9 heterozygous mice. Single dose of Control I mAb (●) at 10 mg/kg; 316P (▲) at 10 mg/kg and 300N (■) at 10 mg/kg.

FIG. 14. Effect of 316P on serum LDL cholesterol levels in Syrian Hamster fed a normal diet. Buffer control (●); 316P 1 mg/kg (■); 316P 3 mg/kg (▲); 316P 5 mg/kg (▼).

DETAILED DESCRIPTION

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.

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. 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.

DEFINITIONS

The term "human proprotein convertase subtilisin/kexin type 9" or "hPCSK9", as used herein, refers to hPCSK9 having the nucleic acid sequence shown in SEQ ID NO:754 and the amino acid sequence of SEQ ID NO:755, or a biologically active fragment thereof.

The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "VH") and a heavy chain constant region (comprised of

domains CH1, CH2 and CH3). Each light chain is comprised of a light chain variable region ("LCVR" or "VL") and a light chain constant region (CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL 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.

Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan et al. (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos et al. 2002 J Mol Biol 320:415-428).

CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences.

The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-6} M or less (e.g., a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds hPCSK9 may, however, exhibit cross-reactivity to other antigens such as PCSK9 molecules from other species. Moreover, multi-specific antibodies (e.g., bispecifics) that bind to hPCSK9 and one or more additional antigens are nonetheless considered antibodies that "specifically bind" hPCSK9, as used herein.

The term "high affinity" antibody refers to those mAbs having a binding affinity to hPCSK9 of at least 10^{-10} M; preferably 10^{-11} M; even more preferably 10^{-12} M, as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

By the term "slow off rate", "K_{off}" or "kd" is meant an antibody that dissociates from hPCSK9 with a rate constant

of 1×10^{-3} s⁻¹ or less, preferably 1×10^{-4} s⁻¹ or less, as determined by surface plasmon resonance, e.g., BIACORE™.

The term "antigen-binding portion" of an antibody (or simply "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hPCSK9. An antibody fragment may include a Fab fragment, a F(ab')₂ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR.

The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other mAbs having different antigenic specificities (e.g., an isolated antibody that specifically binds hPCSK9 is substantially free of mAbs that specifically bind antigens other than hPCSK9). An isolated antibody that specifically binds hPCSK9 may, however, have cross-reactivity to other antigens, such as PCSK9 molecules from other species.

A "neutralizing antibody", as used herein (or an "antibody that neutralizes PCSK9 activity"), is intended to refer to an antibody whose binding to hPCSK9 results in inhibition of at least one biological activity of PCSK9. This inhibition of the biological activity of PCSK9 can be assessed by measuring one or more indicators of PCSK9 biological activity by one or more of several standard in vitro or in vivo assays known in the art (see examples below).

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

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

The term "epitope" is a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

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 90%, and more preferably at least about 95%, 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.

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 90% sequence identity, even more preferably at least 95%,

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 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, which is 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: 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: 1443-45, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

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.

In specific embodiments, the antibody or antibody fragment for use in the method of the invention may be monospecific, bispecific, or multispecific. Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 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 CH3 domain binds Protein A and the second Ig CH3 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 CH3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 mAbs; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 mAbs; 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 mAbs. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

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*).

Preparation of Human Antibodies

Methods for generating human antibodies in transgenic mice are known (see for example, U.S. Pat. No. 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE™). 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. In specific embodiment, the cell is a CHO cell.

Antibodies may be therapeutically useful in blocking a ligand-receptor interaction or inhibiting receptor component interaction, rather than by killing cells through fixation of complement and participation in complement-dependent cytotoxicity (CDC), or killing cells through antibody-dependent cell-mediated cytotoxicity (ADCC). The constant region of an antibody is thus important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an antibody 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.

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 iso-

type 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, CH2 or CH3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

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.

Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As described below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are 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 (for example, SEQ ID NO:751, 752, 753). While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Epitope Mapping and Related Technologies

To screen for antibodies that bind to a particular epitope (e.g., those which block binding of IgE to its high affinity receptor), a routine cross-blocking assay such as that described *Antibodies*, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., N.Y.) can be performed. Other methods include alanine scanning mutants, peptide blots (Reineke (2004) *Methods Mol Biol* 248:443-63) (herein specifically incorporated by reference in its entirety), or 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) (herein specifically incorporated by reference in its entirety).

The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US 2004/0101920, herein specifically incorporated by reference

in its entirety). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical mAbs, such that characterization can be focused on genetically distinct mAbs. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the anti-PCSK9 mAbs of the invention into groups of mAbs binding different epitopes.

In various embodiments, the anti-hPCSK9 antibody or antigen-binding fragment of an antibody binds an epitope within the catalytic domain, which is about 153 to 425 of SEQ ID NO:755); more specifically, an epitope from about 153 to about 250 or from about 250 to about 425; more specifically, the antibody or antibody fragment of the invention binds an epitope within the fragment from about 153 to about 208, from about 200 to about 260, from about 250 to about 300, from about 275 to about 325, from about 300 to about 360, from about 350 to about 400, and/or from about 375 to about 425.

In various embodiments, the anti-h PCSK9 antibody or antigen-binding fragment of an antibody binds an epitope within the propeptide domain (residues 31 to 152 of SEQ ID NO:755); more specifically, an epitope from about residue 31 to about residue 90 or from about residue 90 to about residue 152; more specifically, the antibody or antibody fragment of the invention binds an epitope within the fragment from about residue 31 to about residue 60, from about residue 60 to about residue 90, from about residue 85 to about residue 110, from about residue 100 to about residue 130, from about residue 125 to about residue 150, from about residue 135 to about residue 152, and/or from about residue 140 to about residue 152.

In some embodiments, the anti-h PCSK9 antibody or antigen-binding fragment of an antibody binds an epitope within the C-terminal domain, (residues 426 to 692 of SEQ ID NO:755); more specifically, an epitope from about residue 426 to about residue 570 or from about residue 570 to about residue 692; more specifically, the antibody or antibody fragment of the invention binds an epitope within the fragment from about residue 450 to about residue 500, from about residue 500 to about residue 550, from about residue 550 to about residue 600, and/or from about residue 600 to about residue 692.

In some embodiments, the antibody or antibody fragment binds an epitope which includes more than one of the enumerated epitopes within the catalytic, propeptide or C-terminal domain, and/or within two or three different domains (for example, epitopes within the catalytic and C-terminal domains, or within the propeptide and catalytic domains, or within the propeptide, catalytic and C-terminal domains).

In some embodiments, the antibody or antigen-binding fragment binds an epitope on hPCSK9 comprising amino acid residue 238 of hPCSK9 (SEQ ID NO:755). Experimental results (Table 27) show that when D238 was mutated, the K_D of mAb 316P exhibited >400-fold reduction in binding affinity ($\sim 1 \times 10^{-9}$ M to $\sim 410 \times 10^{-9}$ M) and $T_{1/2}$ decreased >30-fold (from ~ 37 to ~ 1 min). In a specific embodiment, the mutation was D238R. In specific embodiments, the antibody or antigen-binding fragment of the invention binds an epitope of hPCSK9 comprising two or more of amino acid residues at positions 153, 159, 238 and 343.

As shown below, a mutation in amino acid residue 153, 159 or 343 resulted in about a 5- to 10-fold decrease in

affinity or similar shortening in $T_{1/2}$. In specific embodiments, the mutation was S153R, E159R and/or D343R.

In some embodiments, the antibody or antigen-binding fragment binds an epitope on hPCSK9 comprising amino acid residue 366 of hPCSK9 (SEQ ID NO:755). Experimental results (Table 27) show that when E366 was mutated, the affinity of mAb 300N exhibited about 50-fold decrease ($\sim 0.7 \times 10^{-9}$ M to $\sim 36 \times 10^{-9}$ M) and a similar shortening in $T_{1/2}$ (from ~ 120 to ~ 2 min). In a specific embodiment, the mutation is E366K.

The present invention includes anti-PCSK9 antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein. Likewise, the present invention also includes anti-PCSK9 antibodies that compete for binding to PCSK9 or a PCSK9 fragment with any of the specific exemplary antibodies described herein.

One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-PCSK9 antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-PCSK9 antibody of the invention, the reference antibody is allowed to bind to a PCSK9 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the PCSK9 molecule is assessed. If the test antibody is able to bind to PCSK9 following saturation binding with the reference anti-PCSK9 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-PCSK9 antibody. On the other hand, if the test antibody is not able to bind to the PCSK9 molecule following saturation binding with the reference anti-PCSK9 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-PCSK9 antibody of the invention.

To determine if an antibody competes for binding with a reference anti-PCSK9 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a PCSK9 molecule under saturating conditions followed by assessment of binding of the test antibody to the PCSK9 molecule. In a second orientation, the test antibody is allowed to bind to a PCSK9 molecule under saturating conditions followed by assessment of binding of the reference antibody to the PCSK9 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the PCSK9 molecule, then it is concluded that the test antibody and the reference antibody compete for binding to PCSK9. 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 identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, 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 have 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 have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

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, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

In a specific embodiment, the invention comprises an anti-PCSK9 antibody or antigen binding fragment of an antibody that binds an PCSK9 protein of SEQ ID NO:755, wherein the binding between the antibody or fragment thereof to PCSK9 and a variant PCSK9 protein is less than 50% of the binding between the antibody or fragment and the PCSK9 protein of SEQ ID NO:755. In one specific embodiment, the variant PCSK9 protein comprises at least one mutation of a residue at a position selected from the group consisting of 153, 159, 238 and 343. In a more specific embodiment, the at least one mutation is S153R, E159R, D238R, and/or D343R. In another specific embodiment, the variant PCSK9 protein comprises at least one mutation of a residue at a position selected from the group consisting of 366. In one specific embodiment, the variant PCSK9 protein comprises at least one mutation of a residue at a position selected from the group consisting of 147, 366 and 380. In a more specific embodiment, the mutation is S147F, E366K and V380M.

Immunoconjugates

The invention encompasses a human anti-PCSK9 monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxin agents include any agent that is detrimental to cells. Examples of suitable cytotoxin agents and chemotherapeutic agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Bispecifics

The antibodies of the present invention may be monospecific, bispecific, or multispecific. Multispecific mAbs 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. The human anti-PCSK9 mAbs 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 bispecific or a multispecific antibody with a second binding specificity.

An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 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 CH3 domain binds Protein A and the second Ig CH3 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 CH3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 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 bi-specific antibody format described above are contemplated within the scope of the present invention.

Bioequivalents

The anti-PCSK9 antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described mAbs, but that retain the ability to bind human PCSK9. Such variant mAbs 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 mAbs. Likewise, the anti-PCSK9 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-PCSK9 antibody or antibody fragment that is essentially bioequivalent to an anti-PCSK9 antibody or antibody fragment of the invention. Examples of such variant amino acid and DNA sequences are discussed above.

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

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.

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.

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.

Bioequivalent variants of anti-PCSK9 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.

Treatment Population

The methods of the present invention comprise administering to a subject in need thereof a therapeutic composition comprising an anti-PCSK9 antibody. The therapeutic composition can comprise any of the anti-PCSK9 antibodies, or fragments thereof, as disclosed herein. As used herein, the expression "a subject in need thereof" means a human or non-human animal that exhibits one or more symptoms or indicia of hypercholesterolemia or who has been diagnosed with hypercholesterolemia. Specific exemplary populations treatable by the therapeutic methods of the invention include patients indicated for LDL apheresis, subjects with PCSK9-activating (GOF) mutations, patients with heterozygous Familial Hypercholesterolemia (heFH); subjects with primary hypercholesterolemia who are statin intolerant or statin uncontrolled; and subjects at risk for developing hypercholesterolemia who may be preventably treated.

While modifications in lifestyle and conventional drug treatment are often successful in reducing cholesterol levels, not all patients are able to achieve the recommended target cholesterol levels with such approaches. Various conditions, such as familial hypercholesterolemia (FH), appear to be resistant to lowering of LDL-C levels in spite of aggressive use of conventional therapy. Homozygous and heterozygous familial hypercholesterolemia (hoFH, heFH) are conditions associated with premature atherosclerotic vascular disease. However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and upregulating the hepatic LDL receptor, may have little effect in patients whose LDL receptors are non-existent or defective. A mean LDL-C reduction of only less than about 20% has been recently reported in patients with genotype-confirmed hoFH treated with the maximal dose of statins. The addition of ezetimibe 10 mg/day to this regimen resulted in a total reduction of LDL-C levels of 27%, which is still far from optimal. Likewise, many patients are statin non-responsive, poorly controlled with statin therapy, or cannot tolerate statin therapy; in general, these patients are unable to achieve cholesterol control with alternative treatments. There is a large unmet medical need for new treatments that can address the short-comings of current treatment options.

Thus, the invention includes therapeutic methods in which the antibody or antibody fragment of the invention is administered to a patient to treat hypercholesterolemia. Specific non-limiting examples of types of hypercholesterolemia which are treatable in accordance with the methods of the present invention include, e.g., heterozygous Familial Hypercholesterolemia (heFH), homozygous Familial Hypercholesterolemia (hoFH), as well as incidences of hypercholesterolemia that are distinct from Familial Hypercholesterolemia (nonFH).

Therapeutic Administration and Formulations

The invention provides therapeutic compositions comprising the anti-PCSK9 antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and

other agents that are incorporated into formulations to 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™), 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.

The dose may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibody of the present invention is used for treating various conditions and diseases associated with PCSK9, including hypercholesterolemia, disorders associated with LDL and apolipoprotein B, and lipid metabolism disorders, and the like, in an adult patient, it is 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.

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.

The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533; Treat et al. (1989) in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez Berestein and Fidler (eds.), Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

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.), CRC Press, Boca Raton, Fla. (1974). 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, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138, 1984).

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. 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.

Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), 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 certainly are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly).

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.

Dosage

The amount of anti-PCSK9 antibody administered to a subject according to the methods of the present invention is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means a dose of anti-PCSK9 antibody that results in a detectable improvement in one or more symptoms or indicia of hypercholesterolemia, or a dose of anti-PCSK9 antibody that inhibits, prevents, lessens, or delays the progression of hypercholesterolemia in a patient. In the case of an anti-

PCSK9 antibody, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, e.g., about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-PCSK9 antibody.

The amount of anti-PCSK9 antibody contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (i.e., mg/kg). For example, the anti-PCSK9 antibody may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

Administration Regimens

According to certain embodiments of the present invention, multiple doses of anti-PCSK9 antibody 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 anti-PCSK9 antibody. As used herein, "sequentially administering" means that each dose of anti-PCSK9 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-PCSK9 antibody, followed by one or more secondary doses of the anti-PCSK9 antibody, and optionally followed by one or more tertiary doses of the anti-PCSK9 antibody.

The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the anti-PCSK9 antibody. 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-PCSK9 antibody, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of anti-PCSK9 antibody contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

In certain exemplary embodiments of the present invention, each secondary and/or tertiary dose is administered 1 to 30 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more) days after the immediately preceding dose, or 1 to 12 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 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-PCSK9 antibody

which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

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-PCSK9 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.

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 12 weeks after the immediately preceding dose (e.g., once every week [Q1W], once every two weeks [Q2W], once every three weeks [Q3W], once every four weeks [Q4W], once every six weeks [Q6W], once every eight weeks [Q8W], etc.). 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 1 to 12 weeks after the immediately preceding dose (e.g., once every week [Q1W], once every two weeks [Q2W], once every three weeks [Q3W], once every four weeks [Q4W], once every six weeks [Q6W], once every eight weeks [Q8W], etc.). Alternatively, 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.

Non-limiting exemplary administration regimens of the present invention include, e.g., 75 mg of anti-PCSK9 antibody (e.g., 300N or 316P) administered to a subject once every two weeks (Q2W); 100 mg of anti-PCSK9 antibody (e.g., 300N or 316P) administered to a subject once every two weeks (Q2W); and 150 mg of anti-PCSK9 antibody (e.g., 300N or 316P) administered to a subject once every two weeks (Q2W).

The present invention also includes administration regimens comprising administering one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) doses comprising 75 mg of anti-PCSK9 antibody (e.g., 300N or 316P) to a patient, and if the patient has not achieved a satisfactory reduction in LDL-C following administration of one or more of the 75 mg doses (or if an increased dose is otherwise deemed more therapeutically appropriate), then discontinuing the 75 mg doses and administering one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) additional doses comprising 150 mg of the anti-PCSK9 antibody to the patient, wherein each 75 mg and 150 mg dose is administered to the patient once every two weeks (i.e., Q2W dosing). As used herein, the phrase "satisfactory reduction in LDL-C" means that the blood concentration of LDL-C in the patient following administration of one or more doses of anti-PCSK9 antibody is less than about 100 mg/dL or less than about 70 mg/dL.

The present invention also includes administration regimens comprising administering one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) doses comprising 150 mg of anti-PCSK9 antibody (e.g., 300N or 316P) to a patient, followed by discontinuing the 150 mg doses and

25

instead administering one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) additional doses comprising 75 mg of the anti-PCSK9 antibody to the patient, wherein each 150 mg and 75 mg dose is administered to the patient once every two weeks (i.e., Q2W dosing).

The present invention also includes administration regimens comprising administering one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) doses comprising 75 mg of anti-PCSK9 antibody (e.g., 300N or 316P) to a patient, followed by discontinuing the 75 mg doses and instead administering one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) additional doses comprising 150 mg of the anti-PCSK9 antibody to the patient, followed by discontinuing the 150 mg doses and resuming administration of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more) additional doses comprising 75 mg of the anti-PCSK9 antibody to the patient, wherein each 150 mg and 75 mg dose is administered to the patient once every two weeks (i.e., Q2W dosing).

Combination and Adjunct Therapies

The methods of the present invention, according to certain embodiments, may comprise administering a pharmaceutical composition comprising an anti-PCSK9 antibody to a patient who is on a therapeutic regimen for the treatment of hypercholesterolemia at the time of, or just prior to, administration of the pharmaceutical composition of the invention. For example, a patient who has previously been diagnosed with hypercholesterolemia may have been prescribed and is taking a stable therapeutic regimen of another drug prior to and/or concurrent with administration of a pharmaceutical composition comprising an anti-PCSK9 antibody. The prior or concurrent therapeutic regimen may comprise, e.g., (1) an agent which induces a cellular depletion of cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase, such as a statin (e.g., cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, etc.); (2) an agent which inhibits cholesterol uptake and or bile acid re-absorption; (3) an agent which increase lipoprotein catabolism (such as niacin); and/or (4) activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol. In certain embodiments, the patient, prior to or concurrent with administration of an anti-PCSK9 antibody is on a fixed combination of therapeutic agents such as ezetimibe plus simvastatin; a statin with a bile resin (e.g., cholestyramine, colestipol, colestevlam); 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).

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used but some experimental errors and deviations should be accounted for. Unless indicated otherwise, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Generation of Human Antibodies to Human PCSK9

VELOCIMMUNE™ mice were immunized with human PCSK9, and the antibody immune response monitored by

26

antigen-specific immunoassay using serum obtained from these mice. Anti-hPCSK9 expressing B cells were harvested from the spleens of immunized mice shown to have elevated anti-h PCSK9 antibody titers were fused with mouse myeloma cells to form hybridomas. The hybridomas were screened and selected to identify cell lines expressing hPCSK9-specific antibodies using assays as described below. The assays identified several cell lines that produced chimeric anti-hPCSK9 antibodies designated as H1M300, H1M504, H1M505, H1M500, H1M497, H1M498, H1M494, H1M309, H1M312, H1M499, H1M493, H1M496, H1M503, H1M502, H1M508, H1M495 and H1M492.

Human PCSK9-specific antibodies were also isolated directly from antigen-immunized B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1, hereby incorporated by reference in its entirety. Heavy and light chain variable regions were cloned to generate fully human anti-hPCSK9 antibodies designated as H1H313, H1H314, H1H315, H1H316, H1H317, H1H318, H1H320, H1H321 and H1H334. Stable recombinant antibody-expressing CHO cell lines expressing these antibodies were established.

Example 2

Gene Utilization Analysis

To analyze the structure of the mAbs produced, the nucleic acids encoding antibody variable regions were cloned and sequenced. The predicted amino acid sequences of the variable regions were confirmed by N-terminal amino acid sequencing. From the nucleic acid sequence and predicted amino acid sequence of the mAbs, gene usage was identified for each antibody chain.

TABLE 1

Antibody	Heavy Chain Variable Region			Light Chain Variable Region	
	VH	D	JH	VK	JK
H1H313	3-13	1-26	4	3-15	3
H1H314	3-33	3-3	4	1-5	2
H1H315	3-33	3-3	4	4-1	1
H1H316	3-23	7-27	2	4-1	2
H1H317	3-13	1-26	4	1-6	1
H1H318	4-59	3-10	6	1-9	1
H1H320	1-18	2-2	6	2-30	1
H1H321	2-5	1-7	6	2-28	4
H1H334	2-5	6-6	6	2-28	4
H1M300	3-7	2-8	6	2-28	4
H1M504	3-30	2-8	6	2-28	4
H1M505	3-30	2-8	6	2-28	4
H1M500	2-5	5-5	6	2-28	4
H1M497	1-18	2-2	6	2-30	2
H1M498	3-21	2-2	4	1-5	2
H1M494	3-11	5-12	6	3-20	4
H1M309	3-21	6-13	4	1-5	1
H1M312	3-21	6-13	4	1-5	1
H1M499	3-21	6-13	4	1-5	1
H1M493	3-21	6-13	4	1-5	1
H1M496	3-13	6-19	4	3-15	3
H1M503	1-18	2-2	6	2-28	1
H1M502	3-13	6-13	4	3-15	3
H1M508	3-13	6-13	4	3-15	3
H1M495	3-9	4-17	6	1-9	3
H1M492	3-23	3-3	2	3-20	4

27

Example 3

Antigen Binding Affinity Determination

Equilibrium dissociation constants (K_D) for hPCSK9 binding to mAbs generated by hybridoma cell lines described above were determined by surface kinetics in a real-time biosensor surface plasmon resonance assay (BIA-CORE™ T100). Each antibody was captured at a flow rate of 4 μ l/min for 90 sec on a goat anti-mouse IgG polyclonal antibody surface created through direct chemical coupling to a BIA-CORE™ chip to form a captured antibody surface. Human PCSK9-myc-myc-his (hPCSK9-mmh) at a concentration of 50 nM or 12.5 nM was injected over the captured antibody surfaces at a flowrate of 50 μ l/min for 300 sec, and antigen-antibody dissociation was monitored for 15 min at either 25° C. or 37° C. (K_D =pM; $T_{1/2}$ =min).

TABLE 2

Antibody	25° C.		37° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
H1M300	399	170	1510	32
H1M309	29.9	7461	537	326
H1M312	0.225	15568	432	392
H1M493	46.5	4921	522	341
H1M494	870	114	2350	30
H1M495	440	222	7500	19
H1M496	254	257	421	118
H1M497	20.1	5801	480	290
H1M498	6400	30	7500	14
H1M499	106	2253	582	316
H1M500	1400	91	6010	15
H1M502	78.3	958	411	151
H1M503	510	118	1880	30
H1M504	3470	35	11200	6
H1M505	2740	42	9200	6
H1M508	138	572	442	139
H1M510	1070	68	3960	10

Equilibrium dissociation constants (K_D) for hPCSK9 binding to mAbs generated via direct isolation of splenocytes were determined by surface kinetics in a real-time biosensor surface plasmon resonance assay (BIA-CORE™ T100). Each selected antibody was captured at a flowrate of 2 μ l/min for 6 min on a goat anti-human IgG polyclonal antibody surface created through direct chemical coupling to a BIA-CORE™ chip to form a captured antibody surface. Human PCSK9-mmh at a concentration of 50 nM or 12.5 nM was injected over the captured antibody surface at a flowrate of 70 μ l/min for 5 min, and antigen-antibody dissociation was monitored for 15 min at either 25° C. or 37° C. (K_D =pM; $T_{1/2}$ =min).

TABLE 3

Antibody	25° C.		37° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
H1H313P	244	230	780	60
H1H314P	3990	65	3560	43
H1H315P	129	151	413	35
H1H316P	377	42	1080	11
H1H317P	30400	137	18600	70
H1H318P	972	59	1690	28
H1H320P	771	28	1930	8
H1H321P	865	106	3360	23
H1H334P	3750	46	15900	8

28

Dissociation rate (kd) of selected mAbs for tagged rhesus monkey (*Macaca mulata*) PCSK9 (mmPCSK9; SEQ ID NO:756) (mmPCSK9-mmh) at 25° C. was determined as described above.

TABLE 4

Antibody	kd (1/s)	$T_{1/2}$ (min)
H1H313P	2.92×10^{-5}	396
H1H318P	3.69×10^{-3}	3
H1H334P	8.06×10^{-3}	1
H1H315P	2.29×10^{-4}	51
H1H316P	2.29×10^{-4}	51
H1H320P	3.17×10^{-4}	36
H1M300	1.52×10^{-4}	76
H1M504	5.04×10^{-4}	23
H1M497	6.60×10^{-5}	175
H1M503	8.73×10^{-5}	132
H1M496	4.45×10^{-5}	260

Example 4

Effect of pH on Antigen Binding Affinity

The effects of pH on antigen binding affinity for CHO cell-produced fully human anti-hPCSK9 mAbs was assessed as described above. The mAbs tested are fully human versions of H1H316P ("316P") (HCVR/LCVR SEQ ID NO: 90/92; CDR sequences SEQ ID NO: 76/78/80 and 84/86/88) and H1M300N ("300N") (HCVR/LCVR SEQ ID NO: 218/226; CDR sequences SEQ ID NO:220/222/224 and 228/230/232). Human PCSK9-myc-myc-his (hPCSK9-mmh) was captured on an anti-myc mAb surface either at a high density (about 35 to 45 resonance units) (RU) or at a low density (about 5 to 14 RU). Each antibody, at 50 nM in HBST (pH 7.4 or pH 5.5) was injected over the captured hPCSK9 surface at a flow rate of 100 μ l/ml for 1.5 min at 25° C. and antigen-antibody dissociation was monitored for 10 min. Control I: anti-hPCSK9 mAb SEQ ID NO:79/101 (WO 2008/063382) (K_D =pM; $T_{1/2}$ =min).

TABLE 5

Antibody	High hPCSK9 Density Surface				Low hPCSK9 Density Surface			
	pH 7.4		pH 5.5		pH 7.4		pH 5.5	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$
316P	191	74	144	83	339	45	188	58
300N	65	507	1180	26	310	119	1380	13
Control I	20000	29	ND	ND	ND	ND	ND	ND

The antigen binding properties of 316P and 300N at pH 7.4 or pH 5.5 were determined by a modified BIA-CORE™ assay as described above. Briefly, mAbs were immobilized onto BIA-CORE™ CM5 sensor chips via amine coupling. Varying concentrations of myc-myc-his tagged hPCSK9, mouse PCSK9 (mPCSK9, SEQ ID NO:757), hPCSK9 with a gain of function (GOF) point mutation of D374Y (hPCSK9 (D374Y), cynomolgus monkey (*Macaca fascicularis*) PCSK9 (mfPCSK9, SEQ ID NO:761) (mfPCSK9), rat (*Rattus norvegicus*) PCSK9 (rPCSK9, SEQ ID NO:763), and his-tagged Syrian golden hamster (*Mesocricetus auratus*) PCSK9 (maPCSK9, SEQ ID NO:762) (maPCSK9), ranging from 11 to 100 nM, were injected over the antibody surface at the flow rate of 100 μ l/ml for 1.5 min and antigen-antibody dissociation was monitored in real time for 5 min

29

at either 25° C. (Table 6) or 37° C. (Table 7). Control II: anti-hPCSK9 mAbs SEQ ID NO:67/12 (WO 2009/026558) (NB: no binding was observed under the experimental condition) (K_D =pM; $T_{1/2}$ =min).

TABLE 6

pH Effect at 25° C.				
Antigen	pH 7.4		pH 5.5	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
316P				
hPCSK9-mmh	1260	36	22	39
mPCSK9-mmh	4460	10	63	11
hPCSK9(D347Y)-mmh	2490	15	166	13
mfPCSK9-mmh	1420	42	8	23
maPCSK9-h	8350	8	87	8
rPCSK9-mmh	24100	2	349	5
300N				
hPCSK9-mmh	1100	76	3100	5
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	1310	46	9030	3
mfPCSK9-mmh	2170	31	38500	0.4
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB
Control I				
hPCSK9-mmh	33100	14	1740	31
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	71000	11	7320	30
mfPCSK9-mmh	362000	0.2	67200	3
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB
Control II				
hPCSK9-mmh	143	266	2	212
mPCSK9-mmh	3500	11	33	12
hPCSK9(D347Y)-mmh	191	155	49	56
mfPCSK9-mmh	102	262	12	63
maPCSK9-h	6500	3	ND	ND
rPCSK9-mmh	22400	2	106	5

TABLE 7

pH Effect at 37° C.				
Antigen	pH 7.4		pH 5.5	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
316P				
hPCSK9-mmh	4000	9	142	11
mPCSK9-mmh	12200	3	13600	3
hPCSK9(D347Y)-mmh	6660	4	1560	5
mfPCSK9-mmh	3770	11	44	5
maPCSK9-h	21700	2	ND	ND
rPCSK9-mmh	55100	2	399	1
300N				
hPCSK9-mmh	2470	20	11900	1
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	2610	14	28000	1
mfPCSK9-mmh	4810	8	65200	0.1
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB

30

TABLE 7-continued

pH Effect at 37° C.				
Antigen	pH 7.4		pH 5.5	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
Control I				
hPCSK9-mmh	45900	0.1	11300	3
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	169000	0.4	27000	3
mfPCSK9-mmh	500000	0.6	5360	0.3
maPCSK9-h	NB	NB	NB	NB
rPCSK9	NB	NB	NB	NB
Control II				
hPCSK9-mmh	284	87	20	44
mPCSK9-mmh	8680	3	89	3
hPCSK9(D347Y)-mmh	251	57	483	26
mfPCSK9-mmh	180	127	214	65
maPCSK9-h	8830	0.5	ND	ND
rPCSK9p-mmh	30200	1	233	1

Example 5

Anti-hPCSK9 mAbs Binding to hPCSK9 with Point Mutation D374Y

The binding affinity of selected anti-hPCSK9 mAbs to hPCSK9 with a gain of function (GOF) point mutation of D374Y (hPCSK9(D374Y)-mmh) was determined as described above. Each antibody was captured at a flowrate of 40 μ l/min for 8-30 sec on a goat anti-human IgG polyclonal antibody surface created through direct chemical coupling to a BIACORE™ chip to form a captured antibody surface. hPCSK9(D374Y)-mmh at varying concentrations of 1.78 nM to 100 nM was injected over the captured antibody surface at a flowrate of 50 μ l/min for 5 min, and the dissociation of hPCSK9(D374Y)-mmh and antibody was monitored for 15 min at 25° C. Control III: anti-hPCSK9 mAbs SEQ ID NO:49/23 (WO 2009/026558) (K_D =pM; $T_{1/2}$ =min).

TABLE 8

Antibody	K_D	$T_{1/2}$
316P	1780	14
300N	1060	49
Control I	23600	25
Control II	66	216
Control III	1020	126

Example 6

Binding Specificity of Anti-hPCSK9 mAbs

316P, 300N, and Control I anti-hPCSK9 mAbs were captured on an amine-coupled anti-hFc CM5 chip on BIA-CORE™2000. Tagged (myc-myc-his) human PCSK9, human PCSK1 (hPCSK1) (SEQ ID NO:759), human PCSK7 (hPCSK7) (SEQ ID NO:760), or mouse PCSK9 were injected (100 nM) over the captured mAb surface and allowed to bind at 25° C. for 5 min. Changes in RU were recorded. Results: 300N and Control I bound only to hPCSK9, and 316P bound both hPCSK9 and mPCSK9.

31

The binding specificities of anti-hPCSK9 mAbs were determined by ELISA. Briefly, anti-hPCSK9 antibody was coated on a 96-well plate. Human PCSK9-mmh, mPCSK9-mmh, maPCSK9-h, hPCSK1-mmh, or hPCSK7-mmh, at 1.2 nM, were added to antibody-coated plates and incubated at RT for 1 hr. Plate-bound PCSK protein was then detected by HRP-conjugated anti-His antibody. Results show that 316P binds human, mouse, and hamster PCSK9, whereas 300N and Control I only bound hPCSK9. None of the anti-hPCSK9 mAbs exhibited significant binding to hPCSK1 or hPCSK7.

Example 7

Cross-Reactivity of Anti-hPCSK9 mAbs

Cross-reactivity of anti-hPCSK9 mAbs with mmPCSK9, mfPCSK9, mPCSK9, maPCSK9, or rPCSK9 was determined using BIACORE™3000. Briefly, anti-hPCSK9 mAbs were captured on an anti-hFc surface created through direct chemical coupling to a BIACORE™ chip. Purified tagged hPCSK9, hPCSK9(D374Y), mmPCSK9, mfPCSK9, mPCSK9, maPCSK9, or rPCSK9, each at 1.56 nM to 50 nM, was injected over the antibody surface at either 25° C. or 37° C. Binding between 316P, 300N, Control I, Control II, or Control III and the PCSK9 proteins was determined (K_D =pM; $T_{1/2}$ =min) (ND=not determined).

TABLE 9

Antigen	316P mAb			
	37° C.		25° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	1800	9	580	36
hPCSK9(D374Y)-mmh	4200	4	1690	15
mmPCSK9-mmh	1800	21	550	92
mfPCSK9-mmh	1800	11	520	60
mPCSK9-mmh	4700	3	2300	11
maPCSK9-h	19000	1	6810	5
rPCSK9-mmh	37500	1	14500	2

TABLE 10

Antigen	300N mAb			
	37° C.		25° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	2400	22	740	110
hPCSK9(D374Y)-mmh	2200	14	900	65
mmPCSK9-mmh	1600	26	610	79
mfPCSK9-mmh	3800	11	1500	45
mPCSK9-mmh	NB	NB	NB	NB
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB

TABLE 11

Antigen	Control I mAb			
	37° C.		25° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	226000	2	27500	16
hPCSK9(D374Y)-mmh	ND	ND	23600	25

32

TABLE 11-continued

Antigen	Control I mAb			
	37° C.		25° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
mmPCSK9-mmh	420000	3	291000	2
mfPCSK9-mmh	14300	10	24900	14
mPCSK9-mmh	NB	NB	NB	NB
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB

TABLE 12

Antigen	Control II mAb			
	37° C.		25° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	91	162	61	372
hPCSK9(D374Y)-mmh	93	90	66	216
mfPCSK9-mmh	33	252	26	546
mPCSK9-mmh	4700	3	2300	11
maPCSK9-h	60800	0.4	25000	2
rPCSK9-mmh	14100	1	6900	3

TABLE 13

Antigen	Control III mAb			
	37° C.		25° C.	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	380	378	490	450
hPCSK9(D374Y)-mmh	130	660	1000	126
mfPCSK9-mmh	110	750	340	396
mPCSK9-mmh	33500	1	10900	4
maPCSK9-h	780	107	2100	67
rPCSK9-mmh	NB	NB	33200	2

Example 8

Inhibition of Binding Between hPCSK9 and hLDLR Domains

The ability of selected anti-hPCSK9 mAbs to block hPCSK9 binding to human LDLR full length extracellular domain (hLDLR-ecto SEQ ID NO:758), hLDLR EGF-A domain (amino acids 313-355 of SEQ ID NO:758), or hLDLR EGF-AB domains (amino acids of 314-393 of SEQ ID NO:758) (LDLR Genbank number NM_000527) was evaluated using BIACORE™ 3000. Briefly, hLDLR-ecto, EGF-A-hFc, or EGF-AB-hFc protein was amine-coupled on a CM5 chip to create a receptor or receptor fragment surface. Selected anti-hPCSK9 mAbs, at 62.5 nM (2.5 fold excess over antigen), were premixed with 25 nM of hPCSK9-mmh, followed by 40 min incubation at 25° C. to allow antibody-antigen binding to reach equilibrium to form equilibrated solutions. The equilibrated solutions were injected over the receptor or receptor fragment surfaces at 2 μ l/min for 40 min at 25° C. Changes in RU due to the binding of the anti-hPCSK9 mAbs to hLDLR-ecto, EGF-A-hFc, or EGF-AB-hFc were determined. Results show that H1H316P and

33

H1M300N blocked the binding of hPCSK9-mmh to hLDLR-ecto, hLDLR EGF-A domain, and hLDLR EGF-AB domains; H1H320P blocked the binding of hPCSK9-mmh to hLDLR-ecto and hLDLR EGF-A domain; and H1H321P blocked the binding of hPCSK9-mmh to hLDLR EGF-A domain.

The ability of the mAbs to block hPCSK9 binding to hLDLR-ecto, hLDLR EGF-A domain, or hLDLR EGF-AB domains was also evaluated with an ELISA-based immunoassay. Briefly, hLDLR-ecto, hLDLR EGF-A-hFc or hLDLR EGF-AB-hFc, each at 2 µg/ml, was coated on a 96-well plate in PBS buffer overnight at 4° C., and nonspecific binding sites blocked with BSA. This plate was used to measure free hPCSK9-mmh in a PCSK9-mmh solution

34

pre-equilibrated with varying concentrations of anti-hPCSK9 mAbs. A constant amount of hPCSK9-mmh (500 pM) was premixed with varied amounts of antibody, ranging from 0 to ~50 nM in serial dilutions, followed by 1 hr incubation at room temperature (RT) to allow antibody-antigen binding to reach equilibrium. The equilibrated sample solutions were transferred to receptor or receptor fragment coated plates. After 1 hour of binding, the plates were washed and bound hPCSK9-mmh detected using HRP conjugated anti-myc antibody. IC₅₀ values (in pM) were determined as the amount of antibody required to achieve 50% reduction of hPCSK9-mmh bound to the plate-coated receptor or receptor fragment. The results show that specific mAbs functionally block PCSK9 from binding the three receptors at both neutral pH (7.2) and acidic pH (5.5).

TABLE 14

Ab	pH 7.2			pH 5.5		
	Plate Coating Surface					
	hLDLR-ecto	EGF-A	EGF-AB	hLDLR-ecto	EGF-A	EGF-AB
316P	<125	<125	<125	<125	<125	<125
300N	144	146	<125	1492	538	447
Control I	—	>100,000	>100,000	—	>100,000	>100,000
Control II	288	510	274	411	528	508
Control III	303	635	391	742	787	1073

The ability of the mAbs to block hPCSK9 GOF mutant hPCSK9(D374Y)-mmh binding to hLDLR EGF-A domain or hLDLR EGF-AB domain (IC₅₀ values in pM) was also evaluated with the ELISA-based immunoassay described above using a constant amount of 0.05 nM hPCSK9 (D374Y)-mmh.

TABLE 15

		pH 7.2		pH 5.5	
		Plate Coating Surface			
		EGF-A	EGF-AB	EGF-A	EGF-AB
40	316P	203	139	1123	1139
45	300N	135	142	3463	3935
	Control I	>100,000	>100,000	>100,000	>100,000
	Control II	72	57	129	118
	Control III	537	427	803	692

The ability of the mAbs to block either mmPCSK9 or mPCSK9 binding to hLDLR-ecto domain, hLDLR EGF-A domain, or hLDLR EGF-AB domain (IC₅₀ values in pM) was evaluated at neutral pH (7.2) with the ELISA-based immunoassay describe above using a constant amount of 1 nM of mmh-tagged mmPCSK9 or 1 nM of mPCSK9.

TABLE 16

	1 nM mmPCSK9-mmh			1 nM mPCSK9-mmh	
	hLDLR-ecto	EGF-A	EGF-AB	EGF-A	EGF-AB
316P	<250	<250	<250	<250	<250
300N	255	256	290	>33000	>33000

35

The ability of the mAbs to block hPCSK9, mmPCSK9, rPCSK9, maPCSK9, mfPCSK9, or mPCSK9 binding to hLDLR EGF-A domain (IC₅₀ values in pM) was evaluated at neutral pH (7.2) (Table 17) acidic pH (5.5, Table 18) with the ELISA-based immunoassay described above using a constant amount of 0.5 nM of hPCSK9-mmh, 1 nM of mmPCSK9-mmh, 1 nM of rPCSK9-mmh, 1 nM of maPCSK9-h, 0.3 nM of mfPCSK9-mmh, or 1 nM of mPCSK9-mmh.

TABLE 17

	hPCSK9	mmPCSK9	rPCSK9	maPCSK9	mfPCSK9	mPCSK9
316P	<125	<250	2662	349	75	305
300N	182	460	>100000	>100000	473	>100000
Control I	—	>100000	>100000	>100000	>100000	>100000
Control II	146	83	2572	2038	361	855
Control III	249	293	>100000	245	572	>100000

TABLE 18

	hPCSK9	mmPCSK9	rPCSK9	maPCSK9	mPCSK9
316P	<125	<250	42880	1299	991
300N	223	3704	>100000	>100000	>100000
Control I	>10000	>100000	>100000	>100000	>100000
Control II	154	<250	11640	8339	2826
Control III	390	376	>100000	414	>100000

The ability of 316P and Control I to block hPCSK9 binding to hLDLR was also determined. Briefly, either recombinant hLDLR or hLDLR-EGFA-mFc was immobilized onto BIACORE™ CM5 chips via amine coupling. An antigen-antibody mixture of 100 nM hPCSK9-mmh and 316P, Control I mAb, or a non-hPCSK9 specific mAb (each at 250 nM) was incubated at RT for 1 hr, and then injected over the hLDLR or hLDLR-EGFA surface at the flow rate of 10 µl/ml for 15 min at 25° C. Changes in RU due to the binding between the free hPCSK9-mmh in the mixture to either hLDLR or hLDLR-EGFA were recorded. The binding of hPCSK9 to either hLDLR or hLDLR-EGFA was completely blocked by 316P and 300N but not by Control I mAb.

Example 9

Epitope Mapping

In order to determine epitope-binding specificity, three chimeric PCSK9-mmh proteins were generated in which specific human PCSK9 domains were substituted with mouse PCSK9 domains. Chimeric protein #1 consists of a mouse PCSK9 pro-domain (amino acid residues 1-155 of SEQ ID NO:757) followed by a human PCSK9 catalytic domain (residues 153-425 of SEQ ID NO:755) and a mouse PCSK9 C-terminal domain (residues 429-694 SEQ ID NO:757) (mPro-hCat-mC-term-mmh). Chimeric protein #2 consists of a human PCSK9 pro-domain (residues 1-152 of SEQ ID NO:755) followed by a mouse PCSK9 catalytic domain (residues 156-428 of SEQ ID NO:757) and a mouse PCSK9 C-terminal (hPro-mCat-mC-term-mmh). Chimeric protein #3 consists of mouse PCSK9 pro-domain and a mouse PCSK9 catalytic domain followed by a human PCSK9 C-terminal domain (residues 426-692 of SEQ ID NO:755) (mPro-mCat-hC-term-mmh). In addition, hPCSK9 with a point mutation of D374Y (hPCSK9 (D374Y)-mmh) was generated.

36

Binding specificity of mAbs to test proteins hPCSK9-mmh, mouse PCSK9-mmh, chimeric proteins #1, #2, and #3, and hPCSK9 (D374Y)-mmh were tested as follows: the mAbs were coated on a 96-well plate overnight at 4° C., then each test protein (1.2 nM) was added to the plate. After 1 hr binding at RT, the plate was washed and bound test protein detected using HRP-conjugated anti-myc polyclonal antibody (++=OD>1.0; +=OD 0.4-1.0; -=OD<0.4).

TABLE 19

	Antibody	hPCSK9	mPCSK9	Chimeric Protein			hPCSK9(D374Y)
				#1	#2	#3	
25	H1M300	++	-	++	+	-	++
	H1M309	++	-	-	-	++	++
	H1M312	++	-	-	-	++	++
	H1M492	++	-	-	-	-	+
	H1M493	++	-	-	-	++	++
	H1M494	++	-	-	+	++	++
30	H1M495	++	-	-	-	++	++
	H1M496	++	-	-	-	++	++
	H1M497	++	-	-	++	+	++
	H1M498	++	-	-	-	+	++
	H1M499	++	-	-	-	++	++
	H1M500	++	-	++	-	-	++
35	H1M502	++	-	-	-	++	++
	H1M503	++	-	-	++	-	++
	H1M504	++	-	-	-	-	+
	H1M505	++	-	++	+	-	++
	H1M508	++	-	-	-	++	++
	H1H318P	++	-	++	-	-	++
40	H1H334P	++	-	++	-	-	++
	H1H316P	++	++	++	++	++	++
	H1H320P	++	-	-	++	-	++
	Control I	++	-	-	-	++	++

Binding specificity of 316P, 300N and control anti-hPCSK9 mAbs to hPCSK9-mmh, mPCSK9-mmh, mmPCSK9-mmh, mfPCSK9-mmh, rPCSK9-mmh, chimeric proteins #1, #2, and #3, and hPCSK9 (D374Y)-mmh were tested as described above except that the protein concentration is 1.7 nM (=-OD<0.7; +=OD 0.7-1.5; ++=OD>1.5).

TABLE 20

	316P	300N	Control I	Control II	Control III
55	hPCSK9-mmh	++	++	++	++
	mPCSK9-mmh	++	-	++	++
	mmPCSK9-mmh	++	++	++	++
	mfPCSK9-mmh	++	++	++	++
	rPCSK9-mmh	++	-	++	+
	Chimeric Protein #1	++	++	-	++
60	Chimeric Protein #2	++	++	-	++
	Chimeric Protein #3	++	+	++	++
	hPCSK9 (D374Y)	++	++	++	++

Similar results for selected mAbs were obtained by BIA-CORE™ binding assay. Briefly, 316P, 300N, or Control I mAb was captured on an amine-coupled anti-hFc CM5 chip and 100 nM of each protein injected over the mAb-captured

37

surface. Changes in RU due to the binding of each protein to the mAb surface was determined.

TABLE 21

Antibody	hPCSK9	mPCSK9	Chimeric Protein		
			#1	#2	#3
316P	500	505	529	451	467
300N	320	13	243	76	10
Control I	65	7	4	3	69

To further assess the binding specificity of 316P, which cross-reacts with mPCSK9-mmh, a cross-competition ELISA assay was developed to determine binding domain specificity. Briefly, mAbs specific for chimeric protein #1, #2, or #3, were first coated on a 96-well plate overnight at 1 µg/ml. Human PCSK9-mmh (2 µg/ml) was then added to each well followed by 1 hr incubation at RT. 316P (1 µg/ml) was added and incubated for another hour at RT. Plate-bound 316P was detected using HRP-conjugated anti-hFc polyclonal antibody. Although 316P binding to hPCSK9-mmh was not affected by the presence of mAbs specific for either chimeric protein #2 or chimeric protein #3, 316P binding to hPCSK9-mmh was greatly reduced by the presence of antibody specific for chimeric protein #1.

Example 10

BIACORE™-Based Antigen Binding Profile Assessment

Antibody binding profiles were also established for 316P, 300N, Control I, II, and III mAbs using BIACORE™ 1000. Briefly, hPCSK9-mmh was captured on an anti-myc surface. A first anti-hPCSK9 mAb (50 µg/ml) was injected over the PCSK9-bound surface for 10 min, at a flow rate of 10 µl/min at 25° C. A second anti-hPCSK9 mAb (50 µg/ml) was then injected over the first mAb-bound surface for 10 min, at a flow rate of 10 µl/min at 25° C. Ability of the first mAb to block binding of the second mAb was measured and is expressed as percent inhibition.

TABLE 22

First mAb	Second mAb				
	316P	300N	Control I	Control II	Control III
316P	100	101	27	99	101
300N	77	100	12	82	-2
Control I	6	12	100	6	9
Control II	91	102	-6	100	3
Control III	73	10	-12	1	100

Example 11

Increase of LDL Uptake by Anti-hPCSK9 Antibodies

The ability of anti-hPCSK9 mAbs to increase LDL uptake in vitro was determined using a human hepatocellular liver carcinoma cell line (HepG2). HepG2 cells were seeded onto 96-well plates at 9×10^4 cells/well in DMEM complete media and incubated at 37° C., 5% CO₂, for 6 hr to form HepG2 monolayers. Human PCSK9-mmh, at 50 nM in lipoprotein deficient medium (LPDS), and a test mAb was added in various concentrations from 500 nM to 0.98 nM in LPDS

38

medium. Data are expressed as IC₅₀ values for each experiment (IC₅₀=antibody concentration at which increases LDL uptake by 50%). In addition, the experiment also showed that both 316P and 300N were able to completely reverse the inhibitory effect of hPCSK9 on LDL uptake, while Control I mAb or H1M508 anti-hPCSK9 mAb reversed the inhibitory effect by about 50%.

TABLE 23

Antibody	IC ₅₀ (nM)
316P	21.30
300N	22.12
Control I	>250
H1M508	>250

The ability of anti-h PCSK9 mAbs to reverse the inhibitory effect on LDL uptake by PCSK9 protein from different mammalian species was also tested in a HepG2 cell line as described above. Briefly, HepG2 cells were incubated overnight with serial dilutions of antibody in LPDS medium (beginning with 500 nM) and 50 nM of hPCSK9-mmh, mfPCSK9-mmh, mPCSK9-mmh, rPCSK9-mmh, or maPCSK9-h. HepG2 cells were also incubated overnight with serial dilutions of antibody in LPDS (beginning with 50 nM) and 1 nM hPCSK9(D374Y). As shown in Table 24, while 316P was able to completely reverse the inhibitory effect on LDL by all PCSK9 proteins tested, 300N was only able to reverse the inhibitory effect on LDL uptake by hPCSK9, hPCSK9 (D374Y), and mfPCSK9. Values are expressed as nM IC₅₀.

TABLE 24

	316P	300N	Control I	Control II	Control III
hPCSK9-mmh	14.1	12.6	>500	13.4	12.4
hPCSK9(D374Y)-mmh	2.1	1.1	>50	0.7	0.6
mfPCSK9-mmh	14.7	13.4	>500	14.2	13.6
mPCSK9-mmh	21.2	>500	>500	19	>500
rPCSK9-mmh	27.7	>500	>500	21.9	>500
maPCSK9-h	14.4	>500	>500	29.5	12.7

Example 12

Neutralization of Biological Effect of hPCSK9 In Vivo

To assess the biological effect of neutralizing PCSK9, hPCSK9 was over-expressed in C57BL/6 mice by hydrodynamic delivery (HDD) of DNA constructs encoding full-length hPCSK9-mmh. 4 mice (C57BL/6) were injected with empty vector/saline (control), and 16 mice were injected with a 50 µg hPCSK9-mmh-DNA/saline mixture in the tail vein equal to 10% of their body weight. At day 7 after HDD, delivery of hPCSK9 resulted in a 1.6-fold elevation of total cholesterol, 3.4-fold elevation in LDL-cholesterol (LDL-C) and a 1.9-fold elevation in non-HDL cholesterol (relative to control). Serum hPCSK9 levels on day 7 were all greater than 1 µg/ml, as assessed by quantitative ELISA.

Administration of H1M300N on day 6 after HDD to 3 experimental groups (1, 5 or 10 mg/kg) (n=4 per group) via intraperitoneal (i.p.) injection resulted in a significant attenuation of serum cholesterol levels. At 18 hours after administration, total cholesterol was reduced by 9.8%, 26.3% and 26.8%, LDL-C was reduced by 5.1%, 52.3% and 56.7%, and

non-HDL cholesterol was reduced by 7.4%, 33.8% and 28.6% in the 1, 5 or 10 mg/kg H1M300N treated groups, respectively.

Example 13

Pharmacokinetic and Serum Chemistry Study in Monkeys

A pharmacokinetic (PK) study was conducted in naïve male cynomolgus monkeys (*Macaca fascicularis*) with a body weight range between 5-7 kg and aged between 3-5 years.

Group Assignments.

The monkeys were assigned into 5 treatment groups: Treatment Group 1 (n=3) received control buffer (10 mM sodium phosphate, pH 6, 1 ml/kg); Treatment Group 2 (n=3) received 1 ml/kg of 316P (5 mg/ml); Treatment Group 3 (n=3) received 1 ml/kg 300N (5 mg/ml); Treatment Group 4 (n=3) received 1 ml/kg 316P (15 mg/ml); and Treatment Group 5 (n=3) received 1 ml/kg 300N (15 mg/ml). All treatments were administered by IV bolus followed by a 1 ml saline flush. Total dose volume (ml) was calculated on the most recent body weight (each animal was weighed twice during acclimation and once weekly throughout the study). A single dose of test mAb or buffer control was administered on Day 1.

Animal Care.

Animals were housed in a temperature- and humidity-monitored environment. The targeted range of temperature and relative humidity was between 18-29° C. and 30-70%, respectively. An automatic lighting system provided a 12-hour diurnal cycle. The dark cycle could be interrupted for study- or facility-related activities. The animals were individually housed in cages that comply with the Animal Welfare Act and recommendations set forth in The Guide for the Care and Use of Laboratory Animals (National Research Council 1996).

Diet and Feeding.

Animals were fed twice per day according to SNBL USA SOPs. Animals were fasted when required by specific procedures (e.g., prior to blood draws for serum chemistry, urine collection, or when procedures involving sedation are performed). The diet was routinely analyzed for contaminants and found to be within manufacturer's specifications. No contaminants were expected to be present at levels that would interfere with the outcome of the study.

Experimental Design.

An appropriate number of animals were selected from SNBL USA stock. Animals were examined for health by veterinary staff, and had undergone serum chemistry, hematology, and coagulation screening. Sixteen males, confirmed healthy, were assigned to the study. Fifteen males were assigned to specific study groups and the remaining animal was available as a spare. A stratified randomization scheme incorporating serum cholesterol level (based on the average of two draws in acclimation) was used to assign animals to study groups.

Acclimation Period.

Previously quarantined animals were acclimated to the study room for a minimum of 14 days prior to initiation of dosing. Acclimation phase data was collected from all animals, including the spare. All animals were assessed for behavioral abnormalities that could affect performance on study. The spare animal was returned to stock after day 1.

Blood Collection.

Blood was collected by venipuncture from a peripheral vein from restrained, conscious animals. Whenever possible, blood was collected via a single draw and then divided appropriately.

PK Study.

Blood samples (1.5 ml) were collected at pre-dose, 2 min, 15, min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 24 hr, and subsequently once every 24 hr in serum separator tubes (SST). Specimen storage serum is transferred to 2 vials and stored at -60° C. or below.

Serum samples were analyzed using an optimized ELISA (enzyme-linked immunosorbant assay) procedure. Briefly, a microtiter plate was first coated with hPCSK9-mmh. Test mAb 316P or 300N was then captured on the hPCSK9-mmh plate. The captured 316P or 300N was detected using a biotinylated mouse anti-hIgG4 followed by binding to NeutrAvidin-HRP. Varying concentrations of 316P or 300N, ranging from 100 to 1.56 ng/ml, were used as standards. One percent monkey serum (assay matrix) in the absence of 316P or 300N was used as the zero (0 ng/ml) standard. The results, shown in FIG. 2, indicate a dose-dependent increase in serum 316P and 300N levels. PK parameters were analyzed using WinNonlin software (Noncompartmental analysis, Model 201—IV bolus administration).

TABLE 25

PK Parameter	316P		300N	
	5 mg/kg	15 mg/kg	5 mg/kg	15 mg/kg
T _{max} (h)	0.428	0.105	4.02	0.428
C _{max} (µg/ml)	184	527	226	1223
T _{1/2} (h)	83	184	215	366

Serum Chemistry.

Blood samples were collected at pre-dose, 12 hr, 48 hr, and subsequently once every 48 hr, for clinical chemistry analysis, in particular lipid profiles (i.e. cholesterol, LDL-C, HDL-C, triglycerides). With the exception of the 12 hr post-dose sample, all animals were subject to an overnight fast prior to sample collection. The sample volume was approximately 1 ml. Chemistry parameters were determined using an Olympus automated analyzer. Parameters measured (Xybio code): Albumin (ALB); Alkaline Phosphatase (ALP); Alanine Aminotransferase (ALT); Aspartate Transaminase (AST); Total Bilirubin (TBIL); Calcium (Ca); Total Cholesterol (TChol); Creatine Kinase (CK); Creatinine (CRN); Gamma Glutamyltransaminase (GGT); Glucose (GLU); Inorganic Phosphorus (IP); Total Protein (TP); Triglyceride (TRIG); Blood Urea Nitrogen (BUN); Globulin (GLOB); Albumin/Globulin Ratio (A/G); Chloride (Cl); Potassium (K); Sodium (Na); LDL and HDL cholesterol. Residual serum was stored at -20° C. or below and disposed of no sooner than one week after analysis.

Results from samples through Day 105 post-dose time point are shown in FIGS. 3-7. There was a reduction in total cholesterol and LDL-C in animals receiving 316P and 300N, regardless of dose, within 24 hours of the first dose. Serum total cholesterol reduced rapidly and robustly (~35%, FIG. 3). A robust decrease of ~80% was seen in LDL-C (FIGS. 4-5) by day 6. In animals that received a 15 mg/kg dose of 300N, the reduction in both total cholesterol (~10-15% reduction) and LDL-C (~40% reduction) continued to at least day 80 of the study. In addition, HDL-C was elevated in animals that received 316P at 15 mg/kg (FIG. 6). Animals that received a higher dose (15 mg/kg) of either 316P or

300N also showed a reduction in triglycerides during the course of study (FIG. 7). 316P exhibited maximal suppression of LDL-C levels of up to 80% relative to baseline. The length of this suppression was dose-dependent with at least 60% suppression (relative to baseline LDL-C levels) lasting approximately 18 days (5 mg/kg dose) and approximately 45 days (15 mg/kg dose). 300N exhibits a distinct pharmacodynamic profile from 316P. LDL-C suppression by 300N was sustained for a much longer period of time at comparable doses (50% LDL-C suppression for 28 days following a 5 mg/kg dose and 50% LDL-C suppression for approximately 90 days following a 15 mg/kg dose). There was little or no measurable change in liver function as determined by ALT and AST measurements. All animals receiving an anti-PCSK9 antibody in the study exhibited a rapid suppression of LDL-C and total cholesterol.

A similar LDL-C lowering effect of 316P and 300N was also observed in cynomolgous monkeys that received a single subcutaneous (SC) administration of either 5 mg/kg 316P or 5 mg/kg 300N (FIG. 8). Both 316P and 300N dramatically suppressed LDL-C levels and maintained an LDL-C lowering effect for approximately 15 and 30 days, respectively (FIG. 8). The pharmacodynamic effect (approximately 40% LDL-C suppression) approximately correlates with functional antibody levels in monkey serum (FIG. 9). As antibody levels decrease below 10 µg/ml, LDL-C suppression appeared to diminish as well. In addition, 300N demonstrated a substantially longer circulating half-life than 316P and hence a longer observed LDL-C suppression.

TABLE 26

PK Parameter	316P	300N
T_{max} (h)	60	84
C_{max} (µg/ml)	46	63
$T_{1/2}$ (h)	64	286

Example 14

Attenuation of LDL Receptor Degradation by Anti-hPCSK9 Antibodies

To assess the biological effect of PCSK9 on hepatic LDL receptor levels and subsequent effects on serum LDL-C levels, hPCSK9 was administered to mice expressing hPCSK9 but not mPCSK9 (PCSK9^{hu/hu} mice) by intravenous injection. Specifically, PCSK9^{hu/hu} mice were injected with PBS (control), or 1.2 mg/kg hPCSK9-mmh via the tail vein. Six hours after delivery of hPCSK9, a 1.4-fold elevation (relative to baseline level) in total cholesterol and a 2.3-fold elevation in LDL-C in serum were observed. Analysis of hepatic LDL receptor levels in a separate cohort (n=3) of animals 4 hours after hPCSK9 administration revealed a significant reduction in detectable LDL receptor in liver homogenates.

To assess the biological effect of anti-hPCSK9 on hepatic LDL receptor levels and subsequent effects on serum LDL-C levels, 316P and a non-hPCSK9 specific mAb were administered to PCSK9^{hu/hu} mice at equivalent dose (5 mg/kg i.p.) 20 hours prior to the hPCSK9-mmh protein injection described above. Four hours after the hPCSK9 administration, mice were sacrificed and a total of eight tissues (liver, brain, lung, kidney, heart, ileum, adrenal, and pancreas) were collected and levels of LDL receptor were determined

by Western blot. Changes in LDL receptor levels were only observed in liver. In comparison to PBS control dosing, administration of 316P significantly blocked the PCSK9-mediated increases in total cholesterol and LDL cholesterol (LDL-C=2.49 mg/dl at baseline and 3.1 mg/dl 6 hours after PCSK9; a 25% increase compared to 135% with vehicle). Prior administration of the non-hPCSK9 specific mAb blocked LDL-C increases by approximately 27% from PBS alone (LDL-C=4.1 mg/dl compared to PBS 5.6 mg/dl). Analysis of LDL receptor levels in a separate cohort of mice (n=3 per treatment group) revealed a significant reduction in LDL receptor levels with PCSK9 administration, which was blocked by 316P but not by the non-hPCSK9 specific mAb (FIG. 10).

Effect of different doses of 316P was also evaluated in PCSK9^{hu/hu} mice with both elevated LDL-C and elevated hPCSK9 levels. PCSK9^{hu/hu} mice were first placed on a high carbohydrate diet for 8 weeks, resulting in a ~2-fold elevation in both LDL-C and hPCSK9 levels. Either 316P or a non-hPCSK9 specific mAb, each at 1 mg/kg, 5 mg/kg, or 10 mg/kg, were administered to the mice. Sera were collected 24 hours later and LDL-C levels were analyzed. 316P was effective in decreasing LDL-C levels in a dose-dependent manner (FIG. 11). In addition, 316P administered at a dose of 10 mg/kg, rapidly reduced LDL-C levels back to original (pre-diet) values within 24 hours.

Example 15

Mouse PK Studies

A PK study was conducted in 6-week-old C57BL/6 mice and 11-15 week old hPCSK9 heterozygous mice. A single injection of Control I, 316P, or 300N, each at 10 mg/kg, was administered SC. Serum bleeds were measured for hIgG levels at 0 hr (pre-bleed), 6 hr, day 1, 3, 6, 10, 14, 21, 28, 35, 42 and 56, for a total of 12 time points, using an anti-hFc capture and anti-hFc detection sandwich ELISA (FIGS. 12 and 13). All mAbs achieved their T_{max} at approximately 3 days with corresponding C_{max} levels of approximately 47-115 µg/ml for C57BL/6 mice and 55-196 µg/ml for hPCSK9 heterozygous mice. At Day 56, Control I mAb levels were about 12 µg/ml and 300N levels were about 11 µg/ml whereas 316P levels were about less than 0.02 µg/ml in C57BL/6 mice. At Day 56 in hPCSK9 heterozygous mice, Control I mAb levels were about 29 µg/ml, while both 300N and 316P levels were below the quantifiable limit (BQL) of 0.02 µg/ml.

Example 16

Anti-hPCSK9 Antibody Binding to Mutant/Variant hPCSK9

To further assess binding between hPCSK9 and anti-hPCSK9 mAbs, 21 variant hPCSK9 proteins in which each variant contained a single point mutation and two variant hPCSK9 proteins each contained a double mutation were generated. Each selected antibody was captured on a F(ab')₂ anti-hIgG surface created through direct chemical coupling to a BIACORE™ chip to form a captured antibody surface. Each mmh-tagged variant hPCSK9 at varying concentrations from 100 nM to 25 nM was then injected over the captured antibody surface at a flowrate of 60 µl/min for 240 sec, and the dissociation of variant hPCSK9 and antibody was monitored in real time for 20 min at 25° C. nb: no

binding was observed under these experimental conditions (K_D =M $\times 10^{-9}$; $T_{1/2}$ =min; WT=wildtype).

ELISA-based immunoassay. Anti-PCSK9 mAbs were coated on a 96-well plate overnight at 4° C. Each mmh-

TABLE 27

	316P		300N		Control I		Control II		Control III	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$
WT	1.00	37	0.69	120	30.6	16	0.10	333	0.60	481
P70A	1.42	32	1.68	80	19.0	16	0.24	168	0.90	325
S127R	2.40	36	1.87	110	25.0	18	0.26	288	0.55	550
D129G	1.27	36	1.40	88	22.9	18	0.19	257	0.75	445
S147F	1.29	32	9.07	24	21.1	15	0.22	178	0.23	1468
S153R	5.64	4	0.56	141	36.6	17	0.09	322	3.33	60
E159R	6.96	5	0.82	94	31.7	16	0.08	350	2.97	68
T162R	0.98	43	0.58	140	29.0	17	0.09	322	0.48	362
D192R	1.35	28	0.75	119	30.2	15	0.09	326	nb	nb
R194E	0.38	71	0.65	129	31.4	16	0.07	389	nb	nb
E197R	1.42	27	0.67	115	30.2	17	0.09	339	nb	nb
R215H	0.86	41	1.03	98	37.8	17	0.65	49	0.74	272
R215E	0.90	43	1.81	77	44.0	16	4.48	12	0.78	276
F216L	1.83	32	0.99	121	21.2	15	1.35	39	0.33	880
R237E	2.48	15	1.03	109	29.6	15	0.07	481	5.89	43
D238R	410	1	0.78	123	25.9	19	0.24	144	0.14	1273
A341R	1.54	21	0.34	190	28.7	18	0.08	340	0.88	200
D343R	7.88	6	1.18	89	27.0	16	0.08	402	4.13	66
R357H	6.26	30	6.53	66	26.4	13	0.63	165	1.91	896
E366K	2.92	13	36.0	2	28.8	18	0.46	69	0.38	808
D374Y	2.04	15	0.66	83	25.0	17	0.08	285	1.02	161
V380M	0.48	63	2.82	28	25.9	17	0.15	177	0.35	711
P70A, S147F	1.18	34	7.87	24	23.5	18	0.23	164	0.79	348
E366K, V380M	3.33	12	78.3	1	25.5	18	0.59	60	0.52	551

The results show that when residue D238 was mutated, the binding affinity of 316P for hPCSK9 was reduced >400-fold, from a K_D of 1×10^{-9} M to 410×10^{-9} M; and $T_{1/2}$ shortened about 30-fold, from 37 to 1 min, indicating that 316P binds an epitope on hPCSK9 comprising D238 of hPCSK9 (SEQ ID NO:755). Additionally, BIACORE™ assays show that 316P binding affinity and $T_{1/2}$ were reduced about 5- to 10-fold when a residue at 153, 159 or 343 was mutated. Specifically, K_D was reduced from about 1×10^{-9} M to between about $5-8 \times 10^{-9}$ M when any one of S153, E159 or D343 were mutated; while $T_{1/2}$ was decreased from about 37 min to between about 4-6 min.

300N binding to hPCSK9 was reduced about 50-fold when the residue at position 366 was mutated, resulting in a decreased K_D of from about 0.7×10^{-9} M to about 36×10^{-9} M and a shorter $T_{1/2}$ from about 120 to 2 min. These results indicate that 300N binds an epitope on hPCSK9 comprising E366 of hPCSK9 (SEQ ID NO:755). Additionally, the BIACORE™ assays show that 300N binding affinity and $T_{1/2}$ were reduced between 2- to >10-fold when a residue at 147 or 380 was mutated. Specifically, K_D was reduced from about 0.69×10^{-9} M to between about $2-9 \times 10^{-9}$ M when any of S147 or V380 were mutated; while $T_{1/2}$ was shortened from about 120 min to between about 24-66 min. Compared to 316P, 300N binding to hPCSK9 was not reduced by a mutation at residue 238.

In contrast, Control I antibody did not exhibit an altered binding affinity or $T_{1/2}$ in response to any of the positional mutations tested; Control II antibody exhibited a 40-fold decreased affinity when residue 215 was mutated (R215E) (from $\sim 0.1 \times 10^{-9}$ to $\sim 4.5 \times 10^{-9}$), and $T_{1/2}$ was about 27-fold shorter (from ~ 333 to 12 min); while Control III antibody exhibited a decreased affinity when residue 237 was mutated (K_D decreased from $\sim 0.6 \times 10^{-9}$ to $\sim 5.9 \times 10^{-9}$, and $T_{1/2}$ decreased from ~ 481 to ~ 43 min).

Binding specificity of 316P, 300N, and control anti-hPCSK9 mAbs to hPCSK9 variants was tested using an

tagged variant hPCSK9 in CHO-k1 transient transfection lysate supernatants was added to the antibody-coated plate at various concentrations ranging from 0 to 5 nM. After 1 hr binding at RT, the plate was washed and bound variant hPCSK9 was detected using HRP-conjugated anti-myc polyclonal antibody (−OD<0.7; +OD 0.7-1.5; ++OD>1.5).

TABLE 28

hPCSK9 or Variant	316P	300N	Control I	Control II	Control III
hPCSK9(WT)	++	++	++	++	++
hPCSK9(S127R)	++	++	++	++	++
hPCSK9(D129G)	++	++	++	++	++
hPCSK9(S153R)	++	++	++	++	++
hPCSK9(R215H)	++	++	++	++	++
hPCSK9(F216L)	++	++	++	++	++
hPCSK9(R237E)	++	++	++	++	++
hPCSK9(D238R)	−	++	++	++	++
hPCSK9(A341R)	++	++	++	++	++
hPCSK9(D343R)	++	++	++	++	++
hPCSK9(R357H)	++	++	++	++	++
hPCSK9(E159R)	++	++	++	++	++
hPCSK9(T162R)	++	++	++	++	++
hPCSK9(D192R)	++	++	++	++	−
hPCSK9(R194E)	++	++	++	++	−
hPCSK9(E197R)	++	++	++	++	−
hPCSK9(R215E)	++	++	++	++	++
hPCSK9(P70A)	++	++	++	++	++
hPCSK9(S147F)	++	++	++	++	++
hPCSK9(E366K)	++	+	++	++	++
hPCSK9(V380M)	++	++	++	++	++
hPCSK9(P70A, S147F)	++	++	++	++	++
hPCSK9(E366K, V380M)	++	+	++	++	++

Example 17

Effect of 316P on Normolipemic and Hyperlipemic Hamster

The ability of anti-PCSK9 mAb 316P to reduce serum LDL-C was tested in normolipemic or hyperlipemic Gold Syrian hamsters (*Mesocricetus auratus*). Male Syrian Hamsters, age 6-8 weeks, weighing between 80-100 grams, were allowed to acclimate for a period of 7 days before entry into the study. All animals were placed on either a standard chow diet or a hyperlipemic diet of chow supplemented with 0.1% cholesterol and 10% coconut oil. The 316P mAb was delivered to hamsters by a single subcutaneous injection at doses of 1, 3, or 10 mg/kg for normolipemic hamsters and at doses of 3, 10, or 30 mg/kg for hyperlipemic hamsters. Serum samples were taken from all groups at 24 hr and 7, 14, and 22 days post injection, at which time serum lipid levels were assessed and compared to baseline levels taken 7 days prior to the administration of the mAbs. Circulating total cholesterol and LDL-C in normolipemic hamsters was significantly reduced in a dose-dependent manner compared to vehicle injection. As shown in FIG. 14, administration of 316P effectively reduced LDL-C levels by up to 60% seven days post injection at the highest dose (10 mg/kg) tested. Similar cholesterol reducing effect of 316P was not observed in hyperlipemic hamsters.

Example 18

A Randomized, Double-Blind, Placebo-Controlled, Ascending Single-to-Multi-Dose Study of the Safety, Tolerability, and Bioeffect of Subcutaneously Administered Human Anti-PCSK9 Antibody in Patients with and without Concomitant Atorvastatin

The objective of this study was to determine whether a fully human monoclonal antibody to PCSK9 (mAb316P) is

effective and safe as either a primary or adjunctive agent to lower LDLc in patients with Heterozygous Familial Hypercholesterolemia (HeFH) or other forms of primary hypercholesterolemia (nonFH).

This study was a randomized, double-blind, placebo-controlled, multiple ascending dose clinical trial enrolling 61 adults with either documented HeFH (n=21) or nonFH (n=30), on diet plus stable atorvastatin therapy (atorvaRx) or nonFH (n=10) on diet alone. Subjects on stable atorvastatin therapy had LDLc ≥ 2.6 mmol/L and those on diet alone had LDLc ≥ 3.4 mmol/L. mAb316P at doses of 50, 100 and 150 mg was administered subcutaneously (sc) at 1, 29 and 43 days. The primary endpoint was the incidence and severity of treatment emergent adverse events (TEAE). The primary efficacy endpoint was percent and absolute change in serum LDLc from baseline to each visit. Additional endpoints included apolipoprotein (apo) B, total cholesterol, HDLc, VLDLc, and the ratio of apoB to apoA1.

109 patients were screened, and 61 patients were randomized (14 placebo, 47 mAb316P) with 100% completing 148+/-7 days of treatment and follow up. Compared to the nonFH cohort, the FH group was younger (mean 40 vs 52 yrs), had more males (81% vs 57%) and was on higher doses of atorvastatin (52% on 40 mg vs 3%). Baseline LDLc was 3.45, 2.88 and 4.46 mmol/L respectively in the FH, nonFH atorvaRx and nonFH diet only groups respectively. Response to mAb316P (expressed as percent change in calculated serum LDL-C from baseline to each visit) is shown Tables 29 and 30. Treatment with mAb316P resulted in mean % reductions in LDLc on top of statins on day 57 of 35.6%, 50.2% and 57.5% at the 50, 100 and 150 mg doses, respectively, in the combined FH and nonFH populations. There did not appear to be differences in response between FH and nonFH or those on or not on statin therapy.

Favourable changes were also observed in HDLc and apoA1. No serious adverse events were seen and treatment was generally well tolerated. No drug-related adverse effects were seen on liver function testing or other laboratory parameters.

TABLE 29

Percent Change in Calculated Serum LDL-C From Baseline to Each Visit*								
Ab Dose: patients:	FH Patients on Atorvastatin				Non-FH Patients on Atorvastatin			
	PBO# (N = 6)	50 mg (N = 5)	100 mg (N = 5)	150 mg (N = 5)	PBO# (N = 6)	50 mg (N = 8)	100 mg (N = 8)	150 mg (N = 8)
Baseline	—	—	—	—	—	—	—	—
Day 1	—	—	—	—	—	—	—	—
Visit 5	2.03	-0.42	-7.50	-5.88	3.16	-8.98	-10.09	-14.29
Day 2	(6.119)	(4.603)	(6.084)	(10.366)	(9.748)	(5.819)	(11.047)	(8.751)
Visit 6	0.39	-4.81	-20.91	-15.21	5.67	-21.28	-27.27	-21.00
Day 3	(7.522)	(7.306)	(10.160)	(11.538)	(8.135)	(5.678)	(16.699)	(14.256)
Visit 7	-2.79	-30.44	-50.96	-40.81	-6.62	-43.13	-56.95	-46.81
Day 8 ± 3	(5.318)	(10.776)	(16.227)	(20.082)	(8.384)	(6.406)	(19.049)	(19.233)
Visit 8	6.36	-31.42	-53.67	-52.95	4.48	-38.71	-54.36	-62.00
Day 15 ± 3	(19.607)	(18.218)	(12.128)	(17.130)	(7.389)	(11.028)	(7.819)	(16.531)
Visit 9	10.20	-4.99	-21.07	-27.03	-0.63	-2.24	-11.48	-17.64
Day 29 ± 3	(14.274)	(9.479)	(16.407)	(21.567)	(13.983)	(16.704)	(20.396)	(14.132)
Visit 10	1.86	-32.31	-47.59	-44.47	7.54	-30.88	-50.53	-55.72
Day 43 ± 3	(14.283)	(15.685)	(13.104)	(27.321)	(10.473)	(13.053)	(10.389)	(11.393)
Visit 11	3.45	-39.26	-53.64	-55.80	5.84	-33.36	-48.04	-58.52
Day 57 ± 3	(9.693)	(8.294)	(12.404)	(15.596)	(14.883)	(8.700)	(9.366)	(17.918)
Visit 12	2.30	-9.02	-19.17	-23.24	3.54	-2.77	-13.80	-15.84
Day 71 ± 3	(18.929)	(7.955)	(16.643)	(29.233)	(17.026)	(11.065)	(25.640)	(13.593)
Visit 13	-1.70	-2.72	-7.04	-9.82	10.90	-2.01	9.18	6.66
Day 85 ± 3	(14.163)	(16.512)	(15.835)	(21.450)	(23.826)	(10.720)	(28.556)	(14.575)
Visit 14	4.93	5.76	-1.76	4.32	4.62	1.23	-2.53	14.77
Day 99 ± 3	(18.181)	(10.957)	(9.717)	(20.651)	(16.912)	(16.703)	(13.430)	(16.167)
Visit 15	0.21	2.29	0.36	8.26	-0.92	1.76	0.89	13.06

TABLE 29-continued

Ab Dose: patients:	Percent Change in Calculated Serum LDL-C From Baseline to Each Visit*							
	FH Patients on Atorvastatin				Non-FH Patients on Atorvastatin			
	PBO# (N = 6)	50 mg (N = 5)	100 mg (N = 5)	150 mg (N = 5)	PBO# (N = 6)	50 mg (N = 8)	100 mg (N = 8)	150 mg (N = 8)
Day 120 ± 3	(17.738)	(7.043)	(14.954)	(50.237)	(23.154)	(12.863)	(13.837)	(16.902)
Visit 16	4.67	-3.02	5.32	4.23	1.79	5.40	8.63	12.43
Day 148 ± 3	(18.920)	(6.420)	(21.592)	(35.706)	(28.237)	(17.012)	(21.463)	(19.139)

#PBO = placebo

*Values represent Mean percent change from baseline (Standard Deviation)

TABLE 30

Ab Dose: patients:	Percent Change in Calculated Serum LDL-C From Baseline to Each Visit*					
	FH and Non-FH Patients on Atorvastatin, Combined				Non-FH Patients Not on Atorvastatin	
	PBO# (N = 12)	50 mg (N = 13)	100 mg (N = 13)	150 mg (N = 13)	PBO# (N = 2)	150 mg (N = 8)
Baseline	—	—	—	—	—	—
Day 1	—	—	—	—	—	—
Visit 5	2.60	-5.69	-9.10	-11.05	7.13	-7.28
Day 2	(7.782)	(6.753)	(9.233)	(9.930)	(2.911)	(4.156)
Visit 6	3.03	-14.94	-24.82	-18.78	11.64	-11.37
Day 3	(7.963)	(10.302)	(14.403)	(13.097)	(2.323)	(7.661)
Visit 7	-4.70	-38.25	-54.65	-44.50	12.52	-41.59
Day 8 ± 3	(6.985)	(10.193)	(17.567)	(18.959)	(13.260)	(13.106)
Visit 8	5.42	-35.90	-54.09	-58.52	2.75	-44.68
Day 15 ± 3	(14.161)	(13.971)	(9.209)	(16.681)	(17.896)	(15.461)
Visit 9	4.79	-3.30	-15.17	-21.25	15.09	-38.57
Day 29 ± 3	(14.610)	(13.952)	(18.867)	(17.152)	(20.319)	(14.306)
Visit 10	4.70	-31.43	-49.40	-51.39	4.71	-50.88
Day 43 ± 3	(12.304)	(13.488)	(11.064)	(18.893)	(6.661)	(11.674)
Visit 11	4.64	-35.63	-50.19	-57.47	6.09	-54.41
Day 57 ± 3	(12.040)	(8.717)	(10.513)	(16.439)	(28.082)	(12.175)
Visit 12	2.92	-5.17	-15.86	-18.68	16.05	-42.16
Day 71 ± 3	(17.177)	(10.126)	(21.982)	(20.167)	(25.084)	(29.771)
Visit 13	4.60	-2.28	2.94	0.32	14.58	-30.13
Day 85 ± 3	(19.813)	(12.572)	(25.034)	(18.627)	(7.290)	(21.347)
Visit 14	4.78	2.98	-2.23	10.75	7.50	-11.83
Day 99 ± 3	(16.742)	(14.423)	(11.698)	(17.963)	(12.321)	(18.493)
Visit 15	-0.35	1.97	0.68	11.21	25.69	-8.36
Day 120 ± 3	(19.674)	(10.636)	(13.649)	(31.840)	(14.125)	(7.430)
Visit 16	3.23	2.16	7.35	9.28	-6.29	-0.74
Day 148 ± 3	(22.965)	(14.168)	(20.662)	(25.611)	(15.014)	(13.169)

#PBO = placebo

*Values represent Mean percent change from baseline (Standard Deviation)

It can be concluded from this study that mAb316P is an effective therapeutic option for patients with heFH or non-FH, with elevated cholesterol, on statin therapy or on diet alone.

Example 19

Therapeutic Dose Determination of an Anti-PCSK9 Antibody to Treat Hypercholesterolemia

Background

Patient treatment guidelines for dyslipidemia strive to reduce low density lipoprotein cholesterol (LDL-C) levels to goals of ≤ 100 mg/dL or ≤ 70 mg/dL depending on the level of cardiovascular disease risk. Most patients will require ~50% reduction in LDL-C to reach those goals. Despite dramatic reductions in heart disease associated with existing standard-of-care (including statins), substantial proportions of high-risk patients do not attain LDL-C goals. In phase 2 studies of a monoclonal antibody to proprotein convertase

subtilisin/kexin type 9, (mAb316P) 150 mg delivered via single 1 mL subcutaneous injection every 2 weeks (Q2W) demonstrated LDL-C reductions (Least Squares means) independent of baseline levels ranging from 66.2% to 72.4%. The various dosing regimens investigated exhibited a range of LDL-C reductions. Therefore, in this Example, a dose-response modeling analysis was performed to estimate a dose which would lead to ~50% reduction in LDL-C.

Methods

Dose response modeling was performed using a Multiple Comparison Procedures-Modeling approach on Q2W (i.e., once every two week) doses from a double-blind, parallel-group, placebo-controlled, multicenter, dose-ranging clinical trial in patients with LDL-C ≥ 100 mg/dL on stable statin therapy. Three types of candidate dose-response models (linear, umbrella, logistic with 4 model shapes) were fitted to the data.

Results

Based on the selected logistic model, the 75 mg dose is expected to provide a difference vs placebo in percent

LDL-C change from baseline of -49.2% with a 95% confidence interval of [-57.4%; -40.9%]. In prior phase 2 studies (N=274 patients, doses ranging from 50 to 300 mg), the most common adverse events (AEs) were mild injection site reactions with no observed liver or muscle cell toxicity; 7 serious AEs occurred: 4 treatment-related, 1 non-treatment-related, 2 in the placebo group.

CONCLUSION

Phase 3 studies of mAb316P in a range of hypercholesterolemic populations will include evaluation of a starting

dose of 75 mg Q2W to provide ~50% reduction in LDL-C, with flexibility for up-titration to 150 mg Q2W for patients who require higher doses to achieve LDL-C goals.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 763

<210> SEQ ID NO 1

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 1

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tctgtgcag cctctggatt tactctaagt agttacgaca tgcactgggt ccgccaatct      120
acaggaaaag gtctggagtg ggtctcagct attggttcta ccggtgacac atactatcca      180
ggctccgtga agggccgatt caccatcacc agagaaaaag ccaagaactc cgtgtatctt      240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgtaag agaggggtgg      300
gagggtaccct ttgactactg gggccaggga accctgggtca ctgtctcctc a          351
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<210> SEQ ID NO 2

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 2

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Gln Val Gln Leu Val Gln 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 Leu Ser Ser Tyr
 20             25             30
Asp Met His Trp Val Arg Gln Ser Thr Gly Lys Gly Leu Glu Trp Val
 35             40             45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
 50             55             60
Gly Arg Phe Thr Ile Thr Arg Glu Lys Ala Lys Asn Ser Val Tyr Leu
 65             70             75             80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Val
 85             90             95
Arg Glu Gly Trp Glu Val Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100            105            110
Val Thr Val Ser Ser
115
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<210> SEQ ID NO 3

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 3

ggatttactc taagtagtta cgac

24

<210> SEQ ID NO 4

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 4

Gly Phe Thr Leu Ser Ser Tyr Asp

1 5

<210> SEQ ID NO 5

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 5

attggttcta ccggtgacac a

21

<210> SEQ ID NO 6

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 6

Ile Gly Ser Thr Gly Asp Thr

1 5

<210> SEQ ID NO 7

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 7

gtaagagagg ggtgggaggt accctttgac tac

33

<210> SEQ ID NO 8

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 8

Val Arg Glu Gly Trp Glu Val Pro Phe Asp Tyr

1 5 10

<210> SEQ ID NO 9

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 9

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gacatccaga tgaccagtc tccagccacc ctgtctgtgt ctccagggga aagagccgcc      60
ctctctctgca gggccagtca gagggttagc agcaacttag cctggtagca ccagaaacct      120
ggccaggctc ccaggctect catctatggt gcattccacca gggccactgg tatccagcc      180
aggttcagtg gcattggggtc tgggacagag ttcactctca ttatcagcag cctgcagtct      240
gaagattttg cattttatct ctgtcagcag tataataact ggcctccatt cactttcggc      300
cctgggacca aggtggagat caaacga                                           327

```

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<210> SEQ ID NO 10
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 10

```

```

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

```

```

<210> SEQ ID NO 11
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 11

```

```

cagagtgtta gcagcaac

```

18

```

<210> SEQ ID NO 12
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 12

```

```

Gln Ser Val Ser Ser Asn
 1             5

```

```

<210> SEQ ID NO 13
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 13

```

```

ggtgcatcc

```

9

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<210> SEQ ID NO 14
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 14

Gly Ala Ser
 1

<210> SEQ ID NO 15
 <211> LENGTH: 30
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 15

cagcagtata ataactggcc tccattcact

30

<210> SEQ ID NO 16
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 16

Gln Gln Tyr Asn Asn Trp Pro Pro Phe Thr
 1 5 10

<210> SEQ ID NO 17
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 17

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt tactctaagt agttacgaca tgcactgggt ccgccaatct 120
 acaggaaaag gtctggagtg ggtctcagct attggttcta ccggtgacac atactatcca 180
 ggctccgtga agggccgatt caccatcacc agagaaaaag ccaagaactc cgtgtatctt 240
 caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgtaag agaggggtgg 300
 gaggtaccct ttgactactg gggccaggga accctggtca ccgtctctc a 351

<210> SEQ ID NO 18
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 18

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 Leu Ser Ser Tyr
 20 25 30

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

-continued

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

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

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

Arg Glu Gly Trp Glu Val Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 19
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 19

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccgcc	60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtagca ccagaaacct	120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc	180
aggttcagtg gcattgggctc tgggacagag ttcactctca ttatcagcag cctgcagtct	240
gaagattttg cattttattt ctgtcagcag tataataact ggctccatt cactttcggc	300
cctgggacca aagtgatat caaa	324

<210> SEQ ID NO 20
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 20

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

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

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

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Ala Phe Tyr Phe Cys Gln Gln Tyr Asn Asn Trp Pro Pro
 85 90 95

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

<210> SEQ ID NO 21
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 21

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```

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc    60
tcctgtgcag cctctggatt tactctaagt agttacgaca tgcactgggt ccgccaagct    120
acaggaaaag gtctggagtg ggtctcagct attggttcta ccggtgacac atactatcca    180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt    240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgtaag agaggggtgg    300
gaggtaccct ttgactactg gggccaggga accctggtca ccgtctctc a                351

```

```

<210> SEQ ID NO 22
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 22

```

```

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

```

```

<210> SEQ ID NO 23
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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```

<400> SEQUENCE: 23

```

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc    60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtagca gcagaaacct    120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatccagcc    180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct    240
gaagattttg cagtttatta ctgtcagcag tataataact ggcctccatt cactttcggc    300
cctgggacca aagtggatat caaa                324

```

```

<210> SEQ ID NO 24
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 24

```

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly

```

-continued

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

<210> SEQ ID NO 25
 <211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 25

caggtgcagc tgggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc	60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcggtt ataggatttg atggaagtaa tatacattat	180
ggagactccg tgaggggccg aatcatcata tccagagaca attccgagaa cacgttgat	240
ctggaaatga acagcctgag agccgaggac acggcaatgt actattgtgc gagagagaag	300
ggtttagact ggggccaggg aaccacggtc accgtctcct ca	342

<210> SEQ ID NO 26
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 26

Gln Val Gln Leu Val Gln 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 Phe Ile Gly Phe Asp Gly Ser Asn Ile His Tyr Gly Asp Ser Val	50	55	60	
Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr	65	70	75	80
Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys	85	90	95	
Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Thr Val Thr Val	100	105	110	
Ser Ser				

<210> SEQ ID NO 27
 <211> LENGTH: 24
 <212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 27

ggattcacct tcagtagcta tggc

24

<210> SEQ ID NO 28
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 28

Gly Phe Thr Phe Ser Ser Tyr Gly
 1 5

<210> SEQ ID NO 29
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 29

ataggatttg atggaagtaa tata

24

<210> SEQ ID NO 30
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 30

Ile Gly Phe Asp Gly Ser Asn Ile
 1 5

<210> SEQ ID NO 31
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 31

gcgagagaga agggtttaga c

21

<210> SEQ ID NO 32
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 32

Ala Arg Glu Lys Gly Leu Asp
 1 5

<210> SEQ ID NO 33
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 33

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gccatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca gcagaaacca    120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct    240
gatgattttg caacttatta ctgccaacag tataatagtt attacacttt tggccagggg    300
accaaggtgg aaatcaaacg a                                              321

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<210> SEQ ID NO 34

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 34

```

Ala Ile Gln Met Thr Gln Ser Pro Ser Thr 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 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 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
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Tyr Thr
      85             90             95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      100             105

```

<210> SEQ ID NO 35

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 35

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cagagtatta gtagctgg                                              18

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<210> SEQ ID NO 36

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 36

```

Gln Ser Ile Ser Ser Trp
  1             5

```

<210> SEQ ID NO 37

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 37

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aaggcgtct

9

<210> SEQ ID NO 38
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic
 <400> SEQUENCE: 38

Lys Ala Ser
 1

<210> SEQ ID NO 39
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic
 <400> SEQUENCE: 39

caacagtata atagttatta cact

24

<210> SEQ ID NO 40
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic
 <400> SEQUENCE: 40

Gln Gln Tyr Asn Ser Tyr Tyr Thr
 1 5

<210> SEQ ID NO 41
 <211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic
 <400> SEQUENCE: 41

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
 tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
 ccaggcaagg ggctggagtg ggtggcggtt ataggatttg atggaagtaa tatacattat 180
 ggagactccg tgaggggccg aatcatcata tccagagaca attccgagaa cacgttgat 240
 ctggaaatga acagcctgag agccgaggac acggcaatgt actattgtgc gagagagaag 300
 ggtttagact ggggccaggg aaccctggtc accgtctcct ca 342

<210> SEQ ID NO 42
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic
 <400> SEQUENCE: 42

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

-continued

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

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

Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr
 65 70 75 80

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

Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110

Ser Ser

<210> SEQ ID NO 43
 <211> LENGTH: 318
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
 aggttcagcg gcagtggtac tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
 gatgattttg caacttatta ctgccaacag tataatagtt attacacttt tggccagggg 300
 accaagctgg agatcaaa 318

<210> SEQ ID NO 44
 <211> LENGTH: 106
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 44

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 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 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

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

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

<210> SEQ ID NO 45
 <211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 45

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cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctggggaggtc cctgagactc      60
tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt ataggatttg atggaagtaa tatatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagagaag      300
ggttttagact ggggccaggg aaccctggtc accgtctcct ca                          342

```

```

<210> SEQ ID NO 46
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 46

```

```

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 Gly Phe Asp Gly Ser Asn Ile 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 Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
      100            105            110

```

```

Ser Ser

```

```

<210> SEQ ID NO 47
<211> LENGTH: 319
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 47

```

```

gacatccaga tgaccagtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca      180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct      240
gatgattttg caacttatta ctgccaacag tataatagtt attacacttt tggccagggg      300
accaagctgg agatcaaac                          319

```

```

<210> SEQ ID NO 48
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 48

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1         5             10             15

```

-continued

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 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
 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Tyr Thr
 85 90 95
 Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> SEQ ID NO 49
 <211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 49

cagggtgcagc tgcaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
 tctgtgtcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
 ccaggcaagg ggctggagtg ggtggcggtt ataggatttg atggaagtaa tatatattat 180
 ggagactccg tgaggggccg aatcatcata tccagagaca attccgagaa cacgttgtat 240
 ctggaaatga acagcctgag agccgaggac acggcagtgt attattgtgc gagagagaag 300
 ggtttagact ggggccaggg aaccctggtc actgtctcct ca 342

<210> SEQ ID NO 50
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 50

Gln Val Gln Leu Gln 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 Phe Ile Gly Phe Asp Gly Ser Asn Ile Tyr Tyr Gly Asp Ser Val
 50 55 60
 Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr
 65 70 75 80
 Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110

Ser Ser

<210> SEQ ID NO 51
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 51

ggattcacct tcagtagcta tggc

24

<210> SEQ ID NO 52
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 52

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> SEQ ID NO 53
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 53

ataggatttg atggaagtaa tata

24

<210> SEQ ID NO 54
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 54

Ile Gly Phe Asp Gly Ser Asn Ile
1 5

<210> SEQ ID NO 55
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 55

gcgagagaga agggtttaga c

21

<210> SEQ ID NO 56
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 56

Ala Arg Glu Lys Gly Leu Asp
1 5

<210> SEQ ID NO 57
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 57

-continued

```

gccatccaga tgaccacgac tccagactcc ctggtgtgtgt ctctgggcga gagggccacc      60
atcaactgca agtccagcca gagtgttttt cacacctcca acaataagaa ctacttagtt      120
tggtatcagc agaaaccagg acagcctcct aagttgctcc tttactgggc ctctaccgg      180
gaatccgggg tcctcgaccg attcagtggc agcgggtctg ggacagattt cactctcacc      240
atcagcagcc tgcaggtgca agatgtggca aattattact gtcaccaata ttacagtatt      300
ccgtggacgt tcggccaagg gaccaaggtg gagatcaaac ga                          342

```

```

<210> SEQ ID NO 58
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 58

```

```

Ala Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1           5           10          15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Phe His Thr
          20           25           30
Ser Asn Asn Lys Asn Tyr Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln
          35           40           45
Pro Pro Lys Leu Leu Leu 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 Asn Tyr Tyr Cys His Gln
          85           90           95
Tyr Tyr Ser Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
          100          105          110

```

```

Lys Arg

```

```

<210> SEQ ID NO 59
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 59

```

```

cagagtgttt ttcacacctc caacaataag aactac      36

```

```

<210> SEQ ID NO 60
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 60

```

```

Gln Ser Val Phe His Thr Ser Asn Asn Lys Asn Tyr
 1           5           10

```

```

<210> SEQ ID NO 61
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

-continued

<400> SEQUENCE: 61

tgggcctct

9

<210> SEQ ID NO 62

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 62

Trp Ala Ser

1

<210> SEQ ID NO 63

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63

caccaatatt acagtattcc gtggacg

27

<210> SEQ ID NO 64

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 64

His Gln Tyr Tyr Ser Ile Pro Trp Thr

1

5

<210> SEQ ID NO 65

<211> LENGTH: 342

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 65

cagggtgcagc tgggtggagtc tggggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcgttt ataggatttg atggaagtaa tatatattat 180

ggagactccg tgaggggccc aatcatcata tccagagaca attccgagaa cacgttgat 240

ctggaaatga acagcctgag agccgaggac acggcagtggt attattgtgc gagagagaag 300

ggtttagact gggggccaggg aaccctggtc accgtctcct ca 342

<210> SEQ ID NO 66

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 66

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

-continued

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

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

Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr
 65 70 75 80

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

Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110

Ser Ser

<210> SEQ ID NO 67
 <211> LENGTH: 339
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 67

gacatcgtga tgacccagtc tccagactcc ctggtgtgtgt ctctgggcca gagggccacc 60
 atcaactgca agtccagcca gagtgttttt cacacctcca acaataagaa ctacttagtt 120
 tgggtatcagc agaaaccagg acagcctcct aagttgctcc tttactgggc ctctaccggg 180
 gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
 atcagcagcc tgcaggctga agatgtggca aattattact gtcaccaata ttacagtatt 300
 ccgtggacgt tcggccaagg gaccaaggtg gaaatcaaa 339

<210> SEQ ID NO 68
 <211> LENGTH: 113
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 68

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 Lys Ser Ser Gln Ser Val Phe His Thr
 20 25 30

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

Pro Pro Lys Leu Leu Leu 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 Asn Tyr Tyr Cys His Gln
 85 90 95

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

Lys

<210> SEQ ID NO 69
 <211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 69

cagggtgcagc	tggtggagtc	tggtggagtc	gtgttcagc	ctgggagtc	ctgagactc	60
tcctgtgcag	cctctggatt	caccttcagt	agctatggca	tgactgggt	ccgccaggct	120
ccaggcaagg	ggctggagtg	ggtggcagtt	ataggatttg	atggaagtaa	tatatactat	180
gcagactccg	tgaaggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaatga	acagcctgag	agctgaggac	acggctgtgt	attactgtgc	gagagagaag	300
ggtttagact	ggggccagg	aacctgtgc	accgtctcct	ca		342

<210> SEQ ID NO 70

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 70

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 Gly	Phe Asp	Gly Ser	Asn Ile	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	Glu Lys	Gly Leu	Asp Trp	Gly Gln	Gly Thr	Leu Val	Thr Val
	100		105			110	
Ser Ser							

<210> SEQ ID NO 71

<211> LENGTH: 339

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 71

gacatcgtga	tgaccagtc	tccagactcc	ctggctgtgt	ctctgggcca	gagggccacc	60
atcaactgca	agtccagcca	gagtggtttt	cacacctcca	acaataagaa	ctacttagct	120
tggtaccagc	agaaaccagg	acagcctcct	aagctgctca	tttactgggc	ctctaccgg	180
gaatccgggg	tccctgaccg	attcagtggc	agcgggtctg	ggacagattt	cactctcacc	240
atcagcagcc	tcagagctga	agatgtggca	gtttattact	gtcaccaata	ttacagtatt	300
ccgtggacgt	tcggccaagg	gaccaagggtg	gaaatcaaa			339

<210> SEQ ID NO 72

<211> LENGTH: 113

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 72

```

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 Lys Ser Ser Gln Ser Val Phe His Thr
      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 Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln
      85         90        95
Tyr Tyr Ser Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
      100        105       110

```

Lys

<210> SEQ ID NO 73

<211> LENGTH: 354

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 73

```

gaagtgcagc tgggtgcagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc      60
tctctgtcag cctctggatt cacctttaac aactatgccca tgaactgggt ccgccagget      120
ccaggaaagg gactggactg ggtctcaact attagtggta gcggtgttac taaaaactac      180
gcagactccg tgaagggccg ttctattatt tcccagagaca gttccaaaca cagctgtat      240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagattct      300
aactggggaa atttcgatct ctgggggcgt ggcaccacgg tcactgtctc ctca      354

```

<210> SEQ ID NO 74

<211> LENGTH: 118

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 74

```

Glu Val Gln Leu Val Gln 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 Tyr
      20         25        30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
      35         40        45
Ser Thr Ile Ser Gly Ser Gly Gly Thr Thr Asn Tyr Ala Asp Ser Val
      50         55        60
Lys Gly Arg Phe Ile Ile Ser Arg Asp Ser Ser Lys His 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 Ser Asn Trp Gly Asn Phe Asp Leu Trp Gly Arg Gly Thr
      100        105       110
Thr Val Thr Val Ser Ser

```

-continued

115

<210> SEQ ID NO 75
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 75

ggattcacct ttaacaacta tgcc

24

<210> SEQ ID NO 76
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 76

Gly Phe Thr Phe Asn Asn Tyr Ala
1 5

<210> SEQ ID NO 77
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77

attagtggta gcggtggtac taca

24

<210> SEQ ID NO 78
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 78

Ile Ser Gly Ser Gly Gly Thr Thr
1 5

<210> SEQ ID NO 79
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79

gcgaaagatt ctaactgggg aaatttcgat ctc

33

<210> SEQ ID NO 80
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 80

Ala Lys Asp Ser Asn Trp Gly Asn Phe Asp Leu
1 5 10

<210> SEQ ID NO 81

-continued

<211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 81

```

gacatccaga tgacccagtc tccagactcc ctggtgtgtg ctctgggcga gagggccacc    60
atcaactgca agtcagccca gagtgtttta tacaggtcca acaataggaa cttcttaggt    120
tggtaccagc agaaaccagg gcagcctcct aatctactca tttactgggc atctaccgg    180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc    240
atcagcagcc tgcaggtgca agatgtggca gtttattact gtcaacaata ttatactact    300
ccgtacactt ttggccaggg gaccaaggtg gaaatcaaac ga                        342
  
```

<210> SEQ ID NO 82
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82

```

Asp Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1             5             10            15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Arg
          20             25            30
Ser Asn Asn Arg Asn Phe Leu Gly 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 Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100            105            110
Lys Arg
  
```

<210> SEQ ID NO 83
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 83

```

cagagtgttt tatacaggtc caacaatagg aacttc                                36
  
```

<210> SEQ ID NO 84
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 84

```

Gln Ser Val Leu Tyr Arg Ser Asn Asn Arg Asn Phe
 1             5             10
  
```

-continued

<210> SEQ ID NO 85
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 85

tgggcatct

9

<210> SEQ ID NO 86
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 86

Trp Ala Ser
 1

<210> SEQ ID NO 87
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 87

caacaatatt atactactcc gtacact

27

<210> SEQ ID NO 88
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 88

Gln Gln Tyr Tyr Thr Thr Pro Tyr Thr
 1 5

<210> SEQ ID NO 89
 <211> LENGTH: 354
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 89

gagggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttaac aactatgccca tgaactgggt ccgccaggct 120
 ccaggaaagg gactggactg ggtctcaact attagtggta gcggtggtac tacaaactac 180
 gcagactccg tgaagggccg ttctattatt tcccagagaca gttccaaaca cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagattct 300
 aactggggaa atttcgatct ctggggccgt ggcaccctgg tcaactgtctc ctca 354

<210> SEQ ID NO 90
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 90

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 Tyr
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
 35 40 45
 Ser Thr Ile Ser Gly Ser Gly Gly Thr Thr Asn Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Ile Ile Ser Arg Asp Ser Ser Lys His 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 Ser Asn Trp Gly Asn Phe Asp Leu Trp Gly Arg Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 91

<211> LENGTH: 339

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 91

gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
 atcaactgca agtccagcca gagtgtttta tacagggtcca acaataggaa cttcttaggt 120
 tggtagcagc agaaaccagg gcagcctcct aatctactca tttactgggc atctaccggg 180
 gaatccgggg tccttgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
 atcagcagcc tgcaggctga agatgtggca gtttattact gtcaacaata ttatactact 300
 ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

<210> SEQ ID NO 92

<211> LENGTH: 113

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 92

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 Lys Ser Ser Gln Ser Val Leu Tyr Arg
 20 25 30
 Ser Asn Asn Arg Asn Phe Leu Gly 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 Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
 100 105 110

-continued

Lys

<210> SEQ ID NO 93
 <211> LENGTH: 354
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 93

```
gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc      60
tcctgtgcag cctctggatt cacctttaac aactatgcc a tgagctgggt ccgccaggct      120
ccagggaagg ggctggagtg ggtctcagct attagtggta gcggtgggtac tacatactac      180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagattct      300
aactggggaa atttcgatct ctggggccgt ggcaccctgg tcaactgtctc ctca          354
```

<210> SEQ ID NO 94
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 94

```
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 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 Thr 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 Ser Asn Trp Gly Asn Phe Asp Leu Trp Gly Arg Gly Thr
          100         105         110
Leu Val Thr Val Ser Ser
          115
```

<210> SEQ ID NO 95
 <211> LENGTH: 339
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 95

```
gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc      60
atcaactgca agtccagcca gagtgtttta tacagggtcca acaataggaa cttcttagct      120
tggtaccagc agaaaccagg acagcctcct aagctgtctca tttactgggc atctaccgg      180
gaatccgggg tcctgaccg attcagtggc agcgggtctg ggacagatth cactctcacc      240
atcagcagcc tgcaggtgga agatgtggca gtttattact gtcaacaata ttatactact      300
ccgtacactt ttggccaggg gaccaagctg gagatcaaa          339
```

-continued

<210> SEQ ID NO 96
 <211> LENGTH: 113
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 96

```

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 Lys Ser Ser Gln Ser Val Leu Tyr Arg
          20           25           30
Ser Asn Asn Arg Asn Phe 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 Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
          85           90           95
Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
          100          105          110

```

Lys

<210> SEQ ID NO 97
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 97

```

cagggtgcagc tgggtgcagtc tgggggagggc ttggtacagc ctgggggggtc cctgagactc      60
tctgtgtcag tctctggatt caccctcagt agctacgata tgcactgggt cgcaccaacct      120
acaggaaaaag gtctggagtg ggtctcagct attggttcta ctggtgacac atactatcca      180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt      240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggatgg      300
gacgtaccct ttgacttctg gggccaggga accctgggtca ccgtctcctc a      351

```

<210> SEQ ID NO 98
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 98

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Leu Ser Ser Tyr
          20           25           30
Asp Met His Trp Val Arg Gln Pro Thr Gly Lys Gly Leu Glu Trp Val
          35           40           45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
          50           55           60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu

```


-continued

65	70	75	80
----	----	----	----

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

Arg Glu Gly Trp Asp Val Pro Phe Asp Phe Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 99
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 99

ggattcaccc tcagtagcta cgat

24

<210> SEQ ID NO 100
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 100

Gly Phe Thr Leu Ser Ser Tyr Asp
 1 5

<210> SEQ ID NO 101
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 101

attggttcta ctggtgacac a

21

<210> SEQ ID NO 102
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 102

Ile Gly Ser Thr Gly Asp Thr
 1 5

<210> SEQ ID NO 103
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 103

gcaagagagg gatgggacgt accctttgac ttc

33

<210> SEQ ID NO 104
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 104

Ala Arg Glu Gly Trp Asp Val Pro Phe Asp Phe
 1 5 10

<210> SEQ ID NO 105

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 105

gccatccagt tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggcaagtca ggacattaga aatgatttag gctgggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180
 cggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgtctacaa gattacaatt acccgtaggac gttcggccaa 300
 gggaccaagg tggagatcaa acga 324

<210> SEQ ID NO 106

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 106

Ala Ile Gln Leu 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 Asp Ile Arg Asn Asp
 20 25 30
 Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 107

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 107

caggacatta gaaatgat 18

<210> SEQ ID NO 108

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 108

Gln Asp Ile Arg Asn Asp
1 5

<210> SEQ ID NO 109

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 109

gctgcatcc

9

<210> SEQ ID NO 110

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 110

Ala Ala Ser
1

<210> SEQ ID NO 111

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 111

ctacaagatt acaattaccc gtggacg

27

<210> SEQ ID NO 112

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 112

Leu Gln Asp Tyr Asn Tyr Pro Trp Thr
1 5

<210> SEQ ID NO 113

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 113

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgcag tctctggatt caccctcagt agctacgata tgcactgggt ccgccaacct 120

acaggaaaag gtctggagtg ggtctcagct attggttcta ctggtgacac atactatcca 180

ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240

caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggatgg 300

gacgtaccct ttgacttctg gggccaggga accctggtea ccgtctctc a 351

-continued

<210> SEQ ID NO 114
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 114

```

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

```

<210> SEQ ID NO 115
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 115

```

gccatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggcaagtca ggacattaga aatgatttag gctggatatca gcagaaacca    120
gggaaagccc ctaagctcct gatctatgct gcattccagtt taaaaagtgg ggtcccatca    180
cgggttcagcg gcagtggatc tggcacagat ttcactctca ccattcagcag cctgcagcct    240
gaagattttg caacttatta ctgtctacaa gattacaatt acccgtggac gttcggccaa    300
gggaccaagtg tggaaatcaa a                                     321

```

<210> SEQ ID NO 116
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 116

```

Ala 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 Asp Ile Arg Asn Asp
          20             25             30
Leu Gly 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

```

-continued

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

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

<210> SEQ ID NO 117

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 117

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tctgtgcag cctctggatt caccctcagt agctacgata tgcactgggt ccgccaagct 120
 acaggaaaag gtctggagtg ggtctcagct attggttcta ctggtgacac atactatcca 180
 ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
 caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agagggatgg 300
 gacgtaccct ttgacttctg gggccaggga accctgggtca ccgtctcctc a 351

<210> SEQ ID NO 118

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 118

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 Leu Ser Ser Tyr
 20 25 30

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

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

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

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

Arg Glu Gly Trp Asp Val Pro Phe Asp Phe Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 119

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 119

gccatccaga tgaccagtc tccatctctc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggcaagtca ggacattaga aatgatttag gctgggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatgct gcattccagtt taaaaagtgg ggtcccatca 180

-continued

```

aggttcagcg gcagtggtatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa gattacaatt acccggtggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 120
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 120

```

```

Ala 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 Asp Ile Arg Asn Asp
          20             25             30
Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro Trp
          85             90             95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
          100             105

```

```

<210> SEQ ID NO 121
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 121

```

```

caggtgcagc tgcaggagtc ggggccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctgggga ctccatcaat acttactact ggagctgggt ccggcagccc 120
ccaggaagg gactggagtg gattgggtat atctattata gtggaaccac caactacaac 180
ccctccctca agagtcgagt caccatatca atagacacgc ccaggaacca gttctccctg 240
aagctgatct ctgtgaccgc agcggacacg gccgtgtatt actgtgagag agagaggatt 300
actatgattc ggggagttac cctctactat tactcctacg gtatggacgt ctggggccaa 360
gggaccacgg tcacctctc ctca 384

```

```

<210> SEQ ID NO 122
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 122

```

```

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1             5             10             15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Asn Thr Tyr
          20             25             30
Tyr Trp Ser Trp Phe Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
          35             40             45

```

-continued

Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Asn Tyr Asn Pro Ser Leu Lys
 50 55 60
 Ser Arg Val Thr Ile Ser Ile Asp Thr Pro Arg Asn Gln Phe Ser Leu
 65 70 75 80
 Lys Leu Ile Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Glu Arg Ile Thr Met Ile Arg Gly Val Thr Leu Tyr Tyr Tyr Ser
 100 105 110
 Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 123
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 123

ggggactcca tcaatactta ctac

24

<210> SEQ ID NO 124
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 124

Gly Asp Ser Ile Asn Thr Tyr Tyr
 1 5

<210> SEQ ID NO 125
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 125

atctattata gtggaaccac c

21

<210> SEQ ID NO 126
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 126

Ile Tyr Tyr Ser Gly Thr Thr
 1 5

<210> SEQ ID NO 127
 <211> LENGTH: 66
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 127

gcgagagaga ggattactat gattcgggga gttaccctct actattactc ctacggtatg

60

gacgtc

66

-continued

<210> SEQ ID NO 128
 <211> LENGTH: 22
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 128

Ala Arg Glu Arg Ile Thr Met Ile Arg Gly Val Thr Leu Tyr Tyr Tyr
 1 5 10 15

Ser Tyr Gly Met Asp Val
 20

<210> SEQ ID NO 129
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 129

gacatccaga tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgct gggccagtca ggacattagc agttatttag cctgggtatca gcaaaaacca 120
 gggatagccc ctaagctect gatctatgct gcattccactt tgcaaagtgg ggtcccatca 180
 aggttcggcg gcagtggatc tgggacagaa ttactcttca caatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgtcaacag cttaatatgtt accctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa acga 324

<210> SEQ ID NO 130
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 130

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1 5 10 15

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

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

Tyr Ala Ala Ser Thr 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 Gln Gln Leu Asn Ser Tyr Pro Arg
 85 90 95

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

<210> SEQ ID NO 131
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 131

-continued

caggacatta gcagttat

18

<210> SEQ ID NO 132
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 132

Gln Asp Ile Ser Ser Tyr
 1 5

<210> SEQ ID NO 133
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 133

gctgcatcc

9

<210> SEQ ID NO 134
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 134

Ala Ala Ser
 1

<210> SEQ ID NO 135
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 135

caacagctta atagttaccc tcggacg

27

<210> SEQ ID NO 136
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 136

Gln Gln Leu Asn Ser Tyr Pro Arg Thr
 1 5

<210> SEQ ID NO 137
 <211> LENGTH: 384
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 137

cagggtgcagc tgcaggagtc ggggccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctgggga ctccatcaat acttactact ggagctgggt ccggcagccc 120

-continued

```

ccaggaag gactggagt gattgggtat atctattata gtggaaccac caactacaac 180
ccctccctca agagtcgagt caccatatca atagacacgc ccaggaacca gttctccctg 240
aagctgatct ctgtgaccgc agcggacacg gccgtgtatt actgtgcgag agagaggatt 300
actatgattc ggggagttac cctctactat tactectacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

```

```

<210> SEQ ID NO 138
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 138

```

```

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

```

```

<210> SEQ ID NO 139
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 139

```

```

gacatccaga tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtca ggacattagc agttatttag cctgggtatca gcaaaaacca 120
gggatagccc ctaagctcct gatctatgct gcattccactt tgcaaagtgg ggtcccatca 180
aggttcggcg gcagtggatc tgggacagaa ttactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatagtt accctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 140
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 140

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1             5             10            15

```

-continued

Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Ser Tyr
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Thr 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 Gln Gln Leu Asn Ser Tyr Pro Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 141
 <211> LENGTH: 384
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 141

cagggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctcgggagac cctgtccctc 60
 acctgcactg tctctgggga ctccatcaat acttactact ggagctggat ccggcagccc 120
 ccaggaagg gactggagtg gattgggtat atctattata gtggaaccac caactacaac 180
 ccctccctca agagtcgagt caccatata gtagacacgt ccaagaacca gttctccctg 240
 aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgagag agagaggatt 300
 actatgattc ggggagttac cctctactat tactcctacg gtatggacgt ctggggccaa 360
 gggaccacgg tcaccgtctc ctca 384

<210> SEQ ID NO 142
 <211> LENGTH: 128
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 142

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

<210> SEQ ID NO 143

-continued

<211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 143

```

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca ggacattagc agttatttag gctggtatca gcagaaacca    120
gggaaagccc ctaagcgct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct    240
gaagattttg caacttatta ctgtcaacag cttaatagtt accctcggac gttcggccaa    300
gggaccaagg tggaaatcaa a                                           321

```

<210> SEQ ID NO 144
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 144

```

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 Asp Ile Ser Ser Tyr
 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 Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
 85            90            95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100           105

```

<210> SEQ ID NO 145
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 145

```

caggtgcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc    60
tcctgcaagg cttctgggta cacctttacc aactatggta tcagctgggt gcgacaggcc    120
cctggacaag gacttgagtt aatgggatgg attagtggtt acaatggtaa cacaaactat    180
gcacaagaac tccaggccag agtcaccatg accacagaca catccacgag cacagcctac    240
atggagctga ggaacctgag atctgacgac acggccgtat attactgtgc gagagataga    300
gtcgtttagt cagctgctaa ttactacttt tattctatgg acgtctgggg ccaagggacc    360
acggtcaccg tctcctca                                           378

```

<210> SEQ ID NO 146
 <211> LENGTH: 126
 <212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 146

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

<210> SEQ ID NO 147
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 147

ggttacacct ttaccaacta tgggt

24

<210> SEQ ID NO 148
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 148

Gly Tyr Thr Phe Thr Asn Tyr Gly
 1 5

<210> SEQ ID NO 149
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 149

attagtgggtt acaatggtaa caca

24

<210> SEQ ID NO 150
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 150

Ile Ser Gly Tyr Asn Gly Asn Thr
 1 5

-continued

<210> SEQ ID NO 151
 <211> LENGTH: 57
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 151

gcgagagata gactcggtgt agcagctgct aattactact tttattctat ggacgtc 57

<210> SEQ ID NO 152
 <211> LENGTH: 19
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 152

Ala Arg Asp Arg Val Val Val Ala Ala Ala Asn Tyr Tyr Phe Tyr Ser
 1 5 10 15

Met Asp Val

<210> SEQ ID NO 153
 <211> LENGTH: 339
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 153

gccatccaga tgacccagtc tccactctcc ctgtccgtca cccttggaca gccggcctcc 60
 atctctctgca ggtctagtca aagcctcgta tacagtgatg gagacaccta cttgaattgg 120
 ttccagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccgggac 180
 tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgctttcac actgaaaatc 240
 agcgggggtgg aggccaggga tggtgggggt tactactgca tgcaagctac aactcggcct 300
 cggacgttcg gccaaaggac caaggtggaa atcaaacga 339

<210> SEQ ID NO 154
 <211> LENGTH: 113
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 154

Ala Ile Gln Met Thr Gln Ser Pro Leu Ser Leu Ser Val Thr Leu Gly
 1 5 10 15

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

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

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

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

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

Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

-continued

100	105	110
Arg		
<210> SEQ ID NO 155 <211> LENGTH: 33 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 155 caaagcctcg tatacagtga tggagacacc tac		
		33
<210> SEQ ID NO 156 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 156 Gln Ser Leu Val Tyr Ser Asp Gly Asp Thr Tyr 1 5 10		
<210> SEQ ID NO 157 <211> LENGTH: 9 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 157 aaggtttct		
		9
<210> SEQ ID NO 158 <211> LENGTH: 3 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 158 Lys Val Ser 1		
<210> SEQ ID NO 159 <211> LENGTH: 27 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 159 atgcaagcta cacactggcc tcggacg		
		27
<210> SEQ ID NO 160 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 160 Met Gln Ala Thr His Trp Pro Arg Thr 1 5		

-continued

<210> SEQ ID NO 161
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 161

```
caggttcagc tggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc    60
tcctgcaagg cttctgggta cacctttacc aactatggta tcagctgggt gcgacaggcc    120
cctggacaag gacttgagtt aatgggatgg attagtggtt acaatggtaa cacaaactat    180
gcacaagaac tccagggcag agtcaccatg accacagaca catccacgag cacagcctac    240
atggagctga ggaacctgag atctgacgac acggccgtat attactgtgc gagagataga    300
gtcgttgtag cagctgctaa ttactacttt tattctatgg acgtctgggg ccaagggacc    360
acggtcaccg tctcctca                                     378
```

<210> SEQ ID NO 162
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 162

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

<210> SEQ ID NO 163
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 163

```
gatgttgtag tgactcagtc tccactctcc ctgtccgtca cccttggaca gccggcctcc    60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gagacaccta cttgaattgg    120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccggggac    180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgctttcac actgaaaatc    240
agcgggggtgg aggccgagga tgttgggggt tactactgca tgcaagctac aactggcct    300
cggacgttcg gccaaaggac caagtgga atcaaa                                     336
```


-continued

<210> SEQ ID NO 164
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 164

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

<210> SEQ ID NO 165
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 165

cagggttcagc	tggtgcagtc	tggagctgag	gtgaagaagc	ctggggcctc	agtgaaggtc	60
tcctgcaagg	cttctgggta	cacctttacc	aactatggta	tcagctgggt	gcgacaggcc	120
cctggacaag	ggcttgatgt	gatgggatgg	attagtgggt	acaatggtaa	cacaaactat	180
gcacagaagc	tccagggcag	agtcaccatg	accacagaca	catccacgag	cacagcctac	240
atggagctga	ggagcctgag	atctgacgac	acggccgtgt	attactgtgc	gagagataga	300
gtcgtttag	cagctgctaa	ttactacttt	tattctatgg	acgtctgggg	ccaagggacc	360
acggtcaccg	tctcctca					378

<210> SEQ ID NO 166
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 166

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
		20					25					30			
Gly	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40					45				
Gly	Trp	Ile	Ser	Gly	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Leu
	50					55					60				
Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr

-continued

65	70	75	80	
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys				
	85	90	95	
Ala Arg Asp Arg Val Val Val Ala Ala Ala Asn Tyr Tyr Phe Tyr Ser				
	100	105	110	
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser				
	115	120	125	

<210> SEQ ID NO 167
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 167

gatgttgatga tgactcagtc tccactctcc ctgcccgtca cccttgagaca gccggcctcc	60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gagacaccta cttgaattgg	120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccggggac	180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc	240
agcaggggtgg aggctgagga tggtggggtt tattactgca tgcaagctac aactggcct	300
cggacgttcg gccaaaggac caagtgga atcaaa	336

<210> SEQ ID NO 168
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 168

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly	
1 5 10 15	
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser	
20 25 30	
Asp Gly Asp Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser	
35 40 45	
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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	
Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys	
100 105 110	

<210> SEQ ID NO 169
 <211> LENGTH: 375
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 169

caggtccact tgaaggatc tggctcctacg ctggtgaaac ccacacagac cctcacgctg	60
acctgcacct tctctggatt ctcaatcatc actagtggag tgggtgtggg ctggattcgt	120
cagccccccg gaaaggccct ggagtggctt gcaactcattt attggaatgg tgataagcgc	180

-continued

```
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240
gtccttacc aa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacagg 300
ataactgaaa ctagtacta cttctactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375
```

```
<210> SEQ ID NO 170
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 170
```

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

```
<210> SEQ ID NO 171
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 171
```

```
ggattctcac tcatcactag tggagtgggt 30
```

```
<210> SEQ ID NO 172
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 172
```

```
Gly Phe Ser Leu Ile Thr Ser Gly Val Gly
 1             5             10
```

```
<210> SEQ ID NO 173
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 173
```

```
atttattgga atggtgataa g 21
```

-continued

<210> SEQ ID NO 174
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 174

Ile Tyr Trp Asn Gly Asp Lys
1 5

<210> SEQ ID NO 175
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 175

gcacacagga taactgaaac tagttactac ttctactacg gtagggacgt c 51

<210> SEQ ID NO 176
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 176

Ala His Arg Ile Thr Glu Thr Ser Tyr Tyr Phe Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 177
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 177

gacatccaga tgaccagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctctctgca ggtctagtca gagcctctcg catagtcacg gatacgacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatctc atttgggttc taatcggggc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tggtgggggt tattactgca tgcaagctct acaaaactccg 300
ctcactttcg gcggaggggac caaggtggaa atcaaacga 339

<210> SEQ ID NO 178
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 178

Asp Ile Gln 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 Ser
20 25 30

-continued

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

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

Arg

<210> SEQ ID NO 179
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 179

cagagcctcc tgcatagtca tggatacgac tat

33

<210> SEQ ID NO 180
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 180

Gln Ser Leu Leu His Ser His Gly Tyr Asp Tyr
 1 5 10

<210> SEQ ID NO 181
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 181

ttgggttct

9

<210> SEQ ID NO 182
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 182

Leu Gly Ser
 1

<210> SEQ ID NO 183
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 183

atgcaagctc tacaaactcc gctcact

27

-continued

<210> SEQ ID NO 184
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 184

Met Gln Ala Leu Gln Thr Pro Leu Thr
 1 5

<210> SEQ ID NO 185
 <211> LENGTH: 375
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 185

cagatcacct tgaaggagtc tggctcctacg ctggtgaaac ccacacagac cctcacgctg 60
 acctgcacct tctctggatt ctcactcatc actagtggag tgggtgtggg ctggattcgt 120
 cagccccccg gaaaggccct ggagtggctt gcaactcattt attggaatgg tgataagcgc 180
 tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccagggtg 240
 gtccttacaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacagg 300
 ataactgaaa ctagttacta cttctactac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

<210> SEQ ID NO 186
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 186

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

<210> SEQ ID NO 187
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 187

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc      60
atctcctgca ggtctagtca gagectcctg catagtcatg gatacgacta tttggattgg      120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc      180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc      240
agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct aaaaactccg      300
ctcactttcg gcggagggac caaggtggag atcaaa                                336

```

<210> SEQ ID NO 188

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 188

```

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 Ser
      20            25            30
His Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35            40            45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100           105           110

```

<210> SEQ ID NO 189

<211> LENGTH: 375

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 189

```

cagatcacct tgaaggagtc tggctctacg ctggtgaaac ccacacagac cctcacgctg      60
acctgcacct tctctggatt ctcactcatc actagtggag tgggtgtggg ctggatccgt      120
cagccccccg gaaaggccct ggagtggctt gcactcattt attggaatgg tgataagcgc      180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccagggtg      240
gtccttaciaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacagg      300
ataactgaaa ctagtacta cttctactac ggtatggacg tctggggcca agggaccacg      360
gtcacctgtc cctca                                375

```

<210> SEQ ID NO 190

<211> LENGTH: 125

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 190

-continued

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

<210> SEQ ID NO 191
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 191

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctcctgca ggtctagtc gagcctcctg catagtcatg gatacgacta tttggattgg 120
 tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 180
 tccgggggtc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttgggggtt tattactgca tgcaagctct acaaaactccg 300
 ctcactttcg gcggaggggac caaggtggag atcaaa 336

<210> SEQ ID NO 192
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 192

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 Ser
 20 25 30
 His Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> SEQ ID NO 193

-continued

<211> LENGTH: 375
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 193

```
cagatcacct tgaaggagtc tggctcctact ctggtgaaac cctcacagac cctcacgctg    60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt    120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaattc tgataagcgc    180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggta    240
gtccttacaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga    300
catgacagct cgtcctacta cttctactac ggtatggacg tctggggcca agggatcacg    360
gtcacccgtct cctca                                           375
```

<210> SEQ ID NO 194
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 194

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

<210> SEQ ID NO 195
 <211> LENGTH: 30
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 195

```
gggttctcac tcagcactag tggagtgggt    30
```

<210> SEQ ID NO 196
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 196

```
Gly Phe Ser Leu Ser Thr Ser Gly Val Gly
```

-continued

1 5 10

<210> SEQ ID NO 197
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 197

atttattgga attctgataa g 21

<210> SEQ ID NO 198
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 198

Ile Tyr Trp Asn Ser Asp Lys
 1 5

<210> SEQ ID NO 199
 <211> LENGTH: 51
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 199

gcacacagac atgacagctc gtcctactac ttctactacg gtagggacgt c 51

<210> SEQ ID NO 200
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 200

Ala His Arg His Asp Ser Ser Ser Tyr Tyr Phe Tyr Tyr Gly Met Asp
 1 5 10 15

Val

<210> SEQ ID NO 201
 <211> LENGTH: 339
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 201

gacatccaga tgaccagctc tccgctctcc ctgcccgtea cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctctcc catagtcatt gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacaa ctctgatctc atttgggttc taatcggggc 180

tccgggggtcc ctgacagggt cagtggcggt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tggtgggatt tattactgca tgcaagctct acagactcct 300

ctcactttcg gcggagggac caaggtggag atcaaacga 339

<210> SEQ ID NO 202
 <211> LENGTH: 113

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 202

Asp Ile Gln 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 Ser
20 25 30
His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Gly Gly Ser 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 Ala
85 90 95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> SEQ ID NO 203
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 203

cagagcctcc tccatagtca tggatacaac tat

33

<210> SEQ ID NO 204
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 204

Gln Ser Leu Leu His Ser His Gly Tyr Asn Tyr
1 5 10

<210> SEQ ID NO 205
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 205

ttgggttct

9

<210> SEQ ID NO 206
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 206

Leu Gly Ser
1

-continued

<210> SEQ ID NO 207
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 207

atgcaagctc tacagactcc tctcact

27

<210> SEQ ID NO 208
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 208

Met Gln Ala Leu Gln Thr Pro Leu Thr
 1 5

<210> SEQ ID NO 209
 <211> LENGTH: 375
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 209

cagatcacct tgaaggagtc tggctcctact ctggtgaaac cctcacagac cctcacgctg 60
 acctgcacct tctctgggtt ctcaactcagc actagtggag tgggtgtggg ctggatccgt 120
 cagccccag gaaaggccct ggagtggctt gcactcattt attggaattc tgataagcgc 180
 tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggta 240
 gtccttaca tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga 300
 catgacagct cgtcctacta cttctactac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

<210> SEQ ID NO 210
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 210

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

-continued

100	105	110	
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser			
115	120	125	

<210> SEQ ID NO 211
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 211

gatattgtga tgactcagtc tccgctctcc ctgcccgtca cccctggaga gccggcctcc	60
atctcctgca ggtctagtca gagcctctc catagtcatg gatacaacta tttggattgg	120
tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttc taatcgggcc	180
tccgggggtcc ctgacagggt cagtggcggt ggatcaggca cagattttac actgaaaatc	240
agcagagtgg aggctgagga tgttgggatt tattactgca tgcaagctct acagactcct	300
ctcactttcg gcggaggggac caaggtggag atcaaa	336

<210> SEQ ID NO 212
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 212

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 Ser	
20 25 30	
His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro	
50 55 60	
Asp Arg Phe Ser Gly Gly Gly Ser 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 Ala	
85 90 95	
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys	
100 105 110	

<210> SEQ ID NO 213
 <211> LENGTH: 375
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 213

cagatcacct tgaaggagtc tggctcctacg ctggtgaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcaactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcaactcattt attggaattc tgataagcgc	180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccagggtg	240
gtccttaciaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga	300
catgacagct cgtcctacta cttctactac ggtatggacg tctggggcca agggaccacg	360

-continued

gtcaccgtct cctca

375

<210> SEQ ID NO 214
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 214

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

<210> SEQ ID NO 215
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 215

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctctctgca ggtctagtca gagcctctcc catagtcatg gatacaacta tttggattgg 120
 tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 180
 tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct acagactcct 300
 ctcactttcg gcggaggggac caaggtggag atcaaa 336

<210> SEQ ID NO 216
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 216

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 Ser
 20 25 30
 His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro

-continued

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

<210> SEQ ID NO 217
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 217

gagatgcaac tgggtggagtc tggggggaggc ttggtccagc ctgggggggtc cctgagactc	60
tcctgtgcag cctctggatt cacctttagt agtcactgga tgaagtgggt ccgccaggct	120
ccaggaaggg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaatactat	180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgttt	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatatt	300
gtactaatgg tctatgatat ggactactac tactacggta tggacgtctg gggccaaggg	360
accacgggtca ccgtctcctc a	381

<210> SEQ ID NO 218
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 218

Glu Met 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 His	
	20 25 30
Trp Met Lys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
	35 40 45
Ala Asn Ile Asn 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 Phe	
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 Ile Val Leu Met Val Tyr Asp Met Asp Tyr Tyr Tyr Tyr	
	100 105 110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser	
	115 120 125

<210> SEQ ID NO 219
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 219

-continued

ggattcacct ttagtagtca ctgg

24

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

<400> SEQUENCE: 220

Gly Phe Thr Phe Ser Ser His Trp
 1 5

<210> SEQ ID NO 221
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 221

ataaaccaag atggaagtga gaaa

24

<210> SEQ ID NO 222
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 222

Ile Asn Gln Asp Gly Ser Glu Lys
 1 5

<210> SEQ ID NO 223
 <211> LENGTH: 60
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 223

gcgagagata ttgtactaat ggtctatgat atggactact actactacgg tatggacgtc

60

<210> SEQ ID NO 224
 <211> LENGTH: 20
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 224

Ala Arg Asp Ile Val Leu Met Val Tyr Asp Met Asp Tyr Tyr Tyr Tyr
 1 5 10 15

Gly Met Asp Val
 20

<210> SEQ ID NO 225
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 225

gatattgtga tgactcagtc tccactctcc ctgcccgta cccctggaga gccggcctcc

60

-continued

```

atctcctgca ggtctagtca gagectcctg catagtaatg gaaacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggccc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaaactct acaaactccg 300
ctcactttcg gcggaggggac caaggtggag atcaaaa 336

```

```

<210> SEQ ID NO 226
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 226

```

```

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 Ser
      20             25            30
Asn Gly Asn Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35             40            45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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 Thr
      85             90            95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100            105            110

```

```

<210> SEQ ID NO 227
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 227

```

```

cagagcctcc tgcataagtaa tggaacaac tat 33

```

```

<210> SEQ ID NO 228
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 228

```

```

Gln Ser Leu Leu His Ser Asn Gly Asn Asn Tyr
 1             5             10

```

```

<210> SEQ ID NO 229
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 229

```

```

ttgggttct 9

```

-continued

<210> SEQ ID NO 230
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 230

Leu Gly Ser
 1

<210> SEQ ID NO 231
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 231

atgcaaactc tacaaactcc gctcact

27

<210> SEQ ID NO 232
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 232

Met Gln Thr Leu Gln Thr Pro Leu Thr
 1 5

<210> SEQ ID NO 233
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 233

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttagt agtcactgga tgaagtgggt ccgccaggct 120
 ccaggaaggg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaatactat 180
 gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgttt 240
 ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatatt 300
 gtactaatgg tctatgatat ggactactac tactacggta tggacgtctg gggccaaggg 360
 accacgggtca ccgtctcctc a 381

<210> SEQ ID NO 234
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 234

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 His
 20 25 30
 Trp Met Lys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

-continued

35	40	45	
Ala Asn Ile Asn 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 Phe			
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 Ile Val Leu Met Val Tyr Asp Met Asp Tyr Tyr Tyr Tyr			
	100	105	110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser			
	115	120	125

<210> SEQ ID NO 235
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 235

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc	60
atctcctgca ggtctagtca gagcctctcg catagtaatg gaaacaacta tttggattgg	120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc	180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc	240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaaactct acaaaactccg	300
ctcactttcg gcggaggggac caaggtggag atcaaa	336

<210> SEQ ID NO 236
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 236

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1	15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser	
20	30
Asn Gly Asn Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35	45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro	
50	60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile	
65	80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr	
85	95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys	
100	110

<210> SEQ ID NO 237
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 237

-continued

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctggggggtc cctgagactc    60
tcctgtgcag cctctggatt cacctttagt agtcactgga tgagctgggt ccgccaggct    120
ccaggggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaatactat    180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatatt    300
gtactaatgg tctatgatat ggactactac tactacggta tggacgtctg ggggcaaggg    360
accacggtea ccgtctcctc a                                              381

```

```

<210> SEQ ID NO 238
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 238

```

```

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 His
          20          25          30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ala Asn Ile Asn 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 Asp Ile Val Leu Met Val Tyr Asp Met Asp Tyr Tyr Tyr Tyr
          100         105         110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115         120         125

```

```

<210> SEQ ID NO 239
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 239

```

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc    60
atctcctgca ggtctagtca gagcctcctg catagtaatg gaaacaacta tttggattgg    120
tacctgcaga agccagggca gtctccacag ctctgatctt atttgggttc taatcggggc    180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaaac    240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaaactct acaaactccg    300
ctcactttcg gcggagggac caaggtggag atcaaaa                                336

```

```

<210> SEQ ID NO 240
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

-continued

<400> SEQUENCE: 240

```

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 Ser
          20           25           30
Asn Gly Asn Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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 Thr
          85           90           95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105          110

```

<210> SEQ ID NO 241

<211> LENGTH: 381

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 241

```

caggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc      60
tcctgtgcag tctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat      180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat      240
ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt      300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg      360
accacgggtca ccgtctcctc a                                     381

```

<210> SEQ ID NO 242

<211> LENGTH: 127

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 242

```

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 Val 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 Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
          50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
          85           90           95
Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
          100          105          110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

```

-continued

115	120	125
<210> SEQ ID NO 243 <211> LENGTH: 24 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 243 ggattcacct tcagtagcta tggc		
		24
<210> SEQ ID NO 244 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 244 Gly Phe Thr Phe Ser Ser Tyr Gly 1 5		
<210> SEQ ID NO 245 <211> LENGTH: 24 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 245 atatcatatg atggaagtaa taaa		
		24
<210> SEQ ID NO 246 <211> LENGTH: 8 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 246 Ile Ser Tyr Asp Gly Ser Asn Lys 1 5		
<210> SEQ ID NO 247 <211> LENGTH: 60 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 247 gcgaaaaata ttgtactagt gatgtatgat atagactatc actactatgg gatggacgtc		
		60
<210> SEQ ID NO 248 <211> LENGTH: 20 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic <400> SEQUENCE: 248 Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr 1 5 10 15 Gly Met Asp Val 20		

-continued

<210> SEQ ID NO 249
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 249

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc      60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg    120
tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttt taatcggggc     180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc    240
agcagagtgg aggtcagga tgttggggtt tattactgca tgcaagctct aaaaactcct    300
ctcactttcg gcggaggggac caaggtggag atcaga                               336
  
```

<210> SEQ ID NO 250
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 250

```

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 Ser
      20            25            30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35            40            45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg
      100           105           110
  
```

<210> SEQ ID NO 251
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 251

```

cagagcctcc tgcataagtaa tggatacaac tat                                33
  
```

<210> SEQ ID NO 252
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 252

```

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
 1             5             10
  
```

-continued

<210> SEQ ID NO 253
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 253

ttgggtttt

9

<210> SEQ ID NO 254
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 254

Leu Gly Phe

1

<210> SEQ ID NO 255
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 255

atgcaagctc tacaaactcc tctcact

27

<210> SEQ ID NO 256
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 256

Met Gln Ala Leu Gln Thr Pro Leu Thr

1

5

<210> SEQ ID NO 257
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 257

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tctgtgagcag tctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180

gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt 300

gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg 360

accacgggtca ccgtctcctc a 381

<210> SEQ ID NO 258
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 258

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 Val 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 Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
 85 90 95
 Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
 100 105 110
 Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 259

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 259

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctcctgca ggtctagtca gagcctctcg catagtaatg gatacaacta tttggattgg 120
 tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttt taatcggggc 180
 tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttgggtt tattactgca tgcaagctct acaaaactcct 300
 ctcactttcg gcggaggggac caaggtggag atcaaa 336

<210> SEQ ID NO 260

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 260

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 Ser
 20 25 30
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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

-continued

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

<210> SEQ ID NO 261
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 261

```

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc      60
tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaaatatt      300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg ggggcaaggg      360
accacgggtca ccgtctcctc a                                           381

```

<210> SEQ ID NO 262
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 262

```

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 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 Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
      100          105          110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

```

<210> SEQ ID NO 263
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 263

```

gatattgtga tgactcagtc tccactctcc ctgcccgtea cccctggaga gccggcctcc      60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg      120
tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttt taatcggggc      180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc      240

```

-continued

```

agcagagtgg aggctgagga tgttgggggtt tattactgca tgcaagctct acaaaactcct 300
ctcactttcg gcggagggac caaggtggag atcaaaa 336

```

```

<210> SEQ ID NO 264
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 264

```

```

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 Ser
          20           25           30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105          110

```

```

<210> SEQ ID NO 265
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 265

```

```

caggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag tctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg 360
accacgggtca ccgtctcctc a 381

```

```

<210> SEQ ID NO 266
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 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 Ala Val 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 Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val

```

-continued

50	55	60	
Lys Gly Arg Phe Thr	Ile Ser Arg Asp Asn Ser	Lys Lys Thr Leu Tyr	
65	70	75	80
Leu Gln Met Asn Ser	Leu Arg Ala Glu Asp Thr	Ala Val Tyr Asn Cys	
	85	90	95
Ala Lys Asn Ile Val	Leu Val Met Tyr Asp Ile	Asp Tyr His Tyr Tyr	
	100	105	110
Gly Met Asp Val Trp	Gly Gln Gly Thr Thr	Val Thr Val Ser Ser	
	115	120	125

<210> SEQ ID NO 267
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 267

ggattcacct tcagtagcta tggc 24

<210> SEQ ID NO 268
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 268

Gly Phe Thr Phe Ser Ser Tyr Gly
 1 5

<210> SEQ ID NO 269
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 269

atatcatatg atggaagtaa taaa 24

<210> SEQ ID NO 270
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 270

Ile Ser Tyr Asp Gly Ser Asn Lys
 1 5

<210> SEQ ID NO 271
 <211> LENGTH: 60
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 271

gcgaaaaata ttgtactagt gatgtatgat atagactatc actactatgg gatggacgtc 60

<210> SEQ ID NO 272
 <211> LENGTH: 20

-continued

<212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 272

Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
 1 5 10 15

Gly Met Asp Val
 20

<210> SEQ ID NO 273
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 273

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctctctgca ggtctagtca gagcctctcg catagtaatg gatacaacta tttggattgg 120
 tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttt taatcggggc 180
 tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300
 ctcactttcg gcggaggggac caaggtggag atcaga 336

<210> SEQ ID NO 274
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 274

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 Ser
 20 25 30

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

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

<210> SEQ ID NO 275
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 275

cagagcctcc tgcataagtaa tggatacaac tat

33

-continued

<210> SEQ ID NO 276
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 276

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
 1 5 10

<210> SEQ ID NO 277
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 277

ttgggtttt

9

<210> SEQ ID NO 278
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 278

Leu Gly Phe
 1

<210> SEQ ID NO 279
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 279

atgcaagctc tacaaactcc tctcact

27

<210> SEQ ID NO 280
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 280

Met Gln Ala Leu Gln Thr Pro Leu Thr
 1 5

<210> SEQ ID NO 281
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 281

caggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tctgtgtcag tctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180

gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240

-continued

```

ctgcaaatga acagcctgag agctgaggac acggtctgtg ataattgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg 360
accacgggtca cegtctcttc a 381

```

```

<210> SEQ ID NO 282
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 282

```

```

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 Val 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 Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
          50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
          65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
          85          90          95
Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
          100         105         110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115         120         125

```

```

<210> SEQ ID NO 283
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 283

```

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctctcg catagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttt taatcggggc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct acaaactcct 300
ctcactttcg gcggaggggac caaggtggag atcaaa 336

```

```

<210> SEQ ID NO 284
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 284

```

```

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 Ser
          20          25          30

```

-continued

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

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

<210> SEQ ID NO 285
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 285

```

cagggtgcagc tgggtggagtc tggggggaggc gtggtccagc ctgggaggtc cctgagactc      60
tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaaatatt      300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg ggggcaaggg      360
accacgggtca ccgtctcctc a                                     381

```

<210> SEQ ID NO 286
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 286

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 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 Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
 100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 287
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 287

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccttgaga gccggcctcc	60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta ttggattgg	120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttt taatcggggc	180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc	240
agcagagtgg aggtcgagga tgttgggggt tattactgca tgcaagctct acaaaactct	300
ctcactttcg gcggaggggac caagtgagg atcaaa	336

<210> SEQ ID NO 288

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 288

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 Ser	
20 25 30	
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys	
100 105 110	

<210> SEQ ID NO 289

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 289

cagatcacct tgaaggagtc tggctcctacg ctggtaaaac ccacacagac cctcagctg	60
acctgcacct tctctgggtt ctactcagc gctagtggag tgggtgtggg ctggttccgt	120
cagccccag gaaaggccct ggagtggctt gcactcattt attggaatga tgataagcgt	180
tacagcccat ctctaaagaa cagcctcacc atcaccaagg acacctccaa aaaccagggtg	240
gtccttataa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga	300
atacatctat ggtcctactt ctactacggt atggacgtct ggggccaagg gaccacggtc	360
accgtctcct ca	372

<210> SEQ ID NO 290

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 290

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

<210> SEQ ID NO 291

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 291

gggttctcac tcagcgctag tggagtgggt

30

<210> SEQ ID NO 292

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 292

Gly Phe Ser Leu Ser Ala Ser Gly Val Gly
 1 5 10

<210> SEQ ID NO 293

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 293

atttattgga atgatgataa g

21

<210> SEQ ID NO 294

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 294

Ile Tyr Trp Asn Asp Asp Lys
 1 5

<210> SEQ ID NO 295

<211> LENGTH: 48

-continued

<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 295

gcacacagaa tacatctatg gtcctacttc tactacggta tggacgtc 48

<210> SEQ ID NO 296
 <211> LENGTH: 16
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 296

Ala His Arg Ile His Leu Trp Ser Tyr Phe Tyr Tyr Gly Met Asp Val
 1 5 10 15

<210> SEQ ID NO 297
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 297

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctctctgca ggtctagtca gactctctcg catagtaatg gatacaacta tttcgattgg 120
 tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 180
 tccgggggtcc ctgacagatt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttggaatt tattactgca tgcaagctct acaaactcct 300
 ctcactttcg gcggaggggac caaggtggag atcaga 336

<210> SEQ ID NO 298
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 298

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 Thr Leu Leu His Ser
 20 25 30
 Asn Gly Tyr Asn Tyr Phe Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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 Ile Tyr Tyr Cys Met Gln Ala
 85 90 95
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg
 100 105 110

<210> SEQ ID NO 299
 <211> LENGTH: 33
 <212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 299

cagactctcc tgcataagtaa tggatacaac tat

33

<210> SEQ ID NO 300
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 300

Gln Thr Leu Leu His Ser Asn Gly Tyr Asn Tyr
1 5 10

<210> SEQ ID NO 301
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 301

ttgggttct

9

<210> SEQ ID NO 302
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 302

Leu Gly Ser
1

<210> SEQ ID NO 303
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 303

atgcaagctc tacaaactcc tctcact

27

<210> SEQ ID NO 304
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 304

Met Gln Ala Leu Gln Thr Pro Leu Thr
1 5

<210> SEQ ID NO 305
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 305

```

cagatcacct tgaaggagtc tggtcctacg ctggtaaaac ccacacagac cctcacgctg    60
acctgcacct tctctgggtt ctcactcagc gctagtggag tgggtgtggg ctgggttcgt    120
cagcccccag gaaaggccct ggagtggctt gcaactcattt attggaatga tgataagcgt    180
tacagcccat ctctaagaa cagcctcacc atcaccaagg acacctccaa aaaccagggtg    240
gtccttataa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga    300
atacatctat ggtcctactt ctactacggt atggacgtct ggggccaaagg gaccacggtc    360
accgtctcct ca                                     372

```

<210> SEQ ID NO 306

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 306

```

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

```

<210> SEQ ID NO 307

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 307

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc    60
atctcctgca ggtctagtca gactctctcg catagtaatg gatacaacta tttcgattgg    120
tacctgcaga agccagggca gtctccacag ctctgatctt atttgggttc taatcggggc    180
tccgggggtcc ctgacagatt cagtggcagt ggatcaggca cagattttac actgaaaatc    240
agcagagtgg aggctgagga tgttgaattt tattactgca tgcaagctct acaaaactcct    300
ctcactttcg gcggaggggac caaggtggag atcaaaa                                     336

```

<210> SEQ ID NO 308

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 308

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 Thr Leu Leu His Ser
 20 25 30
 Asn Gly Tyr Asn Tyr Phe Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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 Ile Tyr Tyr Cys Met Gln Ala
 85 90 95
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> SEQ ID NO 309

<211> LENGTH: 372

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 309

cagatcacct tgaaggagtc tggctcctacg ctggtgaaac ccacacagac cctcacgctg 60
 acctgcacct tctctggggt ctcactcagc gctagtggag tgggtgtggg ctggatccgt 120
 cagcccccag gaaaggccct ggagtggctt gcaactcattt attggaatga tgataagcgc 180
 tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccagggtg 240
 gtccttaciaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga 300
 atacatctat ggtcctactt ctactacggt atggacgtct ggggggcaagg gaccacggtc 360
 accgtctcct ca 372

<210> SEQ ID NO 310

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 310

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

-continued

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

<210> SEQ ID NO 311
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 311

gatattgtga	tgactcagtc	tccactctcc	ctgcccgtca	ccctggaga	gccggcctcc	60
atctcctgca	ggcttagtca	gactctcctg	catagtaatg	gatacaacta	tttgattgg	120
tacctgcaga	agccagggca	gtctccacag	ctcctgatct	atttgggttc	taatcgggcc	180
tccgggggtcc	ctgacagggt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tgttgggggt	tattactgca	tgcaagctct	acaaactcct	300
ctcactttcg	gcggagggac	caagtgagg	atcaaa			336

<210> SEQ ID NO 312
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 312

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	Thr	Leu	Leu	His	Ser
			20					25					30		
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35					40					45			
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	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	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys
		100					105						110		

<210> SEQ ID NO 313
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 313

cagggttcagc	tggtgcagtc	tggacctgag	gtgaagaacc	ctggggcctc	agtgaaggtc	60
tcctgcaagg	cttctgggta	cacctttacc	acctatggta	tcagttgggt	acgacaggcc	120
cctggacaag	ggcttgagtg	gatgggatgg	atcagcgggt	acaatggtaa	aacaaacgat	180
gcacagaagt	tccaggacag	agtcgccatg	accacagaca	catccacgag	cacagcctac	240
atggagctga	ggagcctgag	atctgacgac	acggccattt	attactgttc	gagagatcgt	300
ttagtagtac	cacctgccct	taattattcc	tactacgtta	tggacgtctg	gggccaaggg	360
accacgggtca	ccgtctcctc	a				381

-continued

<210> SEQ ID NO 314
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 314

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

<210> SEQ ID NO 315
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 315

ggttacacct ttaccaccta tggt

24

<210> SEQ ID NO 316
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 316

Gly	Tyr	Thr	Phe	Thr	Thr	Tyr	Gly
1				5			

<210> SEQ ID NO 317
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 317

atcagcggtt acaatggtaa aaca

24

<210> SEQ ID NO 318
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 318

Ile Ser Gly Tyr Asn Gly Lys Thr
 1 5

<210> SEQ ID NO 319

<211> LENGTH: 60

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 319

tcgagagatc gtttagtagt accacctgcc cttaattatt cctactacgt tatggacgtc 60

<210> SEQ ID NO 320

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 320

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Ser Tyr Tyr
 1 5 10 15

Val Met Asp Val
 20

<210> SEQ ID NO 321

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 321

gatgttgatga tgactcagtc tccactctcc ctgcccgtca cccttgagaca gccggcctcc 60

atctctctgca ggtctagatga aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120

tctcagcaga ggccaggatga atctccaagg cgcctaattt ataagggttc taaccgggac 180

tctgggggtcc cagacagatt cagcggcagc gggtcaggca ctgatttcac actgaaaatc 240

agcaggggtgg aggctgagga tggtgggggtt tattactgca tgcaagggtac acactggccg 300

tacacttttg gccagggggac caagctggag atcaaaa 336

<210> SEQ ID NO 322

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 322

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1 5 10 15

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

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

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

-continued

65	70	75	80
----	----	----	----

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

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

<210> SEQ ID NO 323
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 323

caaagcctcg tatacagtga tggaaacacc tac

33

<210> SEQ ID NO 324
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 324

Gln Ser Leu Val Tyr Ser Asp Gly Asn Thr Tyr
 1 5 10

<210> SEQ ID NO 325
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 325

aaggtttct

9

<210> SEQ ID NO 326
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 326

Lys Val Ser
 1

<210> SEQ ID NO 327
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 327

atgcaaggta cacactggcc gtacact

27

<210> SEQ ID NO 328
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 328

-continued

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 329

<211> LENGTH: 381

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 329

```

cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc   60
tcttgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc   120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat   180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac   240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt   300
ttagtagtac cacctgcctt taattattcc tactacgtta tggacgtctg gggccaaggg   360
accacgggtca ccgtctcctc a                                     381

```

<210> SEQ ID NO 330

<211> LENGTH: 127

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 330

```

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

```

<210> SEQ ID NO 331

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 331

```

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc   60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg   120
tctcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccgggac   180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc   240

```

-continued

```

agcagggtgg aggctgagga tgttggggtt tattactgca tgcaaggtag acactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

```

```

<210> SEQ ID NO 332
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 332

```

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1             5             10             15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20             25             30
Asp Gly Asn Thr Tyr Leu Asn Trp Ser Gln Gln Arg Pro Gly Gln Ser
      35             40             45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
      85             90             95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100            105            110

```

```

<210> SEQ ID NO 333
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 333

```

```

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc acctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgatg gatgggatgg atcagcggtt acaatggtaa aacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300
ttagtagtac cacctgccct taattattcc tactacgtta tggacgtctg ggggcaaggg 360
accacgggtca cgtctcctc a 381

```

```

<210> SEQ ID NO 334
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 334

```

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1             5             10             15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
      20             25             30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35             40             45

```

-continued

Gly Trp Ile Ser Gly Tyr Asn Gly Lys Thr Asn Tyr Ala Gln Lys Leu
50 55 60

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

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

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Ser Tyr Tyr
100 105 110

Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 335
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 335

```

gatgttgatga tgactcagtc tccactctcc ctgcccgtca cccttgagaca gccggcctcc      60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg      120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccggggac      180
tctgggggtcc cagacagatt cagcggcagc gggtcaggca ctgatttcac actgaaaatc      240
agcaggggtgg aggctgagga tggtgggggtt tattactgca tgcaaggtag acactggccg      300
tacacttttg gccagggggac caagctggag atcaaa                                336

```

<210> SEQ ID NO 336
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 336

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

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

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

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
85 90 95

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

<210> SEQ ID NO 337
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 337

```

gaggtgcagc tgggtgagtc tgggggaggc ctggtcaagc ctgggggggtc cctgagactc      60

```

-continued

```

tctctgtcag cctctggatt caccttcagt agctatagca tggactgggt ccgccaggct 120
ccaggaaggg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
gcagactctg tgaagggccg attcaccatc tcagagaca ccgccaagaa ctcaactgtat 240
ctgcaaatga acagcctgag agacgaggac acggctgttt attactgtgc gagagagggc 300
agtagcagac tttttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

```

```

<210> SEQ ID NO 338
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 338

```

```

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 Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20             25             30
Ser Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35             40             45
Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
          50             55             60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ala Lys Asn Ser Leu Tyr
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 Glu Gly Ser Ser Arg Leu Phe Asp Tyr Trp Gly Gln Gly Thr
          100            105            110
Leu Val Thr Val Ser Ser
          115

```

```

<210> SEQ ID NO 339
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 339

```

```

ggattcacct tcagtagcta tagc

```

24

```

<210> SEQ ID NO 340
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 340

```

```

Gly Phe Thr Phe Ser Ser Tyr Ser
 1             5

```

```

<210> SEQ ID NO 341
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 341

```

-continued

attagtagta gtagtagtta cata

24

<210> SEQ ID NO 342
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 342

Ile Ser Ser Ser Ser Ser Tyr Ile
 1 5

<210> SEQ ID NO 343
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 343

gcgagagagg gcagtagcag actttttgac tac

33

<210> SEQ ID NO 344
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 344

Ala Arg Glu Gly Ser Ser Arg Leu Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 345
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 345

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gagtattagt agctgggttg cctggtatca gcagagacca 120

gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaggttg agtcccatca 180

aggttcagcg gcagtggtac tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gaggattttg caacttatta ctgccaacag tataatagtt attggtacac ttttgccag 300

gggaccaagc tggagatcaa a 321

<210> SEQ ID NO 346
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 346

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
 20 25 30

-continued

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

Tyr Lys Ala Ser Ser Leu Glu Gly 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 Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Trp Tyr
 85 90 95

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

<210> SEQ ID NO 347
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 347

cagagtatta gtagctgg

18

<210> SEQ ID NO 348
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 348

Gln Ser Ile Ser Ser Trp
 1 5

<210> SEQ ID NO 349
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 349

aaggcgtct

9

<210> SEQ ID NO 350
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 350

Lys Ala Ser
 1

<210> SEQ ID NO 351
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 351

caacagtata atagttattg gtacact

27

<210> SEQ ID NO 352

-continued

<211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 352

Gln Gln Tyr Asn Ser Tyr Trp Tyr Thr
 1 5

<210> SEQ ID NO 353
 <211> LENGTH: 354
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 353

gaggtgcagc tgggtggagtc tggggggaggc ctggtcaagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt caccttcagt agctatagca tggactgggt ccgccaggct 120
 ccaggaaggg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
 gcagactctg tgaagggccg attcaccatc tccagagaca ccgccaagaa ctactgtat 240
 ctgcaaatga acagcctgag agacgaggac acggctgttt attactgtgc gagagagggc 300
 agtagcagac tttttgacta ctgggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 354
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 354

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 Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ser Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ala Lys Asn Ser Leu Tyr
 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 Glu Gly Ser Ser Arg Leu Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 355
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 355

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60

-continued

```

atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca gcagagacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaagggtg agtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gaggattttg caacttatta ctgccaacag tataatagtt attggtacac ttttggccag 300
gggaccaagc tggagatcaa a 321

```

```

<210> SEQ ID NO 356
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 356

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
      20      25      30
Leu Ala Trp Tyr Gln Gln Arg Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35      40      45
Tyr Lys Ala Ser Ser Leu Glu Gly 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 Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Trp Tyr
      85      90      95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100      105

```

```

<210> SEQ ID NO 357
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 357

```

```

gagggtgcagc tgggtggagtc tggggggaggc ctggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct 120
ccaggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggc 300
agtagcagac tttttgacta ctggggccaa ggaaccctgg tcaccgtctc ctca 354

```

```

<210> SEQ ID NO 358
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 358

```

```

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 Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
      20      25      30

```

-continued

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

Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr 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 Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Ser Ser Arg Leu Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 359

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 359

gacatccaga tgacccagtc tccttcaccc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatacagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag tataatagtt attggtacac ttttggccag 300

gggaccaagc tggagatcaa a 321

<210> SEQ ID NO 360

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 360

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 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 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

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

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

<210> SEQ ID NO 361

<211> LENGTH: 384

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 361

```

caggtgcacc tgggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc    60
tctctgtcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct    120
ccaggaaggg ggctggagtg gatttcatac attagtaatg atggtggtac caaatactat    180
gtggactctg tggaggggcc attcatcatt tccagggaca acgccaagaa ctcattgtat    240
ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag    300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctggggccaa    360
gggaccacgg tcaccgtcgc ctca                                           384

```

<210> SEQ ID NO 362

<211> LENGTH: 128

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 362

```

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

```

<210> SEQ ID NO 363

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 363

```

ggattcacct tcagtacca ctac                                           24

```

<210> SEQ ID NO 364

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 364

```

Gly Phe Thr Phe Ser Asp His Tyr
 1         5

```

<210> SEQ ID NO 365

<211> LENGTH: 24

<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 365

attagtaatg atggtggtac caaa

24

<210> SEQ ID NO 366
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 366

Ile Ser Asn Asp Gly Gly Thr Lys
 1 5

<210> SEQ ID NO 367
 <211> LENGTH: 63
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 367

gcgagagatc agggatatat tggctacgac tcgtattatt actattccta cggtatggac

60

gtc

63

<210> SEQ ID NO 368
 <211> LENGTH: 21
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 368

Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
 1 5 10 15

Tyr Gly Met Asp Val
 20

<210> SEQ ID NO 369
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 369

aaaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc

60

ctctcctgta gggccagtca gagtgttaac aacaaattct tagcctggta ccagcagaaa

120

tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca

180

gacaggttca gtggcagtggt gtctgggacc gacttcactc tcaccatcag cggactggag

240

cctgaagatt ttgaagtgtta ttattgtcaa gtatatggta actcactcac tctcggcgga

300

gggaccaagg tggagatcaa g

321

<210> SEQ ID NO 370
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 370

```

Lys Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1           5           10          15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
          20          25          30
Phe Leu Ala Trp Tyr Gln Gln Lys Ser 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 Gly Leu Glu
65          70          75          80
Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
          85          90          95
Thr Leu Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105

```

<210> SEQ ID NO 371

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 371

cagagtgtta acaacaaatt c

21

<210> SEQ ID NO 372

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 372

```

Gln Ser Val Asn Asn Lys Phe
 1           5

```

<210> SEQ ID NO 373

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 373

ggtgcatcc

9

<210> SEQ ID NO 374

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 374

```

Gly Ala Ser
 1

```

<210> SEQ ID NO 375

<211> LENGTH: 24

<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 375

caagtatatg gtaactcact cact

24

<210> SEQ ID NO 376
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 376

Gln Val Tyr Gly Asn Ser Leu Thr
 1 5

<210> SEQ ID NO 377
 <211> LENGTH: 384
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 377

cagggtgcagc tgggtggagtc tggggggaggc ttggtcaagc ctggaggggc cctgagactc 60
 tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120
 ccaggaaggg ggctggagtg gatttcatac attagtaatg atggtgggtac caaatactat 180
 gtggactctg tggagggccg attcatcatt tccagggaca acgccaagaa ctcatgttat 240
 ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag 300
 ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctggggccaa 360
 gggaccacgg tcaccgtctc ctca 384

<210> SEQ ID NO 378
 <211> LENGTH: 128
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 378

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

-continued

<210> SEQ ID NO 379
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 379

```

gaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc      60
ctctcctgta gggccagtc gagtgtaaac aacaaattct tagcctggta ccagcagaaa      120
tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca      180
gacaggttca gtggcagtggt gtctgggacc gacttcactc tcaccatcag cggactggag      240
cctgaagatt ttgaagtgtg ttattgtcaa gtatatggta actcactcac tctcggcgga      300
gggaccaagg tggagatcaa a                                     321
  
```

<210> SEQ ID NO 380
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 380

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
          20           25           30
Phe Leu Ala Trp Tyr Gln Gln Lys Ser 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 Gly Leu Glu
          65           70           75           80
Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
          85           90           95
Thr Leu Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105
  
```

<210> SEQ ID NO 381
 <211> LENGTH: 384
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 381

```

caggtgcagc tgggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc      60
tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct      120
ccaggaaggg ggctggagtg ggtttcatat attagtaatg atggtggtac caaatactac      180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctactgtat      240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagatcag      300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctgggggcaa      360
gggaccacgg tcaccgtctc ctca                                     384
  
```

<210> SEQ ID NO 382

-continued

<211> LENGTH: 128
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 382

```
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 His
          20           25           30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35           40           45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr 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 Val Tyr Tyr Cys
          85           90           95
Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
          100          105          110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115          120          125
```

<210> SEQ ID NO 383
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 383

```
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc      60
ctctcctgca gggccagtca gagtgtaaac aacaaattct tagcctggta ccagcagaaa      120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca      180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag      240
cctgaagatt ttgcagtgtg ttactgtcaa gtatatggta actcactcac ttctggcgga      300
gggaccaagg tggagatcaa a                                     321
```

<210> SEQ ID NO 384
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 384

```
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 Asn Asn Lys
          20           25           30
Phe 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
```

-continued

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
85 90 95

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

<210> SEQ ID NO 385

<211> LENGTH: 360

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 385

gaggtgcaga aggtggagtc tgggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccaggaag gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaggga cctcggtcac cgtctcctca 360

<210> SEQ ID NO 386

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 386

Glu Val Gln Lys 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 Ser Thr Tyr
20 25 30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 387

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 387

ggattcacct tcagtactta taac

24

<210> SEQ ID NO 388

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 388

Gly Phe Thr Phe Ser Thr Tyr Asn
 1 5

<210> SEQ ID NO 389
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 389

attaggagta gtagtaatta cata

24

<210> SEQ ID NO 390
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 390

Ile Arg Ser Ser Ser Asn Tyr Ile
 1 5

<210> SEQ ID NO 391
 <211> LENGTH: 39
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 391

gcgagagatg gcagcagttg gtacgactac tctgactac

39

<210> SEQ ID NO 392
 <211> LENGTH: 13
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 392

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr
 1 5 10

<210> SEQ ID NO 393
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 393

gacatccaga tgaccagtc tccttcaccc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acagatacca 120

gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcgcct 240

gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

-continued

<210> SEQ ID NO 394
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 394

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
 20        25        30
Leu Ala Trp Tyr Gln Gln Ile 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 Ile Ile Ser Ser Leu Gln Pro
 65        70        75        80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
 85        90        95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100       105

```

<210> SEQ ID NO 395
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 395

cagagtatta gtagctgg

18

<210> SEQ ID NO 396
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 396

```

Gln Ser Ile Ser Ser Trp
 1         5

```

<210> SEQ ID NO 397
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 397

aaggcgtct

9

<210> SEQ ID NO 398
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 398

-continued

Lys Ala Ser
1

<210> SEQ ID NO 399
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 399

caacagtata ttagttattc tcggacg

27

<210> SEQ ID NO 400
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 400

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
1 5

<210> SEQ ID NO 401
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 401

gagggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccaggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctcctca 360

<210> SEQ ID NO 402
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 402

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 Ser Thr Tyr
20 25 30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln

-continued

100	105	110	
Gly Thr Leu Val Thr Val Ser Ser			
115	120		
<210> SEQ ID NO 403			
<211> LENGTH: 321			
<212> TYPE: DNA			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 403			
gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc		60	
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acagatacca		120	
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca		180	
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct		240	
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa		300	
gggaccaagg tggaaatcaa a		321	

<210> SEQ ID NO 404			
<211> LENGTH: 107			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 404			
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp			
20 25 30			
Leu Ala Trp Tyr Gln Gln Ile 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 Ile Ile Ser Ser Leu Gln Pro			
65 70 75 80			
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg			
85 90 95			
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys			
100 105			

<210> SEQ ID NO 405			
<211> LENGTH: 360			
<212> TYPE: DNA			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 405			
gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctggggggtc cctgagactc		60	
tcctgtgcag cctctggatt caccttcagt acttataaca tgaactgggt ccgccaggct		120	
ccaggaaggg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac		180	
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat		240	
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc		300	
agcagttggt acgactactc tgactactgg ggccaaggaa ccctggtcac cgtctctca		360	

-continued

<210> SEQ ID NO 406
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 406

```

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 Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20           25           30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Val Tyr Tyr Cys
 85           90           95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
 100          105          110
Gly Thr Leu Val Thr Val Ser Ser
 115          120

```

<210> SEQ ID NO 407
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 407

```

gacatccaga tgacccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca gcagaaacca    120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct    240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa    300
gggaccaagg tggaaatcaa a                                           321

```

<210> SEQ ID NO 408
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 408

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 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 Ser Gly Val Pro Ser Arg Phe Ser Gly
 50           55           60

```

-continued

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 Ile Ser Tyr Ser Arg
85 90 95

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

<210> SEQ ID NO 409
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 409

gagggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccaggggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccagggaa ccctgggtcac cgtctcctca 360

<210> SEQ ID NO 410
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 410

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 Ser Thr Tyr
20 25 30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 411
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 411

ggattcacct tcagtactta taac

24

<210> SEQ ID NO 412

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<211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 412

Gly Phe Thr Phe Ser Thr Tyr Asn
 1 5

<210> SEQ ID NO 413
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 413

attaggagta gtagtaatta cata

24

<210> SEQ ID NO 414
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 414

Ile Arg Ser Ser Ser Asn Tyr Ile
 1 5

<210> SEQ ID NO 415
 <211> LENGTH: 39
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 415

gcgagagatg gcagcagttg gtacgactac tctgactac

39

<210> SEQ ID NO 416
 <211> LENGTH: 13
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 416

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr
 1 5 10

<210> SEQ ID NO 417
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 417

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acagatacca 120

gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180

aggttcagcg gcagtggtgc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240

-continued

gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 418
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 418

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Ile 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 Ile Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 419
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 419

cagagtatta gtagctgg 18

<210> SEQ ID NO 420
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 420

Gln Ser Ile Ser Ser Trp
 1 5

<210> SEQ ID NO 421
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 421

aaggcgtct 9

<210> SEQ ID NO 422
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 422

Lys Ala Ser
1

<210> SEQ ID NO 423

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 423

caacagtata ttagttattc tcggacg

27

<210> SEQ ID NO 424

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 424

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
1 5

<210> SEQ ID NO 425

<211> LENGTH: 360

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 425

gagggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc 60

tctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccagget 120

ccaggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180

gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat 240

ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300

agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctcctca 360

<210> SEQ ID NO 426

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 426

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60Lys 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 Asp Asp Thr Ala Val Tyr Tyr Cys

-continued

85	90	95	
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln			
100	105	110	
Gly Thr Leu Val Thr Val Ser Ser			
115	120		

<210> SEQ ID NO 427
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 427

gacatccaga tgacccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acagatacca	120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct	240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa	300
gggaccaagg tggaaatcaa a	321

<210> SEQ ID NO 428
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 428

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp	
20 25 30	
Leu Ala Trp Tyr Gln Gln Ile 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 Ile Ile Ser Ser Leu Gln Pro	
65 70 75 80	
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg	
85 90 95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys	
100 105	

<210> SEQ ID NO 429
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 429

gagggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctgggggggc cctgagactc	60
tcctgtgcag cctctggatt caccttcagt acttataaca tgaactgggt ccgccaggct	120
ccaggaaggg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac	180
gcagactcag tgaagggccg attcaccatc tocagagaca acgccaagaa ctactgtat	240

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ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaaggaa ccctggtcac cgtctcctca 360

```

```

<210> SEQ ID NO 430
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 430

```

```

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 Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20        25        30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35        40        45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Val Tyr Tyr Cys
 85        90        95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100       105       110
Gly Thr Leu Val Thr Val Ser Ser
115       120

```

```

<210> SEQ ID NO 431
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 431

```

```

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 432
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 432

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
 20        25        30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35        40        45

```

-continued

Tyr Lys Ala Ser Ser Leu Glu 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

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

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

<210> SEQ ID NO 433
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 433

gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccaggaag gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagag ttcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccagggaa ccctgggtcac cgtctcctca 360

<210> SEQ ID NO 434
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 434

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 Ser Thr Tyr
20 25 30

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

Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser 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 Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 435
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 435

ggattcacct tcagtactta taac

-continued

<210> SEQ ID NO 436
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 436

Gly Phe Thr Phe Ser Thr Tyr Asn
 1 5

<210> SEQ ID NO 437
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 437

attaggagta gtagtaatta cata

24

<210> SEQ ID NO 438
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 438

Ile Arg Ser Ser Ser Asn Tyr Ile
 1 5

<210> SEQ ID NO 439
 <211> LENGTH: 39
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 439

gcgagagatg gcagcagttg gtacgactac tctgactac

39

<210> SEQ ID NO 440
 <211> LENGTH: 13
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 440

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr
 1 5 10

<210> SEQ ID NO 441
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 441

gacatccaga tgacccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acaggtacca 120

gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaatgg ggtcccatca 180

-continued

```

aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 442
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 442

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
        20        25        30
Leu Ala Trp Tyr Gln Gln Val 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 Ile Ile Ser Ser Leu Gln Pro
        65        70        75        80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
        85        90        95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        100       105

```

```

<210> SEQ ID NO 443
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 443

```

```

cagagtatta gtagctgg 18

```

```

<210> SEQ ID NO 444
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 444

```

```

Gln Ser Ile Ser Ser Trp
 1         5

```

```

<210> SEQ ID NO 445
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 445

```

```

aaggcgtct 9

```

```

<210> SEQ ID NO 446
<211> LENGTH: 3
<212> TYPE: PRT

```


-continued

<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 446

Lys Ala Ser
 1

<210> SEQ ID NO 447
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 447

caacagtata ttagttattc tcggacg

27

<210> SEQ ID NO 448
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 448

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
 1 5

<210> SEQ ID NO 449
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 449

gagggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc 60
 tctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
 ccaggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
 gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagag ttcactgtat 240
 ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
 agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctcctca 360

<210> SEQ ID NO 450
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 450

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 Ser Thr Tyr
 20 25 30

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

Ser Ser Ile Arg Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60

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

-continued

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 Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln				
	100	105	110	
Gly Thr Leu Val Thr Val Ser Ser				
	115	120		

<210> SEQ ID NO 451
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 451

gacatccaga tgacccagtc tccttcaccc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acaggtacca	120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct	240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa	300
gggaccaagg tggaaatcaa a	321

<210> SEQ ID NO 452
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 452

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp	
20 25 30	
Leu Ala Trp Tyr Gln Gln Val 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 Ile Ile Ser Ser Leu Gln Pro	
65 70 75 80	
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg	
85 90 95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys	
100 105	

<210> SEQ ID NO 453
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 453

gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctggggggtc cctgagactc	60
tcctgtgcag cctctggatt caccttcagt acttataaca tgaactgggt ccgccaggct	120
ccaggaaggg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac	180

-continued

```
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctcaactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccagggaa ccttggtcac cgtctcctca 360
```

```
<210> SEQ ID NO 454
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 454
```

```
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 Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
          20          25          30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Val Tyr Tyr Cys
          85          90          95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
          100         105         110
Gly Thr Leu Val Thr Val Ser Ser
          115          120
```

```
<210> SEQ ID NO 455
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 455
```

```
gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcaactgcc gggccagtca gagtattagt agctgggttg cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttactctca ccatcagcag cctgcagcct 240
gatgattttg caactatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321
```

```
<210> SEQ ID NO 456
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 456
```

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
          20          25          30
```

-continued

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 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

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

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

<210> SEQ ID NO 457
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 457

gaggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc	60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct	120
ccaggaag gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac	180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttactgtat	240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc	300
agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctcctca	360

<210> SEQ ID NO 458
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 458

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 Ser Thr Tyr
 20 25 30

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

Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 459
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 459

ggattcacct tcagtactta taac

24

<210> SEQ ID NO 460

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 460

Gly Phe Thr Phe Ser Thr Tyr Asn

1 5

<210> SEQ ID NO 461

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 461

attaggagta gtagtaatta cata

24

<210> SEQ ID NO 462

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 462

Ile Arg Ser Ser Ser Asn Tyr Ile

1 5

<210> SEQ ID NO 463

<211> LENGTH: 39

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 463

gcgagagatg gcagcagttg gtacgactac tctgactac

39

<210> SEQ ID NO 464

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 464

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr

1 5 10

<210> SEQ ID NO 465

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 465

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc

60

-continued

```

atcacttgcc gggccagtca gagtattagt agctgggttg cctggatatca acagatacca 120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 466
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 466

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
        20        25        30
Leu Ala Trp Tyr Gln Gln Ile 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 Ile Ile Ser Ser Leu Gln Pro
65        70        75        80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
        85        90        95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        100       105

```

```

<210> SEQ ID NO 467
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 467

```

```

cagagtatta gtagctgg 18

```

```

<210> SEQ ID NO 468
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 468

```

```

Gln Ser Ile Ser Ser Trp
 1         5

```

```

<210> SEQ ID NO 469
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 469

```

```

aaggcgtct 9

```

-continued

```

<210> SEQ ID NO 470
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 470

```

```

Lys Ala Ser
1

```

```

<210> SEQ ID NO 471
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 471

```

```

caacagtata ttagttattc tcggacg

```

27

```

<210> SEQ ID NO 472
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 472

```

```

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
1           5

```

```

<210> SEQ ID NO 473
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 473

```

```

gagggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc   60
tctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct   120
ccaggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac   180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat   240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc   300
agcagttggt acgactactc tgactactgg ggccaggga cctggtcac cgtctcctca   360

```

```

<210> SEQ ID NO 474
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 474

```

```

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 Ser Thr Tyr
20          25          30

```

```

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

```

```

Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val

```

-continued

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 Asp Asp Thr Ala Val Tyr Tyr Cys			
	85	90	95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln			
	100	105	110
Gly Thr Leu Val Thr Val Ser Ser			
	115	120	

<210> SEQ ID NO 475
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 475

gacatccaga tgacccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggccagtca gagtattagt agctgggttg cctgggtatca acagatacca	120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct	240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa	300
gggaccaagg tggaaatcaa a	321

<210> SEQ ID NO 476
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 476

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly	
1	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp	
20	30
Leu Ala Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile	
35	45
Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly	
50	60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro	
65	80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg	
85	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys	
100	105

<210> SEQ ID NO 477
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 477

gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctgggggggtc cctgagactc	60
---	----

-continued

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tctgtgcag cctctggatt caccttcagt acttataaca tgaactgggt cgcgcaggct 120
ccaggggaagg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaaggaa ccctggtcac cgtctcctca 360

```

```

<210> SEQ ID NO 478
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 478

```

```

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 Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
      20        25        30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35        40        45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr 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 Val Tyr Tyr Cys
      85        90        95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
      100       105       110
Gly Thr Leu Val Thr Val Ser Ser
      115        120

```

```

<210> SEQ ID NO 479
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 479

```

```

gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 480
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 480

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1         5         10        15

```

-continued

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 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
 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 481
 <211> LENGTH: 354
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 481

gaggtgcaac tagtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
 tcctgtgtag tctctggatt caccttcggt gactacgaca tgcactgggt ccgtcaagct 120
 acaggaagag gtctggagtg ggtctcaggt attgctcctg ctggtgacac atcctataca 180
 ggctccgtga agggccgatt caccatctcc agagagaatg ccaagaactc cttgcatctt 240
 caaatgaaca gcctgacaac cggggacacg gctatatatt attgtgctag agaggatata 300
 gcagtgccctg gttttgatta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 482
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 482

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

<210> SEQ ID NO 483
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 483

ggattcacct tcggtgacta cgac

24

<210> SEQ ID NO 484
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 484

Gly Phe Thr Phe Gly Asp Tyr Asp
1 5

<210> SEQ ID NO 485
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 485

attgctcctg ctggtgacac a

21

<210> SEQ ID NO 486
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 486

Ile Ala Pro Ala Gly Asp Thr
1 5

<210> SEQ ID NO 487
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 487

gctagagagg atatagcagt gcctgggtttt gattac

36

<210> SEQ ID NO 488
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 488

Ala Arg Glu Asp Ile Ala Val Pro Gly Phe Asp Tyr
1 5 10

<210> SEQ ID NO 489
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 489

-continued

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga acgaggcacc      60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct      120
ggccaggctc ccagactcct catctatggt gcattccacga gggccactgg cttccagacc      180
aggttcagtg gcagtgggct tgggacagag ttcactctca ccatcagcag cctgcagtct      240
gaagattttg cagtttatta ctgtcagcag tataataagt ggctccggt cactttcggc      300
cctggggacca aagtgattt caaa                                           324

```

```

<210> SEQ ID NO 490
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 490

```

```

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

```

```

<210> SEQ ID NO 491
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 491

```

```

cagagtgtta gcagcaac                                           18

```

```

<210> SEQ ID NO 492
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 492

```

```

Gln Ser Val Ser Ser Asn
 1         5

```

```

<210> SEQ ID NO 493
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 493

```

-continued

gggtgcatcc

9

<210> SEQ ID NO 494
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 494

Gly Ala Ser
 1

<210> SEQ ID NO 495
 <211> LENGTH: 30
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 495

cagcagtata ataagtggcc tccgttcact

30

<210> SEQ ID NO 496
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 496

Gln Gln Tyr Asn Lys Trp Pro Pro Phe Thr
 1 5 10

<210> SEQ ID NO 497
 <211> LENGTH: 354
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 497

gagggtgcaac tagtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tctgtgtag tctctggatt caccttcggt gactacgaca tgcaactgggt cctgcaagct 120

acaggaagag gtctggagtg ggtctcaggt attgctcctg ctggtgacac atcctataca 180

ggctccgtga agggccgatt caccatctcc agagagaatg ccaagaactc cttgcatctt 240

caaatgaaca gcctgacaac cggggacacg gctatatatt attgtgctag agaggatata 300

gcagtgcctg gttttgatta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 498
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 498

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 Val Ser Gly Phe Thr Phe Gly Asp Tyr
 20 25 30

Asp Met His Trp Val Arg Gln Ala Thr Gly Arg Gly Leu Glu Trp Val

-continued

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

<210> SEQ ID NO 499

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 499

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga acgaggcacc      60
ctctcctgca gggccagtca gagtgtagc agcaacttag cctggtacca gcagaaacct      120
ggccaggctc ccagactcct catctatggt gcattccacga gggccactgg ctccccagcc      180
aggttcagtg gcagtggggtc tgggacagag ttcactctca ccatcagcag cctgcagtct      240
gaagattttg cagtttatta ctgtcagcag tataataagt ggctccggt cactttcggc      300
cctgggacca aagtgatat caaa                                         324

```

<210> SEQ ID NO 500

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 500

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

<210> SEQ ID NO 501

<211> LENGTH: 354

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 501

-continued

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc    60
tcctgtgcag cctctggatt caccttcggt gactacgaca tgcaactgggt ccgccaagct    120
acaggaaaag gtctggagtg ggtctcagct attgctcctg ctggtgacac atactatcca    180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt    240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgctag agaggatata    300
gcagtgcctg gttttgatta ctggggccaa ggaaccctgg tcaccgtctc ctca        354

```

```

<210> SEQ ID NO 502
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 502

```

```

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

```

```

<210> SEQ ID NO 503
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 503

```

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc    60
ctctcctgca gggccagtcg gagtgtagc agcaacttag cctggtacca gcagaaacct    120
ggccaggctc ccaggtcctt catctatggt gcacccacca gggccactgg tatccagcc    180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct    240
gaagattttt cagtttatta ctgtcagcag tataataagt ggcctccgtt cactttcggc    300
cctgggacca aagtgatat caaa        324

```

```

<210> SEQ ID NO 504
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 504

```

-continued

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

<210> SEQ ID NO 505
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 505

caaattctgc tgggtgcaatc tggacctgag gtgaaggagc ctggggcctc agtgaaggtc 60
 tcctgcaagg cttctgggta cacctttacc aactacgcta tcagctgggt gcgacaggtc 120
 cctggacaag ggcttgatg gatgggatgg gtcagcgctt acaatgggtca cacaaactat 180
 gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240
 atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagaggggggt 300
 gtagtctgtc cagttgtctc ccaactctac aacggtatgg acgtctgggg ccaagggacc 360
 acggtcacgc tctctca 378

<210> SEQ ID NO 506
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 506

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

-continued

<210> SEQ ID NO 507
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 507

ggttacacct ttaccaacta cgct

24

<210> SEQ ID NO 508
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 508

Gly Tyr Thr Phe Thr Asn Tyr Ala
1 5

<210> SEQ ID NO 509
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 509

gtcagcgctt acaatggtca caca

24

<210> SEQ ID NO 510
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 510

Val Ser Ala Tyr Asn Gly His Thr
1 5

<210> SEQ ID NO 511
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 511

gcgagagggg gtgtagtcgt gccagttgct cccacttct acaacggtat ggacgtc

57

<210> SEQ ID NO 512
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 512

Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
1 5 10 15

Met Asp Val

<210> SEQ ID NO 513

-continued

<211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 513

```

gatattgtga tgactcagtt tccactctcc ctgcccgtca cccctggaga gccggcctcc      60
atctcctgca ggtctagtca gagcctctcg catattaatg aatacaacta tttggattgg      120
tacctaaaga agccagggca gtctccacag ctctgatct atttgggttt taatcggggc      180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc      240
agcagagtgg aggctgagga tgttggggtc tattactgca tgcaagctct tcaaaactccg      300
tggacgttag gccaaaggac caaggtggaa atcaaa                                336
  
```

<210> SEQ ID NO 514
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 514

```

Asp Ile Val Met Thr Gln Phe 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 Ile
      20             25            30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser
      35             40            45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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 Leu Gly Gln Gly Thr Lys Val Glu Ile Lys
      100            105           110
  
```

<210> SEQ ID NO 515
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 515

```

cagagcctcc tgcataataa tgaatacaac tat                                33
  
```

<210> SEQ ID NO 516
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 516

```

Gln Ser Leu Leu His Ile Asn Glu Tyr Asn Tyr
 1             5             10
  
```

<210> SEQ ID NO 517
 <211> LENGTH: 9

-continued

<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 517

ttgggtttt

9

<210> SEQ ID NO 518
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 518

Leu Gly Phe
 1

<210> SEQ ID NO 519
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 519

atgcaagctc ttcaaactcc gtggacg

27

<210> SEQ ID NO 520
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 520

Met Gln Ala Leu Gln Thr Pro Trp Thr
 1 5

<210> SEQ ID NO 521
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 521

cagggttcagc tgggtgcagtc tggacctgag gtgaaggagc ctggggcctc agtgaaggtc 60
 tcttgaagg cttctgggta cacctttacc aactacgcta tcagctgggt ggcacaggtc 120
 cctggacaag ggcttgatg gatgggatgg gtcagcgctt acaatggtea cacaaactat 180
 gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240
 atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagagggggg 300
 gtagtcgtgc cagttgtctc ccaacttctac aacggtatgg acgtctgggg ccaagggacc 360
 acggtcacgg tctcctca 378

<210> SEQ ID NO 522
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 522

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

<210> SEQ ID NO 523

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 523

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctcctgca ggtctagtca gagcctctcg catattaatg aatacaacta tttggattgg 120
 tacctaaaga agccagggca gtctccacag ctctgatct atttgggttt taatcgggcc 180
 tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttggggtc tattactgca tgcaagctct tcaaaactccg 300
 tggacgttag gccaaaggac caaggtggaa atcaaa 336

<210> SEQ ID NO 524

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 524

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 Ile
 20 25 30
 Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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 Leu Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

-continued

<210> SEQ ID NO 525
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 525

```
caggttcagc tggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc    60
tcctgcaagg cttctgggta cacctttacc aactacgcta tcagctgggt gcgacaggcc    120
cctggacaag ggcttagatg gatgggatgg gtcagcgctt acaatgggtc cacaaactat    180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac    240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagggggg    300
gtagtctgtc cagttgtctc ccacttctac aacggtatgg acgtctgggg gcaaggggacc    360
acggtcaccg tctcctca                                     378
```

<210> SEQ ID NO 526
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 526

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

<210> SEQ ID NO 527
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 527

```
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc    60
atctcctgca ggtctagtca gagcctcctg catattaatg aatacaacta tttggattgg    120
tacctgcaga agccagggca gtctccacag ctctgatctt atttgggttc taatcggggc    180
tccgggggtc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc    240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct tcaaaactccg    300
tggacgttcg gccaaaggac caagtgga atcaaa                                     336
```

-continued

<210> SEQ ID NO 528
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 528

```

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 Ile
          20           25           30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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> SEQ ID NO 529
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 529

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc      60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagca      120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactataca      180
ggctccgtga tgggccgatt caccatctcc agagacgctg ccaaaaactc cttctatctt      240
gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agaggggaata      300
agaacaccct atgattattg gggccaggga gcccggttca ccgtctcttc a                351

```

<210> SEQ ID NO 530
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 530

```

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 Leu Ser Ser Tyr
          20           25           30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
          35           40           45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Thr Gly Ser Val Met
          50           55           60
Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Ser Phe Tyr Leu
65           70           75           80

```

-continued

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

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

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 531
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 531

ggattcaccc taagtagcta cgac

24

<210> SEQ ID NO 532
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 532

Gly Phe Thr Leu Ser Ser Tyr Asp
 1 5

<210> SEQ ID NO 533
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 533

attggcagta ctggtagacac a

21

<210> SEQ ID NO 534
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 534

Ile Gly Ser Thr Gly Asp Thr
 1 5

<210> SEQ ID NO 535
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 535

gcaagagagg gaataagaac accctatgat tat

33

<210> SEQ ID NO 536
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 536

Ala Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr
 1 5 10

<210> SEQ ID NO 537
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 537

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtca gagtgtagc agcaatgtag cctggtagca gcagaaacct 120
 gggcaggctc ccaggctcct catctatggt gcacccacca gggccactgg tatccagcc 180
 aggttcagtg gcagtggggc tgggacagaa ttcactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataatt ggctccatt cactttcggc 300
 cctgggacca aagtggatat caaa 324

<210> SEQ ID NO 538
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 538

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

<210> SEQ ID NO 539
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 539

cagagtgtta gcagcaat

18

<210> SEQ ID NO 540
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 540

-continued

Gln Ser Val Ser Ser Asn
1 5

<210> SEQ ID NO 541
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 541

ggtgcatcc

9

<210> SEQ ID NO 542
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 542

Gly Ala Ser
1

<210> SEQ ID NO 543
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 543

cagcagtata ataattggcc tccattcact

30

<210> SEQ ID NO 544
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 544

Gln Gln Tyr Asn Asn Trp Pro Pro Phe Thr
1 5 10

<210> SEQ ID NO 545
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 545

gagggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tctgtgagc cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagca 120

acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactatata 180

ggctccgtga tgggccgatt caccatctcc agagacgctg ccaaaaactc cttctatctt 240

gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agaggggaata 300

agaacaccct atgattattg gggccaggga accctggtca ccgtctctc a 351

<210> SEQ ID NO 546
<211> LENGTH: 117

-continued

<212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 546

```

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

```

<210> SEQ ID NO 547
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 547

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc      60
ctctcctgca gggccagtca gagtgttagc agcaatgtag cctggtagca gcagaaacct      120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc      180
aggttcagtg gcagtgggtc tgggacagaa ttcactctca ccatcagcag cctgcagtct      240
gaagattttg cagtttatta ctgtcagcag tataataatt ggctccatt cactttcggc      300
cctgggacca aagtgatat caaa                                324

```

<210> SEQ ID NO 548
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 548

```

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

```

-continued

	85	90	95	
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys				
	100	105		

<210> SEQ ID NO 549
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 549

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc	60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagct	120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactatcca	180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt	240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggaata	300
agaacaccct atgattattg gggccaagga accctgggtca ccgtctcctc a	351

<210> SEQ ID NO 550
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 550

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

<210> SEQ ID NO 551
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 551

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc	60
ctctcctgca gggccagtc gagtgtagc agcaatttag cctggtacca gcagaaacct	120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatccagcc	180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct	240

-continued

```
gaagattttg cagtttatta ctgtcagcag tataataatt ggctccatt cactttcggc 300
cctgggacca aagtgatat caaa 324
```

```
<210> SEQ ID NO 552
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 552
```

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

```
<210> SEQ ID NO 553
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 553
```

```
gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagca 120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactataca 180
ggctccgtga tgggccgatt caccatctcc agagacgctg ccaaaaactc cttctatctt 240
gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agaggggaata 300
agaacaccct atgattattg gggccaggga gcccggtca cgtctctctc a 351
```

```
<210> SEQ ID NO 554
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 554
```

```
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 Leu Ser Ser Tyr
 20        25        30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
 35        40        45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Thr Gly Ser Val Met
 50        55        60
```

-continued

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

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

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

Val Thr Val Ser Ser
115

<210> SEQ ID NO 555
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 555

ggattcaccc taagtagcta cgac

24

<210> SEQ ID NO 556
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 556

Gly Phe Thr Leu Ser Ser Tyr Asp
1 5

<210> SEQ ID NO 557
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 557

attggcagta ctggtgacac a

21

<210> SEQ ID NO 558
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 558

Ile Gly Ser Thr Gly Asp Thr
1 5

<210> SEQ ID NO 559
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 559

gcaagagagg gaataagaac accctatgat tat

33

<210> SEQ ID NO 560
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 560

Ala	Arg	Glu	Gly	Ile	Arg	Thr	Pro	Tyr	Asp	Tyr
1				5					10	

<210> SEQ ID NO 561
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 561

gaaatagtga	tgacgcagtc	tccagccacc	ctgtctgtgt	ctccagggga	aagagccacc	60
ctctcctgca	gggccagtca	gagtgttagc	agcaatgtag	cctggtagca	gcagaaacct	120
ggccaggctc	ccaggtcctc	catctatggt	gcattccacca	gggccactgg	tatccagccc	180
aggttcagtg	gcagtggggc	tgggacagaa	ttcactctca	ccatcagcag	cctgcagtct	240
gaagattttg	cagtttatta	ctgtcagcag	tataataatt	ggcctccatt	cactttcggc	300
cctgggacca	aagtgatat	caaa				324

<210> SEQ ID NO 562
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 562

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

<210> SEQ ID NO 563
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 563

cagagtgtta gcagcaat

18

<210> SEQ ID NO 564
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 564

Gln Ser Val Ser Ser Asn
1 5

<210> SEQ ID NO 565

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 565

ggtgcatcc

9

<210> SEQ ID NO 566

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 566

Gly Ala Ser
1

<210> SEQ ID NO 567

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 567

cagcagtata ataattggcc tccattcact

30

<210> SEQ ID NO 568

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 568

Gln Gln Tyr Asn Asn Trp Pro Pro Phe Thr
1 5 10

<210> SEQ ID NO 569

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 569

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60

tctgtgagc cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagca 120

acaggaaaaa gtctggagtg ggtctcagct attggcagta ctggtgacac atactataca 180

ggctccgtga tgggccgatt caccatctcc agagacgctg ccaaaaaactc cttctatctt 240

gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agaggggaata 300

agaacaccct atgattattg gggccaggga accctgggtca ccgtctctc a 351

-continued

<210> SEQ ID NO 570
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 570

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

<210> SEQ ID NO 571
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 571

```
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc      60
ctctcctgca gggccagtca gagtgtagc agcaatgtag cctggtagca gcagaaacct      120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatccagcc      180
aggttcagtg gcagtgggtc tgggacagaa ttcactctca ccatcagcag cctgcagtct      240
gaagattttg cagtttatta ctgtcagcag tataataatt ggcctccatt cactttcggc      300
cctgggacca aagtgatat caaa                                324
```

<210> SEQ ID NO 572
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 572

```
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
  1             5             10             15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
          20             25             30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
          35             40             45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
          50             55             60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
```


-continued

65	70	75	80	
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro				
	85	90	95	
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys				
	100	105		

<210> SEQ ID NO 573
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 573

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc	60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagct	120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactatcca	180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt	240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggaata	300
agaacaccct atgattattg gggccaagga accctgggtca ccgtctcctc a	351

<210> SEQ ID NO 574
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 574

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

<210> SEQ ID NO 575
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 575

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc	60
ctctcctgca gggccagtca gagtgttagc agcaatttag cctggtacca gcagaaacct	120
ggccaggctc ccaggctcct catctatggt gcattccacca gggccactgg tatccagcc	180

-continued

```

aggttcagtg gcagtggggc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataatt ggctccatt cactttcggc 300
cctgggacca aagtgatat caaa 324

```

```

<210> SEQ ID NO 576
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 576

```

```

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

```

```

<210> SEQ ID NO 577
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 577

```

```

gaagtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgccca tgcactgggt ccggcaagct 120
ccaggaaggg gcctggagtg ggtctcaggt attaatgga acagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagca ctccctgtat 240
ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgt aaaagagggtg 300
actacgggat actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

```

```

<210> SEQ ID NO 578
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 578

```

```

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 Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
      20        25        30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```

-continued

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

<210> SEQ ID NO 579
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 579

ggattcacct ttgatgatta tgcc

24

<210> SEQ ID NO 580
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 580

Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5

<210> SEQ ID NO 581
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 581

attaattgga acagtggtag cata

24

<210> SEQ ID NO 582
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 582

Ile Asn Trp Asn Ser Gly Ser Ile
 1 5

<210> SEQ ID NO 583
 <211> LENGTH: 42
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 583

gtaaaagagg tgactacggg atactactac ggtatggacg tc

42

-continued

<210> SEQ ID NO 584
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 584

Val Lys Glu Val Thr Thr Gly Tyr Tyr Tyr Gly Met Asp Val
 1 5 10

<210> SEQ ID NO 585
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 585

gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgct gggccagtca gggcattagc agttatttag cctggatca gaaaaaacca 120
 gggaaagccc ctaacctcct gatctatgat gcattccatt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagaa ttcactctca cactcagcag cctgcagcct 240
 gaagattttg caacttatta ctgtcaacag cttaatatatt acccattcac ttctggccct 300
 gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 586
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 586

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

<210> SEQ ID NO 587
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 587

cagggcatta gcagttat

-continued

<210> SEQ ID NO 588
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 588

Gln Gly Ile Ser Ser Tyr
 1 5

<210> SEQ ID NO 589
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 589

gatgcatcc

9

<210> SEQ ID NO 590
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 590

Asp Ala Ser
 1

<210> SEQ ID NO 591
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 591

caacagctta atatttacc attcact

27

<210> SEQ ID NO 592
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 592

Gln Gln Leu Asn Ile Tyr Pro Phe Thr
 1 5

<210> SEQ ID NO 593
 <211> LENGTH: 363
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 593

gaagtgcagc tgggtggagtc tggggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tectgtgcag cctctggatt cacctttgat gattatgcc tgcactgggt ccggcaagct 120

ccaggaag gacctggagt ggtctcaggt attaattgga acagtggtag cataggctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagca ctccctgtat 240

-continued

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ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgt aaaagaggtg 300
actacgggat actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

```

```

<210> SEQ ID NO 594
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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```

<400> SEQUENCE: 594

```

```

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

```

```

<210> SEQ ID NO 595
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 595

```

```

gacatccagt tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtc gggcattagc agttatttag cctggtatca gaaaaaacca 120
gggaaagccc ctaacctct gatctatgat gcatccactt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttactctca cactcagcag cctgcagcct 240
gaagattttg caactatta ctgtcaacag cttaatatatt acccattcac ttctggccct 300
gggaccaaag tggatatcaa a 321

```

```

<210> SEQ ID NO 596
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 596

```

```

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1         5         10        15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Gly Ile Ser Ser Tyr
 20        25        30

```

-continued

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

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

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

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

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

<210> SEQ ID NO 597
 <211> LENGTH: 363
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 597

gaagtgacgc tgggtggagtc tggggggagtc ttggtacagc ctggcaggtc cctgagactc	60
tcctgtgcag cctctggatt cacctttgat gattatgccca tgcactgggt ccggcaagct	120
ccaggaaggg gcctggagtg ggtctcaggt attaattgga acagtggtag cataggctat	180
gcggactctg tgaaggggccg attcaccatc tccagagaca acgccaagaa ctccctgtat	240
ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgt aaaagaggtg	300
actacgggat actactacgg tatggacgtc tgggggcaag ggaccacggt caccgtctcc	360
tca	363

<210> SEQ ID NO 598
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 598

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 Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30

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

Ser Gly Ile Asn Trp Asn Ser Gly Ser Ile 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

Val Lys Glu Val Thr Thr Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly
 100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 599
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 599

gacatccagt tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggccagtca gggcattagc agttatttag cctggatatca gcaaaaacca	120
gggaaagccc ctaagctcct gatctatgat gcattccactt tgcaaagtgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct	240
gaagattttg caacttatta ctgtcaacag cttaatatattt acccattcac ttctggccct	300
gggaccaaag tggatatcaa a	321

<210> SEQ ID NO 600

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 600

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly	
1 5 10 15	
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr	
20 25 30	
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	
35 40 45	
Tyr Asp Ala Ser Thr 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 Tyr Tyr Cys Gln Gln Leu Asn Ile Tyr Pro Phe	
85 90 95	
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys	
100 105	

<210> SEQ ID NO 601

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 601

gaggtgcagt tggtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc	60
tctgtgagcag cctctggatt cacgttttagt agctatgccg tgaactgggt ccgccaggct	120
ccaggaagg ggctggattg ggtctcaggt atcagtggta atggtggtag cacctactac	180
gcagactccg tgaagggccg gttcaccatc tccagagaca tttccaagaa cagctgtat	240
gtgcaaatgc acagcctgag agtcgaggac acggccgttt actactgtgc gaaagcccgt	300
tattacgatt ttggggggg gaatttcgat ctctggggcc gtggcaccca ggtcactgtc	360
tctca	366

<210> SEQ ID NO 602

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 602

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

<210> SEQ ID NO 603

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 603

ggattcacgt ttagtagcta tgcc

24

<210> SEQ ID NO 604

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 604

Gly Phe Thr Phe Ser Ser Tyr Ala
 1 5

<210> SEQ ID NO 605

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 605

atcagtggtgta atggtggtag cacc

24

<210> SEQ ID NO 606

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 606

Ile Ser Gly Asn Gly Gly Ser Thr
 1 5

<210> SEQ ID NO 607

<211> LENGTH: 45

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<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 607

gcgaaagccc gttattacga tttttggggg gggaatttcg atctc

45

<210> SEQ ID NO 608
 <211> LENGTH: 15
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 608

Ala Lys Ala Arg Tyr Tyr Asp Phe Trp Gly Gly Asn Phe Asp Leu
 1 5 10 15

<210> SEQ ID NO 609
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 609

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtca gagtgttagc atcaggtact tagcctggta tcagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
 gacaggttca gtgtcagtggt gtctgggaca gacttcactc tcaccatcac tagactggag 240
 cctgaagatt ttgcagteta ttactgtcag caatatggta gttcacgct cactttcggc 300
 ggagggacca aggtggagat caaa 324

<210> SEQ ID NO 610
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 610

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 Ile Arg
 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
 Val Ser Val Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr 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
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 611
 <211> LENGTH: 21
 <212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 611

cagagtgtta gcatcaggta c

21

<210> SEQ ID NO 612
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 612

Gln Ser Val Ser Ile Arg Tyr
1 5

<210> SEQ ID NO 613
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 613

ggtgcatcc

9

<210> SEQ ID NO 614
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 614

Gly Ala Ser
1

<210> SEQ ID NO 615
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 615

cagcaatatg gtagttcacc gctcact

27

<210> SEQ ID NO 616
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 616

Gln Gln Tyr Gly Ser Ser Pro Leu Thr
1 5

<210> SEQ ID NO 617
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 617

```

gaggtgcagt tgttgagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc    60
tctctgtcag cctctggatt cacgtttagt agctatgcc tgaactgggt ccgccaggct    120
ccaggaaggg ggctggattg ggtctcaggt atcagtggtg atggtggtag cacctactac    180
gcagactccg tgaagggccg gtccaccatc tccagagaca tttccaagaa cagctgtat    240
gtgcaaatgc acagcctgag agtcgaggac acggccgttt actactgtgc gaaagcccg    300
tattacgatt tttggggggg gaatttcgat ctctgggggc gtggcaccct ggctcactgc    360
tcctca                                           366

```

<210> SEQ ID NO 618

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 618

```

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

```

<210> SEQ ID NO 619

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 619

```

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc    60
ctctcctgca gggccagtcg gagtggttagc atcagggtact tagcctggta tcagcagaaa    120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca    180
gacaggttca gtgtcagtggt gtctgggaca gacttcactc tcaccatcac tagactggag    240
cctgaagatt ttgcagtcta ttactgtcag caatatggta gttcaccgct cactttcggc    300
ggagggacca aggtggagat caaa                                           324

```

<210> SEQ ID NO 620

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 620

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 Ile Arg
 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
 Val Ser Val Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr 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
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 621

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 621

gaggtgcagc tgttgagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
 tcctgtgcag cctctggatt cacgtttagt agctatgccca tgagctgggt ccgccaggct 120
 ccaggaaggg ggctggagtg ggtctcagct atcagtggta atggtggttag cacctactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagcccgt 300
 tattacgatt ttgggggggg gaatttcgat ctctggggcc gtggcaccct ggtcactgtc 360
 tctca 366

<210> SEQ ID NO 622

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 622

Glu Val Gln Leu Leu 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 Asn 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 Ala Arg Tyr Tyr Asp Phe Trp Gly Gly Asn Phe Asp Leu Trp
 100 105 110

-continued

Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 623
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 623

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc atcaggtact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcaetc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtg ttactgtcag caatatggta gttcacgct cactttcggc 300
ggagggacca aggtggagat caaa 324

<210> SEQ ID NO 624
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 624

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 Ile Arg
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
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 625
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 625

caggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac cacctgccct ttattattcc tactacgtta tggacgtctg gggccaaggg 360
accacgggtca ccgtctcctc a 381

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<210> SEQ ID NO 626
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 626

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

<210> SEQ ID NO 627
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 627

ggttacacct ttaccaccta tggt

24

<210> SEQ ID NO 628
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 628

Gly	Tyr	Thr	Phe	Thr	Thr	Tyr	Gly
1						5	

<210> SEQ ID NO 629
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 629

atcagcgggtt acaatggtaa aaca

24

<210> SEQ ID NO 630
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 630

Ile Ser Gly Tyr Asn Gly Lys Thr
 1 5

<210> SEQ ID NO 631

<211> LENGTH: 60

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 631

tcgagagatc gtttagtagt accacctgcc ctttattatt cctactacgt tatggacgtc 60

<210> SEQ ID NO 632

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 632

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Ser Tyr Tyr
 1 5 10 15

Val Met Asp Val
 20

<210> SEQ ID NO 633

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 633

gatgttgatga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120

tttcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccgggac 180

tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcaggggtgg aggctgagga tggtggggtt tattactgca tgcaagggtac acactggccg 300

tacacttttg gccagggggac caagctggag atcaaa 336

<210> SEQ ID NO 634

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 634

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1 5 10 15

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

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

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

-continued

65	70	75	80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly			
	85	90	95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys			
	100	105	110

<210> SEQ ID NO 635
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 635
 caaagcctcg tatacagtga tggaaacacc tac 33

<210> SEQ ID NO 636
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 636
 Gln Ser Leu Val Tyr Ser Asp Gly Asn Thr Tyr
 1 5 10

<210> SEQ ID NO 637
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 637
 aaggtttct 9

<210> SEQ ID NO 638
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 638
 Lys Val Ser
 1

<210> SEQ ID NO 639
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 639
 atgcaaggta cacactggcc gtacact 27

<210> SEQ ID NO 640
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 640

-continued

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 641

<211> LENGTH: 381

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 641

```
cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac cacctgcctt ttattattcc tactacgtta tggacgtctg gggccaaggg 360
accacgggtca ccgtctcctc a 381
```

<210> SEQ ID NO 642

<211> LENGTH: 127

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 642

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

<210> SEQ ID NO 643

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 643

```
gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccgggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
```

-continued

```

agcagggtgg aggctgagga tgttggggtt tattactgca tgcaaggtag acactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

```

```

<210> SEQ ID NO 644
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 644

```

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1             5             10             15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20             25             30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
      35             40             45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
      85             90             95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100            105            110

```

```

<210> SEQ ID NO 645
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 645

```

```

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc acctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgatg gatgggatgg atcagcggtt acaatggtaa aacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300
ttagtagtac cacctgccct ttattattcc tactacgtta tggacgtctg ggggcaaggg 360
accacgggtca ccgtctcttc a 381

```

```

<210> SEQ ID NO 646
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 646

```

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1             5             10             15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
      20             25             30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35             40             45

```

-continued

Gly Trp Ile Ser Gly Tyr Asn Gly Lys Thr Asn Tyr Ala Gln Lys Leu
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Ser Tyr Tyr
100 105 110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 647
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 647

```

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccttggaaca gccggcctcc      60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg      120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccggggac      180
tctgggggtc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc      240
agcaggggtg aggctgagga tgttgggggt tattactgca tgcaaggtag aactgggccg      300
tacacttttg gccaggggac caagctggag atcaaa                                336

```

<210> SEQ ID NO 648
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 648

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
85 90 95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 649
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 649

```

cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc      60

```

-continued

```

tctgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacagggc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggtt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac cacctgcctt taattattac tactacgtta tggacgtctg gggccaaggg 360
accacgggtca cgtctctctc a 381

```

```

<210> SEQ ID NO 650
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 650

```

```

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

```

```

<210> SEQ ID NO 651
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 651

```

```

ggttacacct ttaccaccta tggt 24

```

```

<210> SEQ ID NO 652
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

```

<400> SEQUENCE: 652

```

```

Gly Tyr Thr Phe Thr Thr Tyr Gly
 1           5

```

```

<210> SEQ ID NO 653
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

```

-continued

<400> SEQUENCE: 653

atcagcggtt acaatggtaa aaca

24

<210> SEQ ID NO 654

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 654

Ile Ser Gly Tyr Asn Gly Lys Thr

1 5

<210> SEQ ID NO 655

<211> LENGTH: 60

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 655

tcgagagatc gtttagtagt accacctgcc cttaattatt actactacgt tatggacgtc

60

<210> SEQ ID NO 656

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 656

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Tyr Tyr Tyr

1 5 10 15

Val Met Asp Val

20

<210> SEQ ID NO 657

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 657

gatgttggtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc

60

atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg

120

tttcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccgggac

180

tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc

240

agcaggggtg aggctgagga tggtggggtt tattactgca tgcaagggtac acactggccg

300

tacacttttg gccaggggac caagctggag atcaaa

336

<210> SEQ ID NO 658

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 658

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

-continued

1	5	10	15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser			
20	25	30	
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser			
35	40	45	
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly			
85	90	95	
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys			
100	105	110	

<210> SEQ ID NO 659
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 659

caaagcctcg tatacagtga tggaaacacc tac

33

<210> SEQ ID NO 660
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 660

Gln Ser Leu Val Tyr Ser Asp Gly Asn Thr Tyr
1 5 10

<210> SEQ ID NO 661
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 661

aaggtttct

9

<210> SEQ ID NO 662
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 662

Lys Val Ser
1

<210> SEQ ID NO 663
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 663

-continued

atgcaaggta cacactggcc gtacact

27

<210> SEQ ID NO 664
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 664

Met Gln Gly Thr His Trp Pro Tyr Thr
 1 5

<210> SEQ ID NO 665
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 665

cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
 tcttgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
 cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
 gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
 atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
 ttagtagtac cacctgccct taattattac tactacgtta tggacgtctg gggccaaggg 360
 accacgggtca ccgtctcctc a 381

<210> SEQ ID NO 666
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 666

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

<210> SEQ ID NO 667
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 667

```

gatgttgatga tgactcagtc tccactctcc ctgcccgtca cccttgagaca gccggcctcc      60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg      120
tttcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccgggac      180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc      240
agcagggtgg aggctgagga tgttgggggtt tattactgca tgcaaggtag aactggccg      300
tacacttttg gccaggggac caagctggag atcaaa      336

```

<210> SEQ ID NO 668

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 668

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1             5             10            15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20             25            30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
      35             40            45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
      85             90            95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100            105           110

```

<210> SEQ ID NO 669

<211> LENGTH: 381

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 669

```

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc      60
tcctgcaagg cttctggtta cacctttacc acctatggta tcagctgggt gcgacaggcc      120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa aacaaactat      180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac      240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt      300
ttagtagtac cacctgccct taattattac tactacgtta tggacgtctg ggggcaaggg      360
accacgggtca ccgtctcctc a      381

```

<210> SEQ ID NO 670

<211> LENGTH: 127

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 670

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

<210> SEQ ID NO 671

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 671

gatgttgtaga tgactcagtc tccactctcc ctgcccgtca cccttgagaca gccggcctcc 60
 atctcctgca ggtctagtaga aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
 ttccagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccggggac 180
 tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
 agcaggggtgg aggctgagga tggtgggggtt tattactgca tgcaaggtac aactgggccg 300
 tacactttttg gccagggggac caagctggag atcaaa 336

<210> SEQ ID NO 672

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 672

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1 5 10 15
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
 20 25 30
 Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
 35 40 45
 Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
 85 90 95
 Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

-continued

<210> SEQ ID NO 673
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 673

```

cagggttcagc tgggtcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc   60
tctcgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc   120
cctggacaag ggcttgagtg gatgggatgg atcagcgggtt acaatggtaa aacaaacgat   180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac   240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt   300
ttagtagtac cacctgcctt ttattattac tactacgtta tggacgtctg gggccaaggg   360
accacgggtca cgtctcctc a                                     381
  
```

<210> SEQ ID NO 674
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 674

```

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

<210> SEQ ID NO 675
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 675

```

ggttacacct ttaccaccta tgggt                                     24
  
```

<210> SEQ ID NO 676
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 676

Gly Tyr Thr Phe Thr Thr Tyr Gly
 1 5

<210> SEQ ID NO 677
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 677

atcagcgggtt acaatggtaa aaca 24

<210> SEQ ID NO 678
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 678

Ile Ser Gly Tyr Asn Gly Lys Thr
 1 5

<210> SEQ ID NO 679
 <211> LENGTH: 60
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 679

tcgagagatc gtttagtagt accacctgcc ctttattatt actactacgt tatggacgtc 60

<210> SEQ ID NO 680
 <211> LENGTH: 20
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 680

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Tyr Tyr Tyr
 1 5 10 15

Val Met Asp Val
 20

<210> SEQ ID NO 681
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 681

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120

tttcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccggggac 180

tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcaggggtgg aggctgagga tgttgggggtt tattactgca tgcaagggtac aactgggccg 300

tacacttttg gccaggggac caagctggag atcaaa 336

-continued

<210> SEQ ID NO 682
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 682

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1         5         10        15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20        25        30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
      35        40        45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
      85        90        95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100       105       110

```

<210> SEQ ID NO 683
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 683

caaagcctcg tatacagtga tggaaacacc tac

33

<210> SEQ ID NO 684
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 684

```

Gln Ser Leu Val Tyr Ser Asp Gly Asn Thr Tyr
 1         5         10

```

<210> SEQ ID NO 685
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 685

aaggtttct

9

<210> SEQ ID NO 686
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 686

-continued

Lys Val Ser
1

<210> SEQ ID NO 687
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 687

atgcaaggta cacactggcc gtacact

27

<210> SEQ ID NO 688
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 688

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> SEQ ID NO 689
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 689

cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggtt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac cacctgcctt ttattattac tactacgtta tggacgtctg gggccaaggg 360
accacgggtca ccgtctcctc a 381

<210> SEQ ID NO 690
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 690

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

-continued

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Tyr Tyr Tyr
 100 105 110

Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 691
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 691

gatgttgtaga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60
 atctcctgca ggtctagtaga aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
 ttccagcaga ggccaggtaga atctccaagg cgcctaattt ataaggtttc taaccgggac 180
 tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
 agcaggggtgg aggctgaggga tggtgggggtt tattactgca tgcaaggtag acactggccg 300
 tacacttttg gccagggggac caagctggag atcaaa 336

<210> SEQ ID NO 692
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 692

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1 5 10 15

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

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

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
 85 90 95

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

<210> SEQ ID NO 693
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 693

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
 tcttgcaagg cttctgggta cacctttacc acctatggta tcagctgggt gcgacaggcc 120
 cctggacaag ggcttgatg gatgggatgg atcagcggtt acaatggtaa aacaaactat 180
 gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
 atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300

-continued

```
ttagtagtac cacctgccct ttattattac tactacgtta tggacgtctg ggggcaaggg 360
accacgggtca ccgtctcttc a 381
```

```
<210> SEQ ID NO 694
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 694
```

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

```
<210> SEQ ID NO 695
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 695
```

```
gatgttggtga tgactcagtc tccactctcc ctgcccggtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccggggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcaggggtgg aggctgagga tgttgggggtt tattactgca tgcaaggtag aactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336
```

```
<210> SEQ ID NO 696
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

```
<400> SEQUENCE: 696
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
  1             5             10             15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
          20             25             30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
          35             40             45
```


-continued

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp 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 Gly
85 90 95

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

<210> SEQ ID NO 697

<211> LENGTH: 384

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 697

```
cagggtgcacc tgggtggagtc tgggggagggc ttggtcaagc ctggaggggtc cctgagactc 60
tctctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccagget 120
ccaggaagg ggctggagtg gatttcatac attagtaatg atggtggtac caaatactat 180
gtggactctg tggagggccg attcatcatt tccagggaca acgccaagaa ctcattgtat 240
ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag 300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtcgc ctca 384
```

<210> SEQ ID NO 698

<211> LENGTH: 128

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 698

Gln Val His 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 His
20 25 30

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

Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Val Asp Ser Val
50 55 60

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

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

Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ala Ser
115 120 125

<210> SEQ ID NO 699

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 699

ggattcacct tcagtgacca ctac

24

<210> SEQ ID NO 700

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 700

Gly Phe Thr Phe Ser Asp His Tyr

1 5

<210> SEQ ID NO 701

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 701

attagtaatg atggtggtac caaa

24

<210> SEQ ID NO 702

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 702

Ile Ser Asn Asp Gly Gly Thr Lys

1 5

<210> SEQ ID NO 703

<211> LENGTH: 63

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 703

gcgagagatc agggatatat tggctacgac tcgtattatt actattccta cggtatggac

60

gtc

63

<210> SEQ ID NO 704

<211> LENGTH: 21

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 704

Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser

1 5 10 15

Tyr Gly Met Asp Val

20

<210> SEQ ID NO 705

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 705

```

aaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc    60
ctctcctgta gggccagtca gagtgttaac aacaaattct tagcctggta ccagcagaaa    120
tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca    180
gacaggttca gtggcagtgg gtctgggacc gacttcactc tcaccatcag cggactggag    240
cctgaagatt ttgaagtgtg ttattgtcaa gtatatggta actcactcac ttccggcgga    300
gggaccaagg tggagatcaa g                                     321

```

<210> SEQ ID NO 706

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 706

```

Lys Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1             5             10             15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
          20             25             30
Phe Leu Ala Trp Tyr Gln Gln Lys Ser 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 Gly Leu Glu
          65             70             75             80
Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
          85             90             95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100             105

```

<210> SEQ ID NO 707

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 707

```

cagagtgtta acaacaaatt c                                     21

```

<210> SEQ ID NO 708

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 708

```

Gln Ser Val Asn Asn Lys Phe
 1             5

```

<210> SEQ ID NO 709

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 709

ggtgcatcc

9

<210> SEQ ID NO 710

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 710

Gly Ala Ser

1

<210> SEQ ID NO 711

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 711

caagtatatg gtaactcact cact

24

<210> SEQ ID NO 712

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 712

Gln Val Tyr Gly Asn Ser Leu Thr

1

5

<210> SEQ ID NO 713

<211> LENGTH: 384

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 713

cagggtgcagc tgggtggagtc tggggggaggc ttggtcaagc ctggaggggc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120

ccaggaaggg ggctggagtg gatttcatac attagtaatg atggtggtac caaatactat 180

gtggactctg tggaggggccc attcatcatt tccagggaca acgccaagaa ctcattgtat 240

ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag 300

ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc ctca 384

<210> SEQ ID NO 714

<211> LENGTH: 128

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 714

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

1

5

10

15

-continued

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

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

Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Val Asp Ser Val
 50 55 60

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

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

Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
 100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 715
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 715

gaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc 60
 ctctcctgta gggccagtca gagtgttaac aacaaattct tagcctggta ccagcagaaa 120
 tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
 gacaggttca gtggcagtgg gtctgggacc gacttcactc tcaccatcag cggactggag 240
 cctgaagatt ttgaagtgtg ttattgtcaa gtatatggta actcactcac ttctggcgga 300
 gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 716
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 716

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1 5 10 15

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

Phe Leu Ala Trp Tyr Gln Gln Lys Ser 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 Gly Leu Glu
 65 70 75 80

Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
 85 90 95

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

<210> SEQ ID NO 717
 <211> LENGTH: 384
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 717

```

cagggtgcagc tgggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc      60
tctgtgtcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccagget      120
ccaggaaggg ggctggagtg ggtttcatat attagtaatg atggtggtac caaatactac      180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat      240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagatcag      300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctgggggcaa      360
gggaccacgg tcaccgtctc ctca                                         384

```

<210> SEQ ID NO 718

<211> LENGTH: 128

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 718

```

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 His
 20        25        30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35        40        45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr 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 Val Tyr Tyr Cys
 85        90        95
Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
100       105       110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115       120       125

```

<210> SEQ ID NO 719

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 719

```

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc      60
ctctcctgca gggccagtca gagtgtaaac aacaaattct tagcctggta ccagcagaaa      120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca      180
gacaggttca gtggcagtggt gtctgggaca gacttcaetc tcaccatcag cagactggag      240
cctgaagatt ttgcagtgtg ttactgtcaa gtatatggta actcactcac ttctggcgga      300
gggaccaagg tggagatcaa a                                         321

```

<210> SEQ ID NO 720

<211> LENGTH: 107

<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 720

```

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 Asn Asn Lys
          20             25            30
Phe 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 Val Tyr Gly Asn Ser Leu
          85             90            95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100            105

```

<210> SEQ ID NO 721
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 721

```

caaattctgc tgggtgcaatc tggacctgag gtgaaggagc ctggggccctc agtgaaggtc      60
tcctgcaagg cttctgggta cacctttacc aactacgcta tcagctgggt gcgacaggtc      120
cctggacaag ggcttgatg gatgggatgg gtcagcgctt acaatgggtca cacaaactat      180
gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac      240
atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagagggggt      300
gtagtcgtgc cagttgtctc ccaactctac aacggtatgg acgtctgggg ccaagggacc      360
acggtcaccg tctcctca

```

<210> SEQ ID NO 722
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 722

```

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

```

-continued

Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
 100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 723
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 723

ggttacacct ttaccaacta cgct

24

<210> SEQ ID NO 724
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 724

Gly Tyr Thr Phe Thr Asn Tyr Ala
 1 5

<210> SEQ ID NO 725
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 725

gtcagcgctt acaatgggtca caca

24

<210> SEQ ID NO 726
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 726

Val Ser Ala Tyr Asn Gly His Thr
 1 5

<210> SEQ ID NO 727
 <211> LENGTH: 57
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 727

gcgagagggg gtgtagtcgt gccagttgct cccacttct acaacgggtat ggacgtc

57

<210> SEQ ID NO 728
 <211> LENGTH: 19
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 728

Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly

-continued

1	5	10	15
Met Asp Val			
<210> SEQ ID NO 729 <211> LENGTH: 336 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 729			
gatattgtga tgactcagtt tccactctcc ctgcccgtca cccctggaga gccggcctcc			60
atctcctgca ggtctagtca gagcctcctg catattaatg aatacaacta tttggattgg			120
tacctaaaga agccagggca gtctccacag ctctgatct atttgggttt taatcggggc			180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc			240
agcagagtgg aggctgagga tgttggggtc tattactgca tgcaagctct tcaaaactccg			300
tggacgttcg gccaaaggac caaggtggaa atcaaa			336
<210> SEQ ID NO 730 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 730			
Asp Ile Val Met Thr Gln Phe 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 Ile			
20 25 30			
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser			
35 40 45			
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn 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> SEQ ID NO 731 <211> LENGTH: 33 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 731			
cagagcctcc tgcataattaa tgaatacaac tat			33
<210> SEQ ID NO 732 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic			
<400> SEQUENCE: 732			

-continued

Gln Ser Leu Leu His Ile Asn Glu Tyr Asn Tyr
 1 5 10

<210> SEQ ID NO 733
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 733

ttgggtttt

9

<210> SEQ ID NO 734
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 734

Leu Gly Phe
 1

<210> SEQ ID NO 735
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 735

atgcaagctc ttcaaactcc gtggacg

27

<210> SEQ ID NO 736
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 736

Met Gln Ala Leu Gln Thr Pro Trp Thr
 1 5

<210> SEQ ID NO 737
 <211> LENGTH: 378
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 737

cagggttcagc tgggtgcagtc tggacctgag gtgaaggagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc aactacgcta tcagctgggt gcgacaggtc 120

cctggacaag ggcttgatg gatgggatgg gtcagcgctt acaatggtca cacaaactat 180

gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagaggggggt 300

gtagtcgtgc cagttgctcc ccacttctac aacgggtatgg acgtctggggg ccaaggggacc 360

acggtcaccg tctcctca 378

<210> SEQ ID NO 738

-continued

<211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 738

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

<210> SEQ ID NO 739
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 739

gatattgtga	tgactcagtc	tccactctcc	ctgcccgtca	cccctggaga	gccggcctcc	60
atctcctgca	ggtctagtca	gagcctctcg	catattaatg	aatacaacta	tttggattgg	120
tacctaaaga	agccagggca	gtctccacag	ctcctgatct	atttgggttt	taatcggggc	180
tccgggggtcc	ctgacagggt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tgttggggtc	tattactgca	tgcaagctct	tcaaactccg	300
tggacgttcg	gccaaaggac	caaggtggaa	atcaaa			336

<210> SEQ ID NO 740
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 740

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 Ile		
	20		25			30			
Asn Glu	Tyr Asn	Tyr Leu	Asp Trp	Tyr Leu	Lys Lys	Pro Gly	Gln Ser		
	35		40			45			
Pro Gln	Leu Leu	Ile Tyr	Leu Gly	Phe Asn	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			

-continued

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> SEQ ID NO 741

<211> LENGTH: 378

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 741

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc aactacgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgatg gatgggatgg gtcagcgctt acaatgggtca cacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggggggt 300
gtagtctgtc cagttgtctc ccacttctac aacggtatgg acgtctgggg gcaaggggacc 360
acggtcacgc tctctca 378

<210> SEQ ID NO 742

<211> LENGTH: 126

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 742

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

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

Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala Gln Lys Leu
50 55 60

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

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

Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 743

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 743

gatattgtga tgactcagtc tccactctcc ctgcccgta cccttgaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catattaatg aatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 180

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tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagatTTTtac actgaaaatc 240
agcagagtgg aggetgagga tgttgggggtt tattactgca tgcaagctct tcaaaactccg 300
tggacgttcg gccaaaggac caagtgga atcaaa 336

```

```

<210> SEQ ID NO 744
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 744

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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 Ile
          20           25           30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn 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> SEQ ID NO 745
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)...(8)
<223> OTHER INFORMATION: Xaa = Any amino acid

```

```

<400> SEQUENCE: 745

```

```

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1           5

```

```

<210> SEQ ID NO 746
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)...(8)
<223> OTHER INFORMATION: Xaa - Any amino acid

```

```

<400> SEQUENCE: 746

```

```

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1           5

```

```

<210> SEQ ID NO 747
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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-continued

```

<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)...(20)
<223> OTHER INFORMATION: Xaa = Any amino acid

<400> SEQUENCE: 747

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1             5             10             15

Xaa Xaa Xaa Xaa
      20

<210> SEQ ID NO 748
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)...(12)
<223> OTHER INFORMATION: Xaa = Any amino acid

<400> SEQUENCE: 748

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1             5             10

<210> SEQ ID NO 749
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)...(3)
<223> OTHER INFORMATION: Xaa = Any amino acid

<400> SEQUENCE: 749

Xaa Xaa Xaa
 1

<210> SEQ ID NO 750
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)...(9)
<223> OTHER INFORMATION: Xaa = Any amino acid

<400> SEQUENCE: 750

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1             5

<210> SEQ ID NO 751
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 751

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

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

```

-continued

```

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
   35                               40               45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
   65                               70               75               80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
   85                               90               95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
  100                               105              110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
  115                               120              125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
  130                               135              140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
  145                               150              155              160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
  165                               170              175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
  180                               185              190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
  195                               200              205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
  210                               215              220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
  225                               230              235              240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
  245                               250              255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
  260                               265              270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
  275                               280              285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
  290                               295              300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
  305                               310              315              320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
  325                               330

```

<210> SEQ ID NO 752

<211> LENGTH: 327

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 752

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
  1           5           10           15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
  20           25           30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
  35           40           45

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

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Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65          70          75          80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
      85          90          95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
      100        105        110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
      115        120        125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
      130        135        140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
      145        150        155        160

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

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
      180        185        190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
      195        200        205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
      210        215        220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
      225        230        235        240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
      245        250        255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
      260        265        270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
      275        280        285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
      290        295        300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
      305        310        315        320

Leu Ser Leu Ser Leu Gly Lys
      325

```

```

<210> SEQ ID NO 753
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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```

<400> SEQUENCE: 753

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```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1          5          10          15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20        25        30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35        40        45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
 65          70          75          80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
      85          90          95

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Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
 100 105 110
 Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 115 120 125
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140
 Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 145 150 155 160
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 180 185 190
 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 195 200 205
 Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 210 215 220
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 225 230 235 240
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 245 250 255
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 260 265 270
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 275 280 285
 Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
 290 295 300
 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 305 310 315 320
 Leu Ser Leu Ser Leu Gly Lys
 325

<210> SEQ ID NO 754

<211> LENGTH: 2076

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 754

```

atgggcaccg tcagctccag gcggtcctgg tggccgctgc cactgctgct gctgctgctg    60
ctgctcctgg gtccccgggg cgcccgctgc caggaggacg aggacggcga ctacgaggag    120
ctggtgctag ccttgcgttc cgaggaggac ggctggccg aagcaccgga gcacggaacc    180
acagccacct tccaccgctg cgccaaggat ccgtaggaggt tgcttgccac ctactgggtg    240
gtgctgaagg aggagaccca cctctgcgag tcagagcgca ctgcccgcg cctgcaggcc    300
caggctgccc gccggggata cctcaccaag atcctgcatg tcttccatgg ccttcttctt    360
ggcttcctgg tgaagatgag tggcgacctg ctggagctgg ccttgaagtt gccccatgtc    420
gactacatcg aggaggactc ctctgtcttt gccagagca tcccgtagga cctggagcgg    480
attacccttc cacggtaccg ggcggatgaa taccagcccc ccgacggagg cagcctggtg    540
gagggtgatc tcctagacac cagcatacag agtgaccacc gggaaatcga gggcagggtc    600
atggtcaccg acttcagaaa tgtgcccag gagacggga cccgcttcca cagacaggcc    660
agcaagtgtg acagtcatgg caccacctg gcaggggtgg tcagcgccg ggatgccggc    720
gtggccaagg gtgccagcat gcgcagcctg cgcgtgctca actgccaagg gaagggcacg    780

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gttagcggca ccctcatagg cctggagttt attcggaaaa gccagctggt ccagcctgtg 840
gggccacttg tgggtgctgt gcccttggtg ggtgggtaca gccgcgtcct caacgccgcc 900
tgccagcgcc tggcgagggc tggggtcgtg ctggtcaccg ctgccggcaa cttccgggac 960
gatgcctgcc tctactcccc agcctcagct cccgaggtca tcacagtggg ggccaccaat 1020
gcccaggacc agccggtgac cctggggact ttggggacca actttggccg ctgtgtggac 1080
ctctttgccc caggggagga catcattggt gcctccagcg actgcagcac ctgctttgtg 1140
tcacagagtg ggacatcaca ggctgctgcc cacgtggctg gcattgcagc catgatgctg 1200
tctgccgagc cggagctcac cctggccgag ttgaggcaga gactgatcca cttctctgcc 1260
aaagatgtca tcaatgaggc ctggttcctt gaggaccagc gggtaactgac ccccaacctg 1320
gtggccgccc tgcccccag caccatggg gcaggttggc agctgttttg caggactgtg 1380
tggtcagcac actcggggcc tacacggatg gccacagcca tcgccgctg cggcccagat 1440
gaggagctgc tgagctgctc cagtttctcc aggagtggga agcggcgggg cgagcgcatg 1500
gaggcccaag ggggcaagct ggtctgccgg gccacaacg cttttggggg tgagggtgtc 1560
tacgccattg ccaggtgctg cctgctaccc caggccaact gcagcgtcca cacagctcca 1620
ccagctgagg ccagcatggg gacccgtgtc cactgccacc aacagggccca cgtcctcaca 1680
ggctgcagct cccactggga ggtggaggac cttggcacc acaagccgcc tgtgtgagg 1740
ccacgaggtc agcccaacca gtgcgtgggc cacagggagg ccagcatcca cgcttcctgc 1800
tgccatgccc caggtctgga atgcaaagtc aaggagcatg gaatcccggc ccctcaggag 1860
caggtgaccg tggcctgcga ggagggtgg accctgactg gctgcagtgc cctccctggg 1920
acctccacg tcctgggggc ctacgccgta gacaacacgt gtgtagttag gagccgggac 1980
gtcagcacta caggcagcac cagcgaagag gccgtgacag ccgttgccat ctgctgccgg 2040
agccggcacc tggcgaggc ctcacaggag ctccag 2076

```

<210> SEQ ID NO 755

<211> LENGTH: 692

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 755

```

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Leu
 1          5          10          15
Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu
 20          25          30
Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
 35          40          45
Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe
 50          55          60
His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 65          70          75          80
Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
 85          90          95
Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
100          105          110
His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
115          120          125
Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
130          135          140

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

Gly	Cys	Ser	Ser	His	Trp	Glu	Val	Glu	Asp	Leu	Gly	Thr	His	Lys	Pro	
				565					570					575		
Pro	Val	Leu	Arg	Pro	Arg	Gly	Gln	Pro	Asn	Gln	Cys	Val	Gly	His	Arg	
				580					585					590		
Glu	Ala	Ser	Ile	His	Ala	Ser	Cys	Cys	His	Ala	Pro	Gly	Leu	Glu	Cys	
				595					600					605		
Lys	Val	Lys	Glu	His	Gly	Ile	Pro	Ala	Pro	Gln	Glu	Gln	Val	Thr	Val	
				610					615					620		
Ala	Cys	Glu	Glu	Gly	Trp	Thr	Leu	Thr	Gly	Cys	Ser	Ala	Leu	Pro	Gly	
				625					630					635		
Thr	Ser	His	Val	Leu	Gly	Ala	Tyr	Ala	Val	Asp	Asn	Thr	Cys	Val	Val	
				645					650					655		
Arg	Ser	Arg	Asp	Val	Ser	Thr	Thr	Gly	Ser	Thr	Ser	Glu	Glu	Ala	Val	
				660					665					670		
Thr	Ala	Val	Ala	Ile	Cys	Cys	Arg	Ser	Arg	His	Leu	Ala	Gln	Ala	Ser	
				675					680					685		
Gln	Glu	Leu	Gln													
				690												

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<210> SEQ ID NO 756
<211> LENGTH: 692
<212> TYPE: PRT
<213> ORGANISM: Macaca mulatta
```

<400> SEQUENCE: 756

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

Val	Ala	Lys	Gly	Ala	Gly	Leu	Arg	Ser	Leu	Arg	Val	Leu	Asn	Cys	Gln	
				245					250					255		
Gly	Lys	Gly	Thr	Val	Ser	Gly	Thr	Leu	Ile	Gly	Leu	Glu	Phe	Ile	Arg	
			260					265					270			
Lys	Ser	Gln	Leu	Val	Gln	Pro	Val	Gly	Pro	Leu	Val	Val	Leu	Leu	Pro	
			275				280					285				
Leu	Ala	Gly	Gly	Tyr	Ser	Arg	Val	Phe	Asn	Ala	Ala	Cys	Gln	Arg	Leu	
	290					295				300						
Ala	Arg	Ala	Gly	Val	Val	Leu	Val	Thr	Ala	Ala	Gly	Asn	Phe	Arg	Asp	
305					310				315						320	
Asp	Ala	Cys	Leu	Tyr	Ser	Pro	Ala	Ser	Ala	Pro	Glu	Val	Ile	Thr	Val	
			325					330					335			
Gly	Ala	Thr	Asn	Ala	Gln	Asp	Gln	Pro	Val	Thr	Leu	Gly	Thr	Leu	Gly	
			340					345					350			
Thr	Asn	Phe	Gly	Arg	Cys	Val	Asp	Leu	Phe	Ala	Pro	Gly	Glu	Asp	Ile	
		355				360						365				
Ile	Gly	Ala	Ser	Ser	Asp	Cys	Ser	Thr	Cys	Phe	Val	Ser	Arg	Ser	Gly	
	370				375					380						
Thr	Ser	Gln	Ala	Ala	Ala	His	Val	Ala	Gly	Ile	Ala	Ala	Met	Met	Leu	
385					390				395						400	
Ser	Ala	Glu	Pro	Glu	Leu	Thr	Leu	Ala	Glu	Leu	Arg	Gln	Arg	Leu	Ile	
			405					410					415			
His	Phe	Ser	Ala	Lys	Asp	Val	Ile	Asn	Glu	Ala	Trp	Phe	Pro	Glu	Asp	
			420					425				430				
Gln	Arg	Val	Leu	Thr	Pro	Asn	Leu	Val	Ala	Ala	Leu	Pro	Pro	Ser	Thr	
		435				440						445				
His	Arg	Ala	Gly	Trp	Gln	Leu	Phe	Cys	Arg	Thr	Val	Trp	Ser	Ala	His	
	450				455					460						
Ser	Gly	Pro	Thr	Arg	Met	Ala	Thr	Ala	Val	Ala	Arg	Cys	Ala	Gln	Asp	
465					470			475							480	
Glu	Glu	Leu	Leu	Ser	Cys	Ser	Ser	Phe	Ser	Arg	Ser	Gly	Lys	Arg	Arg	
			485					490					495			
Gly	Glu	Arg	Ile	Glu	Ala	Gln	Gly	Gly	Lys	Arg	Val	Cys	Arg	Ala	His	
			500					505					510			
Asn	Ala	Phe	Gly	Gly	Glu	Gly	Val	Tyr	Ala	Ile	Ala	Arg	Cys	Cys	Leu	
		515					520					525				
Leu	Pro	Gln	Val	Asn	Cys	Ser	Val	His	Thr	Ala	Pro	Pro	Ala	Gly	Ala	
		530				535					540					
Ser	Met	Gly	Thr	Arg	Val	His	Cys	His	Gln	Gln	Gly	His	Val	Leu	Thr	
545					550				555						560	
Gly	Cys	Ser	Ser	His	Trp	Glu	Val	Glu	Asp	Leu	Gly	Thr	His	Lys	Pro	
			565					570					575			
Pro	Val	Leu	Arg	Pro												

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Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Lys Glu Ala Val
 660 665 670
 Ala Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Val Gln Ala Ser
 675 680 685
 Gln Glu Leu Gln
 690
 <210> SEQ ID NO 757
 <211> LENGTH: 694
 <212> TYPE: PRT
 <213> ORGANISM: Mus muscular
 <400> SEQUENCE: 757
 Met Gly Thr His Cys Ser Ala Trp Leu Arg Trp Pro Leu Leu Pro Leu
 1 5 10 15
 Leu Pro Pro Leu Leu Leu Leu Leu Leu Leu Cys Pro Thr Gly Ala
 20 25 30
 Gly Ala Gln Asp Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu
 35 40 45
 Pro Ser Gln Glu Asp Gly Leu Ala Asp Glu Ala Ala His Val Ala Thr
 50 55 60
 Ala Thr Phe Arg Arg Cys Ser Lys Glu Ala Trp Arg Leu Pro Gly Thr
 65 70 75 80
 Tyr Ile Val Val Leu Met Glu Glu Thr Gln Arg Leu Gln Ile Glu Gln
 85 90 95
 Thr Ala His Arg Leu Gln Thr Arg Ala Ala Arg Arg Gly Tyr Val Ile
 100 105 110
 Lys Val Leu His Ile Phe Tyr Asp Leu Phe Pro Gly Phe Leu Val Lys
 115 120 125
 Met Ser Ser Asp Leu Leu Gly Leu Ala Leu Lys Leu Pro His Val Glu
 130 135 140
 Tyr Ile Glu Glu Asp Ser Phe Val Phe Ala Gln Ser Ile Pro Trp Asn
 145 150 155 160
 Leu Glu Arg Ile Ile Pro Ala Trp His Gln Thr Glu Glu Asp Arg Ser
 165 170 175
 Pro Asp Gly Ser Ser Gln Val Glu Val Tyr Leu Leu Asp Thr Ser Ile
 180 185 190
 Gln Gly Ala His Arg Glu Ile Glu Gly Arg Val Thr Ile Thr Asp Phe
 195 200 205
 Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser
 210 215 220
 Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg
 225 230 235 240
 Asp Ala Gly Val Ala Lys Gly Thr Ser Leu His Ser Leu Arg Val Leu
 245 250 255
 Asn Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu
 260 265 270
 Phe Ile Arg Lys Ser Gln Leu Ile Gln Pro Ser Gly Pro Leu Val Val
 275 280 285
 Leu Leu Pro Leu Ala Gly Gly Tyr Ser Arg Ile Leu Asn Ala Ala Cys
 290 295 300
 Arg His Leu Ala Arg Thr Gly Val Val Leu Val Ala Ala Ala Gly Asn
 305 310 315 320
 Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val
 325 330 335

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

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<210> SEQ ID NO 758

<211> LENGTH: 653

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 758

Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg Gln Phe Val Cys

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

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

<210> SEQ ID NO 759

<211> LENGTH: 753

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 759

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

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

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Arg Ile Gln Asn Glu Gly Arg Ile Val Asn Trp Lys Leu Ile Leu His
 580 585 590
 Gly Thr Ser Ser Gln Pro Glu His Met Lys Gln Pro Arg Val Tyr Thr
 595 600 605
 Ser Tyr Asn Thr Val Gln Asn Asp Arg Arg Gly Val Glu Lys Met Val
 610 615 620
 Asp Pro Gly Glu Glu Gln Pro Thr Gln Glu Asn Pro Lys Glu Asn Thr
 625 630 635 640
 Leu Val Ser Lys Ser Pro Ser Ser Ser Ser Val Gly Gly Arg Arg Asp
 645 650 655
 Glu Leu Glu Glu Gly Ala Pro Ser Gln Ala Met Leu Arg Leu Leu Gln
 660 665 670
 Ser Ala Phe Ser Lys Asn Ser Pro Pro Lys Gln Ser Pro Lys Lys Ser
 675 680 685
 Pro Ser Ala Lys Leu Asn Ile Pro Tyr Glu Asn Phe Tyr Glu Ala Leu
 690 695 700
 Glu Lys Leu Asn Lys Pro Ser Gln Leu Lys Asp Ser Glu Asp Ser Leu
 705 710 715 720
 Tyr Asn Asp Tyr Val Asp Val Phe Tyr Asn Thr Lys Pro Tyr Lys His
 725 730 735
 Arg Asp Asp Arg Leu Leu Gln Ala Leu Val Asp Ile Leu Asn Glu Glu
 740 745 750

Asn

<210> SEQ ID NO 760

<211> LENGTH: 785

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 760

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

Thr	Ile	Gln	Asp	Ile	Ala	Pro	Asn	Tyr	Ser	Pro	Glu	Gly	Ser	Tyr	Asp	
		195					200					205				
Leu	Asn	Ser	Asn	Asp	Pro	Asp	Pro	Met	Pro	His	Pro	Asp	Val	Glu	Asn	
		210			215						220					
Gly	Asn	His	His	Gly	Thr	Arg	Cys	Ala	Gly	Glu	Ile	Ala	Ala	Val	Pro	
		225			230					235						
Asn	Asn	Ser	Phe	Cys	Ala	Val	Gly	Val	Ala	Tyr	Gly	Ser	Arg	Ile	Ala	
				245					250							
Gly	Ile	Arg	Val	Leu	Asp	Gly	Pro	Leu	Thr	Asp	Ser	Met	Glu	Ala	Val	
				260			265						270			
Ala	Phe	Asn	Lys	His	Tyr	Gln	Ile	Asn	Asp	Ile	Tyr	Ser	Cys	Ser	Trp	
		275				280						285				
Gly	Pro	Asp	Asp	Asp	Gly	Lys	Thr	Val	Asp	Gly	Pro	His	Gln	Leu	Gly	
		290				295					300					
Lys	Ala	Ala	Leu	Gln	His	Gly	Val	Ile	Ala	Gly	Arg	Gln	Gly	Phe	Gly	
				310						315						
Ser	Ile	Phe	Val	Val	Ala	Ser	Gly	Asn	Gly	Gly	Gln	His	Asn	Asp	Asn	
				325			330									
Cys	Asn	Tyr	Asp	Gly	Tyr	Ala	Asn	Ser	Ile	Tyr	Thr	Val	Thr	Ile	Gly	
		340						345					350			
Ala	Val	Asp	Glu	Glu	Gly	Arg	Met	Pro	Phe	Tyr	Ala	Glu	Glu	Cys	Ala	
		355				360						365				
Ser	Met	Leu	Ala	Val	Thr	Phe	Ser	Gly	Gly	Asp	Lys	Met	Leu	Arg	Ser	
		370				375					380					
Ile	Val	Thr	Thr	Asp	Trp	Asp	Leu	Gln	Lys	Gly	Thr	Gly	Cys	Thr	Glu	
				390						395						
Gly	His	Thr	Gly	Thr	Ser	Ala	Ala	Ala	Pro	Leu	Ala	Ala	Gly	Met	Ile	
				405					410							
Ala	Leu	Met	Leu	Gln	Val	Arg	Pro	Cys	Leu	Thr	Trp	Arg	Asp	Val	Gln	
				420			425						430			
His	Ile	Ile	Val	Phe	Thr	Ala	Thr	Arg	Tyr	Glu	Asp	Arg	Arg	Ala	Glu	
		435				440						445				
Trp	Val	Thr	Asn	Glu	Ala	Gly	Phe	Ser	His	Ser	His	Gln	His	Gly	Phe	
		450				455					460					
Gly	Leu	Leu	Asn	Ala	Trp	Arg	Leu	Val	Asn	Ala	Ala	Lys	Ile	Trp	Thr	
				470						475						
Ser	Val	Pro	Tyr	Leu	Ala	Ser	Tyr	Val	Ser	Pro	Val	Leu	Lys	Glu	Asn	
				485			490						495			
Lys	Ala	Ile	Pro	Gln	Ser	Pro	Arg	Ser	Leu	Glu	Val	Leu	Trp	Asn	Val	
		500						505					510			
Ser	Arg	Met	Asp	Leu	Glu	Met	Ser	Gly	Leu	Lys	Thr	Leu	Glu	His	Val	
		515				520						525				
Ala	Val	Thr	Val	Ser	Ile	Thr	His	Pro	Arg	Arg	Gly	Ser	Leu	Glu	Leu	
		530				535						540				
Lys	Leu	Phe	Cys	Pro	Ser	Gly	Met	Met	Ser	Leu	Ile	Gly	Ala	Pro	Arg	
				550						555						
Ser	Met	Asp	Ser	Asp	Pro	Asn	Gly	Phe	Asn	Asp	Trp	Thr	Phe	Ser	Thr	
				565					570					575		

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Gln Leu Thr Leu Tyr Gly Ser Val Trp Ser Ala Val Asp Ile Arg Asp
 610 615 620
 Arg Gln Arg Leu Leu Glu Ser Ala Met Ser Gly Lys Tyr Leu His Asp
 625 630 635 640
 Asp Phe Ala Leu Pro Cys Pro Pro Gly Leu Lys Ile Pro Glu Glu Asp
 645 650 655
 Gly Tyr Thr Ile Thr Pro Asn Thr Leu Lys Thr Leu Val Leu Val Gly
 660 665 670
 Cys Phe Thr Val Phe Trp Thr Val Tyr Tyr Met Leu Glu Val Tyr Leu
 675 680 685
 Ser Gln Arg Asn Val Ala Ser Asn Gln Val Cys Arg Ser Gly Pro Cys
 690 695 700
 His Trp Pro His Arg Ser Arg Lys Ala Lys Glu Glu Gly Thr Glu Leu
 705 710 715 720
 Glu Ser Val Pro Leu Cys Ser Ser Lys Asp Pro Asp Glu Val Glu Thr
 725 730 735
 Glu Ser Arg Gly Pro Pro Thr Thr Ser Asp Leu Leu Ala Pro Asp Leu
 740 745 750
 Leu Glu Gln Gly Asp Trp Ser Leu Ser Gln Asn Lys Ser Ala Leu Asp
 755 760 765
 Cys Pro His Gln His Leu Asp Val Pro His Gly Lys Glu Glu Gln Ile
 770 775 780
 Cys
 785

<210> SEQ ID NO 761

<211> LENGTH: 692

<212> TYPE: PRT

<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 761

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

His	Arg	Glu	Ile	Glu	Gly	Arg	Val	Met	Val	Thr	Asp	Phe	Glu	Ser	Val
		195					200					205			
Pro	Glu	Glu	Asp	Gly	Thr	Arg	Phe	His	Arg	Gln	Ala	Ser	Lys	Cys	Asp
	210					215					220				
Ser	His	Gly	Thr	His	Leu	Ala	Gly	Val	Val	Ser	Gly	Arg	Asp	Ala	Gly
225					230					235					240
Val	Ala	Lys	Gly	Ala	Gly	Leu	Arg	Ser	Leu	Arg	Val	Leu	Asn	Cys	Gln
				245					250					255	
Gly	Lys	Gly	Thr	Val	Ser	Gly	Thr	Leu	Ile	Gly	Leu	Glu	Phe	Ile	Arg
			260					265					270		
Lys	Ser	Gln	Leu	Val	Gln	Pro	Val	Gly	Pro	Leu	Val	Val	Leu	Leu	Pro
		275				280						285			
Leu	Ala	Gly	Gly	Tyr	Ser	Arg	Val	Phe	Asn	Ala	Ala	Cys	Gln	Arg	Leu
	290					295					300				
Ala	Arg	Ala	Gly	Val	Val	Leu	Val	Thr	Ala	Ala	Gly	Asn	Phe	Arg	Asp
305					310					315					320
Asp	Ala	Cys	Leu	Tyr	Ser	Pro	Ala	Ser	Ala	Pro	Glu	Val	Ile	Thr	Val
			325						330					335	
Gly	Ala	Thr	Asn	Ala	Gln	Asp	Gln	Pro	Val	Thr	Leu	Gly	Thr	Leu	Gly
			340					345					350		
Thr	Asn	Phe	Gly	Arg	Cys	Val	Asp	Leu	Phe	Ala	Pro	Gly	Glu	Asp	Ile
		355					360					365			
Ile	Gly	Ala	Ser	Ser	Asp	Cys	Ser	Thr	Cys	Phe	Val	Ser	Arg	Ser	Gly
	370				375						380				
Thr	Ser	Gln	Ala	Ala	Ala	His	Val	Ala	Gly	Ile	Ala	Ala	Met	Met	Leu
385					390					395					400
Ser	Ala	Glu	Pro	Glu	Leu	Thr	Leu	Ala	Glu	Leu	Arg	Gln	Arg	Leu	Ile
			405						410					415	
His	Phe	Ser	Ala	Lys	Asp	Val	Ile	Asn	Glu	Ala	Trp	Phe	Pro	Glu	Asp
			420					425					430		
Gln	Arg	Val	Leu	Thr	Pro	Asn	Leu	Val	Ala	Ala	Leu	Pro	Pro	Ser	Thr
		435					440					445			
His	Arg	Ala	Gly	Trp	Gln	Leu	Phe	Cys	Arg	Thr	Val	Trp	Ser	Ala	His
	450				455						460				
Ser	Gly	Pro	Thr	Arg	Met	Ala	Thr	Ala	Val	Ala	Arg	Cys	Ala	Gln	Asp
465					470				475						480
Glu	Glu	Leu	Leu	Ser	Cys	Ser	Ser	Phe	Ser	Arg	Ser	Gly	Lys	Arg	Arg
			485						490					495	
Gly	Glu	Arg	Ile	Glu	Ala	Gln	Gly	Gly	Lys	Arg	Val	Cys	Arg	Ala	His
			500					505					510		
Asn	Ala	Phe	Gly	Gly	Glu	Gly	Val	Tyr	Ala	Ile	Ala	Arg	Cys	Cys	Leu
		515					520					525			
Leu	Pro	Gln	Val	Asn	Cys	Ser	Val	His	Thr	Ala	Pro	Pro	Ala	Gly	Ala
	530					535					540				
Ser	Met	Gly</													

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Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Ile Val
 610 615 620
 Ala Cys Glu Asp Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly
 625 630 635 640
 Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
 645 650 655
 Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu Ala Val
 660 665 670
 Ala Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Val Gln Ala Ser
 675 680 685
 Gln Glu Leu Gln
 690
 <210> SEQ ID NO 762
 <211> LENGTH: 698
 <212> TYPE: PRT
 <213> ORGANISM: Mesocricetus auratus
 <400> SEQUENCE: 762
 Met Gly Thr Ser Cys Ser Ala Arg Pro Arg Trp Leu Leu Ser Pro Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Arg Tyr Met Gly Ala Ser Ala Gln Asp
 20 25 30
 Glu Asp Ala Glu Tyr Glu Glu Leu Met Leu Thr Leu Gln Ser Gln Asp
 35 40 45
 Asp Gly Leu Ala Asp Glu Thr Asp Glu Ala Pro Gln Gly Ala Thr Ala
 50 55 60
 Ala Phe His Arg Cys Pro Glu Glu Ala Trp Arg Val Pro Gly Thr Tyr
 65 70 75 80
 Ile Val Met Leu Ala Glu Glu Ala Gln Trp Val His Ile Glu Gln Thr
 85 90 95
 Met His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly Tyr Val Ile Lys
 100 105 110
 Ile Gln His Ile Phe Tyr Asp Phe Leu Pro Ala Phe Val Val Lys Met
 115 120 125
 Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro His Val Lys Tyr
 130 135 140
 Ile Glu Glu Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu
 145 150 155 160
 Asp Arg Ile Ile Pro Ala Gly Arg Gln Ala Gln Glu Tyr Ser Ser Ser
 165 170 175
 Arg Lys Val Pro Ser Gly Ser Gly Gln Val Glu Val Tyr Leu Leu Asp
 180 185 190
 Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly Arg Val Thr Val
 195 200 205
 Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg
 210 215 220
 Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val
 225 230 235 240
 Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Thr Ile Leu His Gly Leu
 245 250 255
 Arg Val Leu Asn Cys Gln Gly Lys Gly Ile Val Ser Gly Ile Leu Thr
 260 265 270
 Gly Leu Glu Phe Ile Trp Lys Ser Gln Leu Met Gln Pro Ser Gly Pro
 275 280 285

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

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<210> SEQ ID NO 763
<211> LENGTH: 691
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 763

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

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

What is claimed is:

1. A method for treating hypercholesterolemia in a patient, the method comprising administering to the patient a first dose of a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof that specifically binds hPCSK9, wherein the amount of the antibody in the first dose is 75 mg (“the 75 mg dose”);
 and administering to the patient a second dose of a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof that specifically binds hPCSK9, wherein the amount of antibody in the second dose is 150 mg (“the 150 mg dose”);
 wherein the 150 mg dose is administered to the patient two weeks after the 75 mg dose; wherein the antibody

or antigen-binding fragment that specifically binds hPCSK9 comprises the heavy and light chain CDRs of a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs:90/92 and 218/226.

2. The method of claim 1, wherein, after receiving the 75 mg dose, but before receiving the 150 mg dose, the patient has not achieved a reduction in LDL-C level of at least 50% from the patient’s baseline LDL-C level.

3. The method of claim 1, wherein, after receiving the 75 mg dose, but before receiving the 150 mg dose, the patient has not achieved an LDL-C blood concentration of less than or equal to 100 milligrams per deciliter (mg/dL).

471

4. The method of claim 3, wherein, after receiving the 75 mg dose, but before receiving the 150 mg dose, the patient has not achieved an LDL-C blood concentration of less than or equal to 70 mg/dL.

5. The method of claim 1, wherein the antibody or antigen-binding fragment that specifically binds hPCSK9 comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:220, 222, 224, 228, 230 and 232.

6. The method of claim 5, wherein the antibody or antigen-binding fragment comprises an HCVR having the amino acid sequence of SEQ ID NO:218 and an LCVR having the amino acid sequence of SEQ ID NO:226.

7. The method of claim 1, wherein the antibody or antigen-binding fragment that specifically binds hPCSK9 comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:76, 78, 80, 84, 86 and 88.

8. The method of claim 7, wherein the antibody or antigen-binding fragment comprises an HCVR having the amino acid sequence of SEQ ID NO:90 and an LCVR having the amino acid sequence of SEQ ID NO:92.

9. The method of claim 1, wherein the patient is on a therapeutic statin regimen at the time of or just prior to administration of the 75 mg dose.

10. The method of claim 9, wherein the therapeutic statin regimen comprises a statin selected from the group consisting of cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin and pravastatin.

11. The method of claim 10, wherein the statin is atorvastatin.

12. The method of claim 1, wherein the patient is on another lipid lowering agent prior to or concurrent with administration of the antibody or antigen-binding fragment thereof.

13. The method of claim 12, wherein the lipid lowering agent is selected from the group consisting of ezetimibe, a bile acid resin, niacin, and an omega-3 fatty acid.

14. The method of claim 1, wherein the pharmaceutical composition is administered to the patient subcutaneously.

15. The method of claim 1, wherein the patient has heterozygous Familial Hypercholesterolemia (heFH).

16. The method of claim 1, wherein the patient has a form of hypercholesterolemia that is not Familial Hypercholesterolemia (nonFH).

17. A method for reducing LDL-C in a patient in need thereof, the method comprising administering to the patient a first dose of a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof that specifically binds hPCSK9, wherein the amount of the antibody in the first dose is 75 mg ("the 75 mg dose");

and administering to the patient a second dose of a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof that specifically binds hPCSK9, wherein the amount of antibody in the second dose is 150 mg ("the 150 mg dose");

wherein the 150 mg dose is administered to the patient two weeks after the 75 mg dose; wherein the antibody or antigen-binding fragment that specifically binds

472

hPCSK9 comprises the heavy and light chain CDRs of a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs:90/92 and 218/226.

18. The method of claim 17, wherein, after receiving the 75 mg dose, but before receiving the 150 mg dose, the patient has not achieved a reduction in LDL-C level of at least 50% from the patient's baseline LDL-C level.

19. The method of claim 17, wherein, after receiving the 75 mg dose, but before receiving the 150 mg dose, the patient has not achieved an LDL-C blood concentration of less than or equal to 100 milligrams per deciliter (mg/dL).

20. The method of claim 19, wherein, after receiving the 75 mg dose, but before receiving the 150 mg dose, the patient has not achieved an LDL-C blood concentration of less than or equal to 70 mg/dL.

21. The method of claim 17, wherein the antibody or antigen-binding fragment that specifically binds hPCSK9 comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:220, 222, 224, 228, 230 and 232.

22. The method of claim 21, wherein the antibody or antigen-binding fragment comprises an HCVR having the amino acid sequence of SEQ ID NO:218 and an LCVR having the amino acid sequence of SEQ ID NO:226.

23. The method of claim 17, wherein the antibody or antigen-binding fragment that specifically binds hPCSK9 comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:76, 78, 80, 84, 86 and 88.

24. The method of claim 23, wherein the antibody or antigen-binding fragment comprises an HCVR having the amino acid sequence of SEQ ID NO:90 and an LCVR having the amino acid sequence of SEQ ID NO:92.

25. The method of claim 17, wherein the patient is on a therapeutic statin regimen at the time of or just prior to administration of the 75 mg dose.

26. The method of claim 25, wherein the therapeutic statin regimen comprises a statin selected from the group consisting of cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin and pravastatin.

27. The method of claim 26, wherein the statin is atorvastatin.

28. The method of claim 17, wherein the patient is on another lipid lowering agent prior to or concurrent with administration of the antibody or antigen-binding fragment thereof.

29. The method of claim 28, wherein the lipid lowering agent is selected from the group consisting of ezetimibe, a bile acid resin, niacin, and an omega-3 fatty acid.

30. The method of claim 17, wherein the pharmaceutical composition is administered to the patient subcutaneously.

31. The method of claim 17, wherein the patient has heterozygous Familial Hypercholesterolemia (heFH).

32. The method of claim 17, wherein the patient has a form of hypercholesterolemia that is not Familial Hypercholesterolemia (nonFH).

* * * * *