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(54) Title: ANTIBODIES TO PMEL17 AND CONJUGATES THEREOF

(57) Abstract: This application discloses anti-PMEL17 antibodies, antigen binding fragments thereof, and antibody drug conjugates of said antibodies or antigen binding fragments conjugated to a GNAQ/GNA11 inhibitor. The invention also relates to methods of treating or preventing cancer using the antibodies, antigen binding fragments, and antibody drug conjugates. Also disclosed herein are methods of making the antibodies, antigen binding fragments, and antibody drug conjugates, and methods of using the antibodies and antigen binding fragments as diagnostic reagents.

ANTIBODIES TO PMEL17 AND CONJUGATES THEREOF

SEQUENCE LISTING

[0000] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 6, 2019, is named PAT058359-WO-PCT_SL.txt and is 285,253 bytes in size

FIELD OF THE INVENTION

[0001] The present invention generally relates to anti-PMEL17 antibodies, or fragments thereof, conjugates thereof, including GNAQ/GNA11 inhibitor conjugates thereof, and their uses for the treatment or prevention of cancer.

BACKGROUND OF THE INVENTION

[0002] PMEL17 (also referred to as gp100 and SILV) is a single-pass Type I transmembrane protein produced by melanocytes and involved in melanin synthesis. Along its maturation, PMEL17 is transiently expressed at the cell surface before trafficked to melanosomes where PMEL17 is degraded into various domains that multimerizes to form fibrillar sheets. Such pattern then serves as a support for trapping melanin. The melanosomes PMEL17 expression is regulated by MITF, a lineage oncogene, and was found to be up-regulated in a variety of primary and metastatic subcutaneous and uveal melanomas. The transient cell surface expression and subsequent internalization of PMEL17 makes it a suitable target for developing antibody drug conjugate (ADC) for the treatment of melanoma.

PMEL17 and Cancer

[0003] Along its maturation, PMEL17 is heavily processed by pro-protein convertases. The protein is cleaved between V467/K468 forming two subdomains, Mα at the N-term and Mβ at the C-term, supposedly maintained via a disulphide bridge. After leaving the golgi apparatus, some PMEL17 molecules are transiently expressed at the cell surface. Most PMEL17 is then redirected to a melanocyte for further maturation while some PMEL17 appears to be shed. Following additional enzymatic cleavages, PMEL17 is degraded into various domains which reorganize and form fibrillar sheets where melanin polymerizes (Valencia JC, et al. *Sorting of Pmel17 to melanosomes through the plasma membrane by AP1 and AP2: evidence for the*

polarized nature of melanocytes. J Cell Sci. 2006 Mar 15;119(Pt 6):1080-91; Theos AC, et al. *The Silver locus product Pmel17/gp100/Silv/ME20: controversial in name and in function.* Pigment Cell Res. 2005 Oct;18(5):322-36).

[0004] PMEL17 constitutes a potential therapeutic target for the treatment of melanoma. PMEL17 is a direct transcriptional target of MITF, a lineage oncogene in melanoma, as observed by mRNA expression studies (Du J, et al. *MLANA/MART1 and SILV/PMEL17/GP100 are transcriptionally regulated by MITF in melanocytes and melanoma*. Am J Pathol. 2003 Jul;163(1):333-43). PMEL17 expression is restricted to the melanocyte lineage which includes skin melanocytes, hair bulb melanocytes, retinal pigment epithelium, pigmented cilliary epithelium, and possibly the choroid melanocytes in the retina. PMEL17 is also highly expressed in melanocyte lineage tumors such as subcutaneous and uveal melanoma. In contrast, mRNA studies have demonstrated that PMEL17 expression is limited on other tumor types and normal tissues (Wagner SN, Wagner C, Schultewolter T, Goos M. *Analysis of Pmel17/gp100 expression in primary human tissue specimens: implications for melanoma immuno-and gene-therapy*. Cancer Immunol Immunother. 1997 Jun;44(4):239-47). Besides, ADC and ImmTAC compounds targeting PMEL17 have previously been described to specifically induce killing of melanoma in vivo and in vitro and are currently evaluated in clinical trials (Chen Y, et al. *The melanosomal protein PMEL17 as a target for antibody drug conjugate therapy in melanoma.* J Biol Chem. 2012 Jul 13;287(29):24082-91. doi:10.1074/jbc.M112.361485. Epub 2012 May 21).

GNAQ/GNA11 and Cancer

[0005] GNAQ and GNA11 genes encode for the alpha subunit of the heterotrimeric G proteins Gq/11, which are almost ubiquitously expressed and act as binary molecular switches that cycle between active guanosine triphosphate (GTP)-bound and inactive guanosine diphosphate (GDP)-bound states. GTP-bound Gαq and Gα11 activate β-isoforms of phospholipase C, which triggers a number of signal transduction pathways through the generation of second messengers IP3 and DAG. Signaling termination is triggered by GTP hydrolysis mediated by intrinsic GTPase activity of these Gα proteins. Gq and G11 have been shown to be involved in a vast array of physiological functions including platelet activation, myocardial hypertrophy, and smooth muscle tone.

[0006] Oncogenic mutations in either GNAQ or GNA11 occur in up to 90% of cases of uveal melanoma (UM) and in ~2-3% of cutaneous melanoma. Approximately 95% of these mutations affect codons 209 (Q209) in the Ras-like domain, resulting in complete or partial loss of GTPase activity and thereby locking GNAQ/11 into its active state. Q209 GNAQ/11 are

dominant acting oncogenes that transform melanocytes by triggering the activation of multiple pathways including PKC/MAPK, Rho/Rac, β-catenin, and YAP. Although the PKC/MAPK pathway has been shown as one contributing factor to GNAQ-mediated oncogenesis, multiple lines of evidence suggest that mutant GNAQ/11 govern additional pathways that are also likely to play a role in UM tumorigenesis (i.e. YAP, β-catenin). Interestingly, another somatic activating mutation in GNAQ (R183Q) was recently described to be the cause of the Sturge-Weber syndrome (SWS), a neurocutaneous disorder characterized by capillary malformation (port-wine stains), and choroidal and leptomeningeal vascular malformations. Thus, GNAQ and GNA11 constitutes potential therapeutic targets for the treatment of uveal and cutaneous melanoma.

Antibody Drug Conjugates

[0007] Antibody drug conjugates ("ADCs") have been used for the local delivery of cytotoxic agents in the treatment of cancer (*see, e.g.*, Lambert, Curr. Opinion In Pharmacology 5:543-549, 2005). ADCs allow targeted delivery of the drug moiety where maximum efficacy with minimal toxicity may be achieved. ADCs include an antibody selected for its ability to bind to a cell targeted for therapeutic intervention, linked to a drug selected for its cytostatic or cytotoxic activity. Binding of the antibody to the targeted cell thereby delivers the drug to the site where its therapeutic effect is needed.

[0008] Many antibodies that recognize and selectively bind to targeted cells, *e.g.*, cancer cells, have been disclosed for use in ADCs. In spite of the extensive work on ADCs, antibody binding to a particular target of interest is not sufficient to predict success in ADC applications. Examples of factors that can effect therapeutic effectiveness of ADCs (besides target-intrinsic features) include various aspects that need customized fine-tuning, such as the optimal antibody affinity as a balance between target-mediated disposition (TMDD) and efficacy-driving exposure, evaluation of Fc-mediated functions (antibody-dependent cell-mediated cytotoxicity, ADCC), method of conjugation (site-specific or not), the ratio of the drug/payload molecules that conjugate to each antibody ("DAR" or "drug antibody ratio"), the cleavability or stability of the linker, stability of the ADC, and the tendency of an ADC to aggregate.

[0009] There remains a need for antibodies, attachment methods, and cytotoxic payloads with improved properties for use as effective ADC therapeutic compositions and methods.

SUMMARY OF THE INVENTION

[0010] In one embodiment, the present application discloses an antibody or antigen binding fragment thereof that binds PMEL17 comprising:

a. a heavy chain variable region that comprises a heavy chain CDR1 (Complementarity Determining Region 1) of SEQ ID NO:1, 4, 5 or 7, a heavy chain CDR2 (Complementarity Determining Region 2) of SEQ ID NO:2, 6 or 8, and a heavy chain CDR3 (Complementarity Determining Region 3) of SEQ ID NO:3 or 9; and a light chain variable region that comprises a light chain CDR1 (Complementarity Determining Region 1) of SEQ ID NO:14, 17 or 20, a light chain CDR2 (Complementarity Determining Region 2) of SEQ ID NO:15 or 18, and a light chain CDR3 (Complementarity Determining Region 3) of SEQ ID NO:16 or 19;

b. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:33, 36, 37 or 39, a heavy chain CDR2 of SEQ ID NO:34, 38 or 40; a heavy chain CDR3 of SEQ ID NO:35 or 41; a light chain CDR1 of SEQ ID NO:46, 49 or 52; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:48 or 51;

c. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:5, 7, 57 or 60, a heavy chain CDR2 of SEQ ID NO:58, 61 or 62; a heavy chain CDR3 of SEQ ID NO:59 or 63; a light chain CDR1 of SEQ ID NO:68, 71 or 74; a light chain CDR2 of SEQ ID NO:69 or 72; and a light chain CDR3 of SEQ ID NO:70 or 73;

d. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:79, 82, 83 or 85, a heavy chain CDR2 of SEQ ID NO:80, 84 or 86; a heavy chain CDR3 of SEQ ID NO:81 or 87; a light chain CDR1 of SEQ ID NO:92, 95 or 98; a light chain CDR2 of SEQ ID NO:93 or 96; and a light chain CDR3 of SEQ ID NO:94 or 97;

e. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO:104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:105 or 111; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:117 or 118;

f. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:123, 126, 127 or 129, a heavy chain CDR2 of SEQ ID NO:124, 128 or 130; a heavy chain CDR3 of SEQ ID NO:125 or 131; a light chain CDR1 of SEQ ID NO:136,

139 or 142; a light chain CDR2 of SEQ ID NO:137 or 140; and a light chain CDR3 of SEQ ID NO:138 or 141;

g. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:123, 126, 127 or 129, a heavy chain CDR2 of SEQ ID NO:124, 128 or 130; a heavy chain CDR3 of SEQ ID NO:147 or 148; a light chain CDR1 of SEQ ID NO:153, 156 or 158; a light chain CDR2 of SEQ ID NO:50 or 154; and a light chain CDR3 of SEQ ID NO:155 or 157;

h. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO:104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:163 or 164; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:169 or 170;

i. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:175, 178, 179 or 181, a heavy chain CDR2 of SEQ ID NO:176, 180 or 182; a heavy chain CDR3 of SEQ ID NO:177 or 183; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:188 or 189;

j. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO: 103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO: 104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:194 or 195; a light chain CDR1 of SEQ ID NO: 49, 52 or 116; a light chain CDR2 of SEQ ID NO: 47 or 50; and a light chain CDR3 of SEQ ID NO:200 or 201;

k. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:206, 209, 210 or 212, a heavy chain CDR2 of SEQ ID NO:207, 211 or 213; a heavy chain CDR3 of SEQ ID NO:208 or 214; a light chain CDR1 of SEQ ID NO:153, 156 or 158; a light chain CDR2 of SEQ ID NO:50 or 154; and a light chain CDR3 of SEQ ID NO:219 or 220;

l. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO: 206, 209, 210 or 212, a heavy chain CDR2 of SEQ ID NO: 207, 211 or 213; a heavy chain CDR3 of SEQ ID NO:225 or 226; a light chain CDR1 of SEQ ID NO:136, 139

or 142; a light chain CDR2 of SEQ ID NO:137 or 140; and a light chain CDR3 of SEQ ID NO:231 or 232;

m. a heavy chain variable region that comprises a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, 209, 210 or 212, an HCDR2 of SEQ ID NO: 207, 211 or 213, and an HCDR3 of SEQ ID NO:237 or 238; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, 245 or 247, an LCDR2 of SEQ ID NO:47 or 50, and an LCDR3 of SEQ ID NO:244 or 246;

n. a heavy chain variable region that comprises a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, 209, 210 or 212, an HCDR2 of SEQ ID NO: 207, 211 or 213, and an HCDR3 of SEQ ID NO:252 or 253; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, 156 or 158, an LCDR2 of SEQ ID NO:50 or 154, and an LCDR3 of SEQ ID NO:258 or 259;

o. a heavy chain CDR1 of SEQ ID NO:1, a heavy chain CDR2 of SEQ ID NO:2, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:14, a light chain CDR2 of SEQ ID NO:15, and a light chain CDR3 of SEQ ID NO:16;

p. a heavy chain CDR1 of SEQ ID NO: 4, a heavy chain CDR2 of SEQ ID NO:2, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:14, a light chain CDR2 of SEQ ID NO:15, and a light chain CDR3 of SEQ ID NO:16;

q. a heavy chain CDR1 of SEQ ID NO:5, a heavy chain CDR2 of SEQ ID NO:6, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:17, a light chain CDR2 of SEQ ID NO: 18, and a light chain CDR3 of SEQ ID NO: 19;

r. a heavy chain CDR1 of SEQ ID NO:7, a heavy chain CDR2 of SEQ ID NO:8, a heavy chain CDR3 of SEQ ID NO:9, a light chain CDR1 of SEQ ID NO:20, a light chain CDR2 of SEQ ID NO:18, and a light chain CDR3 of SEQ ID NO:16;

s. a heavy chain CDR1 of SEQ ID NO:33, a heavy chain CDR2 of SEQ ID NO:34, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:46, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:48;

t. a heavy chain CDR1 of SEQ ID NO:36, a heavy chain CDR2 of SEQ ID NO:34, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:46, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:48;

u. a heavy chain CDR1 of SEQ ID NO:37, a heavy chain CDR2 of SEQ ID NO:38, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:51;

v. a heavy chain CDR1 of SEQ ID NO: 39, a heavy chain CDR2 of SEQ ID NO:40, a heavy chain CDR3 of SEQ ID NO:41, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:48;

w. a heavy chain CDR1 of SEQ ID NO:57, a heavy chain CDR2 of SEQ ID NO:58, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:68, a light chain CDR2 of SEQ ID NO:69, and a light chain CDR3 of SEQ ID NO:70;

x. a heavy chain CDR1 of SEQ ID NO:60, a heavy chain CDR2 of SEQ ID NO:58, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:68, a light chain CDR2 of SEQ ID NO:69, and a light chain CDR3 of SEQ ID NO:70;

y. a heavy chain CDR1 of SEQ ID NO:5, a heavy chain CDR2 of SEQ ID NO:61, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:71, a light chain CDR2 of SEQ ID NO:72, and a light chain CDR3 of SEQ ID NO:73;

z. a heavy chain CDR1 of SEQ ID NO:7, a heavy chain CDR2 of SEQ ID NO:62, a heavy chain CDR3 of SEQ ID NO:63, a light chain CDR1 of SEQ ID NO:74, a light chain CDR2 of SEQ ID NO:72, and a light chain CDR3 of SEQ ID NO:70;

aa. a heavy chain CDR1 of SEQ ID NO:79, , a heavy chain CDR2 of SEQ ID NO:80, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:92, a light chain CDR2 of SEQ ID NO:93, and a light chain CDR3 of SEQ ID NO:94;

bb. a heavy chain CDR1 of SEQ ID NO:82, a heavy chain CDR2 of SEQ ID NO:80, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:92, a light chain CDR2 of SEQ ID NO:93, and a light chain CDR3 of SEQ ID NO:94;

cc. a heavy chain CDR1 of SEQ ID NO:83, a heavy chain CDR2 of SEQ ID NO:84, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:95, a light chain CDR2 of SEQ ID NO:96, and a light chain CDR3 of SEQ ID NO: 97;

dd. a heavy chain CDR1 of SEQ ID NO: 85, a heavy chain CDR2 of SEQ ID NO:86, a heavy chain CDR3 of SEQ ID NO:87, a light chain CDR1 of SEQ ID NO:98, a light chain CDR2 of SEQ ID NO:96, and a light chain CDR3 of SEQ ID NO:94;

ee. a heavy chain CDR1 of SEQ ID NO:103, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO: 116; a light chain CDR2 of SEQ ID NO:47; and a light chain CDR3 of SEQ ID NO:117;

ff. a heavy chain CDR1 of SEQ ID NO:106, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:117;

gg. a heavy chain CDR1 of SEQ ID NO:107, a heavy chain CDR2 of SEQ ID NO:108, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:118;

hh. a heavy chain CDR1 of SEQ ID NO:109, a heavy chain CDR2 of SEQ ID NO:110, a heavy chain CDR3 of SEQ ID NO:111, a light chain CDR1 of SEQ ID NO:52 a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:117;

ii. a heavy chain CDR1 of SEQ ID NO:123, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137,and a light chain CDR3 of SEQ ID NO:138;

jj. a heavy chain CDR1 of SEQ ID NO:126, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137, and a light chain CDR3 of SEQ ID NO:138;

kk. a heavy chain CDR1 of SEQ ID NO:127, a heavy chain CDR2 of SEQ ID NO:128, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:139, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO: 141;

ll. a heavy chain CDR1 of SEQ ID NO: 129, a heavy chain CDR2 of SEQ ID NO:130, a heavy chain CDR3 of SEQ ID NO:131, a light chain CDR1 of SEQ ID NO:142, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO:138;

mm. a heavy chain CDR1 of SEQ ID NO:123, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO:154, and a light chain CDR3 of SEQ ID NO:155;

nn. a heavy chain CDR1 of SEQ ID NO:126, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO: 154, and a light chain CDR3 of SEQ ID NO:155;

oo. a heavy chain CDR1 of SEQ ID NO:127, a heavy chain CDR2 of SEQ ID NO:128, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:156, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:157;

pp. a heavy chain CDR1 of SEQ ID NO: 129, a heavy chain CDR2 of SEQ ID NO:130, a heavy chain CDR3 of SEQ ID NO:148, a light chain CDR1 of SEQ ID NO:158, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:155;

qq. a heavy chain CDR1 of SEQ ID NO:103, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:169;

rr. a heavy chain CDR1 of SEQ ID NO:106, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:169;

ss. a heavy chain CDR1 of SEQ ID NO:107, a heavy chain CDR2 of SEQ ID NO:108, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:170;

tt. a heavy chain CDR1 of SEQ ID NO: 109, a heavy chain CDR2 of SEQ ID NO:110, a heavy chain CDR3 of SEQ ID NO:164, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:169;

uu. a heavy chain CDR1 of SEQ ID NO:175, a heavy chain CDR2 of SEQ ID NO:176, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:188;

vv. a heavy chain CDR1 of SEQ ID NO:178, a heavy chain CDR2 of SEQ ID NO:176, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:188;

ww. a heavy chain CDR1 of SEQ ID NO:179, a heavy chain CDR2 of SEQ ID NO:180, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:189;

xx. a heavy chain CDR1 of SEQ ID NO: 181, a heavy chain CDR2 of SEQ ID NO:182; a heavy chain CDR3 of SEQ ID NO:183, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:188;

yy. a heavy chain CDR1 of SEQ ID NO: 103, a heavy chain CDR2 of SEQ ID NO: 104, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO: 47, and a light chain CDR3 of SEQ ID NO:200;

zz. a heavy chain CDR1 of SEQ ID NO: 106, a heavy chain CDR2 of SEQ ID NO: 104, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO: 47, and a light chain CDR3 of SEQ ID NO:200;

aaa. a heavy chain CDR1 of SEQ ID NO: 107, a heavy chain CDR2 of SEQ ID NO: 108, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 49, a light chain CDR2 of SEQ ID NO: 50, and a light chain CDR3 of SEQ ID NO: 201;

bbb. a heavy chain CDR1 of SEQ ID NO: 109, a heavy chain CDR2 of SEQ ID NO: 110, a heavy chain CDR3 of SEQ ID NO:195, a light chain CDR1 of SEQ ID NO: 52, a light chain CDR2 of SEQ ID NO: 50, and a light chain CDR3 of SEQ ID NO:200;

ccc. a heavy chain CDR1 of SEQ ID NO:206, a heavy chain CDR2 of SEQ ID NO:207, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO:154, and a light chain CDR3 of SEQ ID NO:219;

ddd. a heavy chain CDR1 of SEQ ID NO:209, a heavy chain CDR2 of SEQ ID NO:207, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO: 154, and a light chain CDR3 of SEQ ID NO:219;

eee. a heavy chain CDR1 of SEQ ID NO:210, a heavy chain CDR2 of SEQ ID NO:211, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:156, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:220;

fff. a heavy chain CDR1 of SEQ ID NO: 212, a heavy chain CDR2 of SEQ ID NO:213, a heavy chain CDR3 of SEQ ID NO:214, a light chain CDR1 of SEQ ID NO:158, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:219;

ggg. a heavy chain CDR1 of SEQ ID NO: 206, a heavy chain CDR2 of SEQ ID NO: 207, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137,and a light chain CDR3 of SEQ ID NO:231;

hhh. a heavy chain CDR1 of SEQ ID NO: 209, a heavy chain CDR2 of SEQ ID NO: 207, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137, and a light chain CDR3 of SEQ ID NO:231;

iii. a heavy chain CDR1 of SEQ ID NO: 210, a heavy chain CDR2 of SEQ ID NO: 211, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:139, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO: 232;

jjj. a heavy chain CDR1 of SEQ ID NO: 212, a heavy chain CDR2 of SEQ ID NO: 213, a heavy chain CDR3 of SEQ ID NO: 226, a light chain CDR1 of SEQ ID NO:142; a light chain CDR2 of SEQ ID NO: 140; and a light chain CDR3 of SEQ ID NO:231;

kkk. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:237,and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, an LCDR2 of SEQ ID NO:47, and an LCDR3 of SEQ ID NO:244;

lll. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 209, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:237, and a light chain

variable region that comprises an LCDR1 of SEQ ID NO:243, an LCDR2 of SEQ ID NO:47, and an LCDR3 of SEQ ID NO:244;

mmm. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 210, an HCDR2 of SEQ ID NO: 211, and an HCDR3 of SEQ ID NO:237, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:245, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:246;

nnn. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 212, an HCDR2 of SEQ ID NO: 213, and an HCDR3 of SEQ ID NO:238; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:247, an LCDR2 of SEQ ID NO: 50, and an LCDR3 of SEQ ID NO:244;

ooo. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:252,and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, an LCDR2 of SEQ ID NO: 154, and an LCDR3 of SEQ ID NO:258;

ppp. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 209, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, an LCDR2 of SEQ ID NO:154, and an LCDR3 of SEQ ID NO:258;

qqq. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 210, an HCDR2 of SEQ ID NO: 211, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:156, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:259; or

rrr. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 212, an HCDR2 of SEQ ID NO: 213, and an HCDR3 of SEQ ID NO: 253; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:158, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:258.

[0011] An antibody or antigen binding fragment thereof that binds PMEL17 of the present application may also comprise:

a. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:21;

b. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:25;

c. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:29;

d. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:42, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:53;

e. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:64, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:75;

f. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:88, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:99;

g. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:112, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:119;

h. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:132, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:143;

i. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:149, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:159;

j. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:165, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:171;

k. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:184, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:190;

l. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:196, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:202;

m. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:215, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:221;

n. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:227, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:233;

o. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:239, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:248; or

p. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:254, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:260.

[0012] In another embodiment, the antibody or antigen binding fragment thereof that binds PMEL17 comprises:

a. A heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:23;

b. A heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:27;

c. A heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:31;

d. A heavy chain comprising the amino acid sequence of SEQ ID NO:44, and a light chain comprising the amino acid sequence of SEQ ID NO:55;

e. A heavy chain comprising the amino acid sequence of SEQ ID NO:66, and a light chain comprising the amino acid sequence of SEQ ID NO:77;

f. A heavy chain comprising the amino acid sequence of SEQ ID NO:90, and a light chain comprising the amino acid sequence of SEQ ID NO:101;

g. A heavy chain comprising the amino acid sequence of SEQ ID NO:114, and a light chain comprising the amino acid sequence of SEQ ID NO:121.;

h. A heavy chain comprising the amino acid sequence of SEQ ID NO:134, and a light chain comprising the amino acid sequence of SEQ ID NO:145;

i. A heavy chain comprising the amino acid sequence of SEQ ID NO:151, and a light chain comprising the amino acid sequence of SEQ ID NO:161;

j. A heavy chain comprising the amino acid sequence of SEQ ID NO:167, and a light chain comprising the amino acid sequence of SEQ ID NO:173;

k. A heavy chain comprising the amino acid sequence of SEQ ID NO:186, and a light chain comprising the amino acid sequence of SEQ ID NO:192;

l. A heavy chain comprising the amino acid sequence of SEQ ID NO:198, and a light chain comprising the amino acid sequence of SEQ ID NO:204;

m. A heavy chain comprising the amino acid sequence of SEQ ID NO:217, and a light chain comprising the amino acid sequence of SEQ ID NO:223;

n. A heavy chain comprising the amino acid sequence of SEQ ID NO:229, and a light chain comprising the amino acid sequence of SEQ ID NO:235;

o. A heavy chain comprising the amino acid sequence of SEQ ID NO:241, and a light chain comprising the amino acid sequence of SEQ ID NO:250; or

p. A heavy chain comprising the amino acid sequence of SEQ ID NO:256, and a light chain comprising the amino acid sequence of SEQ ID NO:262.

[0013] The antibody or antigen binding fragment thereof as described herein may comprise one or more cysteine substitutions. In one embodiment, the antibody or antigen binding fragment thereof comprises one or more cysteine substitutions selected from S152C, S375C, or both S152C and S375C of the heavy chain of the antibody or antigen binding fragment thereof, wherein the position is numbered according to the EU system. An antibody as disclosed herein can be a monoclonal antibody.

[0014] In one aspect, the Antibody Drug Conjugate of the invention is a conjugate of Formula (C):

$$Ab\text{-}(L_A\text{-}(D)_n)_y \qquad (C)$$

wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

L_A is a linker;

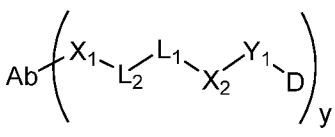
n is 1, 2, 3 or 4, and

y is 1, 2, 3 or 4,

where the Linker-Drug moiety $-(L_A\text{-}(D)_n)$ is covalently attached to the antibody or antigen binding fragment thereof.

[0015] In another aspect of the Antibody Drug Conjugates of Formula (C), L_A is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group, a carbonate group and a bivalent peptide linker.

[0016] In another aspect, the Antibody Drug Conjugate of Formula (C) is a conjugate of Formula (C-1):



(C-1)

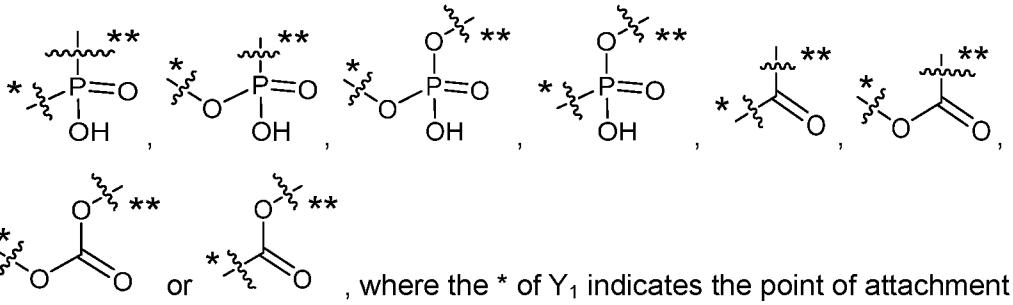
wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

X_2 is a self-immolative spacer;

Y_1 is  , where the * of Y_1 indicates the point of attachment to X_2 and the ** of Y_1 indicates the point of attachment to D;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[0017] The present application also discloses pharmaceutical compositions comprising the antibodies, or antigen binding fragments thereof, disclosed herein and a pharmaceutically acceptable carrier. The present application also discloses pharmaceutical compositions comprising the antibody drug conjugates as disclosed herein and a pharmaceutically acceptable carrier.

[0018] The present application also discloses methods of treating or preventing cancer in a patient in need thereof, comprising administering to said patient the antibody drug conjugates or the pharmaceutical compositions disclosed herein, wherein the cancer expresses PMEL17, contains a mutation of the GNAQ or GNA11 gene, or the cancer expresses PMEL17 and contains a mutation of GNAQ, GNA11, or both.

[0019] In some embodiments of the methods of treatment or preventing cancer, the antibody drug conjugate or pharmaceutical composition are administered to the patient in combination with one or more additional therapeutic compounds. In one embodiment, the one or more additional therapeutic compounds is selected from a standard of care chemotherapeutic, an MDM2 inhibitor, an MRC2 inhibitor, a PKC inhibitor, a MAPK inhibitor, a costimulatory molecule, or a checkpoint inhibitor. In one embodiment, the costimulatory molecule is selected from an agonist of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, STING, or CD83 ligand. In another embodiment, the checkpoint inhibitor is selected from an inhibitor of PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta.

[0020] The present application also discloses the antibody drug conjugates or the pharmaceutical compositions disclosed herein, for use as a medicament. In one embodiment,

the antibody drug conjugates or the pharmaceutical compositions disclosed herein, are for use in the treatment or prevention of a PMEL17 expressing cancer or a cancer that contains a mutation of the GNAQ or GNA11 gene in a patient in need thereof.

[0021] In one embodiment, the application discloses use of the antibodies or antigen binding fragments thereof, the antibody drug conjugates, or the pharmaceutical composition as disclosed herein, to treat or prevent a PMEL17 expressing cancer in a patient in need thereof.

[0022] In one embodiment, the application discloses use of the antibodies or antigen binding fragments thereof, the antibody drug conjugates, or the pharmaceutical compositions as disclosed herein, to treat or prevent a PMEL17 expressing cancer or a cancer that contains a mutation of the GNAQ or GNA11 gene in a patient in need thereof. In one embodiment, the application discloses use of the antibodies or antigen binding fragments thereof, the antibody drug conjugates, or the pharmaceutical compositions as disclosed herein, in the manufacture of a medicament.

[0023] In one embodiment, the cancer expresses PMEL17 or contains a mutation of the GNAQ or GNA11 gene. In one embodiment, the cancer is uveal melanoma, subcutaneous melanoma, hepatocellular carcinoma, or a metastatic cancer thereof.

[0024] The present application also discloses nucleic acids that encodes the antibodies or antigen binding fragments as disclosed herein. In one embodiment, the nucleic acid comprises the nucleotide sequence of SEQ ID NOs: 13, 24, 28, 32, 45, 56, 67, 78, 91, 102, 115, 122, 135, 146, 152, 162, 168, 174, 187, 193, 199, 205, 218, 224, 230, 236, 242, 251, 257, or 26. This application also discloses vectors comprising the nucleic acids, and host cells comprising the vectors or nucleic acids. This application also discloses a process for producing the antibodies or antigen binding fragments disclosed herein comprising cultivating the host cell and recovering the antibody from cell culture. In one embodiment, the process of recovering the antibody from cell culture comprises the steps of:

a) removing cells and filtering the culture;

b) purifying the culture by affinity chromatography ;

c) inactivating any viruses in the culture by adjusting the pH to 3.4-3.6, then readjusting the pH to 5.8-6.2 and filtering the culture;

d) purifying the culture by cation exchange chromatography and performing on-column reduction of the culture;

e) performing anion exchange chromatography on the culture;

f) removing viruses by nanofiltration;

g) filtering the culture containing the antibody; and

h) obtaining purified antibody.

[0025] The present application also discloses a process for producing an anti-PMEL17 antibody drug conjugate comprising:

(a) pre-forming a linker-drug moiety of the following Formula (B):

$$R^8\text{-}L_B\text{-}(D)_n \qquad (B)$$

wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

R^8 is a reactive group;

L_B is a cleavable or non-cleavable linker, and

n is 1, 2, 3 or 4;

(b) conjugating said linker-drug moiety to the antibody recovered from the cell culture using the process for producing an antibody or antigen binding fragment disclosed herein to produce an antibody drug conjugate; and

(c) purifying the antibody drug conjugate.

[0026] The present application also discloses a diagnostic reagent comprising an antibody or antigen binding fragment thereof as disclosed herein. In some embodiments, the antibody or antigen binding fragment thereof is labeled with a radiolabel, a fluorophore, a chromophore, an imaging agent, or a metal ion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] **FIGs. 1A-1B** show exemplary data on in vitro anti-UM activity of GNAQ/11 inhibitors Compound (A1) and Compound (A2).

[0028] **FIG. 2** shows exemplary data on activity of GNAQ/11 inhibitors Compound (A1) and Compound (A2) to induce apoptosis in uveal melanoma cells.

[0029] **FIGs. 3A-3C** show exemplary data on GNAQ/11 inhibition by Compound (A1) and Compound (A2). Compound (A1) and Compound (A2) reduced IP1 levels (FIG. 3A) and relative proliferation (FIG. 3B) in 92.1 cells. Immunoblots of 92.1 cells treated with Compound (A1) and Compound (A2) showed reduced ERK signaling (FIG. 3C).

[0030] **FIGs. 4A-4D** show exemplary data on metabolic stability and PK properties of Compound (A1). Both disappearance of Compound (A1) (FIG. 4A) as well as appearance of the ring-opened form Compound (A8) (FIG. 4B) was monitored over 24h. With the exception of the rat, adding the % remaining Compound (A1) and % formed Compound (A8) shows

stoichiometry over 24h (FIG. 4C). The PK of Compound (A1) after intravenous dosing in mouse is characterized by a very high clearance and moderate to high volume of distribution (FIG. 4D).

[0031] **FIGs. 5A-5D** show exemplary data on metabolic stability and PK properties of Compound (A1) and Compound (A2). In vitro stability of Compound (A2) was tested in plasma and blood from different species (Fig. 5A). Compound (A2) showed good chemical stability in three different systems (Fig. 5B). PK of Compound (A2) in female balb/c mice showed high clearance and a short elimination half-life (Fig. 5C). Compound (A1) and Compound (A2) were stable in buffer at pH 5.6 and in lysosomes over 4h (Fig. 5D).

[0032] **FIGs. 6A-6B** show exemplary data on in vitro anti-uveal melanoma activity of anti-PMEL17-(B1) ADCs. Data presented as mean of 3 independent replicates and relative to PBS-treated cells (control).

[0033] **FIG. 7** shows exemplary data on anti-PMEL17-(B1) ADCs inducing apoptosis in uveal melanoma cells. Data presented as mean of 3 independent replicates.

[0034] **FIGs. 8A-8B** show exemplary data on in vitro anti-uveal melanoma activity of anti-PMEL17-(B2) ADCs and anti-PMEL17 mAbs. Data presented as mean of 3 independent replicates and relative to PBS-treated cells (control).

[0035] **FIG. 9** shows exemplary data on GNAQ/11 inhibition by anti-PMEL17-(B1) and anti-PMEL17-(B2) ADCs in uveal melanoma cells. IP1 levels (nM) are presented as mean of 3 independent replicates.

[0036] **FIGs. 10A-10D** show exemplary data on binding activity of anti-PMEL17 antibodies to intact platelets and uveal melanoma cells.

[0037] **FIGs. 11A-11C** show exemplary data on impact of Compound (A1) and anti-PMEL17-(B1) ADCs on human platelet aggregation.

[0038] **FIGs. 12A-12E** show exemplary data on in vivo anti-tumor activity of anti-PMEL17-(B1) ADCs. G1-(B1) inhibited tumor growth in a dose-dependent manner (Fig. 12A). Values are mean ± SEM; sample size, (n=5-12 mice per group). Initial tumor volume at day 0 was approximately 200-250 mm^3. No body weight loss was observed for up to 14 days after treatment (Fig. 12B). Values are mean ± SEM; sample size, (n=4 mice per group). G1-(B1) treatment resulted in GNAQ signaling inhibition and inhibition of tumor cell proliferation as indicated by reduced levels of pERK and Ki67, respectively (Fig. 12C). In addition, G1-(B1) induced cell apoptosis compared to vehicle- and isotype control 3207-(B1)-treated mice, which correlated with tumor cell accumulation of G1-(B1) ADC as detected by IgG staining (Fig. 12C). No changes were observed in MITF and PMEL17 levels following GNAQ inhibition (Fig. 12C).

No platelet aggregation inhibition was observed in G1-(B1) treated mice for up to 7 days (Figs. 12D & E).

[0039] **FIGs. 13A-13C** show exemplary data on effect of G1-(B1) ADC on a liver and lung metastasis mouse model of uveal melanoma. Individual pictures from each mice are presented at day 45 following i.v. injection of 92.1-luciferase cells (just before the initiation of treatment) and 12 days post treatment (Figs. 13A and 13B); sample size, (n=6 mice per group). Initial BLI for liver metastasis at day 0 was approximately 2.8 *109 p/sec/cm2. Lung tumors (bioluminescence signal) in Fig. 13B are indicated by a black arrow. Corresponding body weight modulation (% vs day 15) was assessed 2-3 times per week prior and post treatment with G1-(B1) 20 mg/kg (grey circles). Values in Fig. 13C are mean ± SEM; sample size, (n=5-6 mice per group). Initial body weight at day 15 was approximately 21 g.

[0040] **FIGs. 14A-14E** show exemplary data on PK properties of G1-(B1) ADCs. The pharmacokinetic profile (total IgG levels) of G1-(B1) showed a slightly over-proportional increase of exposure with dose between 7.5 and 30 mg/kg in nude mice (Fig. 14A). In tumor bearing mice, free payload concentrations were measured after dosing either target binding G1-(B1) or isotype control 3207-(B1). A clear (>4-fold) increase in tumor delivery of Compound (A1) payload could be observed using the targeted ADC (Fig. 14B). The conversion of Compound (A1) (open circles) into its ring-opened form Compound (A8) (filled circles) while being conjugated to the antibody was shown in vivo in mice (Fig. 14C). The exposures in an in vivo efficacy study, comparing two different DAR2 formats with the DAR4 format of G1-(B1) and with the DAR4 Fc-silent format, showed lowest clearance for the DAR2 (E152C) and the DAR4 Fc-silent ADCs, whereas the DAR2 (S375C) exposure decreases faster (Fig. 14D). Fig. 14E shows the concentration of 3207 (isotype control antibody)-(B1) DAR4 (E152C, S375C) and 3207 (isotype control antibody)-(B1) DAR4 Fc-silent conjugates over time.

[0041] **FIGs. 15A-15C** show exemplary data on in vitro stability of anti-PMEL17-GNAQ/11i ADCs in buffer, mouse, rat, and human plasma and in vivo stability of anti-PMEL17-GNAQ/11i ADCs in mouse.

[0042] **FIGs. 16A-16B** show exemplary data on in vivo efficacy of G1-E152C-DAR2-(B1), G1-S375C-DAR2-(B1), Fc-silent G1-(B1) in a xenograft model of uveal melanoma. Values represent mean ± SEM; sample size, (n=5-6 mice per group). Initial tumor volume at day 0 was approximately 300-325 mm^3.

[0043] **FIGs. 17A-17B** show exemplary data on in vitro anti-uveal melanoma activity of anti-PMEL17-(B1) ADCs. Data presented as mean of 3 independent replicates and relative to PBS-treated cells (control).

[0044] **FIG. 18** shows exemplary data show exemplary data on in vivo anti-tumor activity of anti-PMEL17-(B1) ADCs.

[0045] **FIG. 19A-19B** shows exemplary data on an immunohistochemical analysis of tumor biopsies from metastatic uveal melanoma patients.

[0046] **FIGs. 20A-20C** shows exemplary sensorgram data to assess epitope binning of anti-PMEL antibodies. FIG. 20A illustrates the binding steps. FIG. 20B shows the sensorgram when antibody G1 3J LC is immobilized first and 17A9 is flowed over. FIG. 20C shows the sensorgram when 17A9 is immobilized first and G1 3J LC is flowed over. In both cases, binding is observed when the second antibody is flowed over, suggesting that G1 3J LC and 17A9 bind to different epitopes of human PMEL.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0047] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0048] The term "alkyl" refers to a monovalent saturated hydrocarbon chain having the specified number of carbon atoms. For example, C_1-C_6alkyl refers to an alkyl group having from 1 to 6 carbon atoms. Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, isobutyl, sec-butyl, and t-butyl), pentyl (n-pentyl, isopentyl, and neopentyl), and hexyl.

[0049] "Cleavable" as used herein refers to a linking group or linker component that connects two moieties by covalent connections, but breaks down to sever the covalent connection between the moieties under physiologically relevant conditions, typically a cleavable linking group is severed in vivo more rapidly in an intracellular environment than when outside a cell, causing release of the payload to preferentially occur inside a targeted cell. Cleavage may be enzymatic or non-enzymatic, but generally releases a payload from an antibody without degrading the antibody. Cleavage may leave some portion of a linking group or linker component attached to the payload, or it may release the payload without any residue of the linking group.

[0050] "Non-cleavable" as used herein refers to a linking group or linker component that is not especially susceptible to breaking down under physiological conditions, e.g., it is at least as stable as the antibody or antigen binding fragment portion of the conjugate. Such linking

groups are sometimes referred to as 'stable', meaning they are sufficiently resistant to degradation to keep the payload connected to antibody or antigen binding fragment until the antibody or antigen binding fragment is itself at least partially degraded, i.e., the degradation of the antibody or antigen binding fragment precedes cleavage of the linking group in vivo. Degradation of the antibody portion of an ADC having a stable or non-cleavable linking group may leave some or all of the linking group, e.g., one or more amino acid groups from an antibody, attached to the payload or drug moiety that is delivered in vivo.

[0051] The term "antibody" as used herein refers to a polypeptide of the immunoglobulin family that is capable of binding a corresponding antigen non-covalently, reversibly, and in a specific manner. For example, a naturally occurring IgG antibody is a tetramer comprising at least 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 (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, 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, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[0052] The term "antibody" includes, but is not limited to, monoclonal antibodies, human antibodies, humanized antibodies, chimeric antibodies, and anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention). The antibodies can be of any isotype/class (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), or subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2).

[0053] "Complementarity-determining domains" or "complementary-determining regions ("CDRs") interchangeably refer to the hypervariable regions of VL and VH. The CDRs are the target protein-binding site of the antibody chains that harbors specificity for such target protein. There are three CDRs (CDR1-3, numbered sequentially from the N-terminus) in each human VL or VH, constituting about 15-20% of the variable domains. The CDRs are structurally

complementary to the epitope of the target protein and are thus directly responsible for the binding specificity. The remaining stretches of the VL or VH, the so-called framework regions, exhibit less variation in amino acid sequence (Kuby, Immunology, 4th ed., Chapter 4. W.H. Freeman & Co., New York, 2000).

[0054] The positions of the CDRs and framework regions can be determined using various well known definitions in the art, *e.g.*, Kabat, Chothia, international ImMunoGeneTics database (IMGT) (on the worldwide web at www.imgt.org/), and AbM (see, *e.g.*, Johnson *et al.*, Nucleic Acids Res., 29:205-206 (2001); Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987); Chothia *et al.*, Nature, 342:877-883 (1989); Chothia *et al.*, J. Mol. Biol., 227:799-817 (1992); Al-Lazikani *et al.*, J.Mol.Biol., 273:927-748 (1997)). Definitions of antigen combining sites are also described in the following: Ruiz *et al.*, Nucleic Acids Res., 28:219–221 (2000); and Lefranc, M.P., Nucleic Acids Res., 29:207-209 (2001); MacCallum *et al.*, J. Mol. Biol., 262:732-745 (1996); and Martin *et al.*, Proc. Natl. Acad. Sci. USA, 86:9268–9272 (1989); Martin *et al.*, Methods Enzymol., 203:121–153 (1991); and Rees *et al.*, In Sternberg M.J.E. (ed.), Protein Structure Prediction, Oxford University Press, Oxford, 141–172 (1996).

[0055] Both the light and heavy chains are divided into regions of structural and functional homology. The terms “constant” and “variable” are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention, the numbering of the constant region domains increases as they become more distal from the antigen binding site or amino-terminus of the antibody. The N-terminus is a variable region and at the C-terminus is a constant region; the CH3 and CL domains actually comprise the carboxy-terminal domains of the heavy and light chain, respectively.

[0056] The term “antigen binding fragment”, as used herein, refers to one or more portions of an antibody that retain the ability to specifically interact with (*e.g.*, by binding, steric hindrance, stabilizing/destabilizing, spatial distribution) an epitope of an antigen. Examples of binding fragments include, but are not limited to, single-chain Fvs (scFv), camelid antibodies, disulfide-linked Fvs (sdFv), Fab fragments, F(ab') fragments, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, Nature 341:544-546, 1989), which consists of a VH

domain; and an isolated complementarity determining region (CDR), or other epitope-binding fragments of an antibody.

[0057] Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv ("scFv"); *see, e.g.*, Bird *et al.*, Science 242:423-426, 1988; and Huston *et al.*, Proc. Natl. Acad. Sci. 85:5879-5883, 1988). Such single chain antibodies are also intended to be encompassed within the term "antigen binding fragment." These antigen binding fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0058] Antigen binding fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, single domain antibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (*see, e.g.*, Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005). Antigen binding fragments can be grafted into scaffolds based on polypeptides such as fibronectin type III (Fn3) (*see* U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

[0059] Antigen binding fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata *et al.*, Protein Eng. 8:1057-1062, 1995; and U.S. Pat. No. 5,641,870).

[0060] The term "monoclonal antibody" or "monoclonal antibody composition" as used herein refers to polypeptides, including antibodies and antigen binding fragments that have substantially identical amino acid sequence or are derived from the same genetic source. This term also includes preparations of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0061] The term "human antibody", as used herein, includes antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, *e.g.*, human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik *et al.*, J. Mol. Biol. 296:57-86, 2000). Also included are antibodies derived from human sequences wherein

one or more CDRs has been mutated for affinity maturation or for manufacturing/payload conjugation purposes. *See* Kilpatrick *et al.*, "Rapid development of affinity matured monoclonal antibodies using RIMMS," Hybridoma. 1997 Aug;16(4):381-9.

[0062] The human antibodies of the invention may include amino acid residues not encoded by human sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*, or a conservative substitution to promote stability or manufacturing).

[0063] The term "recognize" as used herein refers to an antibody or antigen binding fragment thereof that finds and interacts (*e.g.*, binds) with its epitope, whether that epitope is linear or conformational. The term "epitope" refers to a site on an antigen to which an antibody or antigen binding fragment of the invention specifically binds. 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, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include techniques in the art, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (*see, e.g.*, Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, G. E. Morris, Ed. (1996)).

[0064] The term "affinity" as used herein refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

[0065] The term "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities. An isolated antibody that specifically binds to one antigen may, however, have cross-reactivity to other antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0066] The term "corresponding human germline sequence" refers to the nucleic acid sequence encoding a human variable region amino acid sequence or subsequence that shares the highest determined amino acid sequence identity with a reference variable region amino acid sequence or subsequence in comparison to all other all other known variable region amino acid sequences encoded by human germline immunoglobulin variable region sequences. The corresponding human germline sequence can also refer to the human variable region amino acid sequence or subsequence with the highest amino acid sequence identity with a reference

variable region amino acid sequence or subsequence in comparison to all other evaluated variable region amino acid sequences. The corresponding human germline sequence can be framework regions only, complementarity determining regions only, framework and complementarity determining regions, a variable segment (as defined above), or other combinations of sequences or subsequences that comprise a variable region. Sequence identity can be determined using the methods described herein, for example, aligning two sequences using BLAST, ALIGN, or another alignment algorithm known in the art. The corresponding human germline nucleic acid or amino acid sequence can have at least about 90%, 91, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference variable region nucleic acid or amino acid sequence. Corresponding human germline sequences can be determined, for example, through the publicly available international ImMunoGeneTics database (IMGT) (on the worldwide web at www.imgt.org/) and V-base (on the worldwide web at vbase.mrc-cpe.cam.ac.uk).

[0067] The phrase "specifically binds" or "selectively binds," when used in the context of describing the interaction between an antigen (*e.g.*, a protein) and an antibody, antibody fragment, or antibody-derived binding agent, refers to a binding reaction that is determinative of the presence of the antigen in a heterogeneous population of proteins and other biologics, *e.g.*, in a biological sample, *e.g.*, a blood, serum, plasma or tissue sample. Thus, under certain designated immunoassay conditions, the antibodies or binding agents with a particular binding specificity bind to a particular antigen at least two times the background and do not substantially bind in a significant amount to other antigens present in the sample. In one embodiment, under designated immunoassay conditions, the antibody or binding agent with a particular binding specificity binds to a particular antigen at least ten (10) times the background and does not substantially bind in a significant amount to other antigens present in the sample. Specific binding to an antibody or binding agent under such conditions may require the antibody or agent to have been selected for its specificity for a particular protein. As desired or appropriate, this selection may be achieved by subtracting out antibodies that cross-react with molecules from other species (*e.g.*, mouse or rat) or other subtypes. Alternatively, in some embodiments, antibodies or antibody fragments are selected that cross-react with certain desired molecules.

[0068] A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (*see, e.g.*, Harlow & Lane, Using Antibodies, A Laboratory Manual (1998), for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity). Typically a

specific or selective binding reaction will produce a signal at least twice over the background signal and more typically at least 10 to 100 times over the background.

[0069] The term "equilibrium dissociation constant (KD, M)" refers to the dissociation rate constant (kd, time-1) divided by the association rate constant (ka, time-1, M-1). Equilibrium dissociation constants can be measured using any known method in the art. The antibodies of the present invention generally will have an equilibrium dissociation constant of less than about 10^{-7} or 10^{-8} M, for example, less than about 10^{-9} M or 10^{-10} M, in some embodiments, less than about 10^{-11} M, 10^{-12} M or 10^{-13} M.

[0070] The term "bioavailability" refers to the systemic availability (*i.e.*, blood/plasma levels) of a given amount of drug administered to a patient. Bioavailability is an absolute term that indicates measurement of both the time (rate) and total amount (extent) of drug that reaches the general circulation from an administered dosage form.

[0071] As used herein, the phrase "consisting essentially of" refers to the genera or species of active pharmaceutical agents included in a method or composition, as well as any excipients inactive for the intended purpose of the methods or compositions. In some embodiments, the phrase "consisting essentially of" expressly excludes the inclusion of one or more additional active agents other than an antibody drug conjugate of the invention. In some embodiments, the phrase "consisting essentially of" expressly excludes the inclusion of one or more additional active agents other than an antibody drug conjugate of the invention and a second co-administered agent.

[0072] The term "amino acid" refers to naturally occurring, synthetic, and unnatural amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α-carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0073] The term "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

[0074] For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (*see, e.g.*, Creighton, Proteins (1984)). In some embodiments, the term "conservative sequence modifications" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

[0075] The term "optimized" as used herein refers to a nucleotide sequence that has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a yeast cell, a Pichia cell, a fungal cell, a Trichoderma cell, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide sequence is engineered to retain completely or as much as possible the

amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the "parental" sequence.

[0076] The terms "percent identical" or "percent identity," in the context of two or more nucleic acids or polypeptide sequences, refers to the extent to which two or more sequences or subsequences that are the same. Two sequences are "identical" if they have the same sequence of amino acids or nucleotides over the region being compared. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 30 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

[0077] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0078] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman, Adv. Appl. Math. 2:482c (1970), by the homology alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g.*, Brent *et al.*, Current Protocols in Molecular Biology, 2003).

[0079] Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25:3389-3402, 1977; and Altschul *et al.*, J. Mol. Biol. 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff and Henikoff, (1989) Proc. Natl. Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0080] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0081] The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller, Comput. Appl. Biosci. 4:11-17 (1988) which has

been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch, J. Mol. Biol. 48:444-453 (1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a BLOSUM62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0082] Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0083] The term “nucleic acid” is used herein interchangeably with the term “polynucleotide” and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0084] Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, (1991) Nucleic Acid Res. 19:5081; Ohtsuka *et al.*, (1985) J. Biol. Chem. 260:2605-2608; and Rossolini *et al.*, (1994) Mol. Cell. Probes 8:91-98).

[0085] The term “operably linked” in the context of nucleic acids refers to a functional relationship between two or more polynucleotide (*e.g.*, DNA) segments. Typically, it refers to

the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a transcribed sequence are physically contiguous to the transcribed sequence, *i.e.*, they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[0086] The terms "polypeptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

[0087] The term "antibody drug conjugate" or "immunoconjugate" as used herein refers to the linkage of an antibody or an antigen binding fragment thereof with another agent, such as a chemotherapeutic agent, a toxin, an immunotherapeutic agent, an imaging probe, and the like. The linkage can be covalent bonds, or non-covalent interactions such as through electrostatic forces. Various linkers, known in the art, can be employed in order to form the antibody drug conjugate. Additionally, the antibody drug conjugate can be provided in the form of a fusion protein that may be expressed from a polynucleotide encoding the immunoconjugate. As used herein, "fusion protein" refers to proteins created through the joining of two or more genes or gene fragments which originally coded for separate proteins (including peptides and polypeptides). Translation of the fusion gene results in a single protein with functional properties derived from each of the original proteins.

[0088] The term "subject" includes human and non-human animals. Non-human animals include all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

[0089] The term "cytotoxin", or "cytotoxic agent" as used herein, refers to any agent that is detrimental to the growth and proliferation of cells and may act to reduce, inhibit, or destroy a cell or malignancy.

[0090] The term "anti-cancer agent" as used herein refers to any agent that can be used to treat or prevent a cell proliferative disorder such as cancer, including but not limited to,

cytotoxic agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, and immunotherapeutic agents.

[0091] The term "drug moiety" or "payload" as used herein refers to a chemical moiety that is conjugated to an antibody or antigen binding fragment of the invention, and can include any therapeutic or diagnostic agent, for example, an anti-cancer, anti-inflammatory, anti-infective (e.g., anti-fungal, antibacterial, anti-parasitic, anti-viral), or an anesthetic agent. For example, the drug moiety can be an anti-cancer agent, such as a cytotoxin. In certain embodiments, a drug moiety is a target inhibitor compound. In addition, a payload can be a biophysical probe, a fluorophore, a spin label, an infrared probe, an affinity probe, a chelator, a spectroscopic probe, a radioactive probe, a lipid molecule, a polyethylene glycol, a polymer, a spin label, DNA, RNA, a protein, a peptide, a surface, an antibody, an antibody fragment, a nanoparticle, a quantum dot, a liposome, a PLGA particle, a saccharide or a polysaccharide.

[0092] In some embodiments, the drug moiety or payload is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor). In some embodiments, a GNAQ/11 inhibitor is a molecule that inhibits GNAQ/11-mediated production of IP3 and/or exhibits a dose-response antiproliferative effect in cells dependent on GNAQ/11 signaling (i.e., GNAQ/11 mutant uveal melanoma cells). In some embodiments, a GNAQ/11 inhibitor is a compound that stabilizes GNAQ/11 in the inactive GDP-bound state and prevents GDP release, or binds to the active GTP-bound state and prevents GNAQ/11 interaction with downstream effectors. In some embodiments, a GNAQ/11 inhibitor functions by inhibiting a mutant GNAQ and/or GNA11, such as one comprising a Q209L/P mutation. Methods for attaching such drug moieties to a linker compatible with the targeting moiety are given in the present disclosure, along with the methods known in the art. See, e.g., Singh et al., (2009) Therapeutic Antibodies: Methods and Protocols, vol. 525, 445-457.

[0093] GNAQ (Guanine nucleotide-binding protein G(q) subunit alpha, also known as CMC1, G-ALPHA-q, GAQ, SWS, and G protein subunit alpha q) and GNA11 (Guanine nucleotide-binding protein subunit alpha-11, also known as FBH, FBH2, FHH2, GNA-11, HHC2, HYPOC2, and G protein subunit alpha 11) are closely related GTPases that constitute α subunits of heterotrimeric G proteins acting downstream of G protein-coupled receptors (GPCRs). The α subunits act as a switch for activation of G proteins by exchanging the guanosine diphosphate (GDP) for guanosine triphosphate (GTP), leading to the activation of distinct downstream effectors. The activation is terminated by the intrinsic GTPase activity, as GTP is hydrolyzed to GDP (Van Raamsdonk et al., 2010, N Engl J Med.; 363(23):2191-9). The classical activation of Gq protein cascade occurs via phospholipase C-β (PLC-β), which

hydrolyses phospholipid phosphatidylinositol 4,5-biphosphate to release two potent second messengers: D-myo-inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). Following the transient increase of intracellular Ca^{2+}, IP3 is rapidly transformed into IP2, IP1, and myo-inositol. On the other hand, DAG activates protein kinase C (PKC), leading to a cascade of phosphorylation of RAF, MEK, and ERK, which translocates to the nucleus to regulate cell proliferation and survival (Krantz et al., 2017, Clin Ophthalmol.; 11:279-289).

[0094] The nucleic acid and amino acid sequences of human GNAQ have been published in GenBank with the following Accession Nos.:

[0095] NP_002063 (SEQ ID NO:268)

1 mtlesimacc lseeakearr indeierqlr rdkrdarrel kllllgtges gkstfikqmr
61 iihgsgysde dkrgftklvy qniftamqam iramdtlkip ykyehnkaha qlvrevdvek
121 vsafenpyvd aikslwndpg iqecydrrre yqlsdstkyy lndldrvadp aylptqqdvl
181 rvrvpttgii eypfdlqsvi frmvdvggqr serrkwihcf envtsimflv alseydqvlv
241 esdnenrmee skalfrtiit ypwfqnssvi lflnkkdlle ekimyshlvd yfpeydgpqr
301 daqaarefil kmfvdlnpds dkiiyshftc atdtenirfv faavkdtilq lnlkeynlv

[0096] NM_002072 (SEQ ID NO:269)

1 agactatccg ctcccaccgc gccccggcc cacctggtgg ccccggccct ggccgccgcc
61 cccgcggcgg ttcccggagc tcgtcccgga cgcgcgcccg ggcggcgggg gctcggcggc
121 caccgctgcc tcgggggagc gagggcggga gggtgtgtgt gcgcgctgtg agcaggggt
181 gccggcgggg ctgcagcgga ggcactttgg aagaatgact ctggagtcca tcatggcgtg
241 ctgcctgagc gaggaggcca aggaagcccg gcggatcaac gacgagatcg agcggcagct
301 ccgcagggac aagcgggacg cccgccggga gctcaagctg ctgctgctcg ggacaggaga
361 gagtggcaag agtacgttta tcaagcagat gagaatcatc catgggtcag gatactctga
421 tgaagataaa aggggcttca ccaagctggt gtatcagaac atcttcacgg ccatgcaggc
481 catgatcaga gccatggaca cactcaagat cccatacaag tatgagcaca ataaggctca
541 tgcacaatta gttcgagaag ttgatgtgga gaaggtgtct gcttttgaga atccatatgt
601 agatgcaata aagagtttat ggaatgatcc tggaatccag gaatgctatg atagacgacg
661 agaatatcaa ttatctgact ctaccaaata ctatcttaat gacttggacc gcgtagctga
721 ccctgcctac ctgcctacgc aacaagatgt gcttagagtt cgagtcccca ccacagggat
781 catcgaatac ccctttgact tacaaagtgt cattttcaga atggtcgatg taggggcca
841 aaggtcagag agaagaaaat ggatacactg ctttgaaaat gtcacctcta tcatgtttct
901 agtagcgctt agtgaatatg atcaagttct cgtggagtca gacaatgaga accgaatgga
961 ggaaagcaag gctctcttta gaacaattat cacatacccc tggttccaga actcctcggt
1021 tattctgttc ttaaacaaga aagatcttct agaggagaaa atcatgtatt cccatctagt
1081 cgactacttc ccagaatatg atggacccca gagagatgcc caggcagccc gagaattcat
1141 tctgaagatg ttcgtggacc tgaacccaga cagtgacaaa attatctact cccacttcac
1201 gtgcgccaca gacaccgaga atatccgctt tgtctttgct gccgtcaagg acaccatcct
1261 ccagttgaac ctgaaggagt acaatctggt ctaattgtgc ctcctagaca cccgccctgc
1321 ccttccctgg tgggctattg aagatacaca agagggactg tatttctgtg gaaaacaatt
1381 tgcataatac taatttattg ccgtcctgga ctctgtgtga gcgtgtccac agagtttgta
1441 gtaaatatta tgattttatt taaactattc agaggaaaaa cagaggatgc tgaagtacag
1501 tcccagcaca tttcctctct atctttttt taggcaaaac cttgtgactc agtgtatttt
1561 aaattctcag tcatgcactc acaaagataa gacttgtttc tttctgtctc tctctctttt

1621 tcttttctat ggagcaaaac aaagctgatt tccctttttt cttcccccgc taattcatac
1681 ctccctcctg atgtttttcc caggttacaa tggcctttat cctagttcca ttcttggtca
1741 agtttttctc tcaaatgata cagtcaggac acatcgttcg atttaagcca tcatcagctt
1801 aatttaagtt tgtagttttt gctgaaggat tatatgtatt aatacttacg gttttaaatg
1861 tgttgctttg gatacacaca tagtttcttt tttaatagaa tatactgtct tgtctcactt
1921 tggactggga cagtggatgc ccatctaaaa gttaagtgtc atttctttta gatgtttacc
1981 ttcagccata gcttgattgc tcagagaaat atgcagaagg caggatcaaa gacacacagg
2041 agtcctttct tttgaaatgc cacgtgccat tgtctttcct cccttctttg cttctttttc
2101 ttaccctctc tttcaattgc agatgccaaa aaagatgcca acagacacta cattacccta
2161 atggctgcta cccagaacct ttttataggt tgttcttaat ttttttgttg ttgttgttca
2221 agcttttcct ttctttttt tcttggtgtt tgggccacga ttttaaaatg acttttatta
2281 tgggtatgtg ttgccaaagc tggctttttg tcaaataaaa tgaatacgaa cttaaaaaat
2341 aaaagctggt atcttaaaat gtaagagagt aagactgtga agcctaaaat gactggctga
2401 gaatgaacca gaaatgccat ttgccaaaca gttgtaacta gaaatttgat tctcacggtc
2461 cattcttttc tttgtcctta agatgacatt gttagtgttc acgtcccatg ttcagtgtcc
2521 aaaccggcaa tgtaaaaagt atcctgtgtg gtttaacagg aaatctgttt atgtctcttt
2581 atttgaaacc agttttactc tcagtggttc tttaagttca atgaagtctg ccaggaacat
2641 tggttggtag tattattccg acacctttaa tttccaaaat ctgaagttcc tgctagttta
2701 ccaccttcat gatcttcttg aactggtaac tgattaggtt gaacttatgg aagatttgtg
2761 gacttaactc aaaagtaacc tctcagtgtt ctatagaaca tgtatttgtg taactgaacc
2821 taccaggaga aatgtttgga attctatatg tgcaattttt caacaaatgc aaaaaaaata
2881 cagcacatgt attgacaagc ttctgtcaag cagcttgagt tgaaatttga tttaagaaaa
2941 taaatcatga ttgttcaaag ctgctgggac gttagaatta ggccatgata ctggtctcat
3001 tttaactaca gtggtatttg gcactagtgt aaacttccat ataaatcact cttttggaac
3061 aacaaagggg gagggagaaa aatcacggcc tgttaaatga gtaccaaagc cgcccaacag
3121 taatgagatg ttctcatcct tgattctccc agcctcaaac aacacagctt actttttttt
3181 tcccttgctc agaaagtacc tgtaatttaa caaacagact gcctgtaggt atagtgcaat
3241 tacaaatgct ctaatcattg tacatacatc tctcttgata ttgcagcatc catactggct
3301 ttgtaatcat taatttttg gcagattgaa tgtgctgtat tgatatgtat ctatgtaatt
3361 gtattgtatg tctatagcta attcacgttt tgaataatgt tattttattt actttttaa
3421 gagaggagaa tgtaaatttg tcagtttatt tctgactagg gatattttct ttccatttag
3481 aaaagaagaa aaaaaaaaaa ccttactgtc atacagagcg gtactagcgt cgtgctgtat
3541 aaaatcattt gcacattcct gagtagaggt atactgatta taagacccaa aggtaatttc
3601 atagcaaaat acataaaatc agtcggagct tttatacaaa catggaaacc aactttgtag
3661 aacttttgcc atttgatcta ggattggaat atgagctttt atacaattca tattcttatt
3721 tggcaaatgc acagtttagt attacctctc tgatggcctt tactagaaag gcagttttag
3781 aagctattgt gatccactaa ggaaatgttt taacagctag agaccactgc ttgcctgaaa
3841 gggcgttctt aaatttggtg cagcaaaaaa aaaaaaaaaa aaaaaaaaaa ttaaacaaca
3901 acatttgaag gcctacagtg tgtatagaga aaacctcatc acaagatcat aagtgttaca
3961 gttttaggga atcaagatat tctatttaat agagctatag taaatgtagt caattaaacc
4021 tgatctcaaa gcttgaagaa gctgagcaaa acagggaaag attgttatat ttgtctttat
4081 gaaattggga tggaatttgc tatgcagaat tgaggtttgt ggcttcgctg ttcctgtagg
4141 gtgcatgaca agatcccttc tcttgagaaa ggaaaaaatt gatcacccta gcagcagtga
4201 tgcatagaaa cctaatttta gccacaccag tcaatcgaag ctaaaggatt ttctttttg
4261 tttcttcggg gttttattga aggggctagg ggcgggacgg gattcttttc agttttgtat
4321 aaaaacaaag tttactcatg ctttatatta tattgtgatt gcaagcgtta taagcgtgtg
4381 ccactggcct cctattgttg atgcttaggt aatggaggcc tgtggtgagt tttatggtga
4441 cttgggcatg tcttattcaa aaacaaaaac ataaaacaca gaaacctttc ttcagcatac
4501 caaggcaagc agccatttca tgactcactt aacacattgc agtgtaccag tttacagatg
4561 atttttccct ttttgcgtga catggcagtt ctaaccccca gagaattcct tatttgtaaa
4621 ttggaagttt ctactatgcc ttacagagct taaattcaga agtttgtgcc tcatatctga

4681 aacaaaggga aataacacac ccattcaaaa gtaaataaat ctcctagaag tttttgtttt
4741 taacatttcc atataaagag ctctgttgaa tgtcatgaat agactggaaa aaaaaatttt
4801 aagaacctgc atatgttgtt tactagcaga tgacaactac aaaaggaatc tgaagaacac
4861 gtaaaacttg tatttttttt tttttggtag attaactagc aggcctattt taaaaaggta
4921 attcagctaa agggcaattt actttttgt acttcagact atcttgattg tcaaagtgta
4981 cgaactgtaa ttttaaaatt tatactgcca catgattgta aattttagtt gtcttaagtt
5041 aggaattggt gaaaagctat ttatgctgga tttgggtcaa aatgacttat ttgcaaaaaa
5101 ataaataatg ggaagaaagg gctgtataat gaaatactgc aagactcaca tattggttgg
5161 aaatttccct caaatcacct accgattacc cttgatttcc ctttgttttc agtttctcaa
5221 aacgaatgaa atgaaatata gcagaatgtt aacccatata aaaataaagt gtacccaaat
5281 attgtaatgt atattgctgc tcttcttcaa attaaataag ggtttaaaac cacttaattg
5341 gtaatcaaca tctcaattga tacaaataag gtgtgcttgg tatacattaa tattttcttc
5401 caaagatata tctttggtta gaaacacaaa aaaataaaac tagtaatatt gtatgtttat
5461 ctatctctac atatttccag catatgtagc gttaatagat ctgtcctggt aactgtgtct
5521 ttgggatttc attttggttc catcaaatta ggaaaagaaa tggcttagtt gtatatgatt
5581 agctagagat ttttggagcc agacacctgc tgtttagtag ataacttagt acagacccta
5641 aacttgtcat ttgtttttct cacagaatag ccatttcctg ctgtcttccc aatgatcact
5701 gcccctttcaa taacactctt gcctctagaa tcatatgttc aaagtatgaa tacacaccta
5761 gcacatagta ggtgctcaaa tattaatttc ctccttgcct tccttatcta ccctgtgtcc
5821 tccatttccc cgtatgattc caacccaata tagcaaatga catttacatg ttatgaaaac
5881 atctattggg taaaatcaga tcttggataa agaaattctg acttttatat aagcttttgg
5941 tagacagaaa aaacagaaag gtattcgttg gtagaacatt tttaagttca ggaaagaaag
6001 ctggaataat actacgtaac tttgtccagg ttactttgac tgaaacacgt ttttggtgga
6061 tttcttttcc tcaaagaact ctctaaatgc aactccttgc tggattcctc acccatcatc
6121 ctgttggaaa cccttactag acctatgtat ttagggagtt ttgtcagaaa acatttttaa
6181 cttgcagtat ttaaaagaat atttactgtt cctaaaatgt cattcaaatg catgtactgt
6241 ctattgtttg gggatgggaa ctagttttgc aaaaaacacc taatgttgta taataatgcc
6301 ccaatgatct tgctggttaa aaatacagta ttttttggcca taa

[0097] The nucleic acid and amino acid sequence of human GNA11 have been published in GenBank with the following Accession Nos.:

[0098] NP_002058 (SEQ ID NO:270)

1 mtlesmmacc lsdevkeskr inaeiekqlr rdkrdarrel kllllgtges gkstfikqmr
61 iihgagysee dkrgftklvy qniftamqam irametlkil ykyeqnkana llirevdvek
121 vttfehqyvs aiktlwedpg iqecydrrre yqlsdsakyy ltdvdriatl gylptqqdvl
181 rvrvpttgii eypfdlenii frmvdvggqr serrkwihcf envtsimflv alseydqvlv
241 esdnenrmee skalfrtiit ypwfqnssvi lflnkkdlle dkilyshlvd yfpefdgpqr
301 daqaarefil kmfvdlnpds dkiiyshftc atdtenirfv faavkdtilq lnlkeynlv

[0099] NM_002067 (SEQ ID NO:271)

1 aggttgtccg gcgctgtcgc tcggttgcgg cggctgcggt tggcggtggc tgcggcggcg
61 gcgcgggctg agtgcggccg cgcgggagtc cgcggctggc gcggcccgag cggggacccg
121 gcggctcgcc aggcggcggc cgaggcgggg cgggccggcc cggggccgag ggccggtggc
181 cgaggccgga gggccgcggc gggcggcggc cgaggcggct ccggccaggg ccgggccggg
241 ggccgggggg cggcggcggg caggcggccg cgtcggccgg ggccgggacg atgactctgg

301 agtccatgat ggcgtgttgc ctgagcgatg aggtgaagga gtccaagcgg atcaacgccg
361 agatcgagaa gcagctgcgg cgggacaagc gcgacgcccg gcgcgagctc aagctgctgc
421 tgctcggcac gggcgagagc gggaagagca cgttcatcaa gcagatgcgc atcatccacg
481 gcgccggcta ctcggaggag gacaagcgcg gcttcaccaa gctcgtctac cagaacatct
541 tcaccgccat gcaggccatg atccgggcca tggagacgct caagatcctc tacaagtacg
601 agcagaacaa ggccaatgcg ctcctgatcc gggaggtgga cgtggagaag gtgaccacct
661 tcgagcatca gtacgtcagt gccatcaaga ccctgtggga ggacccgggc atccaggaat
721 gctacgaccg caggcgcgag taccagctct ccgactctgc caagtactac ctgaccgacg
781 ttgaccgcat cgccaccttg ggctacctgc ccacccagca ggacgtgctg cgggtccgcg
841 tgcccaccac cggcatcatc gagtaccctt tcgacctgga gaacatcatc ttccggatgg
901 tggatgtggg gggccagcgg tcggagcgga ggaagtggat ccactgcttt gagaacgtga
961 catccatcat gtttctcgtc gccctcagcg aatacgacca agtcctggtg gagtcggaca
1021 acgagaaccg gatggaggag agcaaagccc tgttccggac catcatcacc tacccctggt
1081 tccagaactc ctccgtcatc ctcttcctca acaagaagga cctgctggag gacaagatcc
1141 tgtactcgca cctggtggac tacttccccg agttcgatgg tccccagcgg gacgcccagg
1201 cggcgcggga gttcatcctg aagatgttcg tggacctgaa ccccgacagc gacaagatca
1261 tctactcaca cttcacgtgt gccaccgaca cggagaacat ccgcttcgtg ttcgcggccg
1321 tgaaggacac catcctgcag ctcaacctca aggagtacaa cctggtctga gcgcccaggc
1381 ccagggagac gggatggaga cacggggcag gaccttcctt ccacggagcc tgcggctgcc
1441 gggcgggtgg cgctgccgag tccgggccgg ggcctctgcc cgcgggagga gatttttttt
1501 tttcatattt ttaacaaatg gtttttattt cacagttatc aggggatgta catctctccc
1561 tccgtacact tcgcgcacct tctcaccttt tgtcaacggc aaaggcagcc tttttctggc
1621 cttgacttat ggctcgcttt tttctaaaaa aaaaaaaaaa agaaagaaag aaaaaaagca
1681 acgaaacata aaacacacaa gcgccccgtg cccccagtga ctctgggcct cacagagccc
1741 ccgccagcca gcatggggcc ccgccctgca gccagtcacg cgcccccaca ccgcagcccc
1801 ccgtggctgt ccttccaacc ccacgtgctt tttctttctc ctgcccgctt cttttcttca
1861 tcacaaaagg cgtggagact cggagacgga cgtttttccc ctttttaag ttattgacgc
1921 ccagcgcgcc tcgcctcttc acccatcaac gctgtgcttt gcccactgga ctcctgaaga
1981 gggggtgggg ggctccctcg gtcgcccacc ctgggaagtg cctaaccttt tattttattt
2041 tatttttttg aggaaaaaga acgcctgact cacaggttga agaaacaccc tgggccctct
2101 ctcatggccg ggttccccgt ccctctgcag aggctgggaa gggtccccgg gctggagcca
2161 cgggggcttc tctgggctgt gcctccgggg ccaacactgg ctgcttgggg ctgcccgggg
2221 actccagagg gctgcacggc caccctgccc tggctagagc gcaccccacc ggagcccacg
2281 tgggctgggc ggctggaggg atggtccccc ggtgacactg ggagaaaggc cacttggatg
2341 ggggcgtttc tgttttgttc cgctttgtga tgtcaccaat ttggaaacag cgagggtggg
2401 tggggacttt tacagaatat tctcaggtgt gtacccgaga ggcagagaga gggacgtggc
2461 cggcagctct gtgcgtggcc ttgtcccaag cacttgcgcc cgcccccgag cgccgccccc
2521 ggggagcggg aagccagcac tcgcactttg gccaggggcg cgtggaaggt ggtggcaggc
2581 accggcctgg gcagcttcca ggcctggctg gccacgacca cggcccgagg gggagcccgc
2641 caggccacgc cgcactgagc cacagccccg ggggccgcct cccggggccc cttgaggcac
2701 tgaggcaccg agactggttc tccccgagag actcggaagg tggggaacga ggggactgtg
2761 tttggggagg tggctttttc gtctgctgtt gactgaacac tacagcgccc tgtggttccg
2821 ggcttcgcac agctgtccca gggatggatc gcctgtgctg ccttcgcccg ccgccacacc
2881 gggaccctgc acggctgctt ctggcctcga cagatgacaa aagaaacagc cccaaaatac
2941 gaccactcca accagcagtt cccgcctgcc tgcccgccac tgtcaggcct gccctggcct
3001 cctcgtccgc agggctgtct gctggcttct gggggcagaa gagcggggag ccccgtggaa
3061 gggtcagggg agaccaggtc agggcagcta catttctggt gatcagcccc atggggagac
3121 ggggctggcg ggataccccc cccccggctt ccccacacca cttctgtctc acccggaagc
3181 gtccttttt tgtgccaggt gtctacctaa gagggttggt gccagaagcc ccccatggcg
3241 agtgctgggg cccggcggtg ccctggggga gcagatgggg ccacccctgg cagggccgct
3301 acaacctttt ccagcagcgg agccctctgg ggggcctgtg cttgtggcat ctctgagggc

3361 ctagattgca caaggtgacc tggccgtggc ctgagggtgg agtcgcccag cacgcaggcc
3421 ggggcgctgc ggggctaagt attaggcctt cccagggagg gggcgtgcca agcatcccag
3481 agccgggctg ggaccgccaa aacgtcgtgg cctggatcct ctgggtctga gtgcctgatc
3541 ccctgccccc caaaaaagca gaggtaggtg ttgcaggccc agggcagggg tgcctgcccc
3601 aggagagtcc caggcagtgg ttctcgtgcc agtggcaccc aggggcaagg acagccaacc
3661 cccacccttg ccacgtgtgg ggccacgtgg gcatgtgggg tgtgtgtttt taccttggtg
3721 aatctcacct gccaacgatt tctcgtgagt gccgaccacc ttctccgacc atgttacgcc
3781 cgggcggcag cagcccccgg ccactgcaaa cccatgccct gggtcccccg gctcccccag
3841 ggaggcatcc ccgtgccaat gtcccccagt ggtggcagca gatcctgtgg ccggcctggc
3901 ggacgggacc cagtgatact tgtatattac acagtcctga tttcagacaa tttcaacctt
3961 aatctattta aaaaagaata ttctatacaa gctgttttta agccttttac catttgaaat
4021 gcatgtgttg tgcgcgttgg ggatgggagg aggggctgag gagcggctca gtgtcacctc
4081 ccacagccac cggccctgac ccttaatcca gacaccgatg gaagtcgact tttcatatct
4141 ttctcctgaa atgaactctg ttttaaattg gaataaattt tgttcctaaa

[00100] "Tumor" refers to neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

[00101] The term "anti-tumor activity" means a reduction in the rate of tumor cell proliferation, viability, or metastatic activity. For example, anti-tumor activity can be shown by a decline in growth rate of abnormal cells that arises during therapy or tumor size stability or reduction, or longer survival due to therapy as compared to control without therapy. Such activity can be assessed using accepted in vitro or in vivo tumor models, including but not limited to xenograft models, allograft models, MMTV models, and other known models known in the art to investigate anti-tumor activity.

[00102] The term "malignancy" refers to a non-benign tumor or a cancer. As used herein, the term "cancer" includes a malignancy characterized by deregulated or uncontrolled cell growth. Exemplary cancers include: carcinomas, sarcomas, leukemias, and lymphomas.

[00103] The term "cancer" includes primary malignant tumors (*e.g.*, those whose cells have not migrated to sites in the subject's body other than the site of the original tumor) and secondary malignant tumors (*e.g.*, those arising from metastasis, the migration of tumor cells to secondary sites that are different from the site of the original tumor).

[00104] The term "PMEL17" (also referred to as premelanosome protein (PMEL), D12S53E, ME20, ME20-M, ME20M, P1, P100, gp100, SI, SIL, and silver locus protein homolog (SILV)) refers to a single-pass Type I transmembrane protein produced by melanocytes and involved in melanin synthesis. The nucleic acid and amino acid sequence of human PMEL17 have been published in GenBank with the following Accession Nos.: NP_008859, NP_001307050, NP_001307051, NP_001186982, NP_001186983 (amino acid sequences), and NM_006928, NM_001200053, NM_001200054, NM_001320121, NM_001320122

(nucleotide sequences). As used herein, the term “PMEL17” is used to refer collectively to all naturally occurring isoforms of PMEL17 protein, or a variant thereof.

[00105] NP_008859 (SEQ ID NO:272)

1 mdlvlkrcll hlavigalla vgatkvprnq dwlgvsrqlr tkawnrqlyp ewteaqrldc
61 wrggqvslkv sndgptliga nasfsialnf pgsqkvlpdg qviwvnntii ngsqvwggqp
121 vypqetddac ifpdggpcps gswsqkrsfv yvwktwgqyw qvlggpvsgl sigtgramlg
181 thtmevtvyh rrgsrsyvpl ahsssaftit dqvpfsvsvs qlraldggnk hflrnqpltf
241 alqlhdpsgy laeadlsytw dfgdssgtli sralvvthty lepgpvtaqv vlqaaiplts
301 cgsspvpgtt dghrptaeap nttagqvptt evvgttpgqa ptaepsgtts vqvpttevis
361 tapvqmptae stgmtpekvp vsevmgttla emstpeatgm tpaevsivvl sgttaaqvtt
421 tewvettare lpipepegpd assimstesi tgslgplldg tatlrlvkrq vpldcvlyry
481 gsfsvtldiv qgiesaeilq avpsgegdaf eltvscqggl pkeacmeiss pgcqppaqrl
541 cqpvlpspac qlvlhqilkg gsgtyclnvs ladtnslavv stqlimpgqe aglgqvpliv
601 gillvlmavv lasliyrrrl mkqdfsvpql phssshwlrl prifcscpig enspllsgqq
661 v

[00106] NP_001307050 (SEQ ID NO:273)

1 mdlvlkrcll hlavigalla vgatkvprnq dwlgvsrqlr tkawnrqlyp ewteaqrldc
61 wrggqvslkv sndgptliga nasfsialnf pgsqkvlpdg qviwvnntii ngsqvwggqp
121 vypqetddac ifpdggpcps gswsqkrsfv yvwktwgqyw qvlggpvsgl sigtgramlg
181 thtmevtvyh rrgsrsyvpl ahsssaftit dqvpfsvsvs qlraldggnk hflrnqpltf
241 alqlhdpsgy laeadlsytw dfgdssgtli sralvvthty lepgpvtaqv vlqaaiplts
301 cgsspvpgtt dghrptaeap nttagqvptt evvgttpgqa ptaepsgtts vqvpttevis
361 tapvqmptae staaqvttte wvettarelp ipepegpdas simstesitg slgplldgta
421 tlrlvkrqvp ldcvlyrygs fsvtldivqg iesaeilqav psgegdafel tvscqgglpk
481 eacmeisspg cqppaqrlcq pvlpspacql vlhqilkggs gtyclnvsla dtnslavvst
541 qlimpvpgil ltgqeaglgq vplivgillv lmavvlasli yrrrlmkqdf svpqlphsss
601 hwlrlprifc scpigenspl lsgqqv

[00107] NP_001307051 (SEQ ID NO:274)

1 mdlvlkrcll hlavigalla vgatkvprnq dwlgvsrqlr tkawnrqlyp ewteaqrldc
61 wrggqvslkv sndgptliga nasfsialnf pgsqkvlpdg qviwvnntii ngsqvwggqp
121 vypqetddac ifpdggpcps gswsqkrsfv yvwktwgqyw qvlggpvsgl sigtgramlg
181 thtmevtvyh rrgsrsyvpl ahsssaftit dqvpfsvsvs qlraldggnk hflrnqpltf
241 alqlhdpsgy laeadlsytw dfgdssgtli sralvvthty lepgpvtaqv vlqaaiplts
301 cgsspvpgtt dghrptaeap nttagqvptt evvgttpgqa ptaepsgtts vqvpttevis
361 tapvqmptae staaqvttte wvettarelp ipepegpdas simstesitg slgplldgta
421 tlrlvkrqvp ldcvlyrygs fsvtldivqg iesaeilqav psgegdafel tvscqgglpk
481 eacmeisspg cqppaqrlcq pvlpspacql vlhqilkggs gtyclnvsla dtnslavvst
541 qlimpgqeag lgqvplivgi llvlmavvla sliyrrrlmk qdfsvpqlph ssshwlrlpr
601 ifcscpigen spllsgqqv

[00108] NP_001186982 (SEQ ID NO:275)

1 mdlvlkrcll hlavigalla vgatkgsqvw ggqpvypqet ddacifpdgg pcpsgswsqk

61 rsfvyvwktw gqywqvlggp vsglsigtgr amlgthtmev tvyhrrgsrs yvplahsssa
121 ftitdqvpfs vsvsqlrald ggnkhflrnq pltfalqlhd psgylaeadl sytwdfgdss
181 gtlisralvv thtylepgpv taqvvlqaai pltscgsspv pgttdghrpt aeapnttagq
241 vpttevvgtt pgqaptaeps gttsvqvptt evistapvqm ptaestgmtp ekvpvsevmg
301 ttlaemstpe atgmtpaevs ivvlsgttaa qvtttewvet tarelpipep egpdassims
361 tesitgslgp lldgtatlrl vkrqvpldcv lyrygsfsvt ldivqgiesa eilqavpsge
421 gdafeltvsc qgglpkeacm eisspgcqpp aqrlcqpvlp spacqlvlhq ilkggsgtyc
481 lnvsladtns lavvstqlim pgqeaglgqv plivgillvl mavvlasliy rrrlmkqdfs
541 vpqlphsssh wlrlprifcs cpigenspll sgqqv

[00109] NP_001186983 (SEQ ID NO:276)

1 mdlvlkrcll hlavigalla vgatkvprnq dwlgvsrqlr tkawnrqlyp ewteaqrldc
61 wrggqvslkv sndgptliga nasfsialnf pgsqkvlpdg qviwvnntii ngsqvwggqp
121 vypqetddac ifpdggpcps gswsqkrsfv yvwktwgqyw qvlggpvsgl sigtgramlg
181 thtmevtvyh rrgsrsyvpl ahsssaftit dqvpfsvsvs qlraldggnk hflrnqpltf
241 alqlhdpsgy laeadlsytw dfgdssgtli sralvvthty lepgpvtaqv vlqaaiplts
301 cgsspvpgtt dghrptaeap nttagqvptt evvgttpgqa ptaepsgtts vqvpttevis
361 tapvqmptae stgmtpekvp vsevmgttla emstpeatgm tpaevsivvl sgttaaqvtt
421 tewvettare lpipepegpd assimstesi tgslgplldg tatlrlvkrq vpldcvlyry
481 gsfsvtldiv qgiesaeilq avpsgegdaf eltvscqggl pkeacmeiss pgcqppaqrl
541 cqpvlpspac qlvlhqilkg gsgtyclnvs ladtnslavv stqlimpvpg illtgqeagl
601 gqvplivgil lvlmavvlas liyrrrlmkq dfsvpqlphs sshwlrlpri fcscpigens
661 pllsgqqv

[00110] NM_006928 (SEQ ID NO:277)

1 cccagcgctc ctccccgcaa atgatcccgc cccaggggcc tatcccagtc cccccagtgc
61 ctttggttgc tggagggaag aacacaatgg atctggtgct aaaaagatgc cttcttcatt
121 tggctgtgat aggtgctttg ctggctgtgg gggctacaaa agtacccaga aaccaggact
181 ggcttggtgt ctcaaggcaa ctcagaacca aagcctggaa caggcagctg tatccagagt
241 ggacagaagc ccagagactt gactgctgga gaggtggtca agtgtccctc aaggtcagta
301 atgatgggcc tacactgatt ggtgcaaatg cctccttctc tattgccttg aacttccctg
361 gaagccaaaa ggtattgcca gatgggcagg ttatctgggt caacaatacc atcatcaatg
421 ggagccaggt gtggggagga cagccagtgt atccccagga aactgacgat gcctgcatct
481 tccctgatgg tggaccttgc ccatctggct cttggtctca gaagagaagc tttgtttatg
541 tctggaagac ctggggccaa tactggcaag ttctaggggg cccagtgtct gggctgagca
601 ttgggacagg cagggcaatg ctgggcacac acaccatgga agtgactgtc taccatcgcc
661 ggggatcccg gagctatgtg cctcttgctc attccagctc agccttcacc attactgacc
721 aggtgccttt ctccgtgagc gtgtcccagt tgcgggcctt ggatggaggg aacaagcact
781 tcctgagaaa tcagcctctg acctttgccc tccagctcca tgaccccagt ggctatctgg
841 ctgaagctga cctctcctac acctgggact ttggagacag tagtggaacc ctgatctctc
901 gggcacttgt ggtcactcat acttacctgg agcctggccc agtcactgcc caggtggtcc
961 tgcaggctgc cattcctctc acctcctgtg gctcctcccc agttccaggc accacagatg
1021 ggcacaggcc aactgcagag gcccctaaca ccacagctgg ccaagtgcct actacagaag
1081 ttgtgggtac tacacctggt caggcgccaa ctgcagagcc ctctggaacc acatctgtgc
1141 aggtgccaac cactgaagtc ataagcactg cacctgtgca gatgccaact gcagagagca
1201 caggtatgac acctgagaag gtgccagttt cagaggtcat gggtaccaca ctggcagaga
1261 tgtcaactcc agaggctaca ggtatgacac ctgcagaggt atcaattgtg gtgctttctg

1321 gaaccacagc tgcacaggta acaactacag agtgggtgga gaccacagct agagagctac
1381 ctatccctga gcctgaaggt ccagatgcca gctcaatcat gtctacggaa agtattacag
1441 gttccctggg ccccctgctg gatggtacag ccaccttaag gctggtgaag agacaagtcc
1501 ccctggattg tgttctgtat cgatatggtt ccttttccgt caccctggac attgtccagg
1561 gtattgaaag tgccgagatc ctgcaggctg tgccgtccgg tgaggggggat gcatttgagc
1621 tgactgtgtc ctgccaaggc gggctgccca aggaagcctg catggagatc tcatcgccag
1681 ggtgccagcc ccctgcccag cggctgtgcc agcctgtgct acccagccca gcctgccagc
1741 tggttctgca ccagatactg aagggtggct cggggacata ctgcctcaat gtgtctctgg
1801 ctgataccaa cagcctggca gtggtcagca cccagcttat catgcctggt caagaagcag
1861 gccttgggca ggttccgctg atcgtgggca tcttgctggt gttgatggct gtggtccttg
1921 catctctgat atataggcgc agacttatga agcaagactt ctccgtaccc cagttgccac
1981 atagcagcag tcactggctg cgtctacccc gcatcttctg ctcttgtccc attggtgaga
2041 acagcccccc cctcagtggg cagcaggtct gagtactctc atatgatgct gtgatttttcc
2101 tggagttgac agaaacacct atatttcccc cagtcttccc tgggagacta ctattaactg
2161 aaataaatac tcagagcctg aaaaaaaaaa aaaaa

[00111] NM_001200053 (SEQ ID NO:278)

1 gggcctatcc cagtcccccc agtgcctttg gttgctggag ggaagaacac aatggatctg
61 gtgctaaaaa gatgccttct tcatttggct gtgataggtg ctttgctggc tgtgggggct
121 acaaaaggga gccaggtgtg gggaggacag ccagtgtatc cccaggaaac tgacgatgcc
181 tgcatcttcc ctgatggtgg accttgccca tctggctctt ggtctcagaa gagaagcttt
241 gtttatgtct ggaagacctg gggccaatac tggcaagttc taggggccc agtgtctggg
301 ctgagcattg ggacaggcag ggcaatgctg ggcacacaca ccatggaagt gactgtctac
361 catcgccggg gatcccggag ctatgtgcct cttgctcatt ccagctcagc cttcaccatt
421 actgaccagg tgcctttctc cgtgagcgtg tcccagttgc gggccttgga tggagggaac
481 aagcacttcc tgagaaatca gcctctgacc tttgccctcc agctccatga ccccagtggc
541 tatctggctg aagctgacct ctcctacacc tgggactttg gagacagtag tggaaccctg
601 atctctcggg cacttgtggt cactcatact tacctggagc ctggcccagt cactgcccag
661 gtggtcctgc aggctgccat tcctctcacc tcctgtggct cctccccagt tccaggcacc
721 acagatgggc acaggccaac tgcagaggcc cctaacacca cagctggcca agtgcctact
781 acagaagttg tgggtactac acctggtcag gcgccaactg cagagccctc tggaaccaca
841 tctgtgcagg tgccaaccac tgaagtcata agcactgcac ctgtgcagat gccaactgca
901 gagagcacag gtatgacacc tgagaaggtg ccagtttcag aggtcatggg taccacactg
961 gcagagatgt caactccaga ggctacaggt atgacacctg cagaggtatc aattgtggtg
1021 ctttctggaa ccacagctgc acaggtaaca actacagagt gggtggagac cacagctaga
1081 gagctaccta tccctgagcc tgaaggtcca gatgccagct caatcatgtc tacggaaagt
1141 attacaggtt ccctgggccc cctgctggat ggtacagcca ccttaaggct ggtgaagaga
1201 caagtccccc tggattgtgt tctgtatcga tatggttcct tttccgtcac cctggacatt
1261 gtccagggta ttgaaagtgc cgagatcctg caggctgtgc cgtccggtga gggggatgca
1321 tttgagctga ctgtgtcctg ccaaggcggg ctgcccaagg aagcctgcat ggagatctca
1381 tcgccagggt gccagccccc tgcccagcgg ctgtgccagc ctgtgctacc cagcccagcc
1441 tgccagctgg ttctgcacca gatactgaag ggtggctcgg ggacatactg cctcaatgtg
1501 tctctggctg ataccaacag cctggcagtg gtcagcaccc agcttatcat gcctggtcaa
1561 gaagcaggcc ttgggcaggt tccgctgatc gtgggcatct tgctggtgtt gatggctgtg
1621 gtccttgcat ctctgatata taggcgcaga cttatgaagc aagacttctc cgtaccccag
1681 ttgccacata gcagcagtca ctggctgcgt ctaccccgca tcttctgctc ttgtcccatt
1741 ggtgagaaca gccccctcct cagtgggcag caggtctgag tactctcata tgatgctgtg
1801 attttcctgg agttgacaga aacacctata tttcccccag tcttccctgg gagactacta

1861 ttaactgaaa taaatactca gagcctgaaa aaaaaaaaaa aa

[00112] NM_001200054 (SEQ ID NO:279)

1 gggcctatcc cagtcccccc agtgcctttg gttgctggag ggaagaacac aatggatctg
61 gtgctaaaaa gatgccttct tcatttggct gtgataggtg ctttgctggc tgtgggggct
121 acaaaagtac ccagaaacca ggactggctt ggtgtctcaa ggcaactcag aaccaaagcc
181 tggaacaggc agctgtatcc agagtggaca gaagcccaga gacttgactg ctggagaggt
241 ggtcaagtgt ccctcaaggt cagtaatgat gggcctacac tgattggtgc aaatgcctcc
301 ttctctattg ccttgaactt ccctggaagc caaaaggtat tgccagatgg gcaggttatc
361 tgggtcaaca ataccatcat caatgggagc caggtgtggg gaggacagcc agtgtatccc
421 caggaaactg acgatgcctg catcttccct gatggtggac cttgcccatc tggctcttgg
481 tctcagaaga gaagctttgt ttatgtctgg aagacctggg gccaatactg gcaagttcta
541 gggggcccag tgtctgggct gagcattggg acaggcaggg caatgctggg cacacacacc
601 atggaagtga ctgtctacca tcgccgggga tcccggagct atgtgcctct tgctcattcc
661 agctcagcct tcaccattac tgaccaggtg cctttctccg tgagcgtgtc ccagttgcgg
721 gccttggatg gagggaacaa gcacttcctg agaaatcagc ctctgacctt tgccctccag
781 ctccatgacc ccagtggcta tctggctgaa gctgacctct cctacacctg ggactttgga
841 gacagtagtg gaaccctgat ctctcgggca cttgtggtca ctcatactta cctggagcct
901 ggcccagtca ctgcccaggt ggtcctgcag gctgccattc ctctcacctc ctgtggctcc
961 tccccagttc caggcaccac agatgggcac aggccaactg cagaggcccc taacaccaca
1021 gctggccaag tgcctactac agaagttgtg ggtactacac ctggtcaggc gccaactgca
1081 gagccctctg gaaccacatc tgtgcaggtg ccaaccactg aagtcataag cactgcacct
1141 gtgcagatgc caactgcaga gagcacaggt atgacacctg agaaggtgcc agtttcagag
1201 gtcatgggta ccacactggc agagatgtca actccagagg ctacaggtat gacacctgca
1261 gaggtatcaa ttgtggtgct ttctggaacc acagctgcac aggtaacaac tacagagtgg
1321 gtggagacca cagctagaga gctacctatc cctgagcctg aaggtccaga tgccagctca
1381 atcatgtcta cggaaagtat tacaggttcc ctgggccccc tgctggatgg tacagccacc
1441 ttaaggctgg tgaagagaca agtccccctg gattgtgttc tgtatcgata tggttccttt
1501 tccgtcaccc tggacattgt ccagggtatt gaaagtgccg agatcctgca ggctgtgccg
1561 tccggtgagg gggatgcatt tgagctgact gtgtcctgcc aaggcgggct gcccaaggaa
1621 gcctgcatgg agatctcatc gccagggtgc cagccccctg cccagcggct gtgccagcct
1681 gtgctaccca gcccagcctg ccagctggtt ctgcaccaga tactgaaggg tggctcgggg
1741 acatactgcc tcaatgtgtc tctggctgat accaacagcc tggcagtggt cagcacccag
1801 cttatcatgc ctgtgcctgg gattcttctc acaggtcaag aagcaggcct tgggcaggtt
1861 ccgctgatcg tgggcatctt gctggtgttg atggctgtgg tccttgcatc tctgatatat
1921 aggcgcagac ttatgaagca agacttctcc gtaccccagt tgccacatag cagcagtcac
1981 tggctgcgtc taccccgcat cttctgctct tgtcccattg gtgagaacag ccccctcctc
2041 agtgggcagc aggtctgagt actctcatat gatgctgtga ttttcctgga gttgacagaa
2101 acacctatat ttcccccagt cttccctggg agactactat taactgaaat aaatactcag
2161 agcctgaaaa aaaaaaaaaa a

[00113] NM_001320121 (SEQ ID NO:280)

1 gggcctatcc cagtcccccc agtgcctttg gttgctggag ggaagaacac aatggatctg
61 gtgctaaaaa gatgccttct tcatttggct gtgataggtg ctttgctggc tgtgggggct
121 acaaaagtac ccagaaacca ggactggctt ggtgtctcaa ggcaactcag aaccaaagcc
181 tggaacaggc agctgtatcc agagtggaca gaagcccaga gacttgactg ctggagaggt
241 ggtcaagtgt ccctcaaggt cagtaatgat gggcctacac tgattggtgc aaatgcctcc

301 ttctctattg ccttgaactt ccctggaagc caaaaggtat tgccagatgg gcaggttatc
361 tgggtcaaca ataccatcat caatgggagc caggtgtggg gaggacagcc agtgtatccc
421 caggaaactg acgatgcctg catcttccct gatggtggac cttgcccatc tggctcttgg
481 tctcagaaga gaagctttgt ttatgtctgg aagacctggg gccaatactg gcaagttcta
541 gggggcccag tgtctgggct gagcattggg acaggcaggg caatgctggg cacacacacc
601 atggaagtga ctgtctacca tcgccgggga tcccggagct atgtgcctct tgctcattcc
661 agctcagcct tcaccattac tgaccaggtg cctttctccg tgagcgtgtc ccagttgcgg
721 gccttggatg gagggaacaa gcacttcctg agaaatcagc ctctgacctt tgccctccag
781 ctccatgacc ccagtggcta tctggctgaa gctgacctct cctacacctg ggactttgga
841 gacagtagtg gaaccctgat ctctcgggca cttgtggtca ctcatactta cctggagcct
901 ggcccagtca ctgcccaggt ggtcctgcag gctgccattc ctctcacctc ctgtggctcc
961 tccccagttc caggcaccac agatgggcac aggccaactg cagaggcccc taacaccaca
1021 gctggccaag tgcctactac agaagttgtg ggtactacac ctggtcaggc gccaactgca
1081 gagccctctg gaaccacatc tgtgcaggtg ccaaccactg aagtcataag cactgcacct
1141 gtgcagatgc caactgcaga gagcacagct gcacaggtaa caactacaga gtgggtggag
1201 accacagcta gagagctacc tatccctgag cctgaaggtc cagatgccag ctcaatcatg
1261 tctacggaaa gtattacagg ttccctgggc cccctgctgg atggtacagc caccttaagg
1321 ctggtgaaga gacaagtccc cctggattgt gttctgtatc gatatggttc cttttccgtc
1381 accctggaca ttgtccaggg tattgaaagt gccgagatcc tgcaggctgt gccgtccggt
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1501 atggagatct catcgccagg gtgccagccc cctgcccagc ggctgtgcca gcctgtgcta
1561 cccagcccag cctgccagct ggttctgcac cagatactga agggtggctc ggggacatac
1621 tgcctcaatg tgtctctggc tgataccaac agcctggcag tggtcagcac ccagcttatc
1681 atgcctgtgc ctgggattct tctcacaggt caagaagcag gccttgggca ggttccgctg
1741 atcgtgggca tcttgctggt gttgatggct gtggtccttg catctctgat atataggcgc
1801 agacttatga agcaagactt ctccgtaccc cagttgccac atagcagcag tcactggctg
1861 cgtctacccc gcatcttctg ctcttgtccc attggtgaga acagcccct cctcagtggg
1921 cagcaggtct gagtactctc atatgatgct gtgattttcc tggagttgac agaaacacct
1981 atatttcccc cagtcttccc tgggagacta ctattaactg aaataaatac tcagagcctg
2041 a

[00114] NM_001320122 (SEQ ID NO:281)

1 gggcctatcc cagtcccccc agtgcctttg gttgctggag ggaagaacac aatggatctg
61 gtgctaaaaa gatgccttct tcatttggct gtgataggtg ctttgctggc tgtgggggct
121 acaaaagtac ccagaaacca ggactggctt ggtgtctcaa ggcaactcag aaccaaagcc
181 tggaacaggc agctgtatcc agagtggaca gaagcccaga gacttgactg ctggagaggt
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541 gggggcccag tgtctgggct gagcattggg acaggcaggg caatgctggg cacacacacc
601 atggaagtga ctgtctacca tcgccgggga tcccggagct atgtgcctct tgctcattcc
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721 gccttggatg gagggaacaa gcacttcctg agaaatcagc ctctgacctt tgccctccag
781 ctccatgacc ccagtggcta tctggctgaa gctgacctct cctacacctg ggactttgga
841 gacagtagtg gaaccctgat ctctcgggca cttgtggtca ctcatactta cctggagcct
901 ggcccagtca ctgcccaggt ggtcctgcag gctgccattc ctctcacctc ctgtggctcc
961 tccccagttc caggcaccac agatgggcac aggccaactg cagaggcccc taacaccaca

1021 gctggccaag tgcctactac agaagttgtg ggtactacac ctggtcaggc gccaactgca
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1261 tctacggaaa gtattacagg ttccctgggc cccctgctgg atggtacagc caccttaagg
1321 ctggtgaaga gacaagtccc cctggattgt gttctgtatc gatatggttc cttttccgtc
1381 accctggaca ttgtccaggg tattgaaagt gccgagatcc tgcaggctgt gccgtccggt
1441 gagggggatg catttgagct gactgtgtcc tgccaaggcg ggctgcccaa ggaagcctgc
1501 atggagatct catcgccagg gtgccagccc cctgcccagc ggctgtgcca gcctgtgcta
1561 cccagcccag cctgccagct ggttctgcac cagatactga agggtggctc ggggacatac
1621 tgcctcaatg tgtctctggc tgataccaac agcctggcag tggtcagcac ccagcttatc
1681 atgcctggtc aagaagcagg ccttgggcag gttccgctga tcgtgggcat cttgctggtg
1741 ttgatggctg tggtccttgc atctctgata tataggcgca gacttatgaa gcaagacttc
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1861 tcttgtccca ttggtgagaa cagccccctc ctcagtgggc agcaggtctg agtactctca
1921 tatgatgctg tgattttcct ggagttgaca gaaacaccta tatttccccc agtcttccct
1981 gggagactac tattaactga aataaatact cagagcctga

[00115] The term “variant” refers to a polypeptide that has a substantially identical amino acid sequence to a reference polypeptide, or is encoded by a substantially identical nucleotide sequence, and is capable of having one or more activities of the reference polypeptide. For example, a variant can have about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher sequence identity to a reference polypeptide, while retain one or more activities of the reference polypeptide.

[00116] As used herein, the terms “treat,” “treating,” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment, “treat,” “treating,” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat,” “treating,” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both.

[00117] As used herein, the term “prevent”, “preventing" or “prevention” of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder

[00118] The term “therapeutically acceptable amount” or “therapeutically effective dose” interchangeably refers to an amount sufficient to effect the desired result (i.e., a reduction in tumor size, inhibition of tumor growth, prevention of metastasis, inhibition or prevention of viral, bacterial, fungal or parasitic infection). In some embodiments, a therapeutically acceptable amount does not induce or cause undesirable side effects. In some embodiments, a

therapeutically acceptable amount induces or causes side effects but only those that are acceptable by the healthcare providers in view of a patient's condition. A therapeutically acceptable amount can be determined by first administering a low dose, and then incrementally increasing that dose until the desired effect is achieved. A "prophylactically effective dosage," and a "therapeutically effective dosage," of the molecules of the invention can prevent the onset of, or result in a decrease in severity of, respectively, disease symptoms, including symptoms associated with cancer.

[00119] The term "co-administer" refers to the presence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

[00120] The present invention provides antibodies, antibody fragments (*e.g.*, antigen binding fragments), and drug conjugates thereof, *i.e.*, antibody drug conjugates or ADCs, that bind to PMEL17. In particular, the present invention provides antibodies and antibody fragments (*e.g.*, antigen binding fragments) that bind to PMEL17, and internalize upon such binding. The antibodies and antibody fragments (*e.g.*, antigen binding fragments) of the present invention can be used for producing antibody drug conjugates. Furthermore, the present invention provides antibody drug conjugates that have desirable pharmacokinetic characteristics and other desirable attributes, and thus can be used for treating or preventing a cancer expressing PMEL17. The present invention further provides pharmaceutical compositions comprising the antibody drug conjugates of the invention, and methods of making and using such pharmaceutical compositions for the treatment or prevention of cancer.

Drug Moiety (D)

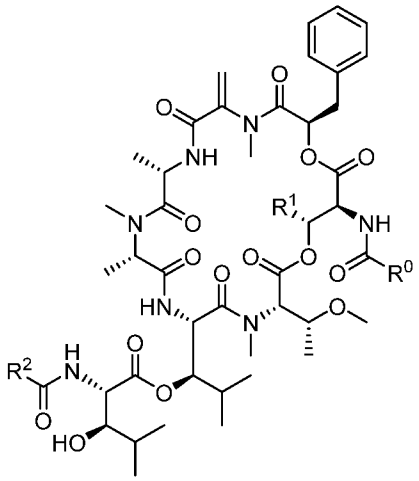
[00121] In one aspect, the Drug moiety (D) of the Antibody Drug Conjugate of the invention is a GNAQ inhibitor, a GNA11 inhibitor, or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

[00122] In another aspect, the Drug moiety (D) of the Antibody Drug Conjugate of the invention is a GNAQ inhibitor.

[00123] In another aspect, the Drug moiety (D) of the Antibody Drug Conjugate of the invention is a GNA11 inhibitor.

[00124] In another aspect, the Drug moiety (D) of the Antibody Drug Conjugate of the invention is an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

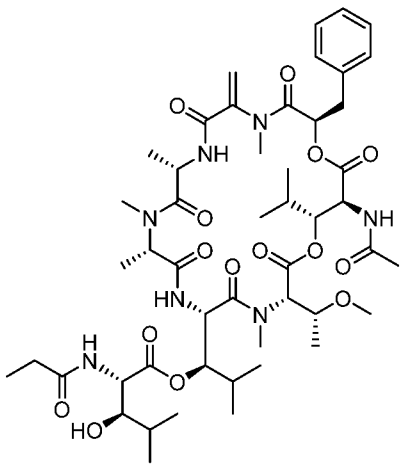
[00125] In another aspect, the Drug moiety of the Antibody Drug Conjugate of the invention is a compound having the structure of Formula (A):



(A),

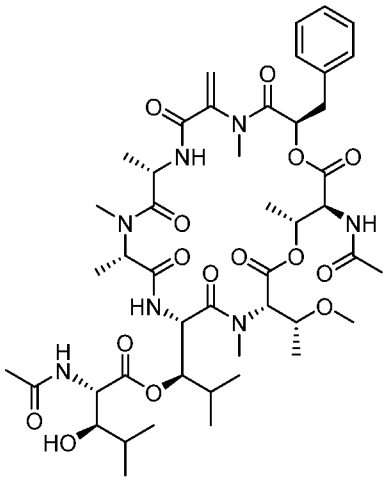
wherein R_0 is methyl or ethyl, R_1 is methyl or i-propyl, and R_2 is methyl or ethyl.

[00126] In another aspect, Drug moiety of the Antibody Drug Conjugate of the invention is compound (A1) having the following structure:



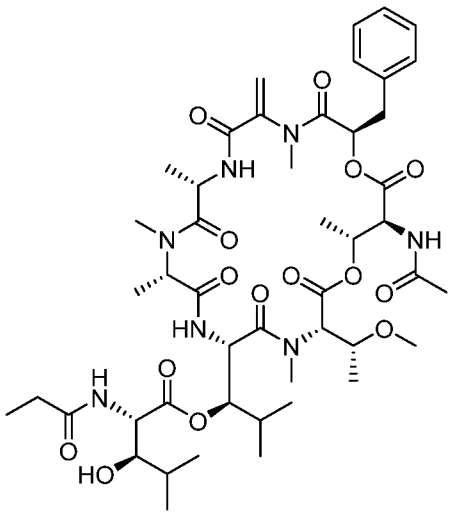
(A1).

[00127] In another aspect, Drug moiety of the Antibody Drug Conjugate of the invention is compound (A2) having the following structure:



(A2).

[00128] In another aspect, Drug moiety of the Antibody Drug Conjugate of the invention is compound (A3) having the following structure:



(A3).

Table 1 gives the inhibitory activity of compounds (A1), (A2) and (A3) obtained using the assay described in Example 5.

Table 1

Compound	GI_{50} (nM) 92.1GNAQ ^{Q209L}
A1	0.467
A2	22.1

Compound	GI_{50} (nM) 92.1GNAQ ^{Q209L}
A3	9.3

Linker-Drug Moiety (L_A-$(D)_n$)

[00129] In a second aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the one or more Drug moieties are each independently selected from a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

[00130] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the one or more Drug moieties are each independently selected from a GNAQ inhibitor.

[00131] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties attached to a linker (L_A), wherein the one or more Drug moieties are each independently selected from a GNA11 inhibitor.

[00132] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the one or more Drug moieties are each independently selected from an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

[00133] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a cleavable linker and the one or more Drug moieties are each independently selected from a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

[00134] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a cleavable linker and the one or more Drug moieties are each independently selected from a GNAQ inhibitor.

[00135] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$)), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker

(L_A), wherein the linker (L_A) is a cleavable linker and the one or more Drug moieties are each independently selected from a GNA11 inhibitor.

[00136] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$))), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a cleavable linker and the one or more Drug moieties are each independently selected from an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

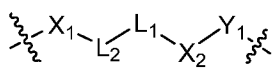
[00137] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$))), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a non-cleavable linker and the one or more Drug moieties are each independently selected from a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

[00138] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$))), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a non-cleavable linker and the one or more Drug moieties are each independently selected from a GNAQ inhibitor.

[00139] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$))), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a non-cleavable linker and the one or more Drug moieties are each independently selected from a GNA11 inhibitor.

[00140] In another aspect, the Linker-Drug moiety, ((L_A-$(D)_n$))), of the Antibody Drug Conjugate of the invention comprises one or more Drug moieties covalently attached to a linker (L_A), wherein the linker (L_A) is a non-cleavable linker and the one or more Drug moieties are each independently selected from an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor).

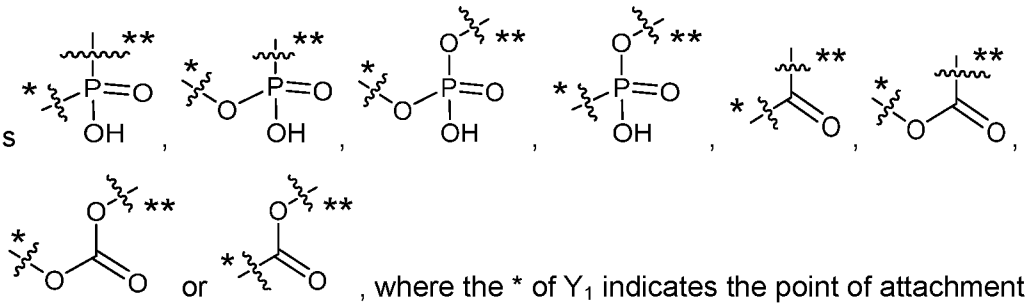
[00141] In another aspect, the linker (L_A) of the Linker-Drug moiety, ((L_A-$(D)_n$))), of the Antibody Drug Conjugate of the invention has the following formula:



wherein:

X_1 is a bivalent coupling group;

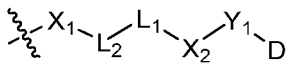
X_2 is a self-immolative spacer;

Y_1 is  , where the * of Y_1 indicates the point of attachment to X_2 and the ** of Y_1 indicates the other point of attachment;

L_1 is a bivalent peptide linker, and

L_2 is a bond or a linker.

[00142] In another aspect, the Linker-Drug moiety, $((L_A\text{-}(D)_n))$, of the Antibody Drug Conjugate of the invention has the following formula:

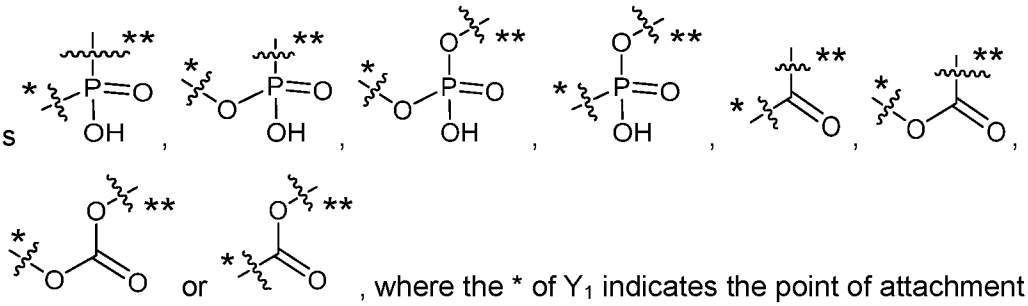


wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

X_1 is a bivalent coupling group;

X_2 is a self-immolative spacer;

Y_1 is  , where the * of Y_1 indicates the point of attachment to X_2 and the ** of Y_1 indicates the point of attachment to D;

L_1 is a bivalent peptide linker, and

L_2 is a bond or a linker.

Linker-Drug Compounds $(L_B\text{-}(D)_n)$

[00143] In one aspect the Linker-Drug of the invention is a compound having the structure of Formula (B), or stereoisomers or pharmaceutically acceptable salts thereof,

$$R^8\text{-}L_B\text{-}(D)_n \qquad (B)$$

wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

R^8 is a reactive group;

L_B is a cleavable linker or non-cleavable linker, and

n is 1, 2, 3 or 4.

[00144] In one aspect the Linker-Drug of the invention having the structure of Formula (B), or stereoisomers or pharmaceutically acceptable salts thereof, wherein

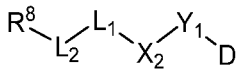
D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

R^8 is a reactive group;

L_B is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group, a carbonate group and a bivalent peptide linker, and

n is 1, 2, 3 or 4.

[00145] In one aspect the Linker-Drug of the invention is a compound having the structure of Formula (B-1), or stereoisomers or pharmaceutically acceptable salts thereof,



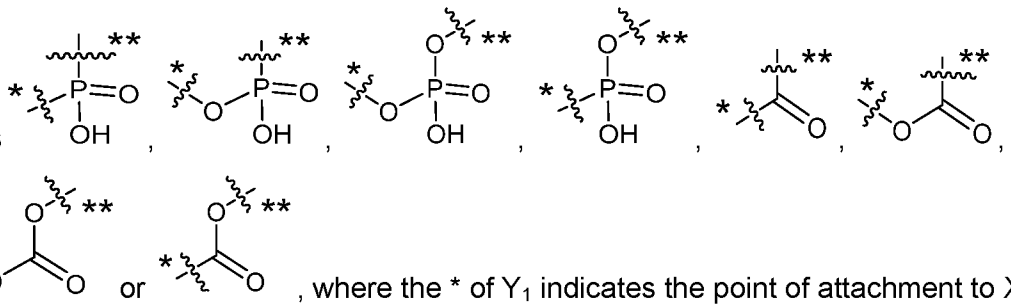
(B-1)

wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

R^8 is a reactive group;

X_2 is a self-immolative spacer;

Y_1 is  where the * of Y_1 indicates the point of attachment to X_2 and the ** of Y_1 indicates the point of attachment to D;

L_1 is a bivalent peptide linker, and

L_2 is a bond or a linker.

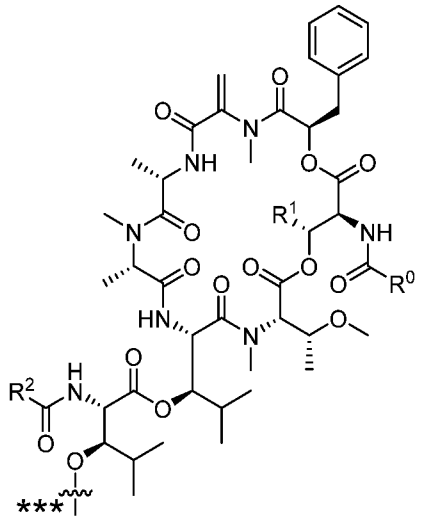
[00146] Certain aspects and examples of the Linker-Drug compounds of the invention are provided in the following listing of additional, enumerated embodiments. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

[00147] Embodiment 1. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is a GNAQ inhibitor.

[00148] Embodiment 2. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is a GNA11 inhibitor.

[00149] Embodiment 3. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is an inhibitor of GNAQ and GNA11.

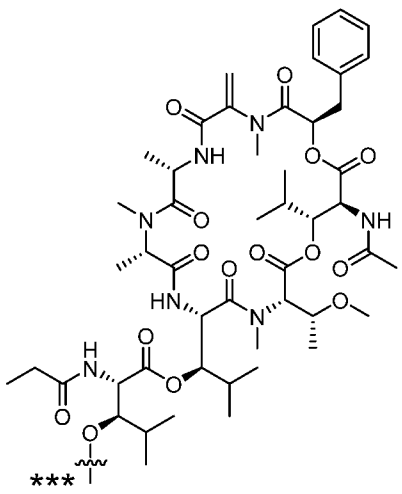
[00150] Embodiment 4. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is



,

wherein R^0 is methyl or ethyl, R^1 is methyl or isopropyl, R^2 is methyl or ethyl, and the *** indicates the point of attachment to L_B or Y_1.

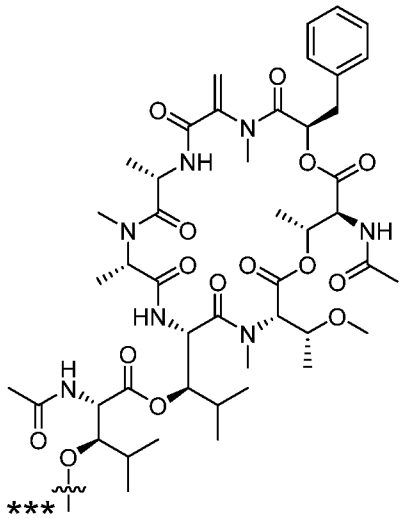
[00151] Embodiment 5. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is



,

where the *** indicates the point of attachment to L_B or Y_1.

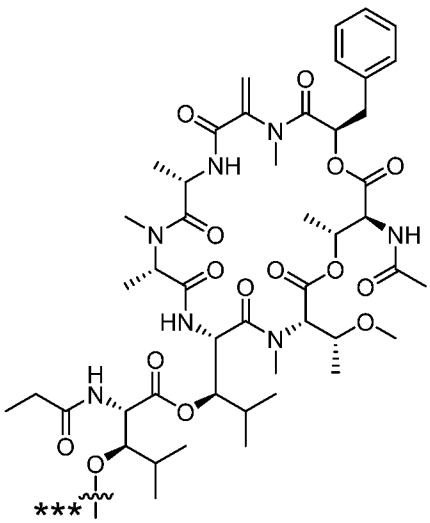
[00152] Embodiment 6. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is



,

where the *** indicates the point of attachment to L_B or Y_1.

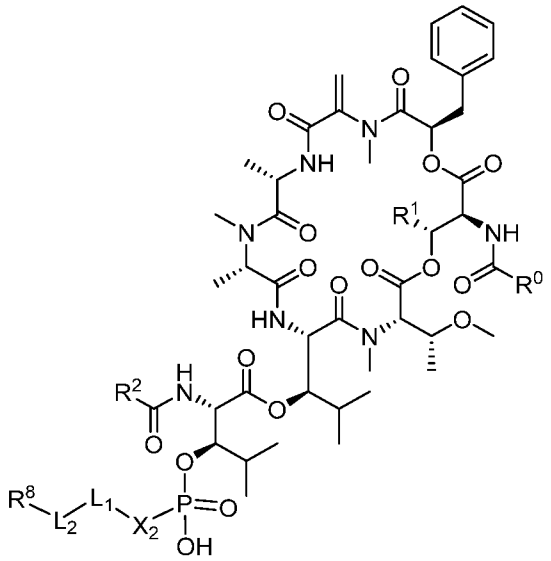
[00153] Embodiment 7. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, wherein D is



,

where the *** indicates the point of attachment to L_B or Y_1.

[00154] Embodiment 8. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-2), or a pharmaceutically acceptable salt thereof:



(B-2),

wherein:

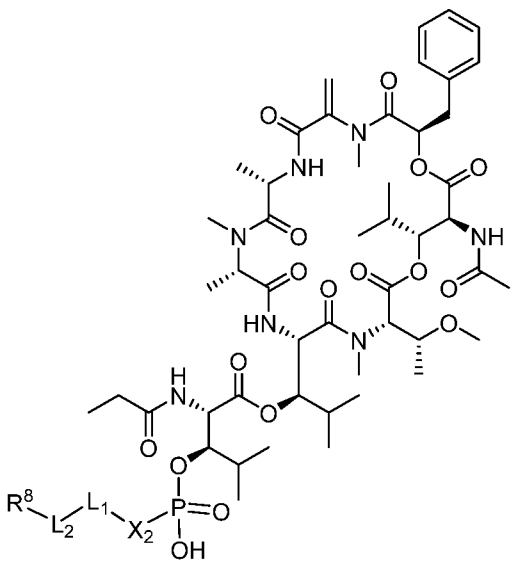
R^0 is methyl or ethyl,;

R^1 is methyl or isopropyl;

R^2 is methyl or ethyl, and

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00155] Embodiment 9. The compound of Formula (B), Formula (B-1) or Formula (B-2), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-2a), or a pharmaceutically acceptable salt thereof:

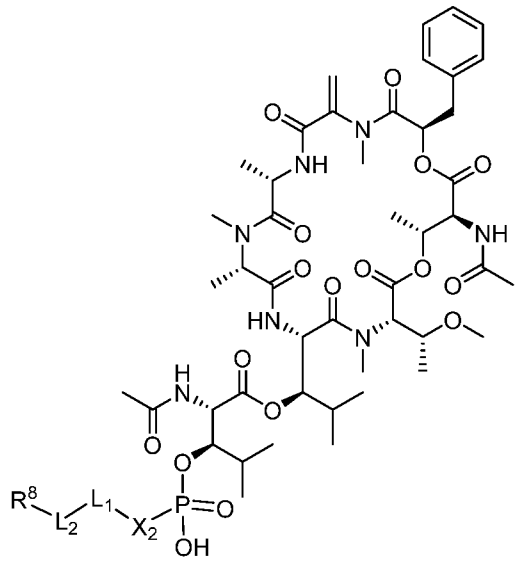


(B-2a),

wherein:

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00156] Embodiment 10. The compound of Formula (B), Formula (B-1) or Formula (B-2), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-2b), or a pharmaceutically acceptable salt thereof:

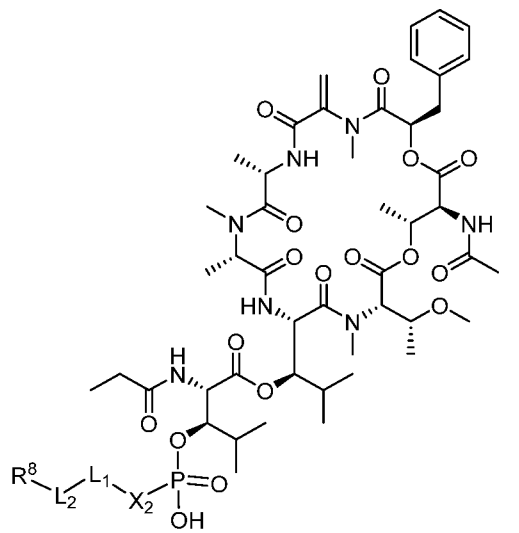


(B-2b),

wherein:

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00157] Embodiment 11. The compound of Formula (B), Formula (B-1) or Formula (B-2), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-2c), or a pharmaceutically acceptable salt thereof:

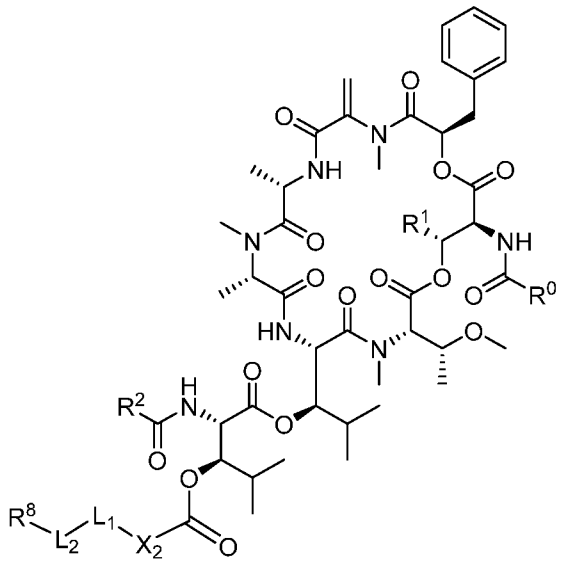


(B-2c),

wherein:

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00158] Embodiment 12. The compound of Formula (B) or Formula (B-1), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-3), or a pharmaceutically acceptable salt thereof:



(B-3),

wherein:

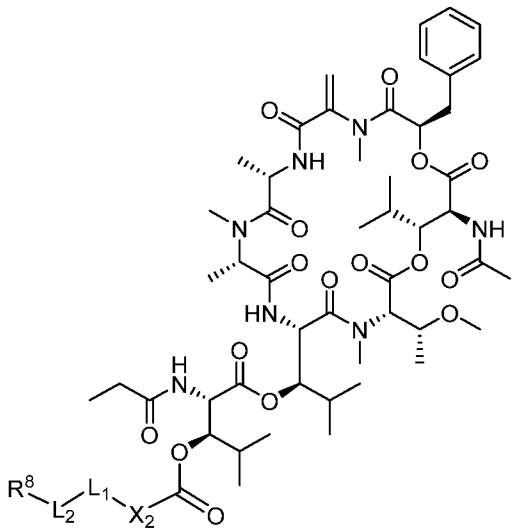
R^0 is methyl or ethyl,;

R^1 is methyl or isopropyl;

R^2 is methyl or ethyl, and

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00159] Embodiment 13. The compound of Formula (B), Formula (B-1) or Formula (B-3), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-3a), or a pharmaceutically acceptable salt thereof:

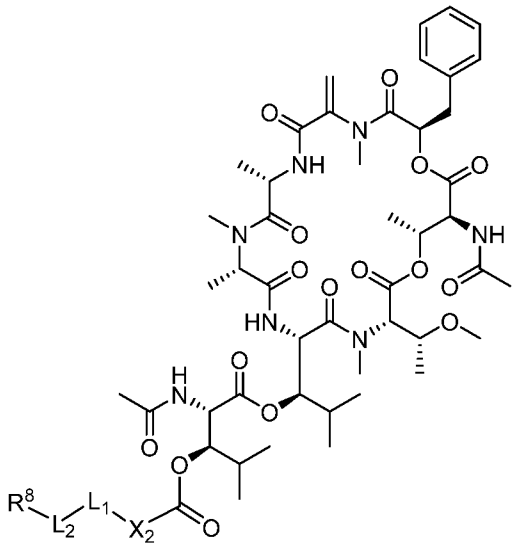


(B-3a),

wherein:

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00160] Embodiment 14. The compound of Formula (B), Formula (B-1) or Formula (B-3), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-3b), or a pharmaceutically acceptable salt thereof:

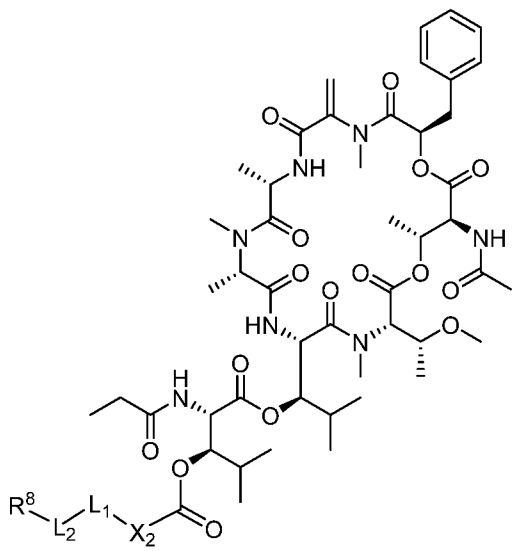


(B-3b),

wherein:

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

[00161] Embodiment 15. The compound of Formula (B), Formula (B-1) or Formula (B-3), or stereoisomers or a pharmaceutically acceptable salt thereof, having the structure of Formula (B-3c), or a pharmaceutically acceptable salt thereof:



(B-3c),

wherein:

X_2, L_1, L_2 and R^8 are as define in compounds of Formula (B-1) above.

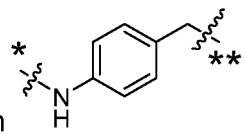
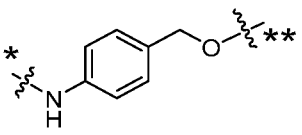
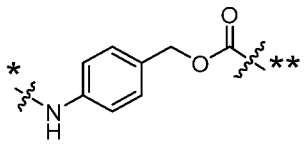
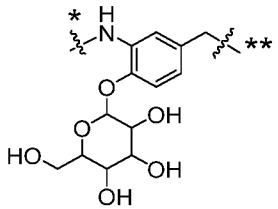
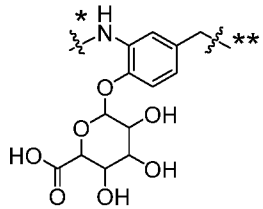
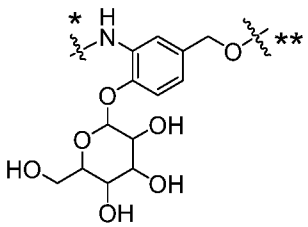
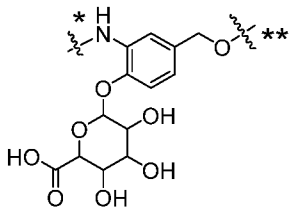
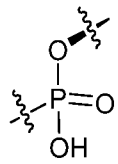
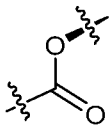
[00162] Embodiment 16. The compound of Formula (B-2) of Embodiment 8, Formula (B-3) of Embodiment 12, or a pharmaceutically acceptable salt thereof:

wherein:

R^0 is methyl or ethyl;

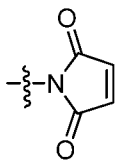
R^1 is methyl or isopropyl;

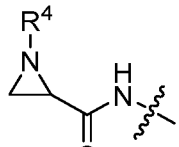
R^2 is methyl or ethyl;

X_2 is a self-immolative spacer selected from  ,  ,  ,  ,  ,  and  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to the  group or the point of attachment to  group;

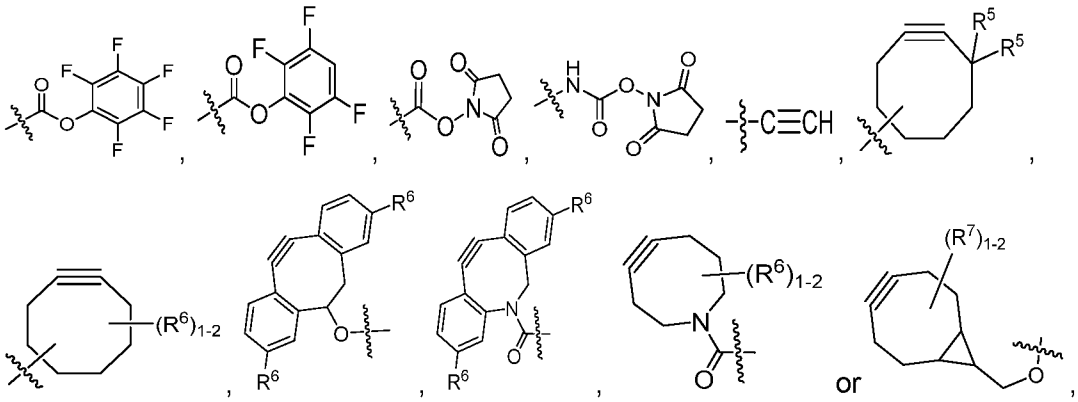
L_1 is a bivalent peptide linker comprising 2 to 4 amino acid residues;

L_2 is a linker,

R^8 is selected from  , $-N_3$, $-ONH_2$, $-NR^4C(=O)CH=CH_2$, SH, $-SSR^{13}$, $-S(=O)_2(CH=CH_2)$, $-NR^4S(=O)_2(CH=CH_2)$, $-NR^4C(=O)CH_2Br$, $-NR^4C(=O)CH_2I$, -



$NHC(=O)CH_2Br$, $-NHC(=O)CH_2I$, $-C(=O)NHNH_2$, , $-CO_2H$, $-NH_2$,



wherein:

each R^4 is independently selected from H and C_1-C_6alkyl;

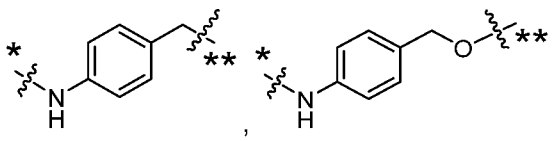
each R^5 is independently selected from H, C_1-C_6alkyl, F, Cl, and –OH;

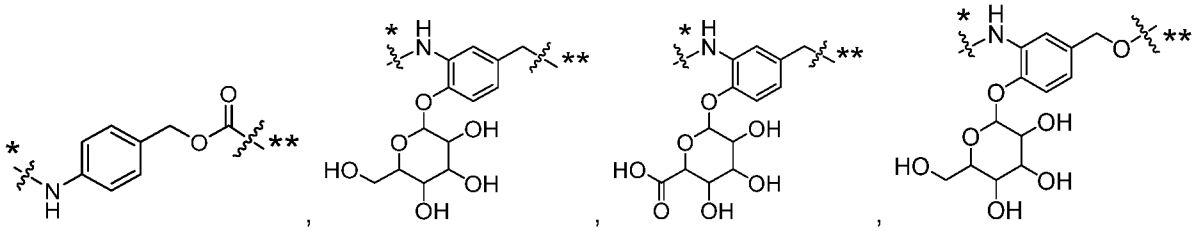
each R^6 is independently selected from H, C_1-C_6alkyl, F, Cl, $-NH_2$, $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, -CN, $-NO_2$ and –OH,

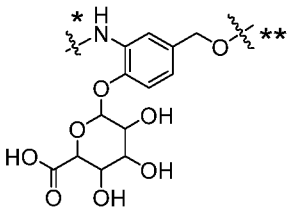
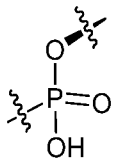
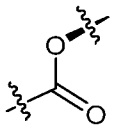
and

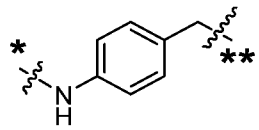
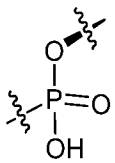
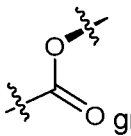
each R^7 is independently selected from H, C_{1-6}alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4}alkoxy substituted with –C(=O)OH and C_{1-4}alkyl substituted with –C(=O)OH.

[00163] Embodiment 17. The compound of any one of Embodiments 1 to 16, wherein X_2 is a self-immolative spacer selected from





and  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to Y_1, the point of attachment to the  group or the point of attachment to  group.

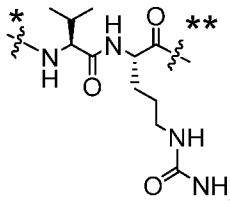
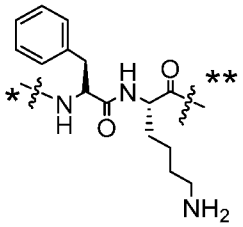
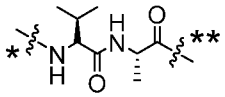
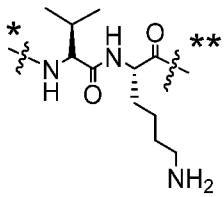
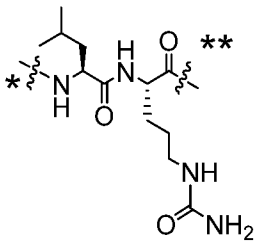
[00164] Embodiment 18. The compound of any one of Embodiments 1 to 17, wherein X_2 is  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to Y_1, the point of attachment to the  group or the point of attachment to  group.

[00165] Embodiment 19. The compound of any one of Embodiments 1 to 18, wherein L_1 is a bivalent peptide linker comprising 2 to 4 amino acid residues.

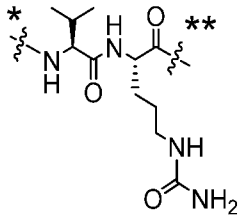
[00166] Embodiment 20. The compound of any one of Embodiments 1 to 18, wherein L_1 is a is a bivalent peptide linker comprising an amino acid residue selected from valine, citrulline, lysine, isoleucine, phenylalanine, methionine, asparagine, proline, alanine, leucine, tryptophan, and tyrosine.

[00167] Embodiment 21. The compound of any one of Embodiments 1 to 18, wherein L_1 is a bivalent peptide linker comprising at least one valine (Val) or citrulline (Cit) residue.

[00168] Embodiment 22. The compound of any one of Embodiments 1 to 18, wherein L_1 is a bivalent dipeptide linker selected from ValCit, PheLys, ValAla and ValLys.

[00169] Embodiment 23. The compound of any one of Embodiments 1 to 18, wherein L_1 is a bivalent dipeptide linker selected from  (ValCit),  (PheLys),  (ValAla),  (ValLys) and  (LeuCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2.

[00170] Embodiment 24. The compound of any one of Embodiments 1 to 18, wherein L_1 is ValCit.

[00171] Embodiment 25. The compound of any one of Embodiments 1 to 18, wherein L_1 is  (ValCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2.

[00172] Embodiment 26. The compound of any one of Embodiments 1 to 25, wherein L_2 is a linker.

[00173] Embodiment 27. The compound of any one of Embodiments 1 to 25, wherein L_2 is a linker selected from:

-*C(=O)((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -*C(=O)(CH$_2$)$_m$**-, -*C(=O)(CH$_2$)$_n$NHC(=O)(CH$_2$)$_m$**-, -*C(=O)(CH$_2$)$_m$NHC(=O)((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -* ((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -* ((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -(CH$_2$)$_m$-, -*(CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$**-, -* (CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$C(=O)NH(CH$_2$)$_m$**-, -* ((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$**-, -* *((CH$_2$)$_m$O)$_p$CH$_2$)$_m$C(=O)NH(CH$_2$)$_m$**-, -* (CH$_2$)$_m$C(R$_3$)$_2$**-, and -* (CH$_2$)$_m$C(R$_3$)$_2$SS(CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$**-, where the * of L_2 indicates the attachment point to L_1 and the ** of L_2 indicates the point of attachment to R_8;

and wherein:

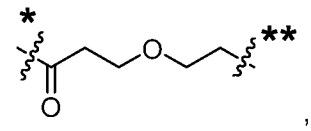
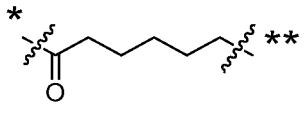
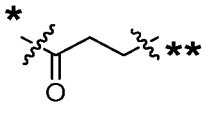
each R_3 is independently selected from H and C_1-C_6alkyl;

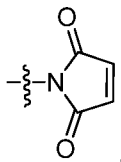
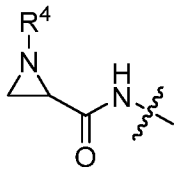
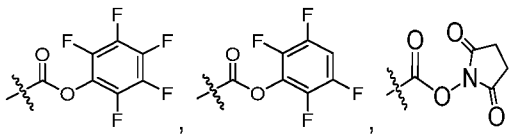
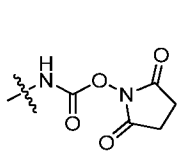
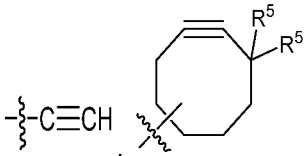
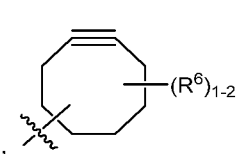
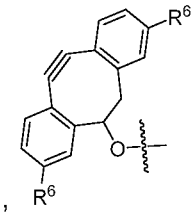
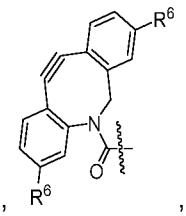
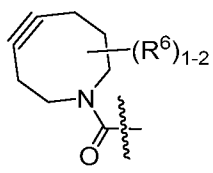
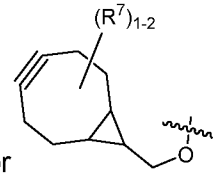
each m is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

each p is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14.

[00174] Embodiment 28. The compound of any one of Embodiments 1 to 25, wherein L_2 is -*C(=O)((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**- or -*C(=O)(CH$_2$)$_m$**-, where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to R_8,

and wherein each m is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14.

[00175] Embodiment 29. The compound of any one of Embodiments 1 to 25, wherein L_2 is  ,  , or  , where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to R_8.

[00176] Embodiment 30. The compound of any one of Embodiments 1 to 29, wherein R^8 is  , -N$_3$, -ONH$_2$, -NR^{4}C(=O)CH=CH$_2$, SH, -SSR^{13}, -S(=O)$_2$(CH=CH$_2$), -NR^{4}S(=O)$_2$(CH=CH$_2$), -NR^{4}C(=O)CH$_2$Br, -NR^{4}C(=O)CH$_2$I, -NHC(=O)CH$_2$Br, -NHC(=O)CH$_2$I, -C(=O)NHNH$_2$,  , -CO$_2$H, -NH$_2$,  ,  ,  ,  ,  ,  ,  or  , wherein:

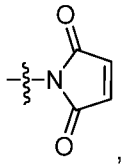
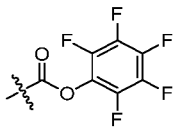
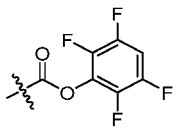
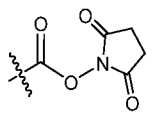
each R^4 is independently selected from H and C_1-C_6alkyl;

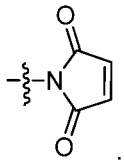
each R^5 is independently selected from H, C_1-C_6alkyl, F, Cl, and –OH;

each R^6 is independently selected from H, C_1-C_6alkyl, F, Cl, $-NH_2$, $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, -CN, $-NO_2$ and –OH,

and

each R^7 is independently selected from H, C_{1-6}alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4}alkoxy substituted with –C(=O)OH and C_{1-4}alkyl substituted with –C(=O)OH.

[00177] Embodiment 31. The compound of any one of Embodiments 1 to 29, wherein R^8 is  , $-ONH_2$,  ,  or  .

[00178] Embodiment 32. The compound of any one of Embodiments 1 to 29, wherein R^8 is  .

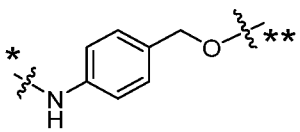
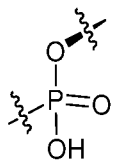
[00179] Embodiment 33. The compound of Formula (B-2) of Embodiment 8, or a pharmaceutically acceptable salt thereof:

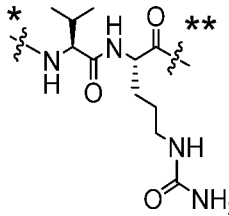
wherein:

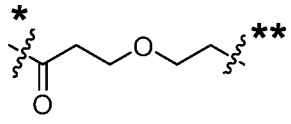
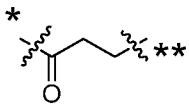
R^0 is methyl or ethyl;

R^1 is methyl or isopropyl;

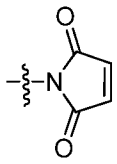
R^2 is methyl or ethyl;

X_2 is  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to the  group;

L_1 is  (ValCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2;

L_2 is  or  , where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to R_8,

and

R^8 is  .

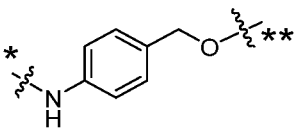
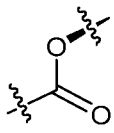
[00180] Embodiment 34. The compound of Formula (B-3) of Embodiment 12, or a pharmaceutically acceptable salt thereof:

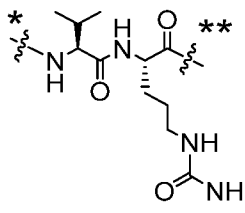
wherein:

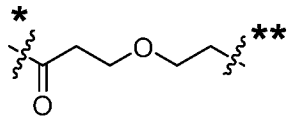
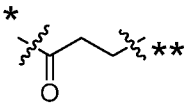
R^0 is methyl or ethyl;

R^1 is methyl or isopropyl;

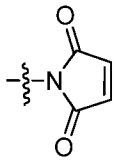
R^2 is methyl or ethyl;

X_2 is  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to the  group;

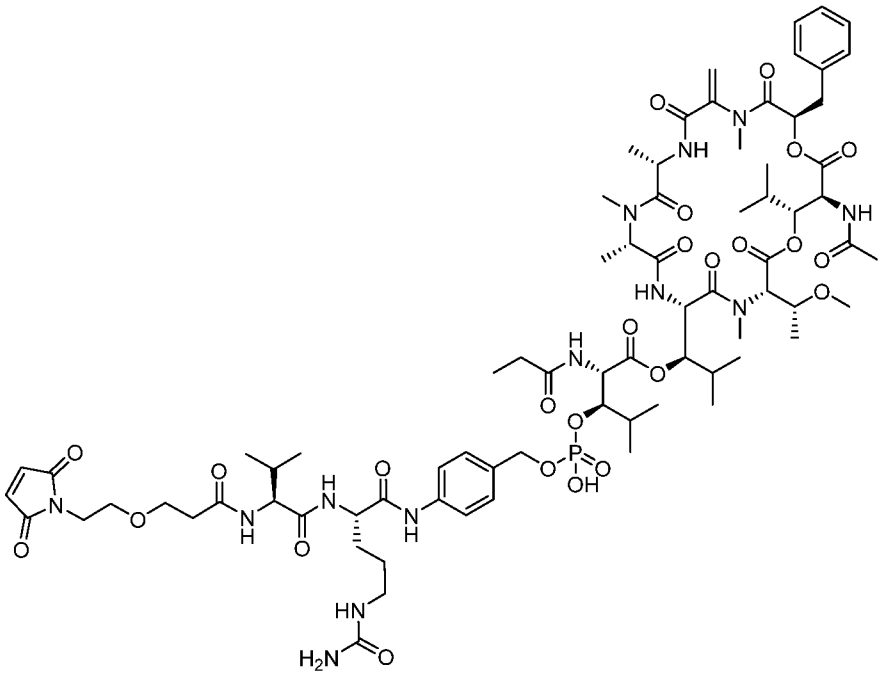
L_1 is  (ValCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2;

L_2 is  or  , where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to R_8,

and

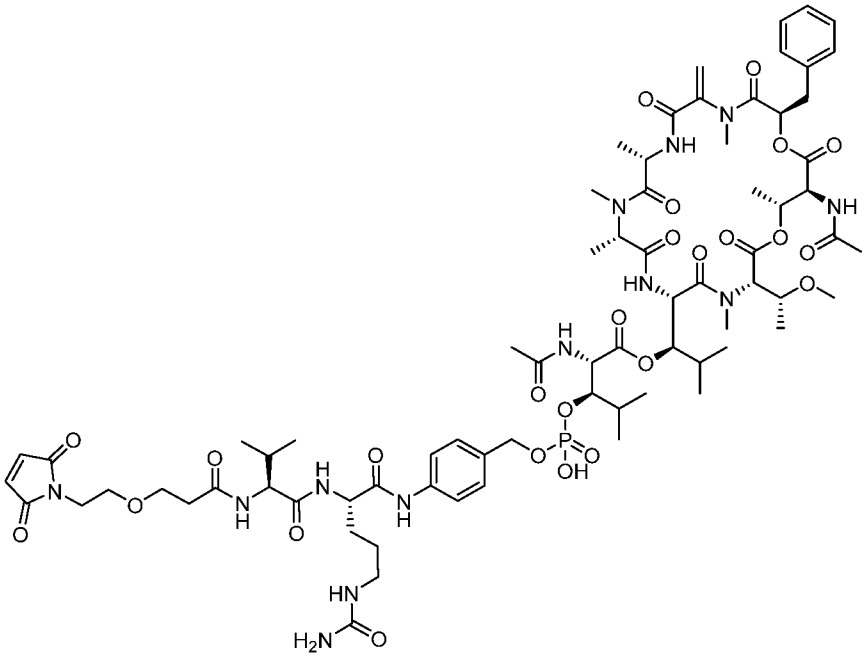
R^8 is  .

[00181] Embodiment 35. The compound of Formula (B), Formula (B-1) or Formula (B-2), wherein the compound is



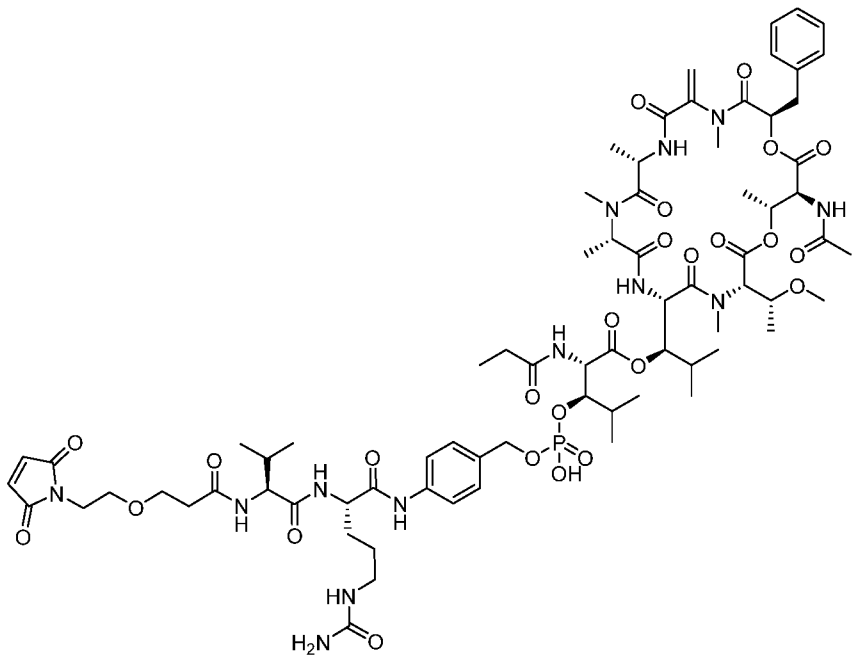
(B1).

[00182] Embodiment 36. The compound of Formula (B), Formula (B-1) or Formula (B-2), wherein the compound is



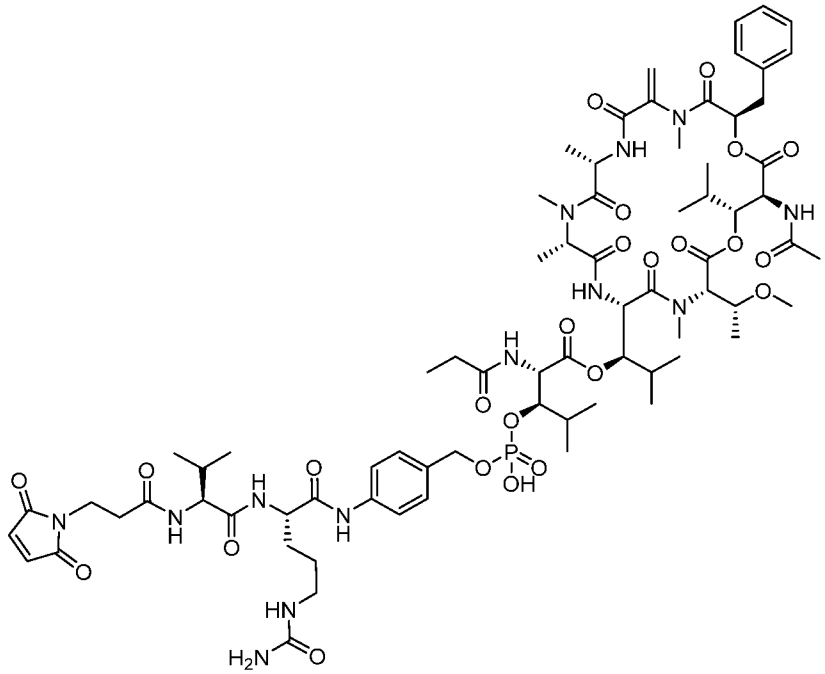
(B2).

[00183] Embodiment 37. The compound of Formula (B), Formula (B-1) or Formula (B-2), wherein the compound is



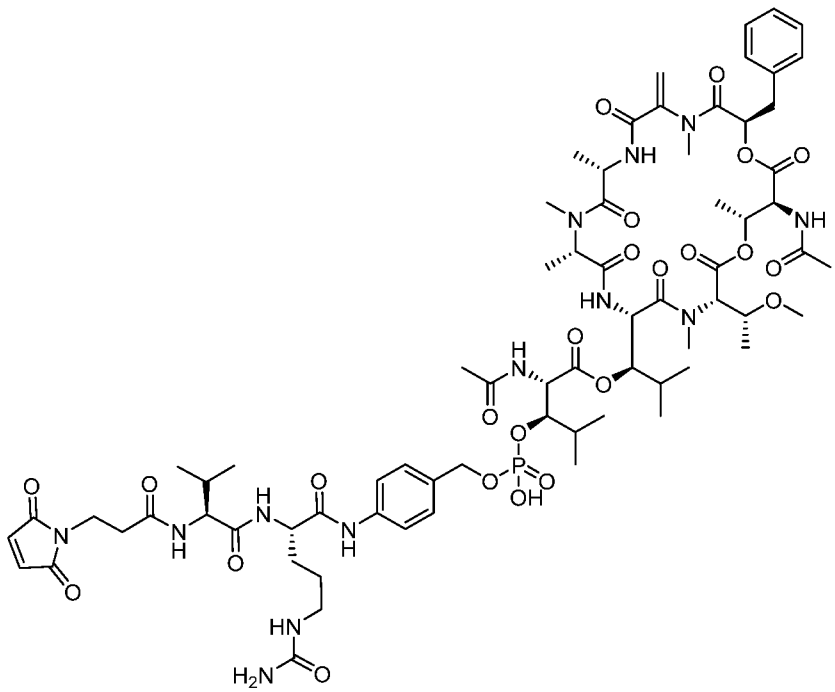
(B3).

[00184] Embodiment 38. The compound of Formula (B), Formula (B-1) or Formula (B-2), wherein the compound is



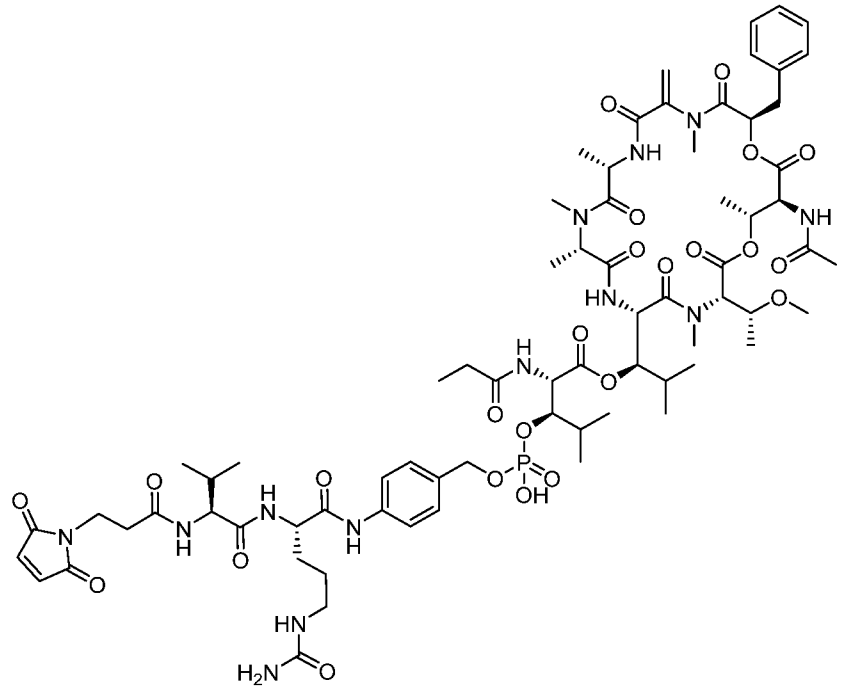
(B4).

[00185] Embodiment 39. The compound of Formula (B), Formula (B-1) or Formula (B-2), wherein the compound is



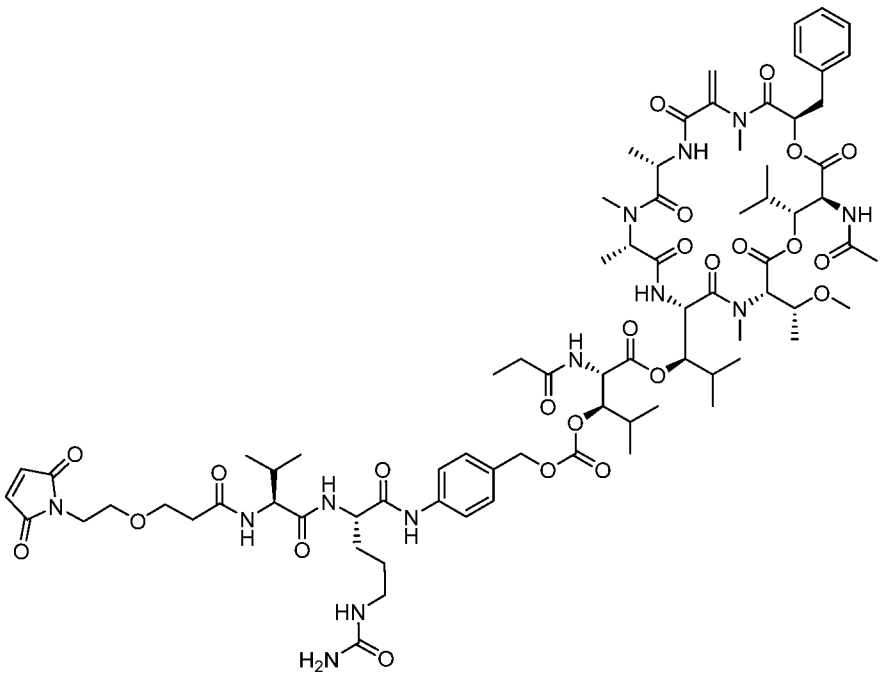
(B5).

[00186] Embodiment 40. The compound of Formula (B), Formula (B-1) or Formula (B-2), wherein the compound is



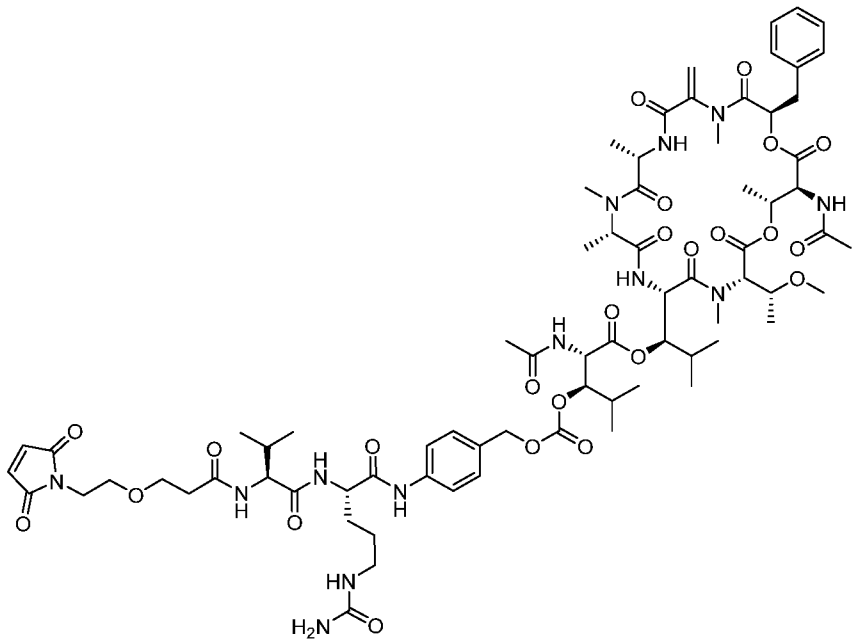
(B6).

[00187] Embodiment 41. The compound of Formula (B), Formula (B-1) or Formula (B-3), wherein the compound is



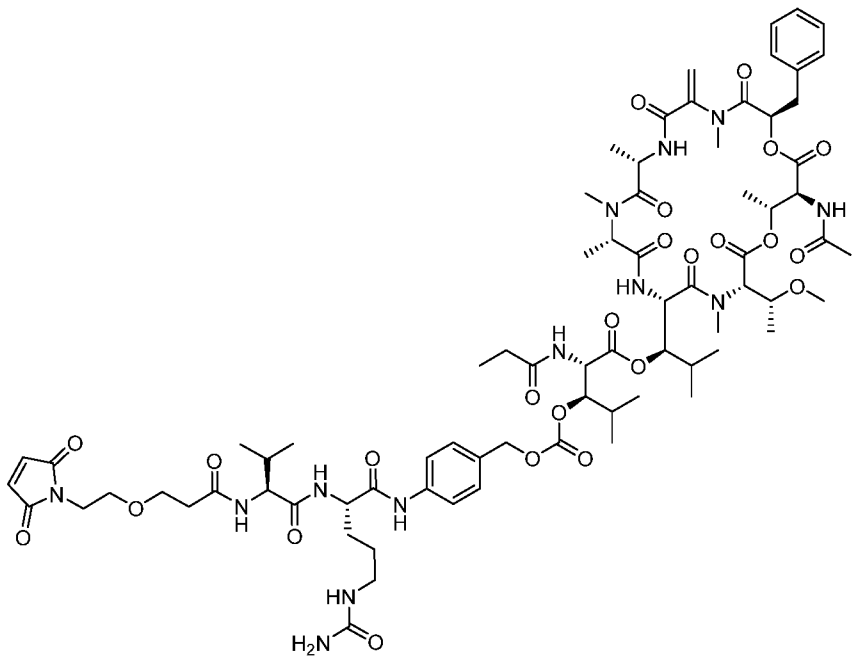
(B7).

[00188] Embodiment 42. The compound of Formula (B), Formula (B-1) or Formula (B-3), wherein the compound is



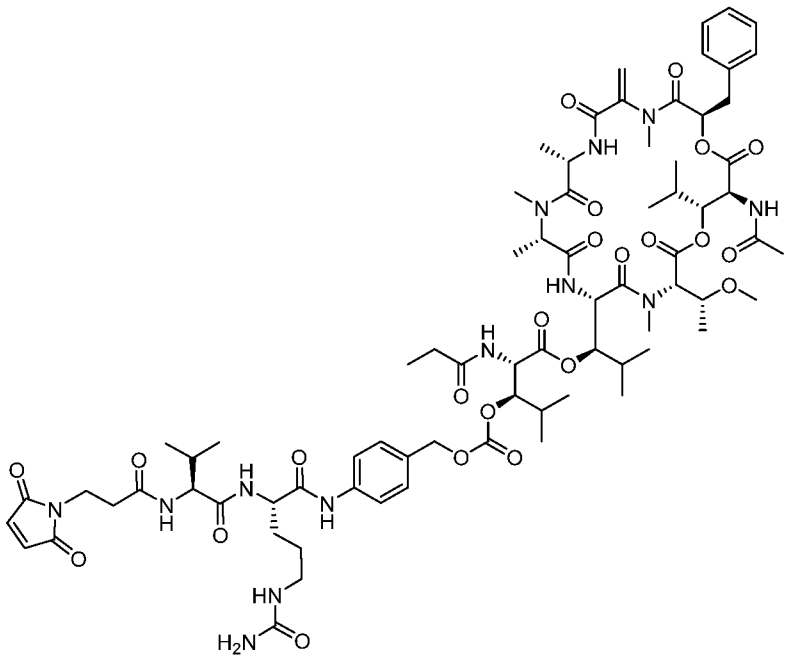
(B8).

[00189] Embodiment 43. The compound of Formula (B), Formula (B-1) or Formula (B-3), wherein the compound is



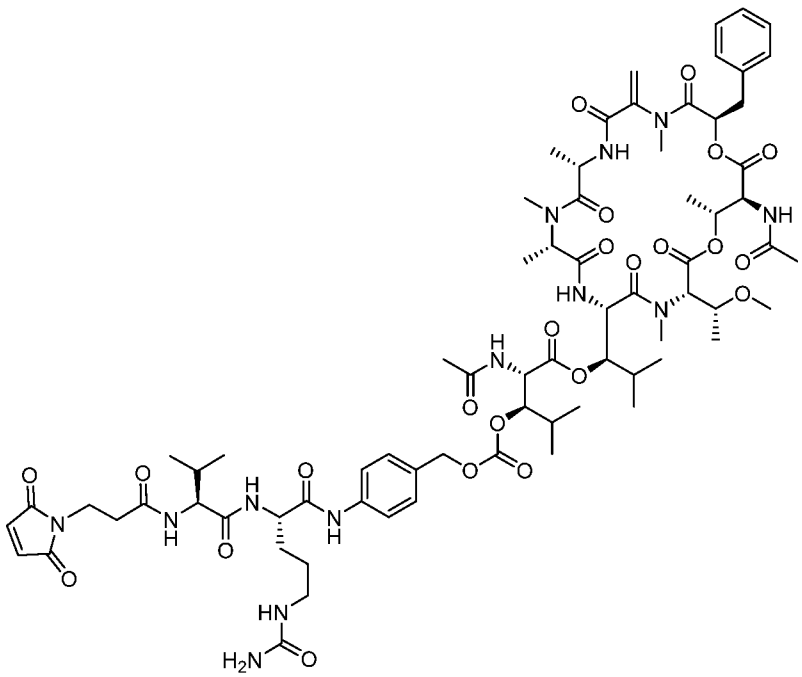
(B9).

[00190] Embodiment 44. The compound of Formula (B), Formula (B-1) or Formula (B-3), wherein the compound is



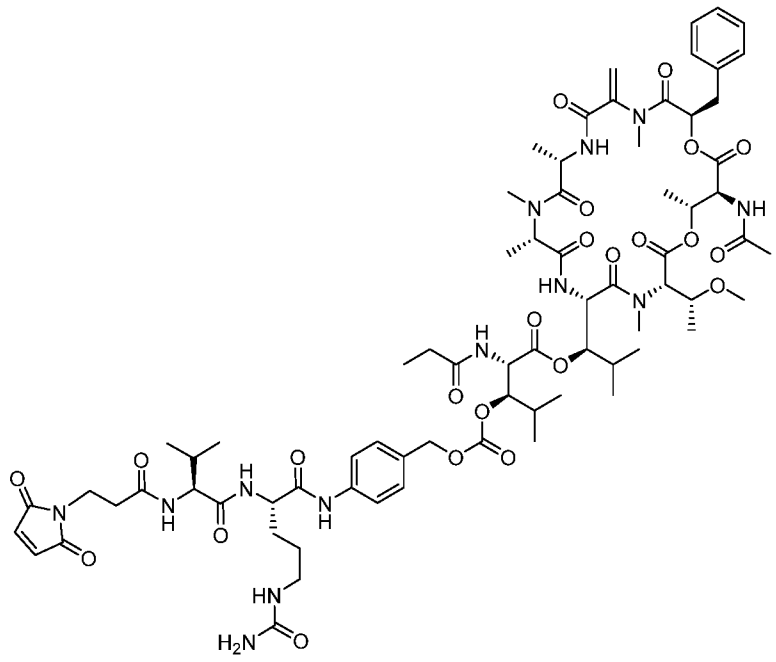
(B10).

[00191] Embodiment 45. The compound of Formula (B), Formula (B-1) or Formula (B-3), wherein the compound is



(B11).

[00192] Embodiment 46. The compound of Formula (B), Formula (B-1) or Formula (B-3), wherein the compound is



(B12).

Antibody Drug Conjugates

[00193] In one aspect, the Antibody Drug Conjugate of the invention is a conjugate of Formula (C):

$$Ab\text{-}(L_A\text{-}(D)_n)_y \qquad (C)$$

wherein:

D is a drug moiety;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

L_A is a linker;

n is 1, 2, 3 or 4, and

y is 1, 2, 3 or 4,

where the Linker-Drug moiety (L_A-$(D)_n$) is covalently attached to the antibody or antigen binding fragment thereof.

[00194] In one aspect, the Antibody Drug Conjugate of the invention having the structure of Formula (C), wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

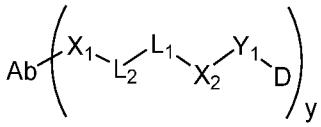
L_A is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group, a carbonate group and a bivalent peptide linker;

n is 1, 2, 3 or 4, and

y is 1, 2, 3 or 4,

where the Linker-Drug moiety (L_A-$(D)_n$) is covalently attached to the antibody or antigen binding fragment thereof.

[00195] In one aspect, the Antibody Drug Conjugate of Formula (C) is a conjugate of Formula (C-1):



(C-1)

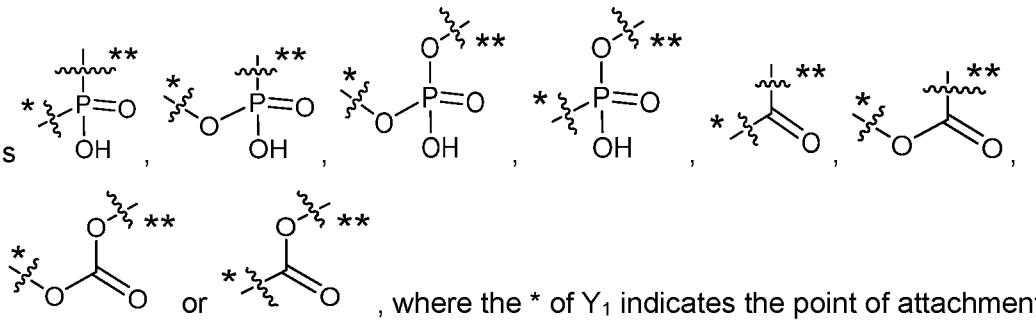
wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

X_2 is a self-immolative spacer;

Y_1 is  where the * of Y_1 indicates the point of attachment to X_2 and the ** of Y_1 indicates the point of attachment to D;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00196] In the conjugates of Formula (C), one or more Linker-Drug moiety (L_B-$(D)_n$) can be covalently attached to the antibody or antigen binding fragment thereof, Ab, thereby covalently attaching one or more drug moieties, D, to the antibody or antigen binding fragment thereof, Ab, through linker, L_A. L_A is any chemical moiety that is capable of linking the antibody or antigen binding fragment thereof, Ab, to one or more drug moieties, D. The conjugates of Formula (C), wherein one or more drug moieties, D, are covalently linked to an antibody or antigen binding fragment thereof, Ab, can be formed using a bifunctional or multifunctional linker reagent having one or more reactive functional groups that are the same or different. One of the reactive functional groups of the bifunctional or multifunctional linker reagent is used to react with a group on the antibody or antigen binding fragment thereof, Ab, by way of example, a thiol

or an amine (e.g. a cysteine, an N-terminus or amino acid side chain such as lysine) to form a covalent linkage with one end of the linker L_A. Such reactive functional groups of the bifunctional or multifunctional linker reagent include, but are not limited to, a maleimide, a thiol and an NHS ester. The other reactive functional group or groups of the bifunctional or multifunctional linker reagent are used to covalently attached one or more drug moieties, D, to linker L_A.

[00197] In one aspect, L_A is a cleavable linker. In another aspect, L_A is a non-cleavable linker. In some aspects, L_A is an acid-labile linker, photo-labile linker, peptidase cleavable linker, esterase cleavable linker, glycosidase cleavable linker, phosphodiesterase cleavable linker, a disulfide bond reducible linker, a hydrophilic linker, or a dicarboxylic acid based linker.

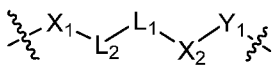
[00198] In one aspect, L_A is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group, a carbonate group and a bivalent peptide linker.

[00199] In one aspect, L_A is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group, a carbonate group, a bivalent peptide linker and a bivalent coupling group.

[00200] In one aspect, L_A is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group and a bivalent peptide linker.

[00201] In one aspect, L_A is a cleavable linker comprising one or more linker components selected from a self-immolative spacer, a phosphate group, a bivalent peptide linker and a bivalent coupling group.

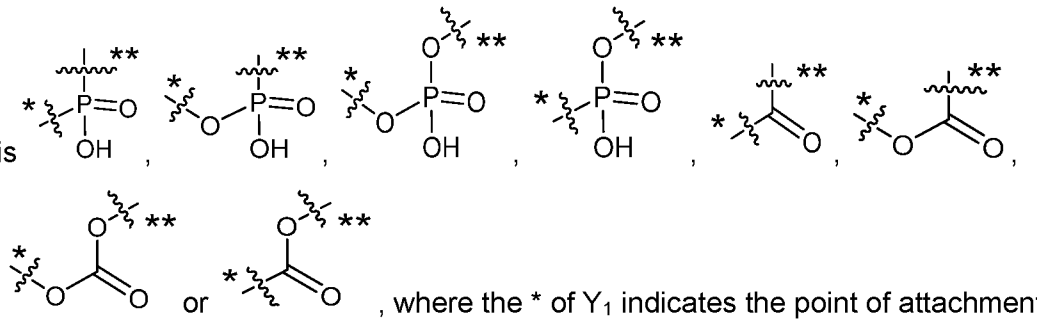
[00202] In another aspect, the linker (L_A) has the following formula:



wherein:

X_1 is a bivalent coupling group;

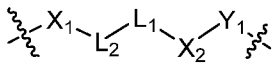
X_2 is a self-immolative spacer;

Y_1 is  , where the * of Y_1 indicates the point of attachment to X_2, and the ** of Y_1 indicates the other point of attachment;

L_1 is a bivalent peptide linker, and

L_2 is a bond or a linker.

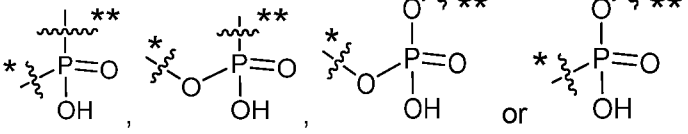
[00203] In another aspect, the linker (L_A) has the following formula:



wherein:

X_1 is a bivalent coupling group;

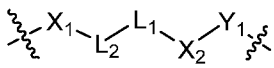
X_2 is a self-immolative spacer;

Y_1 is  , where the * of Y_1 indicates the point of attachment to X_2;

L_1 is a bivalent peptide linker, and

L_2 is a bond or a linker.

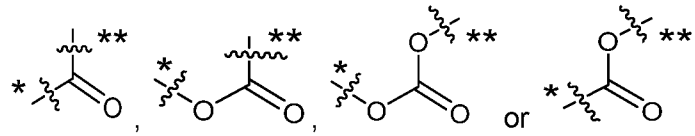
[00204] In another aspect, the linker (L_A) has the following formula:



wherein:

X_1 is a bivalent coupling group;

X_2 is a self-immolative spacer;

Y_1 is  , where the * of Y_1 indicates the point of attachment to X_2;

L_1 is a bivalent peptide linker, and

L_2 is a bond or a linker.

[00205] While the drug to antibody ratio has an exact integer value for a specific conjugate molecule (e.g., the product of n and y in Formula (C), it is understood that the value will often be an average value when used to describe a sample containing many molecules, due to some degree of heterogeneity, typically associated with the conjugation step. The average loading for a sample of a conjugate is referred to herein as the drug to antibody ratio, or "DAR." In some aspects, the DAR is between about 1 and about 5, and typically is about 1, 2, 3, or 4. In some aspects, at least 50% of a sample by weight is compound having the average DAR plus

or minus 2, and preferably at least 50% of the sample is a conjugate that contains the average DAR plus or minus 1. Other aspects include conjugates wherein the DAR is about 2. In some aspects, a DAR of 'about y' means the measured value for DAR is within 20% of the product of n and y in Formula (I). In some aspects, a DAR of 'about n' means the measured value for DAR is within 20% of n in Formula (II).

[00206] In one aspect, the average molar ratio of the drug to the antibody in the conjugates of Formula (C) (*i.e.*, average value of the product of n and y, also known as drug to antibody ratio (DAR)) is about 1 to about 10, about 1 to about 6 (*e.g.*, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0), about 1 to about 5, about 1.5 to about 4.5, or about 2 to about 4.

[00207] In one aspect provided by the disclosure, the conjugate has substantially high purity and has one or more of the following features: (a) greater than about 90% (*e.g.*, greater than or equal to about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%), preferably greater than about 95%, of conjugate species are monomeric, (b) unconjugated linker level in the conjugate preparation is less than about 10% (*e.g.*, less than or equal to about 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0%) (relative to total linker), (c) less than 10% of conjugate species are crosslinked (*e.g.*, less than or equal to about 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0%), (d) free drug (ADP-induced platelet aggregation inhibitor, *e.g.*, a GNAQ inhibitor, a GNA11 inhibitor, or a GNAQ and a GNA11 inhibitor) level in the conjugate preparation is less than about 2% (*e.g.*, less than or equal to about 1.5%, 1.4%, 1.3%, 1.2%, 1.1%, 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, or 0%) (mol/mol relative to total drug).

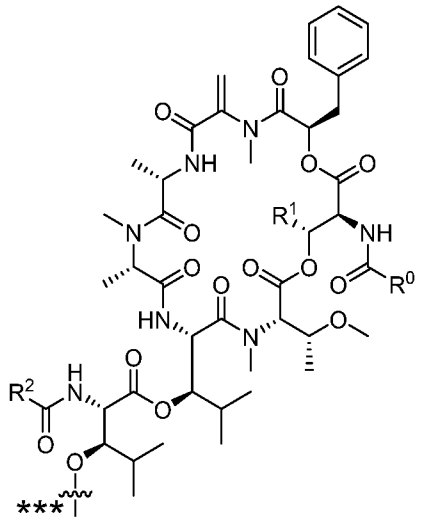
[00208] Certain aspects and examples of the Antibody Drug Conjugates of the invention are provided in the following listing of additional, enumerated embodiments. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

[00209] Embodiment 47. The conjugate of Formula (C) or Formula (C-1), wherein D is a GNAQ inhibitor.

[00210] Embodiment 48. The conjugate of Formula (C) or Formula (C-1), wherein D is a GNA11 inhibitor.

[00211] Embodiment 49. The conjugate of Formula (C) or Formula (C-1), wherein D is an inhibitor of GNAQ and GNA11.

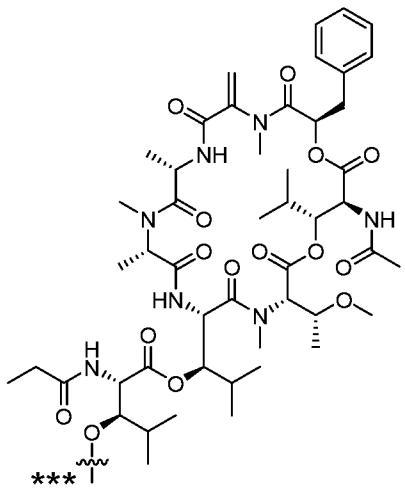
[00212] Embodiment 50. The conjugate of Formula (C) or Formula (C-1), wherein D is



,

wherein R^0 is methyl or ethyl, R_1 is methyl or isopropyl, R_2 is methyl or ethyl, and the *** indicates the point of attachment to L_A or Y_1.

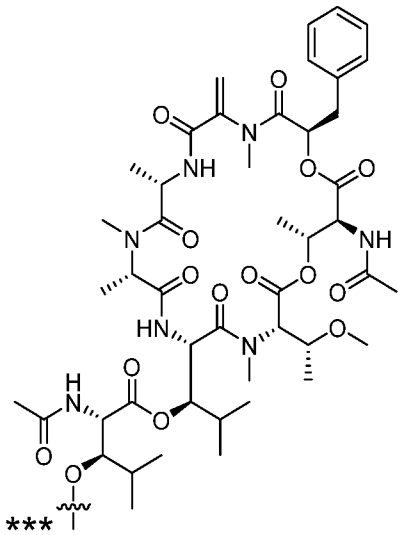
[00213] Embodiment 51. The conjugate of Formula (C) or Formula (C-1), wherein D is



,

where the *** indicates the point of attachment to L_A or Y_1.

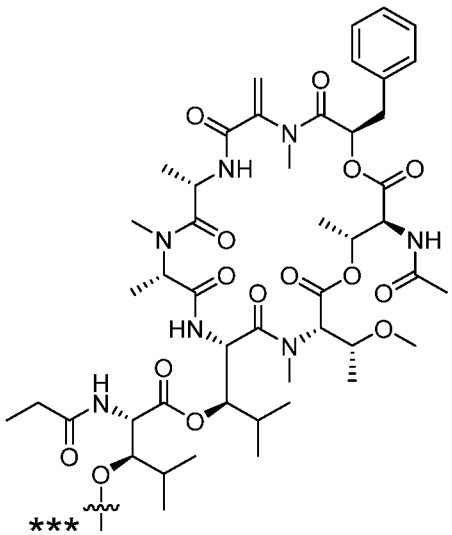
[00214] Embodiment 52. The conjugate of Formula (C) or Formula (C-1), wherein D is



,

where the *** indicates the point of attachment to L_A or Y_1.

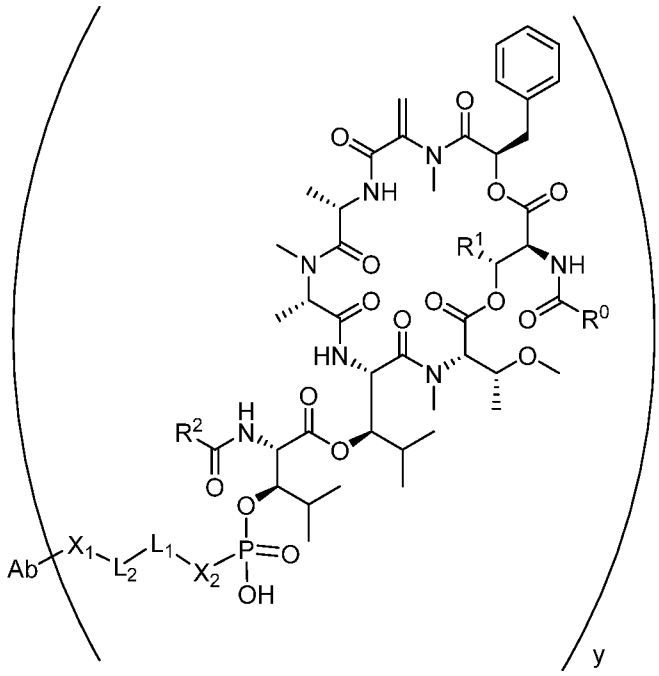
[00215] Embodiment 53. The conjugate of Formula (C) or Formula (C-1), wherein D is



,

where the *** indicates the point of attachment to L_A or Y_1.

[00216] Embodiment 54. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-2):



(C-2),

wherein:

R^0 is methyl or ethyl;

R^1 is methyl or isopropyl;

R^2 is methyl or ethyl;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

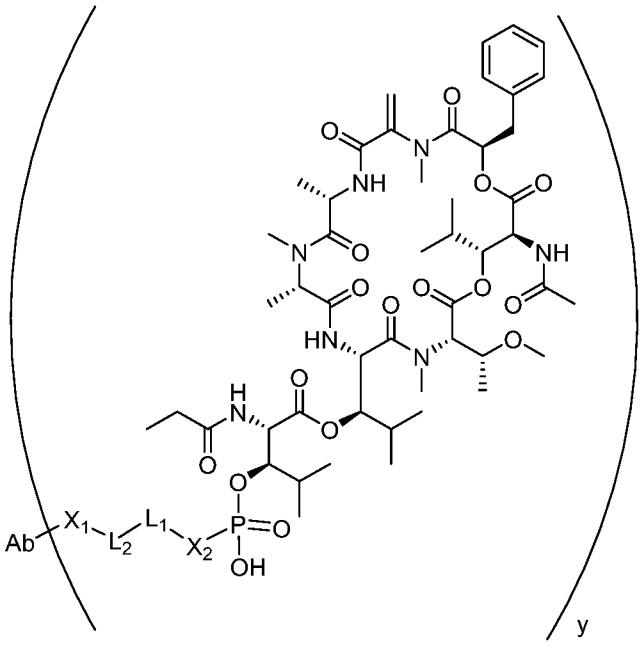
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00217] Embodiment 55. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-2a):



(C-2a),

wherein:

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

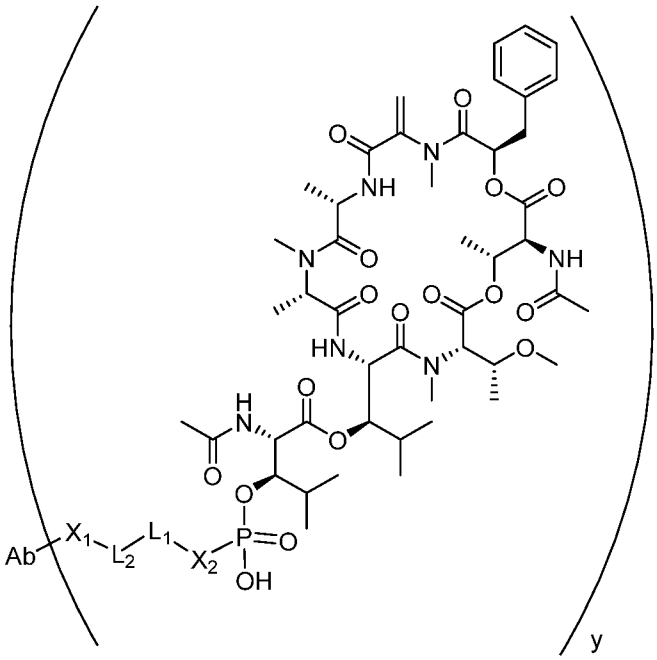
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00218] Embodiment 56. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-2b):



(C-2b),

wherein:

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

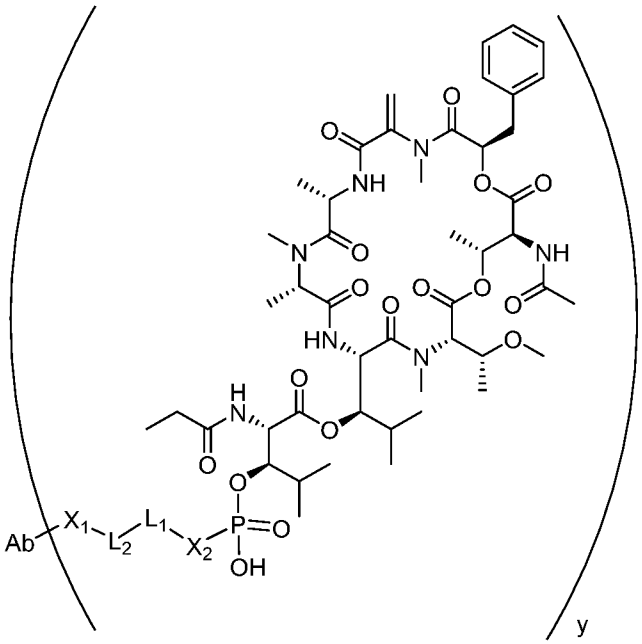
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00219] Embodiment 57. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-2c):



(C-2c),

wherein:

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

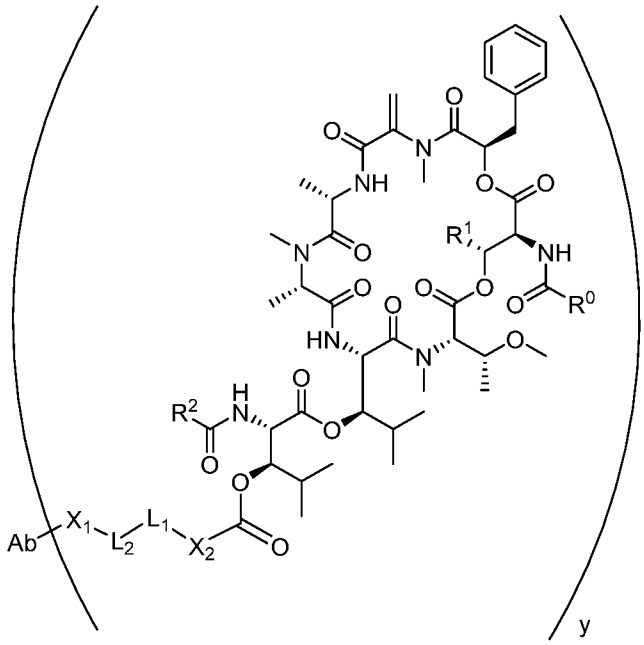
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00220] Embodiment 58. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-3):



(C-3),

wherein:

R^0 is methyl or ethyl;

R^1 is methyl or isopropyl;

R^2 is methyl or ethyl;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

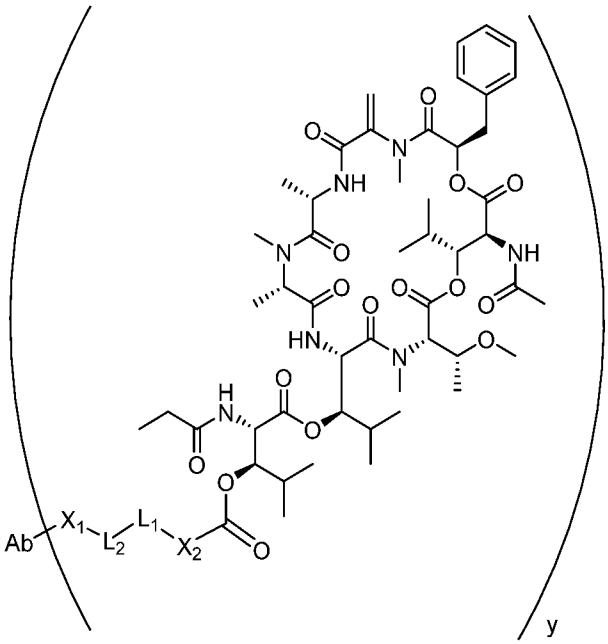
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00221] Embodiment 59. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-3a):



(C-3a),

wherein:

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

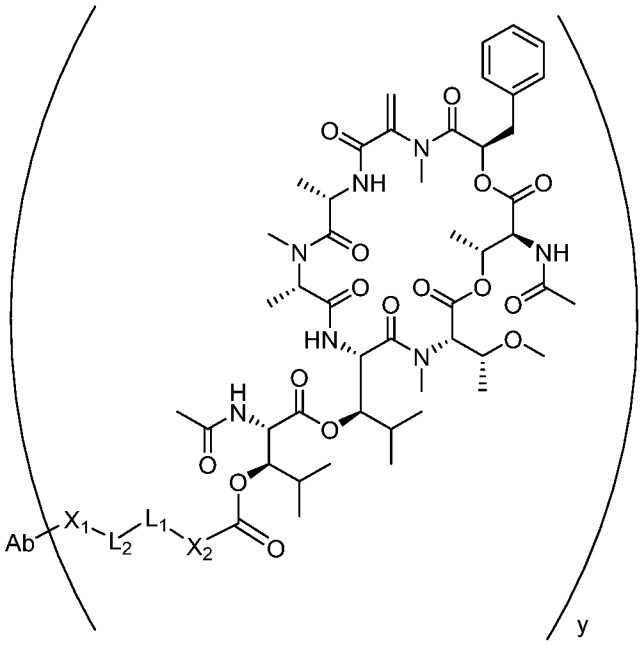
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00222] Embodiment 60. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-3b):



(C-3b),

wherein:

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

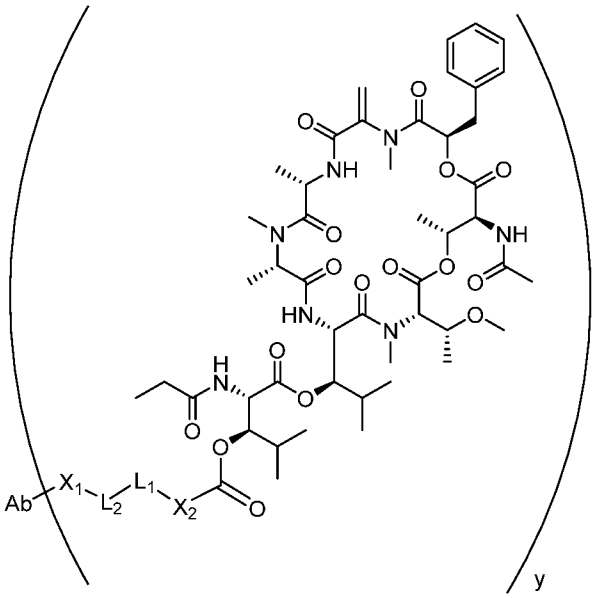
X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00223] Embodiment 61. The conjugate of Formula (C) or Formula (C-1), having the structure of Formula (C-3c):



(C-3c),

wherein:

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;

X_2 is a self-immolative spacer;

L_1 is a bivalent peptide linker;

L_2 is a bond or a linker, and

y is 1, 2, 3 or 4.

[00224] Embodiment 62. The conjugate of Formula (C-2) of Embodiment 54 or the conjugate of Formula (C-3) of Embodiment 58:

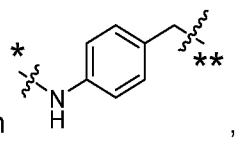
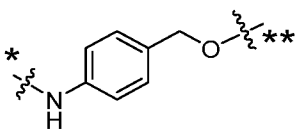
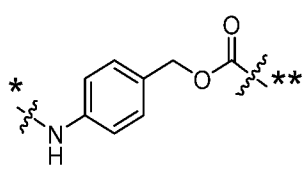
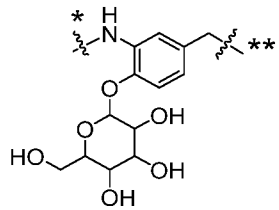
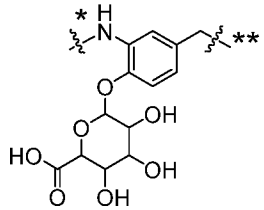
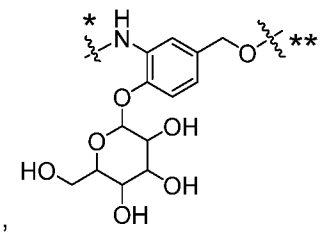
wherein:

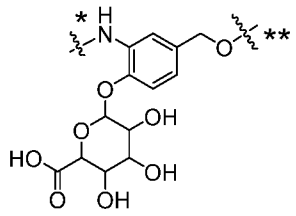
R^0 is methyl or ethyl;

R^1 is methyl or isopropyl;

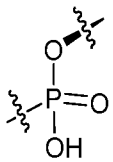
R^2 is methyl or ethyl;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

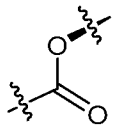
X_2 is a self-immolative spacer selected from  ,  ,  ,  ,  , 



and , where the * of X_2 indicates the point of attachment to L_1 and the



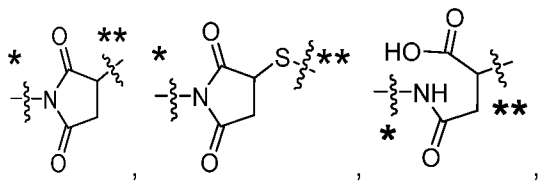
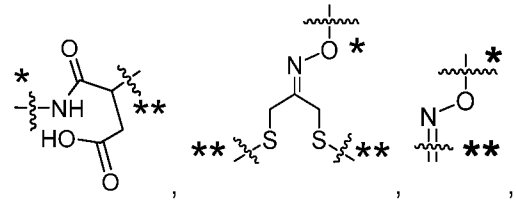
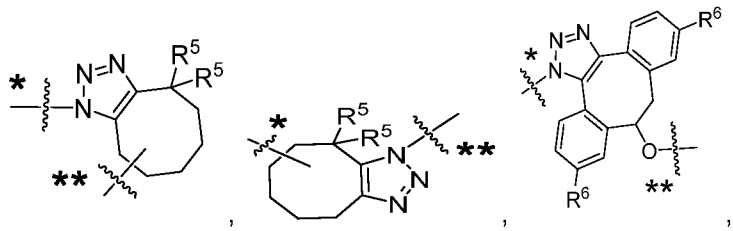
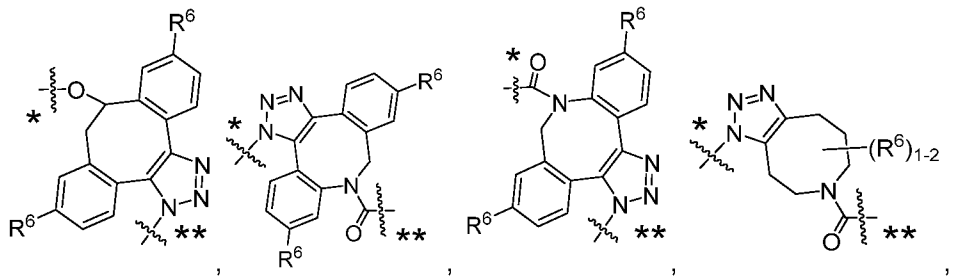
** of X_2 indicates the point of attachment to the group or the point of attachment to

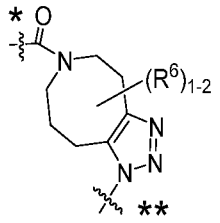
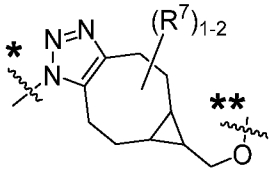


group;

L_1 is a bivalent peptide linker comprising 2 to 4 amino acid residues;

L_2 is a linker;

X_1 is a bivalent coupling group selected from  ,  , -*$NR^4C(=O)CH_2$**-, -*$NHC(=O)CH_2$**-, -*$S(=O)_2CH_2CH_2$**-, -* $(CH_2)_2S(=O)_2CH_2CH_2$**-, -*$NR^4S(=O)_2CH_2CH_2$**-, -*$NR^4C(=O)CH_2CH_2$**-, -NH-, -C(=O)-, -*NHC(=O) **-, -*$CH_2NHCH_2CH_2$**-, -*$NHCH_2CH_2$**-, -S-,  , 

, **-, where the * of X_1 indicates the point of attachment to L_2 and the ** of X_1 indicates the point of attachment to Ab;

and wherein:

each R^4 is independently selected from H and C_1-C_6alkyl;

each R^5 is independently selected from H, C_1-C_6alkyl, F, Cl, and –OH;

each R^6 is independently selected from H, C_1-C_6alkyl, F, Cl, $-NH_2$, $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, -CN, $-NO_2$ and –OH,

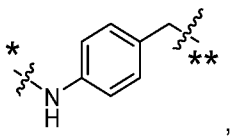
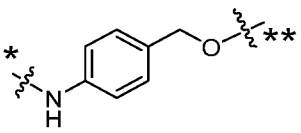
and

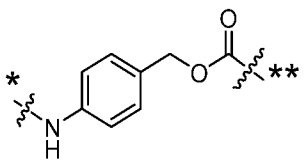
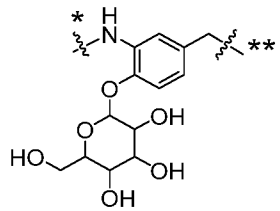
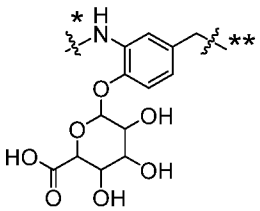
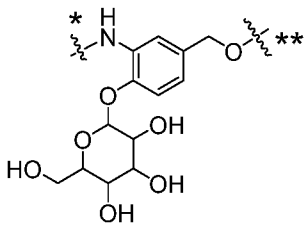
each R^7 is independently selected from H, C_{1-6}alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4}alkoxy substituted with –C(=O)OH and C_{1-4}alkyl substituted with –C(=O)OH,

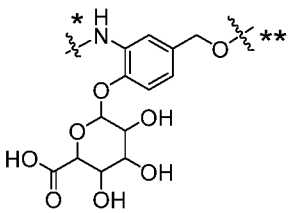
and

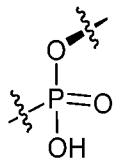
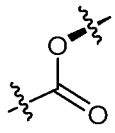
y is 1, 2, 3 or 4.

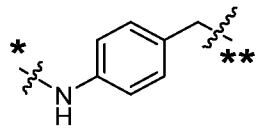
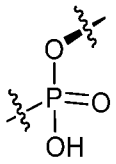
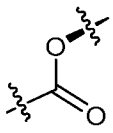
[00225] Embodiment 63. The conjugate of any one of Embodiments 54 to 62, wherein X_2 is a self-immolative spacer selected from

and  , where the * of X_2 indicates the point of attachment to L_1 and the **

of X_2 indicates the point of attachment to Y_1 or the point of attachment to the  group or the point of attachment to  group.

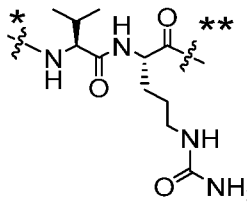
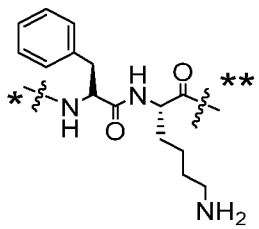
[00226] Embodiment 64. The conjugate of any one of Embodiments 54 to 63, wherein X_2 is  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to Y_1 or the point of attachment to the  group or the point of attachment to  group.

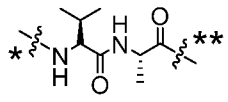
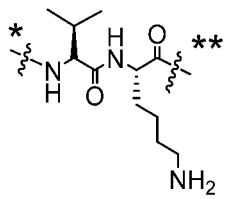
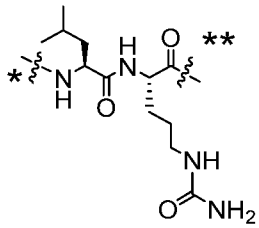
[00227] Embodiment 65. The conjugate of any one of Embodiments 54 to 64, wherein L_1 is a bivalent peptide linker comprising 2 to 4 amino acid residues.

[00228] Embodiment 66. The conjugate of any one of Embodiments 54 to 65, wherein L_1 is a is a bivalent peptide linker comprising an amino acid residue selected from valine, citrulline, lysine, isoleucine, phenylalanine, methionine, asparagine, proline, alanine, leucine, tryptophan, and tyrosine.

[00229] Embodiment 67. The conjugate of any one of Embodiments 54-64, wherein L_1 is a bivalent peptide linker comprising at least one valine (Val) or citrulline (Cit) residue.

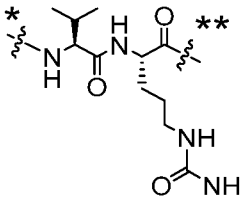
[00230] Embodiment 68. The conjugate of any one of Embodiments 54 to 64, wherein L_1 is a bivalent dipeptide linker selected from ValCit, PheLys, ValAla and ValLys.

[00231] Embodiment 69. The conjugate of any one of Embodiments 54 to 64, wherein L_1 is a bivalent dipeptide linker selected from  (ValCit), 

(PheLys),  (ValAla),  (ValLys) and  (LeuCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2.

[00232] Embodiment 70. The conjugate of any one of Embodiments 54 to 64, wherein L_1 is ValCit.

[00233] Embodiment 71. The conjugate of any one of Embodiments 54 to 64, wherein

L_1 is  (ValCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2.

[00234] Embodiment 72. The conjugate of any one of Embodiments 54 to 71, wherein L_2 is a linker.

[00235] Embodiment 73. The conjugate of any one of Embodiments 54 to 71, wherein L_2 is a linker selected from:

-*C(=O)((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -*C(=O)(CH$_2$)$_m$**-, -*C(=O)(CH$_2$)$_n$NHC(=O)(CH$_2$)$_m$**-, -*C(=O)(CH$_2$)$_m$NHC(=O)((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -* ((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -* ((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**-, -(CH$_2$)$_m$-, -*(CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$**-, -* (CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$C(=O)NH(CH$_2$)$_m$**-, -* ((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$**-, -* *((CH$_2$)$_m$O)$_p$CH$_2$)$_m$C(=O)NH(CH$_2$)$_m$**-, -* (CH$_2$)$_m$C(R$_3$)$_2$**-, and -* (CH$_2$)$_m$C(R$_3$)$_2$SS(CH$_2$)$_m$NHC(=O)(CH$_2$)$_m$**-, where the * of L_2 indicates the attachment point to L_1 and the ** of L_2 indicates the point of attachment to X_1;

and wherein:

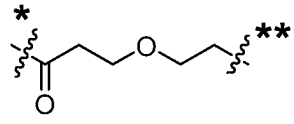
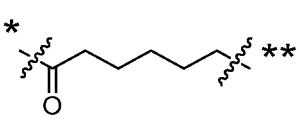
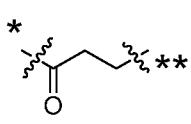
each R_3 is independently selected from H and C_1-C_6alkyl;

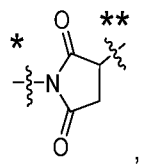
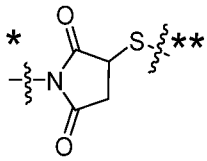
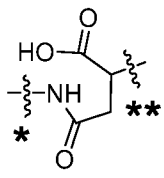
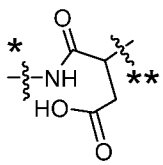
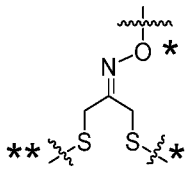
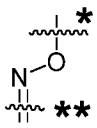
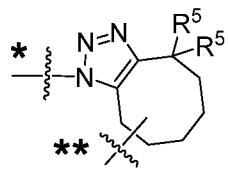
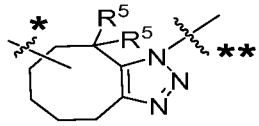
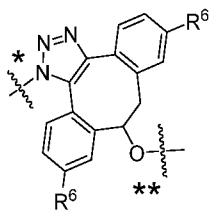
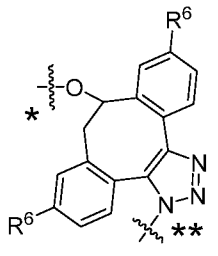
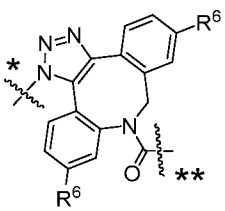
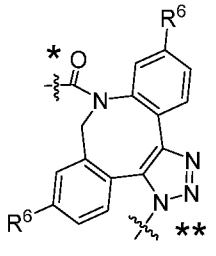
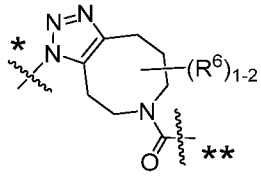
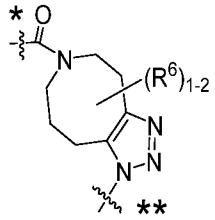
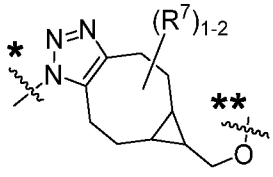
each m is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

each p is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14.

[00236] Embodiment 74. The conjugate of any one of Embodiments 54 to 71, wherein L_2 is -*C(=O)((CH$_2$)$_m$O)$_p$(CH$_2$)$_m$**- or -*C(=O)(CH$_2$)$_m$**-, where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to X_1,

and wherein each m is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14.

[00237] Embodiment 75. The conjugate of any one of Embodiments 54 to 71, wherein L_2 is  ,  or  , where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to X_1.

[00238] Embodiment 76. The conjugate of any one of Embodiments 54 to 75, wherein X_1 is is a bivalent coupling group selected from  ,  ,  ,  ,  ,  , -*NR^{4}C(=O)CH$_2$**-, -*NHC(=O)CH$_2$**-, -*S(=O)$_2$CH$_2$CH$_2$**-, -* (CH$_2$)$_2$S(=O)$_2$CH$_2$CH$_2$**-, -*NR^{4}S(=O)$_2$CH$_2$CH$_2$**-, -*NR^{4}C(=O)CH$_2$CH$_2$**-, -NH-, -C(=O)-, -*NHC(=O) **-, -*CH$_2$NHCH$_2$CH$_2$**-, -*NHCH$_2$CH$_2$**-, -S-,  ,  ,  ,  ,  ,  ,  ,  ,  , **-, where the * of X_1

indicates the point of attachment to L_2 and the ** of X_1 indicates the point of attachment to Ab;

and wherein:

each R^4 is independently selected from H and C_1-C_6alkyl;

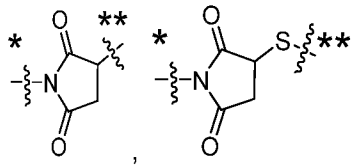
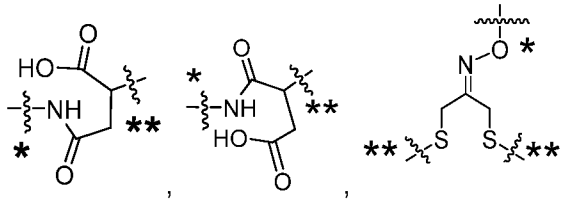
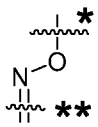
each R^5 is independently selected from H, C_1-C_6alkyl, F, Cl, and –OH;

each R^6 is independently selected from H, C_1-C_6alkyl, F, Cl, $-NH_2$, $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, -CN, $-NO_2$ and –OH,

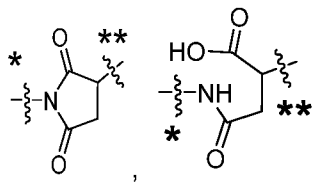
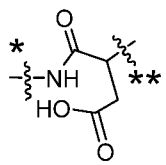
and

each R^7 is independently selected from H, C_{1-6}alkyl, fluoro, benzyloxy substituted with –C(=O)OH, benzyl substituted with –C(=O)OH, C_{1-4}alkoxy substituted with –C(=O)OH and C_{1-4}alkyl substituted with –C(=O)OH.

[00239] Embodiment 77. The conjugate of any one of Embodiments 54 to 75,

wherein X_1 is is a bivalent coupling group selected from  ,  , and  , where the * of X_1 indicates the point of attachment to L_2 and the ** of X_1 indicates the point of attachment to Ab.

[00240] Embodiment 78. The conjugate of any one of Embodiments 54 to 75,

wherein X_1 is is a bivalent coupling group selected from  , and  , where the * of X_1 indicates the point of attachment to L_2 and the ** of X_1 indicates the point of attachment to Ab.

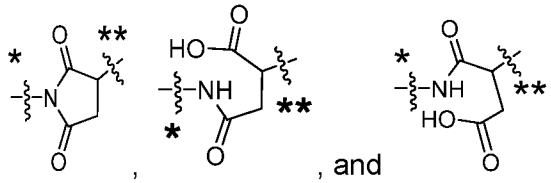
[00241] Embodiment 79. The conjugate of Formula (C-2) of Embodiment 54 wherein:

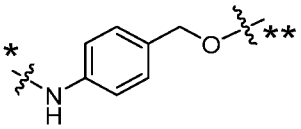
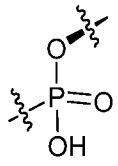
Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

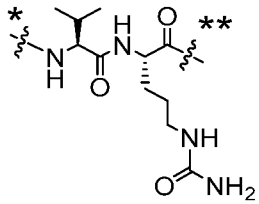
R^0 is methyl or ethyl;

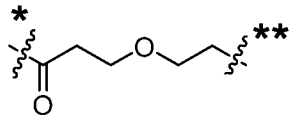
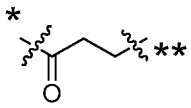
R^1 is methyl or isopropyl;

R^2 is methyl or ethyl;

X_1 is is a bivalent coupling group selected from  , where the * of X_1 indicates the point of attachment to L_2 and the ** of X_1 indicates the point of attachment to Ab

X_2 is  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to the  group;

L_1 is  (ValCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2;

L_2 is  or  , where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to R_8,

and

y is 1, 2, 3 or 4.

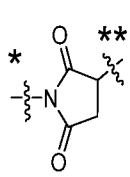
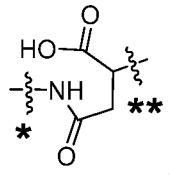
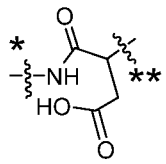
[00242] Embodiment 80. The conjugate of Formula (C-3) of Embodiment 58 wherein:

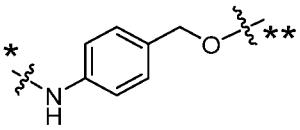
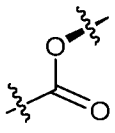
Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

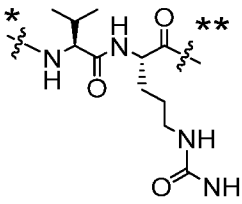
R^0 is methyl or ethyl;

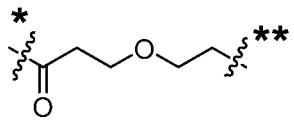
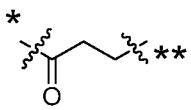
R^1 is methyl or isopropyl;

R^2 is methyl or ethyl;

X_1 is is a bivalent coupling group selected from  ,  , and  , where the * of X_1 indicates the point of attachment to L_2 and the ** of X_1 indicates the point of attachment to Ab

X_2 is  , where the * of X_2 indicates the point of attachment to L_1 and the ** of X_2 indicates the point of attachment to the  group;

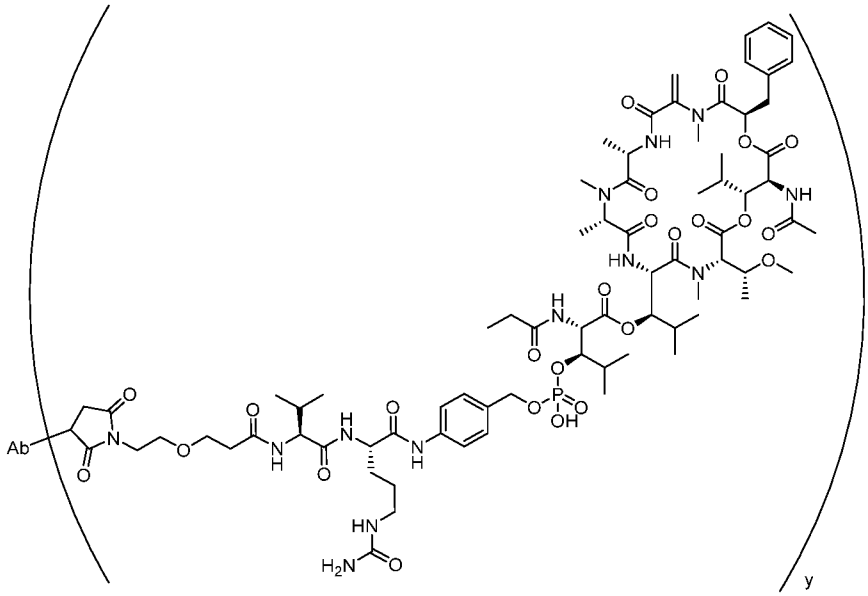
L_1 is  (ValCit), where the * of L_1 indicates the attachment point to L_2 and the ** of L_1 indicates the attachment point to X_2;

L_2 is  or  , where the * of L_2 indicates the point of attachment to L_1 and the ** of L_2 indicates the point of attachment to R_8,

and

y is 1, 2, 3 or 4.

[00243] Embodiment 81. The conjugate of Formula (C), Formula (C-1) or Formula (C-2) having the structure:

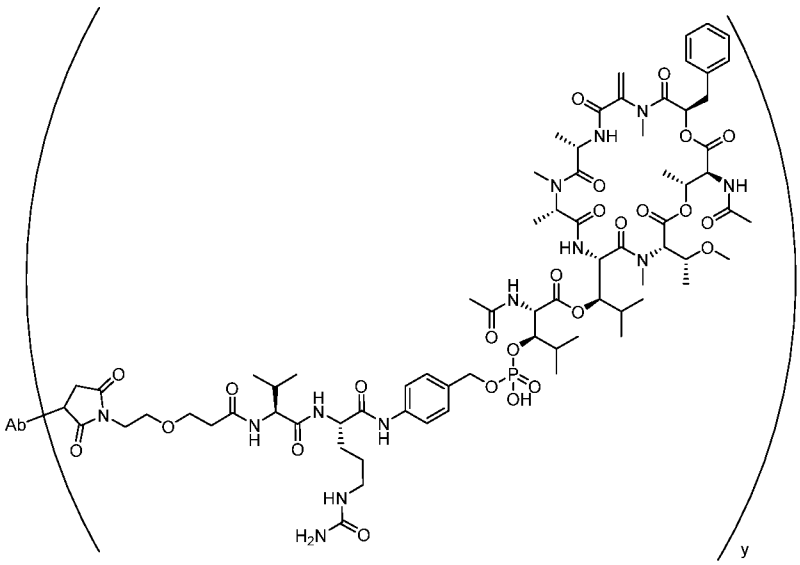


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00244] Embodiment 82. The conjugate of Formula (C), Formula (C-1) or Formula (C-2) having the structure:

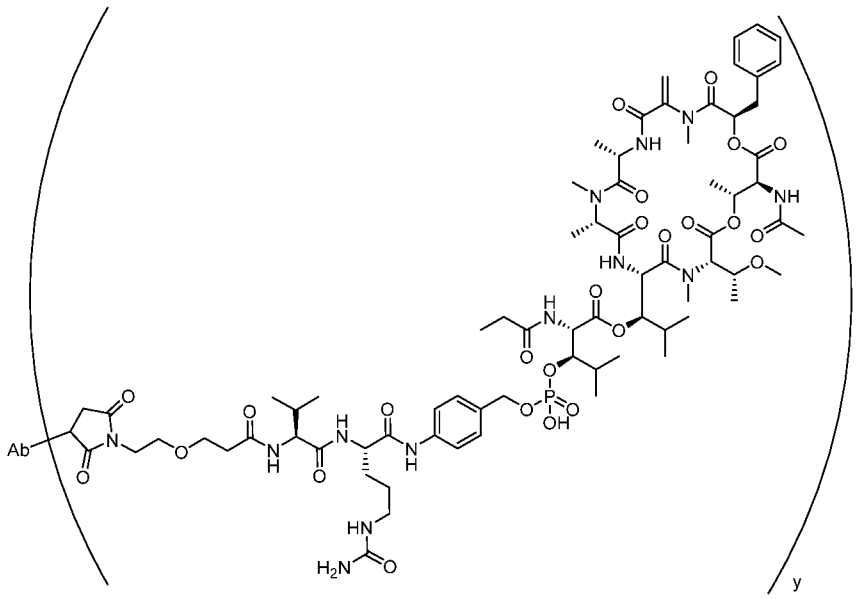


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00245] Embodiment 83. The conjugate of Formula (C), Formula (C-1) or Formula (C-2) having the structure:

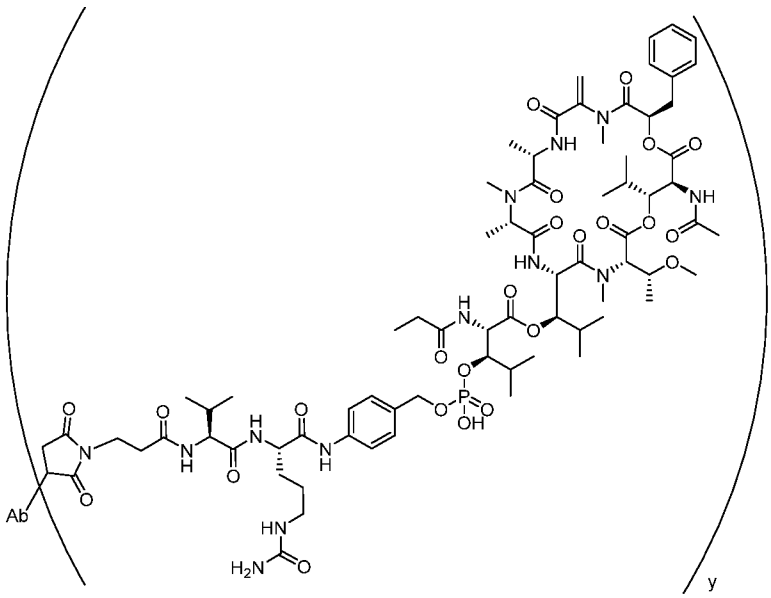


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00246] Embodiment 84. The conjugate of Formula (C), Formula (C-1) or Formula (C-2) having the structure:

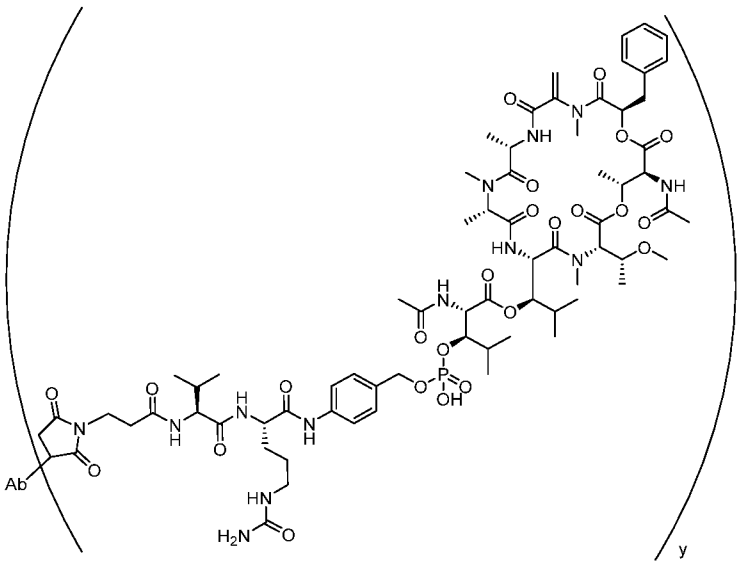


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00247] Embodiment 85. The conjugate of Formula (C), Formula (C-1) or Formula (C-2) having the structure:

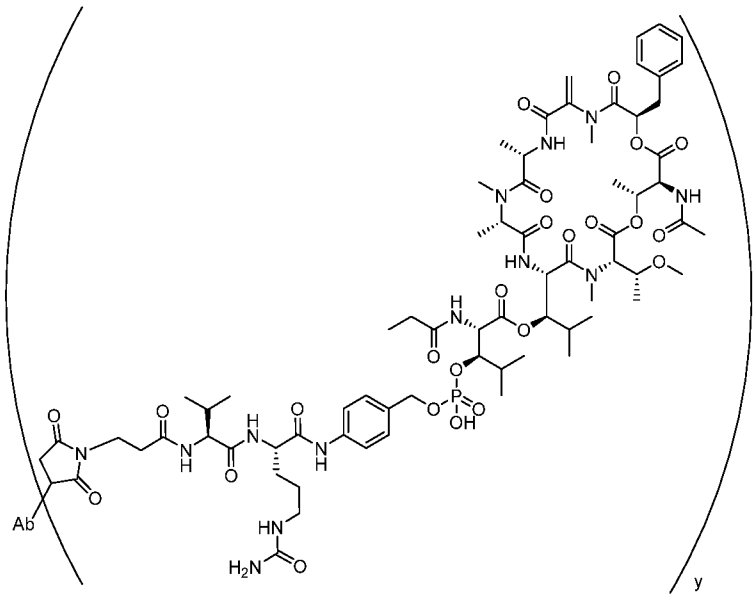


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00248] Embodiment 86. The conjugate of Formula (C), Formula (C-1) or Formula (C-2) having the structure:

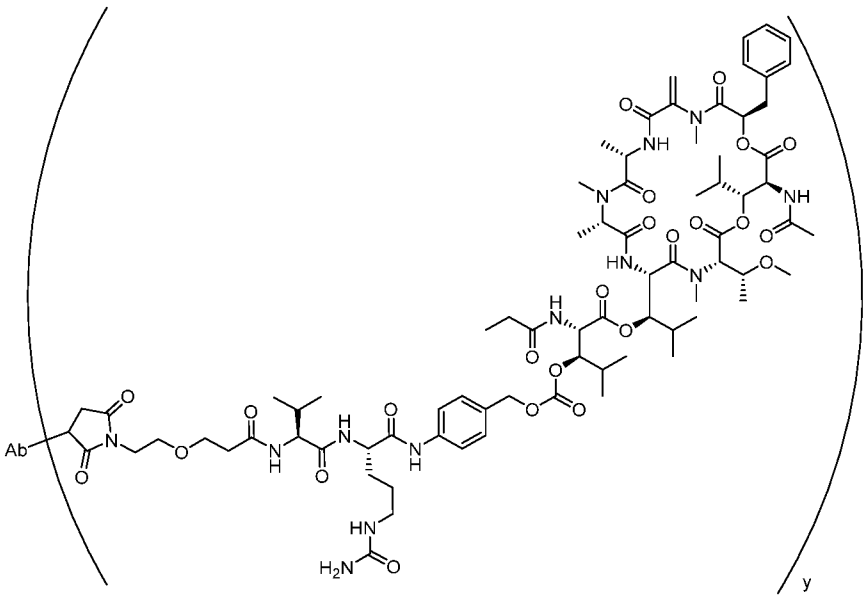


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00249] Embodiment 87. The conjugate of Formula (C), Formula (C-1) or Formula (C-3) having the structure:

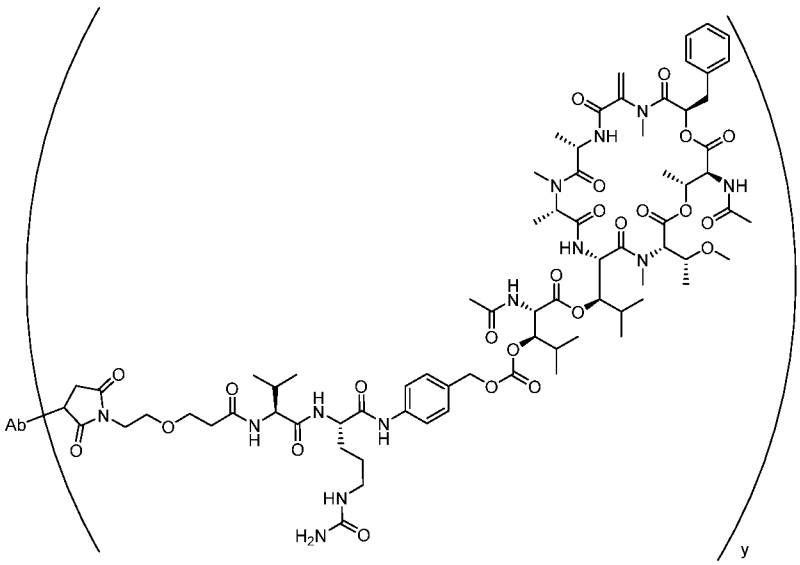


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00250] Embodiment 88. The conjugate of Formula (C), Formula (C-1) or Formula (C-3) having the structure:

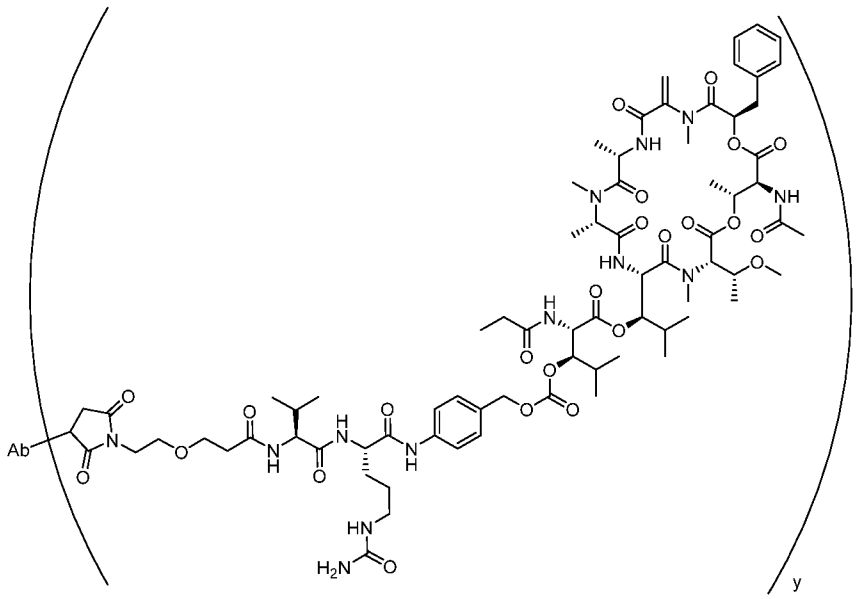


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00251] Embodiment 89. The conjugate of Formula (C), Formula (C-1) or Formula (C-3) having the structure:

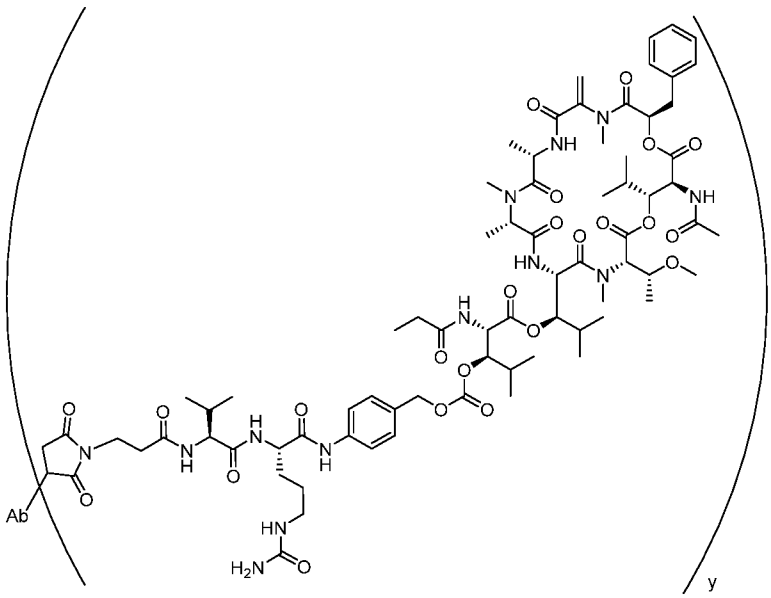


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00252] Embodiment 90. The conjugate of Formula (C), Formula (C-1) or Formula (C-3) having the structure:

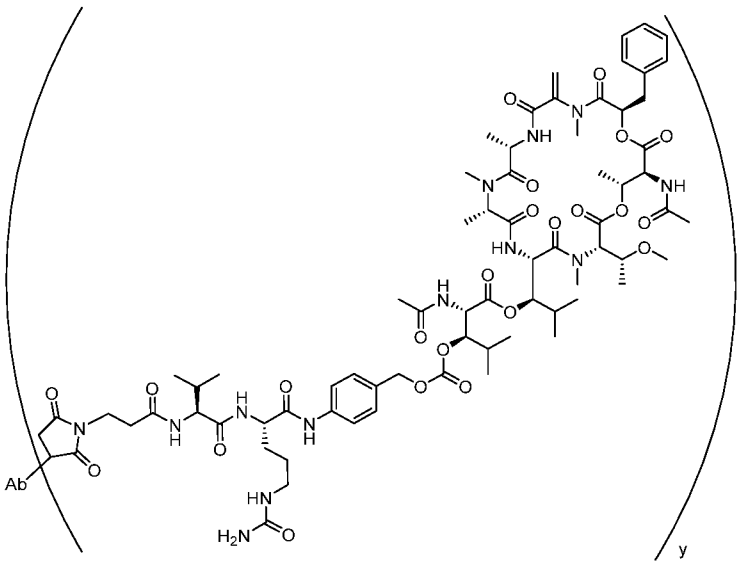


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00253] Embodiment 91. The conjugate of Formula (C), Formula (C-1) or Formula (C-3) having the structure:

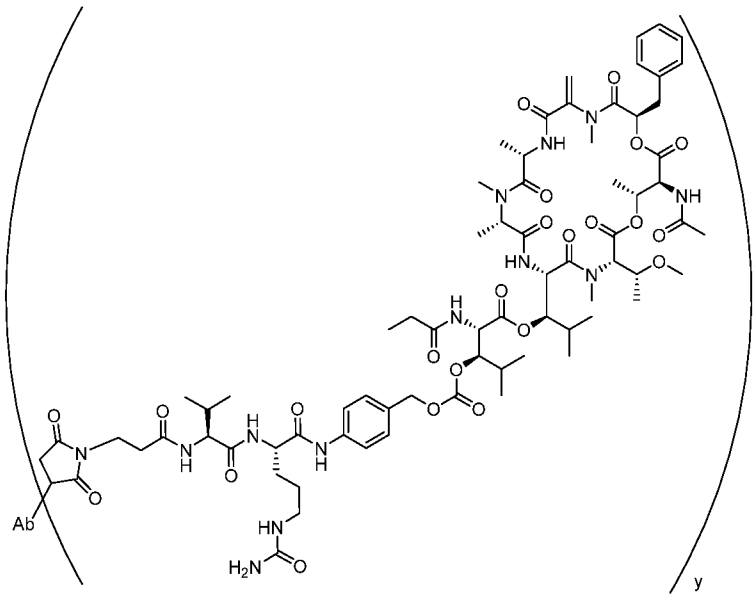


wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00254] Embodiment 92. The conjugate of Formula (C), Formula (C-1) or Formula (C-3) having the structure:



wherein:

y is 2 or 4 and

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein.

[00255] Further, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present invention may be conjugated to a drug moiety that modifies a given biological response. Drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin, a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, a cytokine, an apoptotic agent, an anti-angiogenic agent, or, a biological response modifier such as, for example, a lymphokine.

[00256] In one embodiment, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present invention are conjugated to a drug moiety, such as a cytotoxin, a drug (*e.g.*, an immunosuppressant) or a radiotoxin. Examples of cytotoxins include but are not limited to, taxanes (*see, e.g.*, International (PCT) Patent Application Nos. WO 01/38318 and PCT/US03/02675), DNA-alkylating agents (*e.g.*, CC-1065 analogs), anthracyclines, tubulysin analogs, duocarmycin analogs, auristatin E, auristatin F, maytansinoids, pyrrolobenzodiazipines (PBDs), and cytotoxic agents comprising a reactive polyethylene glycol moiety (*see, e.g.*, Sasse *et al.*, J. Antibiot. (Tokyo), 53, 879-85 (2000), Suzawa *et al.*, Bioorg. Med. Chem., 8, 2175-84 (2000), Ichimura *et al.*, J. Antibiot. (Tokyo), 44, 1045-53 (1991), Francisco *et al.*, Blood (2003) (electronic publication prior to print publication), U.S. Pat. Nos. 5,475,092, 6,340,701, 6,372,738, and 6,436,931, U.S. Patent Application Publication No. 2001/0036923 A1, Pending U.S. patent application Ser. Nos. 10/024,290 and 10/116,053, and International (PCT) Patent Application No. WO 01/49698), taxon, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, t. colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents also include, for example, anti-metabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), ablating agents (*e.g.*, mechlorethamine, thiotepa chlorambucil, meiphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin, anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine). (See *e.g.*, Seattle Genetics US20090304721).

[00257] Other examples of cytotoxins that can be conjugated to the antibodies, antibody fragments (antigen binding fragments) or functional equivalents of the invention include duocarmycins, calicheamicins, maytansines and auristatins, and derivatives thereof.

[00258] Various types of cytotoxins, linkers and methods for conjugating therapeutic agents to antibodies are known in the art, *see, e.g.*, Saito *et al.*, (2003) Adv. Drug Deliv. Rev. 55:199-215; Trail *et al.*, (2003) Cancer Immunol. Immunother. 52:328-337; Payne, (2003) Cancer Cell 3:207-212; Allen, (2002) Nat. Rev. Cancer 2:750-763; Pastan and Kreitman, (2002) Curr. Opin. Investig. Drugs 3:1089-1091; Senter and Springer, (2001) Adv. Drug Deliv. Rev. 53:247-264.

[00259] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present invention can also be conjugated to a radioactive isotope to generate cytotoxic radiopharmaceuticals, referred to as radioimmunoconjugates. Examples of radioactive isotopes that can be conjugated to antibodies for use diagnostically or therapeutically include, but are not limited to, iodine-131, indium-111, yttrium-90, and lutetium-177. Methods for preparing radioimmunoconjugates are established in the art. Examples of radioimmunoconjugates are commercially available, including Zevalin™ (DEC Pharmaceuticals) and Bexxar™ (Corixa Pharmaceuticals), and similar methods can be used to prepare radioimmunoconjugates using the antibodies of the invention. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo *et al.*, (1998) Clin Cancer Res. 4(10):2483-90; Peterson *et al.*, (1999) Bioconjug. Chem. 10(4):553-7; and Zimmerman *et al.*, (1999) Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

[00260] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present invention can also conjugated to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antibody fragment (*e.g.*, antigen binding fragment) described herein (*e.g.*, a Fab fragment, Fd fragment, Fv fragment, $F(ab)_2$ fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide.

[00261] Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention

or fragments thereof (*e.g.*, antibodies or fragments thereof with higher affinities and lower dissociation rates). *See, generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten *et al.*, (1997) Curr. Opinion Biotechnol. 8:724-33; Harayama, (1998) Trends Biotechnol. 16(2):76-82; Hansson *et al.*, (1999) J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, (1998) Biotechniques 24(2):308- 313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody or fragment thereof that specifically binds to an antigen may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[00262] Moreover, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present invention can be conjugated to marker sequences, such as a peptide, to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide (SEQ ID NO: 267), such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, (1989) Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine (SEQ ID NO: 267) provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, (1984) Cell 37:767), and the "FLAG" tag (A. Einhauer *et al.*, J. Biochem. Biophys. Methods 49: 455–465, 2001). According to the present invention, antibodies or antigen binding fragments can also be conjugated to tumor-penetrating peptides in order to enhance their efficacy.

[00263] In other embodiments, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present invention are conjugated to a diagnostic or detectable agent. Such immunoconjugates can be useful for monitoring or prognosing the onset, development, progression and/or severity of a disease or disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can be accomplished by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, Alexa Fluor 350, Alexa Fluor 405, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 500, Alexa

Fluor 514, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 610, Alexa Fluor 633, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, Alexa Fluor 750, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, and ^{121}I,), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, and ^{111}In,), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{64}Cu, ^{113}Sn, and ^{117}Sn; and positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

[00264] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the invention may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

3. Conjugation and Preparation of ADCs

Processes for Making Antibody conjugates of Formula (C), Formula (C-1) and Formula (C-2)

[00265] A general reaction scheme for the formation of conjugates of Formula (C) is shown in Scheme 1 below:

Scheme 1

$$\mathrm{Ab{-}(RG_1)_y} + y\left(\mathrm{R^8{-}L_B\text{-}(D)_n}\right) \longrightarrow \mathrm{Ab\text{-}(L_A\text{-}(D)_n)_y}$$

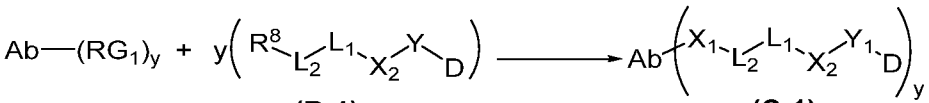
(B) **(C)**

where: RG_1 is a reactive group on the antibody or antigen binding fragment thereof, Ab, by way of example only a thiol, amine or ketone, which reacts with a compatible reactive group, R^8, attached to the linker-drug compound thereby covalently linking antibody or antigen binding fragment thereof, Ab, to one or more linker-drug moieties. Non-limiting examples of such reactions of RG_1 and R^8 groups are a maleimide (R^8) reacting with a thiol (RG_1) to give a succinimide ring, or a hydroxylamine (R^8) reacting with a ketone (RG_1) to give an oxime.

In one embodiment, D is a GNAQ inhibitor, a GNA11 inhibitor, or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor), L_a is a linker further comprising a bivalent coupling group formed when RG_1 and R^8 react, n is 1, 2, 3 or 4, and y is 1, 2, 3 or 4.

[00266] A general reaction scheme for the formation of conjugates of Formula (C-1) is shown in Scheme 2 below:

Scheme 2



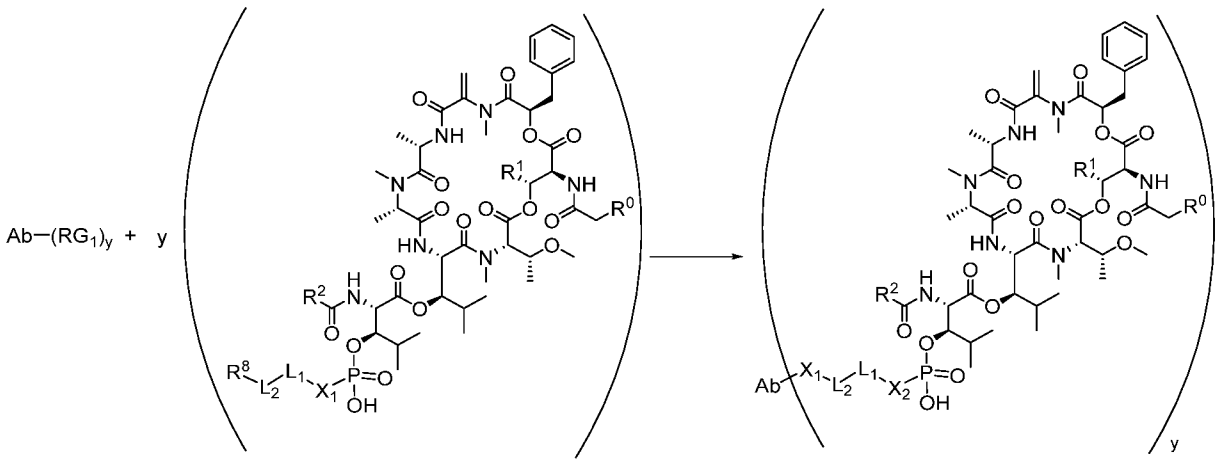
(B-1) **(C-1)**

where: RG_1 is a reactive group on the antibody or antigen binding fragment thereof, Ab, by way of example only a thiol, amine or ketone, which reacts with a compatible reactive group, R^8, attached to the linker-drug moiety thereby covalently linking antibody or antigen binding fragment thereof, Ab, to one or more linker-drug moieties. Non-limiting examples of such reactions of RG_1 and R^8 groups are a maleimide (R^8) reacting with a thiol (RG_1) to give a succinimide ring, or a hydroxylamine (R^8) reacting with a ketone (RG_1) to give an oxime.

In one embodiment, D is a GNAQ inhibitor, a GNA11 inhibitor, or an inhibitor of GNAQ and GNA11 (GNAQ/GNA11 inhibitor), X_1 is a bivalent coupling group formed when RG_1 and R^8 react (e.g. a succinimide ring or an oxime), Y_1 is a phosphate group, X_2 is a self-immolative spacer, L_1 is a bivalent peptide linker, L_2 is a bond or a linker, and y is 1, 2, 3 or 4.

[00267] A general reaction scheme for the formation of conjugates of Formula (C-2) is shown in Scheme 3 below:

Scheme 3



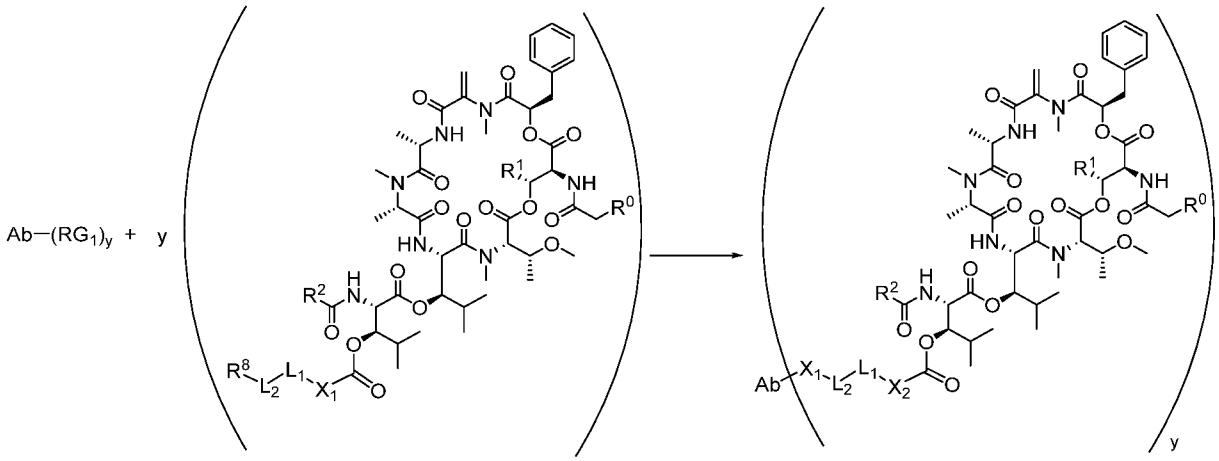
(B-2) **(C-2)**

where: RG_1 is a reactive group on the antibody or antigen binding fragment thereof, Ab, by way of example only a thiol, amine or ketone, which reacts with a compatible reactive group, R^8, attached to the linker-drug moiety thereby covalently linking antibody or antigen binding fragment thereof, Ab, to one or more linker-drug moieties. Non-limiting examples of such reactions of RG_1 and R^8 groups are a maleimide (R^8) reacting with a thiol (RG_1) to give a succinimide ring, or a hydroxylamine (R^8) reacting with a ketone (RG_1) to give an oxime.

Here R^0 is methyl or ethyl, R^1 is methyl or isopropyl, R^2 is methyl or ethyl, X_1 is a bivalent coupling group formed when RG_1 and R^8 react (e.g. a succinimide ring or an oxime), X_2 is a self-immolative spacer, L_1 is a bivalent peptide linker, L_2 is a bond or a linker, and y is 1, 2, 3 or 4.

[00268] A general reaction scheme for the formation of conjugates of Formula (C-2) is shown in Scheme 4 below:

Scheme 4



where: RG_1 is a reactive group on the antibody or antigen binding fragment thereof, Ab, by way of example only a thiol, amine or ketone, which reacts with a compatible reactive group, R^8, attached to the linker-drug moiety thereby covalently linking antibody or antigen binding fragment thereof, Ab, to one or more linker-drug moieties. Non-limiting examples of such reactions of RG_1 and R^8 groups are a maleimide (R^8) reacting with a thiol (RG_1) to give a succinimide ring, or a hydroxylamine (R^8) reacting with a ketone (RG_1) to give an oxime.

Here R^0 is methyl or ethyl, R^1 is methyl or isopropyl, R^2 is methyl or ethyl, X_1 is a bivalent coupling group formed when RG_1 and R^8 react (e.g. a succinimide ring or an oxime), X_2

is a self-immolative spacer, L_1 is a bivalent peptide linker, L_2 is a bond or a linker, and y is 1, 2, 3 or 4.

Process For Conjugation to Engineered Cysteine Antibody Residues

[00269] Conjugates of the invention can be prepared using cysteine residues engineered into an antibody by, for example, site-directed mutagenesis. Such site-specific conjugates are homogenous and have improved properties (Junutula JR, Raab H, Clark S, Bhakta S, Leipold DD, Weir S, Chen Y, Simpson M, Tsai SP, Dennis MS, Lu Y, Meng YG, Ng C, Yang J, Lee CC, Duenas E, Gorrell J, Katta V, Kim A, McDorman K, Flagella K, Venook R, Ross S, Spencer SD, Lee Wong W, Lowman HB, Vandlen R, Sliwkowski MX, Scheller RH, Polakis P, Mallet W. (2008) Nature Biotechnology 26:925-932.)

[00270] Because engineered cysteines in antibodies expressed in mammalian cells are modified by adducts (disulfides) such as glutathione (GSH) and/or cysteine during their biosynthesis (Chen *et al*. 2009), the engineered cysteine residues in the product as initially expressed are unreactive to thiol reactive reagents such as maleimido or bromo-or iodo-acetamide groups. To conjugate payload to an engineered cysteine after expression, glutathione or cysteine adducts need to be removed by reducing these disulfide adducts, which generally entails also reducing native disulfides in the expressed protein. Deprotection of adducted engineered cysteines can be accomplished by first exposing antibody to a reducing agent, e.g., dithiothreitol (DTT), TCEP, or reduced cysteine, followed by a procedure that allows for re-oxidation of all native disulfide bonds of an antibody to restore and/or stabilize the functional antibody structure.

[00271] Several methods can be employed to reduce and re-oxidize antibodies with engineered cysteine residues for preparation of antibody drug conjugates. Attempts to follow re-oxidation protocols previously described in the literature using high concentration of $CuSO_4$ resulted in protein precipitation (Junutula JR, Raab H, Clark S, Bhakta S, Leipold DD, Weir S, Chen Y, Simpson M, Tsai SP, Dennis MS, Lu Y, Meng YG, Ng C, Yang J, Lee CC, Duenas E, Gorrell J, Katta V, Kim A, McDorman K, Flagella K, Venook R, Ross S, Spencer SD, Lee Wong W, Lowman HB, Vandlen R, Sliwkowski MX, Scheller RH, Polakis P, Mallet W. (2008) Nature Biotechnology 26:925). We have successfully prepared and obtained antibody drug conjugates with several different methods for reduction and antibody re-oxidation.

[00272] The following is a method to reduce and re-oxidize antibodies with engineered cysteine residues for preparation of antibody drug conjugates: Freshly prepared DTT is added to purified Cys mutant antibodies to a final concentration of 10 mM. After incubation with DTT at room temperature for 1 hour, mixture is dialyzed at 4°C against PBS for three days with daily

buffer exchange to remove DTT and re-oxidize native disulfide bonds of the antibody. An alternative method is to remove reducing reagents through a desalting column such as Sephadex G-25, equilibrated with PBS. Once protein is fully reduced, 1 mM oxidized ascorbate (dehydro-ascorbic acid) is optionally added to desalted samples and re-oxidation incubations are carried out for 20-24 hours.

[00273] In another exemplary method, deprotection of engineered Cys residues is accomplished by adding fully reduced cysteine at 20 mM concentration to antibodies bound to protein A-Sepharose resin. Reduction of the Cys adducts is achieved by incubation for approximately 30-60 minutes at room temperature, then reductant is rapidly removed by washing resin with 50 beds of PBS. Re-oxidation of the reduced antibody is achieved by incubating washed slurry at room temperature with or without addition of 50-2000 nM $CuCl_2$ as an accelerant. With the exception of use of copper sulfate, examples herein use each of the protocols described herein with similar results. Reoxidation restores intra-chain disulfides, while dialysis, desalting or protein A chromatography removes reducing agent as well as cysteines and glutathiones initially connected to engineered cysteine(s) of the antibody. HPLC reverse phase chromatography is typically used to monitor the reoxidation process: Antibodies are loaded onto a PLRP-S column (4000 Å, 50 mm x 2.1 mm, Agilent) heated to 80° C and eluted using a linear gradient of 30-45% CH3CN in water containing 0.1% TFA at 1.5 mL/min. and peak detection at 215, 254, and 280 nm.

[00274] After re-oxidation, the antibody is conjugated to a linker-drug compound of , by way of example, compounds of Formula (B), Formula (B-1), Formula (B-2) or Formula (B-3) (see schemes 1-4). By way of example, a compound of Formula (B), Formula (B-1), Formula (B-2) or Formula (B-3) is added to re-oxidized Cys mutant antibody at 5-10 molar equivalents relative to antibody in PBS buffer (pH 7.2). Incubations are carried out for 1-2 hours. The conjugation process is monitored by reverse-phase HPLC, which is able to separate conjugated antibodies from non-conjugated ones. Conjugation reaction mixtures are analyzed on a PRLP-S column (4000 Å, 50 mm x 2.1 mm, Agilent) heated to 80°C and elution of the column are carried out by a linear gradient of 30-60% acetonitrile in water containing 0.1% TFA at a flow rate of 1.5 ml/min. Elution of proteins from the column is monitored at 280 nm, 254 nm and 215 nm.

[00275] Alternatively, for antibodies bound to a Protein A resin, once the antibody is re-oxidized, the resin is washed with 10 column volumes PBS and the resin is then resuspended in equal volume PBS and an 8x excess of a compound of Formula (B), Formula (B-1), Formula (B-2) or Formula (B-3) (in DMSO) is added and incubated at room temperature for 2 hours. The

resin is then washed with 50 column volumes of PBS and the resulting antibody drug conjugate is eluted from the Protein A resin, neutralized with 1/10 volume 1 M Tris pH 9.0 and buffer exchanged into appropriate buffer to perform preparative size exclusion chromatography (if needed).

[00276] Immunoconjugates are also characterized in terms of average loading of a drug moiety to antibody binding moiety, generally referred to as drug-to-antibody ratio (DAR). The DAR value is extrapolated, for example, from LC-MS data for reduced and deglycosylated samples. LC/MS allows quantitation of the average number of molecules of payload (drug moiety) attached to an antibody in an ADC. HPLC separates an antibody into light and heavy chains, and also separates heavy chain (HC) and light chain (LC) according to the number of Linker-Payload groups per chain. Mass spectral data enables identification of the component species in the mixture, e.g., LC, LC+1, LC+2, HC, HC+1, HC+2, etc. From average loading of LC and HC chains, the average DAR can be calculated for an ADC. The DAR for a given immunoconjugate sample represents the average number of drug (payload) molecules attached to a tetrameric antibody containing two light chains and two heavy chains.

[00277] Throughout the text of this application, should there be a discrepancy between the text of the specification and the sequence listing, the text of the specification shall prevail.

Table 2. Examples of Anti-PMEL17 Antibodies of the Present Invention

G1 E152C_S375C_wt LC		
SEQ ID NO: 1	HCDR1 (Combined)	GGTFSDYAIT
SEQ ID NO: 2	HCDR2 (Combined)	GIIPIFGTANYAQKFQG
SEQ ID NO: 3	HCDR3 (Combined)	EGGLLTDISYSRYWFAY
SEQ ID NO: 4	HCDR1 (Kabat)	DYAIT
SEQ ID NO: 2	HCDR2 (Kabat)	GIIPIFGTANYAQKFQG
SEQ ID NO: 3	HCDR3 (Kabat)	EGGLLTDISYSRYWFAY
SEQ ID NO: 5	HCDR1 (Chothia)	GGTFSDY
SEQ ID NO: 6	HCDR2 (Chothia)	IPIFGT
SEQ ID NO: 3	HCDR3 (Chothia)	EGGLLTDISYSRYWFAY

SEQ ID NO: 7	HCDR1 (IMGT)	GGTFSDYA
SEQ ID NO: 8	HCDR2 (IMGT)	IIPIFGTA
SEQ ID NO: 9	HCDR3 (IMGT)	AREGGLLTDISYSRYWFAY
SEQ ID NO: 10	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAITWVRQAPGQGLEWMGGIIPIFGTANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REGGLLTDISYSRYWFAYWGQGTLVTVSS
SEQ ID NO: 11	DNA VH	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTGA CTACGCTATCACTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTAT CATCCCGATCTTCGGCACTGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGGTGGTCTG CTGACTGACATCTCTTACTCTCGTTACTGGTT CGCTTACTGGGGCCAAGGCACCCTGGTGAC TGTTAGCTCA
SEQ ID NO: 12	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAITWVRQAPGQGLEWMGGIIPIFGTANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REGGLLTDISYSRYWFAYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPC PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPCDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
SEQ ID NO: 13	DNA Heavy Chain	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTGA CTACGCTATCACTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTAT CATCCCGATCTTCGGCACTGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGGTGGTCTG CTGACTGACATCTCTTACTCTCGTTACTGGTT CGCTTACTGGGGCCAAGGCACCCTGGTGAC

		TGTTAGCTCAGCTAGCACCAAGGGCCCAAGT GTGTTTCCCCTGGCCCCCAGCAGCAAGTCTA CTTCCGGCGGAACTGCTGCCCTGGGTTGCC TGGTGAAGGACTACTTCCCCTGTCCCGTGAC AGTGTCCTGGAACTCTGGGGCTCTGACTTCC GGCGTGCACACCTTCCCCGCCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGAGCAGCGTG GTGACAGTGCCCTCCAGCTCTCTGGGAACC CAGACCTATATCTGCAACGTGAACCACAAGC CCAGCAACACCAAGGTGGACAAGAGAGTGG AGCCCAAGAGCTGCGACAAGACCCACACCT GCCCCCCCTGCCCAGCTCCAGAACTGCTGG GAGGGCCTTCCGTGTTCCTGTTCCCCCCCAA GCCCAAGGACACCCTGATGATCAGCAGGAC CCCCGAGGTGACCTGCGTGGTGGTGGACGT GTCCCACGAGGACCCAGAGGTGAAGTTCAA CTGGTACGTGGACGGCGTGGAGGTGCACAA CGCCAAGACCAAGCCCAGAGAGGAGCAGTA CAACAGCACCTACAGGGTGGTGTCCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGG CAAAGAATACAAGTGCAAAGTCTCCAACAAG GCCCTGCCAGCCCCAATCGAAAAGACAATCA GCAAGGCCAAGGGCCAGCCACGGGAGCCC CAGGTGTACACCCTGCCCCCCAGCCGGGAG GAGATGACCAAGAACCAGGTGTCCCTGACCT GTCTGGTGAAGGGCTTCTACCCCTGTGATAT CGCCGTGGAGTGGGAGAGCAACGGCCAGCC CGAGAACAACTACAAGACCACCCCCCCAGTG CTGGACAGCGACGGCAGCTTCTTCCTGTACA GCAAGCTGACCGTGGACAAGTCCAGGTGGC AGCAGGGCAACGTGTTCAGCTGCAGCGTGA TGCACGAGGCCCTGCACAACCACTACACCCA GAAGTCCCTGAGCCTGAGCCCCGGCAAG
SEQ ID NO: 14	LCDR1 (Combined)	SGDALRDKFVY
SEQ ID NO: 15	LCDR2 (Combined)	DDNNRPS
SEQ ID NO: 16	LCDR3 (Combined)	QSWDHSYSLVV
SEQ ID NO: 14	LCDR1 (Kabat)	SGDALRDKFVY
SEQ ID NO: 15	LCDR2 (Kabat)	DDNNRPS
SEQ ID NO: 16	LCDR3 (Kabat)	QSWDHSYSLVV
SEQ ID NO: 17	LCDR1 (Chothia)	DALRDKF
SEQ ID NO: 18	LCDR2 (Chothia)	DDN

SEQ ID NO: 19	LCDR3 (Chothia)	WDHSYSLV
SEQ ID NO: 20	LCDR1 (IMGT)	ALRDKF
SEQ ID NO: 18	LCDR2 (IMGT)	DDN
SEQ ID NO: 16	LCDR3 (IMGT)	QSWDHSYSLVV
SEQ ID NO: 21	VL	DIELTQPPSVSVSPGQTASITCSGDALRDKFVY WYQQKPGQAPVLVIYDDNNRPSGIPERFSGSN SGNTATLTISGTQAEDEADYYCQSWDHSYSLV VFGGGTKLTVL
SEQ ID NO: 22	DNA VL	GATATCGAACTGACCCAGCCGCCGAGCGTG AGCGTGAGCCCGGGCCAGACCGCGAGCATT ACCTGTAGCGGCGATGCTCTGCGTGACAAAT TCGTTTACTGGTACCAGCAGAAACCGGGCCA GGCGCCGGTGCTGGTGATCTACGACGACAA CAACCGTCCGAGCGGCATCCCGGAACGTTTT AGCGGATCCAACAGCGGCAACACCGCGACC CTGACCATTAGCGGCACCCAGGCGGAAGAC GAAGCGGATTATTACTGCCAGTCTTGGGACC ATTCTTACTCTCTGGTTGTGTTTGGCGGCGG CACGAAGTTAACTGTCCTG
SEQ ID NO: 23	Light Chain	DIELTQPPSVSVSPGQTASITCSGDALRDKFVY WYQQKPGQAPVLVIYDDNNRPSGIPERFSGSN SGNTATLTISGTQAEDEADYYCQSWDHSYSLV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
SEQ ID NO: 24	DNA Light Chain	GATATCGAACTGACCCAGCCGCCGAGCGTG AGCGTGAGCCCGGGCCAGACCGCGAGCATT ACCTGTAGCGGCGATGCTCTGCGTGACAAAT TCGTTTACTGGTACCAGCAGAAACCGGGCCA GGCGCCGGTGCTGGTGATCTACGACGACAA CAACCGTCCGAGCGGCATCCCGGAACGTTTT AGCGGATCCAACAGCGGCAACACCGCGACC CTGACCATTAGCGGCACCCAGGCGGAAGAC GAAGCGGATTATTACTGCCAGTCTTGGGACC ATTCTTACTCTCTGGTTGTGTTTGGCGGCGG CACGAAGTTAACTGTCCTGGGACAACCTAAG GCCGCTCCCTCCGTGACCCTGTTCCCCCCC AGCTCCGAGGAACTGCAGGCCAACAAGGCC ACCCTGGTGTGCCTGATCAGCGACTTCTACC CTGGCGCCGTGACCGTGGCCTGGAAGGCCG ACAGCAGCCCCGTGAAGGCCGGCGTGGAGA CAACCACCCCCAGCAAGCAGAGCAACAACAA GTACGCCGCCAGCAGCTACCTGAGCCTGAC CCCCGAGCAGTGGAAGAGCCACAGAAGCTA CAGCTGCCAGGTCACCCACGAGGGCAGCAC

		CGTGGAGAAAACCGTGGCCCCCACCGAGTG CAGC
G1 E152C_S375C_3J LC		
SEQ ID NO: 1	HCDR1 (Combined)	GGTFSDYAIT
SEQ ID NO: 2	HCDR2 (Combined)	GIIPIFGTANYAQKFQG
SEQ ID NO: 3	HCDR3 (Combined)	EGGLLTDISYSRYWFAY
SEQ ID NO: 4	HCDR1 (Kabat)	DYAIT
SEQ ID NO: 2	HCDR2 (Kabat)	GIIPIFGTANYAQKFQG
SEQ ID NO: 3	HCDR3 (Kabat)	EGGLLTDISYSRYWFAY
SEQ ID NO: 5	HCDR1 (Chothia)	GGTFSDY
SEQ ID NO: 6	HCDR2 (Chothia)	IPIFGT
SEQ ID NO: 3	HCDR3(Ch othia)	EGGLLTDISYSRYWFAY
SEQ ID NO: 7	HCDR1 (IMGT)	GGTFSDYA
SEQ ID NO: 8	HCDR2 (IMGT)	IIPIFGTA
SEQ ID NO: 9	HCDR3 (IMGT)	AREGGLLTDISYSRYWFAY
SEQ ID NO: 10	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAITWVRQAPGQGLEWMGGIIPIFGTANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REGGLLTDISYSRYWFAYWGQGTLVTVSS
SEQ ID NO: 11	DNA VH	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTGA CTACGCTATCACTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTAT CATCCCGATCTTCGGCACTGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGGTGGTCTG CTGACTGACATCTCTTACTCTCGTTACTGGTT CGCTTACTGGGGCCAAGGCACCCTGGTGAC TGTTAGCTCA
SEQ ID NO: 12	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAITWVRQAPGQGLEWMGGIIPIFGTANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REGGLLTDISYSRYWFAYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPC PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS

		VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPCDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
SEQ ID NO: 13	DNA Heavy Chain	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTGA CTACGCTATCACTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTAT CATCCCGATCTTCGGCACTGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGGTGGTCTG CTGACTGACATCTCTTACTCTCGTTACTGGTT CGCTTACTGGGGCCAAGGCACCCTGGTGAC TGTTAGCTCAGCTAGCACCAAGGGCCCAAGT GTGTTTCCCCTGGCCCCCAGCAGCAAGTCTA CTTCCGGCGGAACTGCTGCCCTGGGTTGCC TGGTGAAGGACTACTTCCCCTGTCCCGTGAC AGTGTCCTGGAACTCTGGGGCTCTGACTTCC GGCGTGCACACCTTCCCCGCCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGAGCAGCGTG GTGACAGTGCCCTCCAGCTCTCTGGGAACCC AGACCTATATCTGCAACGTGAACCACAAGCC CAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTG CCCCCCCTGCCCAGCTCCAGAACTGCTGGG AGGGCCTTCCGTGTTCCTGTTCCCCCCCAAG CCCAAGGACACCCTGATGATCAGCAGGACC CCCGAGGTGACCTGCGTGGTGGTGGACGTG TCCCACGAGGACCCAGAGGTGAAGTTCAACT GGTACGTGGACGGCGTGGAGGTGCACAACG CCAAGACCAAGCCCAGAGAGGAGCAGTACA ACAGCACCTACAGGGTGGTGTCCGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCA AAGAATACAAGTGCAAAGTCTCCAACAAGGC CCTGCCAGCCCCAATCGAAAAGACAATCAGC AAGGCCAAGGGCCAGCCACGGGAGCCCCAG GTGTACACCCTGCCCCCCAGCCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTC TGGTGAAGGGCTTCTACCCCTGTGATATCGC CGTGGAGTGGGAGAGCAACGGCCAGCCCGA GAACAACTACAAGACCACCCCCCCAGTGCTG GACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGTCCAGGTGGCAGC

		AGGGCAACGTGTTCAGCTGCAGCGTGATGC ACGAGGCCCTGCACAACCACTACACCCAGAA GTCCCTGAGCCTGAGCCCCGGCAAG
SEQ ID NO: 14	LCDR1 (Combined)	SGDALRDKFVY
SEQ ID NO: 15	LCDR2 (Combined)	DDNNRPS
SEQ ID NO: 16	LCDR3 (Combined)	QSWDHSYSLVV
SEQ ID NO: 14	LCDR1 (Kabat)	SGDALRDKFVY
SEQ ID NO: 15	LCDR2 (Kabat)	DDNNRPS
SEQ ID NO: 16	LCDR3 (Kabat)	QSWDHSYSLVV
SEQ ID NO: 17	LCDR1 (Chothia)	DALRDKF
SEQ ID NO: 18	LCDR2 (Chothia)	DDN
SEQ ID NO: 19	LCDR3 (Chothia)	WDHSYSLV
SEQ ID NO: 20	LCDR1 (IMGT)	ALRDKF
SEQ ID NO: 18	LCDR2 (IMGT)	DDN
SEQ ID NO: 16	LCDR3 (IMGT)	QSWDHSYSLVV
SEQ ID NO: 25	VL	SYELTQPLSVSVALGQTARITCSGDALRDKFVY WYQQKPGQAPVLVIYDDNNRPSGIPERFSGSN SGNTATLTISRAQAGDEADYYCQSWDHSYSLV VFGGGTKLTVL
SEQ ID NO: 26	DNA VL	AGCTACGAGCTGACCCAGCCGCTGTCGGTG TCAGTCGCCCTGGGACAAACTGCCAGGATCA CTTGTTCCGGGGACGCATTGCGGGACAAGTT CGTGTACTGGTACCAGCAGAAGCCGGGTCA AGCCCCAGTGCTCGTGATCTACGACGACAAC AACCGGCCTTCCGGTATCCCCGAACGCTTCT CCGGATCCAATAGCGGAAACACCGCCACCCT GACCATTTCGAGAGCTCAGGCCGGGGATGA AGCGGACTACTACTGCCAGTCATGGGATCAC TCGTACTCCCTCGTCGTGTTTGGAGGCGGCA CGAAGCTTACTGTGCTG
SEQ ID NO: 27	Light Chain	SYELTQPLSVSVALGQTARITCSGDALRDKFVY WYQQKPGQAPVLVIYDDNNRPSGIPERFSGSN SGNTATLTISRAQAGDEADYYCQSWDHSYSLV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS

SEQ ID NO: 28	DNA Light Chain	AGCTACGAGCTGACCCAGCCGCTGTCGGTG TCAGTCGCCCTGGGACAAACTGCCAGGATCA CTTGTTCCGGGGACGCATTGCGGGACAAGTT CGTGTACTGGTACCAGCAGAAGCCGGGTCA AGCCCCAGTGCTCGTGATCTACGACGACAAC AACCGGCCTTCCGGTATCCCCGAACGCTTCT CCGGATCCAATAGCGGAAACACCGCCACCCT GACCATTTCGAGAGCTCAGGCCGGGGATGA AGCGGACTACTACTGCCAGTCATGGGATCAC TCGTACTCCCTCGTCGTGTTTGGAGGCGGCA CGAAGCTTACTGTGCTGGGCCAGCCTAAGG CCGCTCCCTCCGTGACCCTGTTCCCCCCCAG CTCCGAGGAACTGCAGGCCAACAAGGCCAC CCTGGTGTGCCTGATCAGCGACTTCTACCCT GGCGCCGTGACCGTGGCCTGGAAGGCCGAC AGCAGCCCCGTGAAGGCCGGCGTGGAGACA ACCACCCCCAGCAAGCAGAGCAACAACAAGT ACGCCGCCAGCAGCTACCTGAGCCTGACCC CCGAGCAGTGGAAGAGCCACAGAAGCTACA GCTGCCAGGTCACCCACGAGGGCAGCACCG TGGAGAAAACCGTGGCCCCCACCGAGTGCA GC
G1 E152C_S375C_3R LC		
SEQ ID NO: 1	HCDR1 (Combined)	GGTFSDYAIT
SEQ ID NO: 2	HCDR2 (Combined)	GIIPIFGTANYAQKFQG
SEQ ID NO: 3	HCDR3 (Combined)	EGGLLTDISYSRYWFAY
SEQ ID NO: 4	HCDR1 (Kabat)	DYAIT
SEQ ID NO: 2	HCDR2 (Kabat)	GIIPIFGTANYAQKFQG
SEQ ID NO: 3	HCDR3 (Kabat)	EGGLLTDISYSRYWFAY
SEQ ID NO: 5	HCDR1 (Chothia)	GGTFSDY
SEQ ID NO: 6	HCDR2 (Chothia)	IPIFGT
SEQ ID NO: 3	HCDR3(Chothia)	EGGLLTDISYSRYWFAY
SEQ ID NO: 7	HCDR1 (IMGT)	GGTFSDYA
SEQ ID NO: 8	HCDR2 (IMGT)	IIPIFGTA
SEQ ID NO: 9	HCDR3 (IMGT)	AREGGLLTDISYSRYWFAY
SEQ ID NO: 10	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAITWVRQAPGQGLEWMGGIIPIFGTANYAQKF

		QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REGGLLTDISYSRYWFAYWGQGTLVTVSS
SEQ ID NO: 11	DNA VH	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTGA CTACGCTATCACTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTAT CATCCCGATCTTCGGCACTGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGGTGGTCTG CTGACTGACATCTCTTACTCTCGTTACTGGTT CGCTTACTGGGGCCAAGGCACCCTGGTGAC TGTTAGCTCA
SEQ ID NO: 12	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAITWVRQAPGQGLEWMGGIIPIFGTANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REGGLLTDISYSRYWFAYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPC PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPCDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
SEQ ID NO: 13	DNA Heavy Chain	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTGA CTACGCTATCACTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTAT CATCCCGATCTTCGGCACTGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGGTGGTCTG CTGACTGACATCTCTTACTCTCGTTACTGGTT CGCTTACTGGGGCCAAGGCACCCTGGTGAC TGTTAGCTCAGCTAGCACCAAGGGCCCAAGT GTGTTTCCCCTGGCCCCCAGCAGCAAGTCTA CTTCCGGCGGAACTGCTGCCCTGGGTTGCC TGGTGAAGGACTACTTCCCCTGTCCCGTGAC AGTGTCCTGGAACTCTGGGGCTCTGACTTCC GGCGTGCACACCTTCCCCGCCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGAGCAGCGTG GTGACAGTGCCCTCCAGCTCTCTGGGAACCC AGACCTATATCTGCAACGTGAACCACAAGCC

		CAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTG CCCCCCCTGCCCAGCTCCAGAACTGCTGGG AGGGCCTTCCGTGTTCCTGTTCCCCCCCAAG CCCAAGGACACCCTGATGATCAGCAGGACC CCCGAGGTGACCTGCGTGGTGGTGGACGTG TCCCACGAGGACCCAGAGGTGAAGTTCAACT GGTACGTGGACGGCGTGGAGGTGCACAACG CCAAGACCAAGCCCAGAGAGGAGCAGTACA ACAGCACCTACAGGGTGGTGTCCGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCA AAGAATACAAGTGCAAAGTCTCCAACAAGGC CCTGCCAGCCCCAATCGAAAAGACAATCAGC AAGGCCAAGGGCCAGCCACGGGAGCCCCAG GTGTACACCCTGCCCCCCAGCCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTC TGGTGAAGGGCTTCTACCCCTGTGATATCGC CGTGGAGTGGGAGAGCAACGGCCAGCCCGA GAACAACTACAAGACCACCCCCCCAGTGCTG GACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGTCCAGGTGGCAGC AGGGCAACGTGTTCAGCTGCAGCGTGATGC ACGAGGCCCTGCACAACCACTACACCCAGAA GTCCCTGAGCCTGAGCCCCGGCAAG
SEQ ID NO: 14	LCDR1 (Combined)	SGDALRDKFVY
SEQ ID NO: 15	LCDR2 (Combined)	DDNNRPS
SEQ ID NO: 16	LCDR3 (Combined)	QSWDHSYSLVV
SEQ ID NO: 14	LCDR1 (Kabat)	SGDALRDKFVY
SEQ ID NO: 15	LCDR2 (Kabat)	DDNNRPS
SEQ ID NO: 16	LCDR3 (Kabat)	QSWDHSYSLVV
SEQ ID NO: 17	LCDR1 (Chothia)	DALRDKF
SEQ ID NO: 18	LCDR2 (Chothia)	DDN
SEQ ID NO: 19	LCDR3 (Chothia)	WDHSYSLV
SEQ ID NO: 20	LCDR1 (IMGT)	ALRDKF
SEQ ID NO: 18	LCDR2 (IMGT)	DDN
SEQ ID NO: 16	LCDR3 (IMGT)	QSWDHSYSLVV
SEQ ID NO: 29	VL	SYELTQPPSVSVSPGQTASITCSGDALRDKFVY WYQQKPGQSPVLVIYDDNNRPSGIPERFSGSN

		SGNTATLTISGTQAMDEADYYCQSWDHSYSLV VFGGGTKLTVL
SEQ ID NO: 30	DNA VL	TCGTACGAGCTCACTCAACCGCCTTCTGTGT CCGTGTCACCCGGGCAGACTGCCTCCATTAC CTGTTCGGGAGATGCCCTGCGCGACAAGTTT GTGTACTGGTACCAGCAGAAGCCCGGACAG TCGCCAGTGCTCGTCATCTATGACGACAACA ACAGACCTTCCGGTATCCCGGAACGGTTCAG CGGAAGCAATTCCGGCAACACCGCTACCCTG ACCATTAGCGGCACTCAGGCCATGGACGAA GCGGATTACTACTGCCAATCCTGGGACCACT CATACTCCCTTGTGGTGTTCGGTGGCGGAAC GAAGCTGACCGTCCTG
SEQ ID NO: 31	Light Chain	SYELTQPPSVSVSPGQTASITCSGDALRDKFVY WYQQKPGQSPVLVIYDDNNRPSGIPERFSGSN SGNTATLTISGTQAMDEADYYCQSWDHSYSLV VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
SEQ ID NO: 32	DNA Light Chain	TCGTACGAGCTCACTCAACCGCCTTCTGTGT CCGTGTCACCCGGGCAGACTGCCTCCATTAC CTGTTCGGGAGATGCCCTGCGCGACAAGTTT GTGTACTGGTACCAGCAGAAGCCCGGACAG TCGCCAGTGCTCGTCATCTATGACGACAACA ACAGACCTTCCGGTATCCCGGAACGGTTCAG CGGAAGCAATTCCGGCAACACCGCTACCCTG ACCATTAGCGGCACTCAGGCCATGGACGAA GCGGATTACTACTGCCAATCCTGGGACCACT CATACTCCCTTGTGGTGTTCGGTGGCGGAAC GAAGCTGACCGTCCTGGGCCAGCCTAAGGC CGCTCCCTCCGTGACCCTGTTCCCCCCCAGC TCCGAGGAACTGCAGGCCAACAAGGCCACC CTGGTGTGCCTGATCAGCGACTTCTACCCTG GCGCCGTGACCGTGGCCTGGAAGGCCGACA GCAGCCCCGTGAAGGCCGGCGTGGAGACAA CCACCCCCAGCAAGCAGAGCAACAACAAGTA CGCCGCCAGCAGCTACCTGAGCCTGACCCC CGAGCAGTGGAAGAGCCACAGAAGCTACAG CTGCCAGGTCACCCACGAGGGCAGCACCGT GGAGAAAACCGTGGCCCCCACCGAGTGCAG C
G4 E152_S375C		
SEQ ID NO: 33	HCDR1 (Combined)	GGTFSTYAIS
SEQ ID NO: 34	HCDR2 (Combined)	RIIPILGIANYAQKFQG
SEQ ID NO: 35	HCDR3 (Combined)	EVRMIFDY

SEQ ID NO: 36	HCDR1 (Kabat)	TYAIS
SEQ ID NO: 34	HCDR2 (Kabat)	RIIPILGIANYAQKFQG
SEQ ID NO: 35	HCDR3 (Kabat)	EVRMIFDY
SEQ ID NO: 37	HCDR1 (Chothia)	GGTFSTY
SEQ ID NO: 38	HCDR2 (Chothia)	IPILGI
SEQ ID NO: 35	HCDR3(Chothia)	EVRMIFDY
SEQ ID NO: 39	HCDR1 (IMGT)	GGTFSTYA
SEQ ID NO: 40	HCDR2 (IMGT)	IIPILGIA
SEQ ID NO: 41	HCDR3 (IMGT)	AREVRMIFDY
SEQ ID NO: 42	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFST YAISWVRQAPGQGLEWMGRIIPILGIANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REVRMIFDYWGQGTLVTVSS
SEQ ID NO: 43	DNA VH	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA GCTGCAAAGCATCCGGAGGGACGTTTTCTAC TTACGCTATCTCTTGGGTGCGCCAGGCCCCG GGCCAGGGCCTCGAGTGGATGGGCCGTATC ATCCCGATCCTGGGCATCGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGTTCGTATG ATCTTCGATTACTGGGGCCAAGGCACCCTGG TGACTGTTAGCTCA
SEQ ID NO: 44	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFST YAISWVRQAPGQGLEWMGRIIPILGIANYAQKF QGRVTITADESTSTAYMELSSLRSEDTAVYYCA REVRMIFDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPCPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPCDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 45	DNA Heavy Chain	CAGGTGCAATTGGTGCAGAGCGGTGCCGAA GTGAAAAAACCGGGCAGCAGCGTGAAAGTTA

		GCTGCAAAGCATCCGGAGGGACGTTTTCTAC TTACGCTATCTCTTGGGTGCGCCAGGCCCCG GGCCAGGGCCTCGAGTGGATGGGCCGTATC ATCCCGATCCTGGGCATCGCGAACTACGCC CAGAAATTTCAGGGCCGGGTGACCATTACCG CCGATGAAAGCACCAGCACCGCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGC CGTGTATTATTGCGCGCGTGAAGTTCGTATG ATCTTCGATTACTGGGGCCAAGGCACCCTGG TGACTGTTAGCTCAGCCTCTACGAAAGGCCC AAGCGTATTTCCCCTGGCTCCTTCTAGTAAAT CAACCTCAGGTGGTACAGCAGCCCTTGGCT GCCTGGTCAAAGACTATTTCCCCTGTCCGGT GACCGTCTCATGGAACTCAGGTGCTTTGACA TCTGGTGTGCATACATTCCCAGCTGTGCTGC AAAGTAGTGGACTGTACAGCCTTTCCAGCGT GGTCACGGTGCCAAGTAGCTCCTTGGGTACT CAGACTTATATCTGCAATGTGAACCACAAGC CCTCTAACACGAAGGTGGACAAGCGCGTGG AGCCCAAATCTTGCGATAAGACGCATACTTG TCCCCCATGCCCTGCTCCTGAGCTGTTGGGA GGCCCGTCAGTGTTCTTGTTCCCTCCGAAGC CTAAGGACACTTTGATGATAAGTAGGACACC AGAGGTGACTTGCGTGGTGGTTGATGTGTCC CATGAAGATCCCGAGGTCAAATTTAATTGGT ACGTAGATGGTGTCGAAGTTCACAATGCTAA GACTAAGCCAAGGGAAGAGCAGTACAACAGT ACATATAGGGTAGTCTCCGTGCTGACAGTCC TCCACCAGGACTGGTTGAACGGCAAGGAATA CAAATGTAAGGTGTCAAACAAAGCTCTGCCT GCTCCCATTGAGAAAACAATCTCTAAAGCCA AAGGCCAGCCGAGAGAGCCCCAAGTCTACA CTTTGCCCCCGAGCAGGGAGGAAATGACCA AGAATCAGGTGAGTCTGACGTGCCTCGTCAA AGGATTTTATCCATGCGATATTGCAGTTGAAT GGGAGAGCAATGGCCAGCCAGAGAACAACT ATAAAACCACACCACCCGTGCTCGACTCTGA TGGCAGCTTCTTCCTCTATAGCAAGCTGACA GTCGATAAATCTCGCTGGCAGCAAGGCAATG TGTTCTCCTGCTCCGTCATGCACGAGGCTTT GCATAACCATTATACTCAAAAATCTCTGTCCC TGTCACCTGGTAAA
SEQ ID NO: 46	LCDR1 (Combined)	RASQSISSYLA
SEQ ID NO: 47	LCDR2 (Combined)	AASSLQS
SEQ ID NO: 48	LCDR3 (Combined)	QQSYDYYT
SEQ ID NO: 46	LCDR1 (Kabat)	RASQSISSYLA

SEQ ID NO: 47	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 48	LCDR3 (Kabat)	QQSYDYYT
SEQ ID NO: 49	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 51	LCDR3 (Chothia)	SYDYY
SEQ ID NO: 52	LCDR1 (IMGT)	QSISSY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 48	LCDR3 (IMGT)	QQSYDYYT
SEQ ID NO: 53	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL AWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQSYDYYTFG QGTKVEIK
SEQ ID NO: 54	DNA VL	GATATCCAGATGACCCAGAGCCCGAGCAGC CTGAGCGCCAGCGTGGGCGATCGCGTGACC ATTACCTGCAGAGCCAGCCAGTCTATTTCTT CTTACCTGGCTTGGTACCAGCAGAAACCGGG CAAAGCGCCGAAACTATTAATCTACGCTGCT TCTTCTCTGCAAAGCGGCGTGCCGAGCCGC TTTAGCGGCAGCGGATCCGGCACCGATTTCA CCCTGACCATTAGCTCTCTGCAACCGGAAGA CTTTGCGACCTATTATTGCCAGCAGTCTTAC GACTACTACACCTTTGGCCAGGGCACGAAAG TTGAAATTAAA
SEQ ID NO: 55	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL AWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQSYDYYTFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC
SEQ ID NO: 56	DNA Light Chain	GATATCCAGATGACCCAGAGCCCGAGCAGC CTGAGCGCCAGCGTGGGCGATCGCGTGACC ATTACCTGCAGAGCCAGCCAGTCTATTTCTT CTTACCTGGCTTGGTACCAGCAGAAACCGGG CAAAGCGCCGAAACTATTAATCTACGCTGCT TCTTCTCTGCAAAGCGGCGTGCCGAGCCGC TTTAGCGGCAGCGGATCCGGCACCGATTTCA CCCTGACCATTAGCTCTCTGCAACCGGAAGA CTTTGCGACCTATTATTGCCAGCAGTCTTAC GACTACTACACCTTTGGCCAGGGCACGAAAG TTGAAATTAAACGTACGGTGGCAGCTCCGTC TGTTTTCATCTTTCCACCTAGCGACGAGCAA

		CTCAAAAGTGGTACAGCATCCGTGGTTTGTC TGCTGAACAATTTTTACCCCAGGGAGGCTAA GGTCCAGTGGAAAGTCGATAACGCTCTTCAG TCTGGCAACAGTCAGGAGAGCGTCACAGAG CAGGACTCTAAGGATAGCACTTATAGTCTGT CCTCCACGCTGACACTGTCTAAAGCGGATTA TGAGAAGCACAAGGTTTACGCCTGTGAGGTA ACGCACCAAGGACTCTCCTCCCCAGTTACCA AATCTTTCAACAGAGGAGAATGT
MOR024353 E152C_S375C		
SEQ ID NO: 57	HCDR1 (Combined)	GGTFSDYAIS
SEQ ID NO: 58	HCDR2 (Combined)	GIIPIFGDANYAQKFQG
SEQ ID NO: 59	HCDR3 (Combined)	EGSSYFYMAY
SEQ ID NO: 60	HCDR1 (Kabat)	DYAIS
SEQ ID NO: 58	HCDR2 (Kabat)	GIIPIFGDANYAQKFQG
SEQ ID NO: 59	HCDR3 (Kabat)	EGSSYFYMAY
SEQ ID NO: 5	HCDR1 (Chothia)	GGTFSDY
SEQ ID NO: 61	HCDR2 (Chothia)	IPIFGD
SEQ ID NO: 59	HCDR3(Chothia)	EGSSYFYMAY
SEQ ID NO: 7	HCDR1 (IMGT)	GGTFSDYA
SEQ ID NO: 62	HCDR2 (IMGT)	IIPIFGDA
SEQ ID NO: 63	HCDR3 (IMGT)	AREGSSYFYMAY
SEQ ID NO: 64	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAISWVRQAPGQGLEWMGGIIPIFGDANYAQK FQGRVTITADESTSTAYMELSSLRSEDTAVYYC AREGSSYFYMAYWGQGTLVTVSS
SEQ ID NO: 65	DNA VH	CAGGTTCAGCTGGTGCAGTCTGGCGCCGAA GTGAAGAAACCTGGCAGCAGCGTGAAGGTG TCCTGCAAAGCAAGCGGCGGCACCTTCAGC GATTACGCCATCTCTTGGGTCCGACAGGCCC CTGGACAAGGCTTGGAATGGATGGGCGGCA TCATCCCCATCTTCGGCGACGCCAATTACGC CCAGAAATTCCAGGGCAGAGTGACCATCACC GCCGACGAGTCTACAAGCACCGCCTACATG GAACTGAGCAGCCTGAGAAGCGAGGACACC GCCGTGTACTACTGTGCCAGAGAGGGCAGC

		AGCTACTTCTACATGGCCTATTGGGGCCAGG GCACCCTGGTCACAGTTAGCTCT
SEQ ID NO: 66	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSD YAISWVRQAPGQGLEWMGGIIPIFGDANYAQK FQGRVTITADESTSTAYMELSSLRSEDTAVYYC AREGSSYFYMAYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPCPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPCDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO: 67	DNA Heavy Chain	CAGGTTCAGCTGGTGCAGTCTGGCGCCGAA GTGAAGAAACCTGGCAGCAGCGTGAAGGTG TCCTGCAAAGCAAGCGGCGGCACCTTCAGC GATTACGCCATCTCTTGGGTCCGACAGGCCC CTGGACAAGGCTTGGAATGGATGGGCGGCA TCATCCCCATCTTCGGCGACGCCAATTACGC CCAGAAATTCCAGGGCAGAGTGACCATCACC GCCGACGAGTCTACAAGCACCGCCTACATG GAACTGAGCAGCCTGAGAAGCGAGGACACC GCCGTGTACTACTGTGCCAGAGAGGGCAGC AGCTACTTCTACATGGCCTATTGGGGCCAGG GCACCCTGGTCACAGTTAGCTCTGCTAGCAC CAAGGGCCCAAGTGTGTTTCCCCTGGCCCC CAGCAGCAAGTCTACTTCCGGCGGAACTGCT GCCCTGGGTTGCCTGGTGAAGGACTACTTCC CCTGTCCCGTGACAGTGTCCTGGAACTCTGG GGCTCTGACTTCCGGCGTGCACACCTTCCCC GCCGTGCTGCAGAGCAGCGGCCTGTACAGC CTGAGCAGCGTGGTGACAGTGCCCTCCAGC TCTCTGGGAACCCAGACCTATATCTGCAACG TGAACCACAAGCCCAGCAACACCAAGGTGG ACAAGAGAGTGGAGCCCAAGAGCTGCGACA AGACCCACACCTGCCCCCCCTGCCCAGCTC CAGAACTGCTGGGAGGGCCTTCCGTGTTCCT GTTCCCCCCCAAGCCCAAGGACACCCTGAT GATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGGACGTGTCCCACGAGGACCCAGA GGTGAAGTTCAACTGGTACGTGGACGGCGT GGAGGTGCACAACGCCAAGACCAAGCCCAG AGAGGAGCAGTACAACAGCACCTACAGGGT GGTGTCCGTGCTGACCGTGCTGCACCAGGA CTGGCTGAACGGCAAAGAATACAAGTGCAAA GTCTCCAACAAGGCCCTGCCAGCCCCAATC GAAAAGACAATCAGCAAGGCCAAGGGCCAG

		CCACGGGAGCCCCAGGTGTACACCCTGCCC CCCAGCCGGGAGGAGATGACCAAGAACCAG GTGTCCCTGACCTGTCTGGTGAAGGGCTTCT ACCCCTGTGATATCGCCGTGGAGTGGGAGA GCAACGGCCAGCCCGAGAACAACTACAAGA CCACCCCCCCAGTGCTGGACAGCGACGGCA GCTTCTTCCTGTACAGCAAGCTGACCGTGGA CAAGTCCAGGTGGCAGCAGGGCAACGTGTT CAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGTCCCTGAGCCTG AGCCCCGGCAAG
SEQ ID NO: 68	LCDR1 (Combined)	SGDNIGSKLAS
SEQ ID NO: 69	LCDR2 (Combined)	DDSNRPS
SEQ ID NO: 70	LCDR3 (Combined)	AATAGDRWAYV
SEQ ID NO: 68	LCDR1 (Kabat)	SGDNIGSKLAS
SEQ ID NO: 69	LCDR2 (Kabat)	DDSNRPS
SEQ ID NO: 70	LCDR3 (Kabat)	AATAGDRWAYV
SEQ ID NO: 71	LCDR1 (Chothia)	DNIGSKL
SEQ ID NO: 72	LCDR2 (Chothia)	DDS
SEQ ID NO: 73	LCDR3 (Chothia)	TAGDRWAY
SEQ ID NO: 74	LCDR1 (IMGT)	NIGSKL
SEQ ID NO: 72	LCDR2 (IMGT)	DDS
SEQ ID NO: 70	LCDR3 (IMGT)	AATAGDRWAYV
SEQ ID NO: 75	VL	SYELTQPLSVSVALGQTARITCSGDNIGSKLAS WYQQKPGQAPVLVIYDDSNRPSGIPERFSGSN SGNTATLTISRAQAGDEADYYCAATAGDRWAY VFGGGTKLTVL
SEQ ID NO: 76	DNA VL	AGCTATGAGCTGACACAGCCTCTGTCCGTGT CTGTGGCTCTGGGACAGACCGCCAGAATCA CCTGTAGCGGCGACAACATCGGCAGCAAGC TGGCCTCTTGGTATCAGCAGAAGCCTGGACA GGCCCCTGTGCTGGTCATCTACGACGACAG CAATAGACCCAGCGGCATCCCCGAGAGATTC AGCGGCAGCAATAGCGGCAATACCGCCACA CTGACCATCAGCAGAGCACAGGCTGGCGAC GAGGCCGATTACTATTGTGCTGCCACAGCCG GCGACAGATGGGCCTATGTTTTTGGCGGCG GAACAAAGCTGACCGTGCTG

SEQ ID NO: 77	Light Chain	SYELTQPLSVSVALGQTARITCSGDNIGSKLAS WYQQKPGQAPVLVIYDDSNRPSGIPERFSGSN SGNTATLTISRAQAGDEADYYCAATAGDRWAY VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
SEQ ID NO: 78	DNA Light Chain	AGCTATGAGCTGACACAGCCTCTGTCCGTGT CTGTGGCTCTGGGACAGACCGCCAGAATCA CCTGTAGCGGCGACAACATCGGCAGCAAGC TGGCCTCTTGGTATCAGCAGAAGCCTGGACA GGCCCCTGTGCTGGTCATCTACGACGACAG CAATAGACCCAGCGGCATCCCCGAGAGATTC AGCGGCAGCAATAGCGGCAATACCGCCACA CTGACCATCAGCAGAGCACAGGCTGGCGAC GAGGCCGATTACTATTGTGCTGCCACAGCCG GCGACAGATGGGCCTATGTTTTTGGCGGCG GAACAAAGCTGACCGTGCTGGGACAGCCTA AGGCCGCTCCCTCCGTGACCCTGTTCCCCC CCAGCTCCGAGGAACTGCAGGCCAACAAGG CCACCCTGGTGTGCCTGATCAGCGACTTCTA CCCTGGCGCCGTGACCGTGGCCTGGAAGGC CGACAGCAGCCCCGTGAAGGCCGGCGTGGA GACAACCACCCCCAGCAAGCAGAGCAACAA CAAGTACGCCGCCAGCAGCTACCTGAGCCT GACCCCCGAGCAGTGGAAGAGCCACAGAAG CTACAGCTGCCAGGTCACCCACGAGGGCAG CACCGTGGAGAAAACCGTGGCCCCCACCGA GTGCAGC
MOR024354 E152C_S375C		
SEQ ID NO: 79	HCDR1 (Combined)	GFTFSSFGMS
SEQ ID NO: 80	HCDR2 (Combined)	AISYSGSDTYYADSVKG
SEQ ID NO: 81	HCDR3 (Combined)	DVGVMDY
SEQ ID NO: 82	HCDR1 (Kabat)	SFGMS
SEQ ID NO: 80	HCDR2 (Kabat)	AISYSGSDTYYADSVKG
SEQ ID NO: 81	HCDR3 (Kabat)	DVGVMDY
SEQ ID NO: 83	HCDR1 (Chothia)	GFTFSSF
SEQ ID NO: 84	HCDR2 (Chothia)	SYSGSD
SEQ ID NO: 81	HCDR3(Chothia)	DVGVMDY

SEQ ID NO: 85	HCDR1 (IMGT)	GFTFSSFG
SEQ ID NO: 86	HCDR2 (IMGT)	ISYSGSDT
SEQ ID NO: 87	HCDR3 (IMGT)	ARDVGVMDY
SEQ ID NO: 88	VH	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSF GMSWVRQAPGKGLEWVSAISYSGSDTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARDVGVMDYWGQGTLVTVSS
SEQ ID NO: 89	DNA VH	CAGGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTCAGCAG CTTTGGCATGAGCTGGGTCCGACAGGCCCC TGGCAAAGGACTTGAATGGGTGTCCGCCATC AGCTACAGCGGCAGCGATACCTACTACGCC GACAGCGTGAAGGGCAGATTCACCATCTCCA GAGACAACAGCAAGAACACCCTGTACCTGCA GATGAACAGCCTGAGAGCCGAGGACACCGC CGTGTACTACTGTGCCAGAGATGTGGGCGT GATGGACTATTGGGGCCAGGGCACACTGGT CACCGTTAGCTCT
SEQ ID NO: 90	Heavy Chain	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSF GMSWVRQAPGKGLEWVSAISYSGSDTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARDVGVMDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPCPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPCDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 91	DNA Heavy Chain	CAGGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTCAGCAG CTTTGGCATGAGCTGGGTCCGACAGGCCCC TGGCAAAGGACTTGAATGGGTGTCCGCCATC AGCTACAGCGGCAGCGATACCTACTACGCC GACAGCGTGAAGGGCAGATTCACCATCTCCA GAGACAACAGCAAGAACACCCTGTACCTGCA GATGAACAGCCTGAGAGCCGAGGACACCGC CGTGTACTACTGTGCCAGAGATGTGGGCGT GATGGACTATTGGGGCCAGGGCACACTGGT CACCGTTAGCTCTGCTAGCACCAAGGGCCCA AGTGTGTTTCCCCTGGCCCCCAGCAGCAAGT CTACTTCCGGCGGAACTGCTGCCCTGGGTT

		GCCTGGTGAAGGACTACTTCCCCTGTCCCGT GACAGTGTCCTGGAACTCTGGGGCTCTGACT TCCGGCGTGCACACCTTCCCCGCCGTGCTG CAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACAGTGCCCTCCAGCTCTCTGGGA ACCCAGACCTATATCTGCAACGTGAACCACA AGCCCAGCAACACCAAGGTGGACAAGAGAG TGGAGCCCAAGAGCTGCGACAAGACCCACA CCTGCCCCCCCTGCCCAGCTCCAGAACTGC TGGGAGGGCCTTCCGTGTTCCTGTTCCCCCC CAAGCCCAAGGACACCCTGATGATCAGCAG GACCCCCGAGGTGACCTGCGTGGTGGTGGA CGTGTCCCACGAGGACCCAGAGGTGAAGTT CAACTGGTACGTGGACGGCGTGGAGGTGCA CAACGCCAAGACCAAGCCCAGAGAGGAGCA GTACAACAGCACCTACAGGGTGGTGTCCGT GCTGACCGTGCTGCACCAGGACTGGCTGAA CGGCAAAGAATACAAGTGCAAAGTCTCCAAC AAGGCCCTGCCAGCCCCAATCGAAAAGACAA TCAGCAAGGCCAAGGGCCAGCCACGGGAGC CCCAGGTGTACACCCTGCCCCCCAGCCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGA CCTGTCTGGTGAAGGGCTTCTACCCCTGTGA TATCGCCGTGGAGTGGGAGAGCAACGGCCA GCCCGAGAACAACTACAAGACCACCCCCCC AGTGCTGGACAGCGACGGCAGCTTCTTCCT GTACAGCAAGCTGACCGTGGACAAGTCCAG GTGGCAGCAGGGCAACGTGTTCAGCTGCAG CGTGATGCACGAGGCCCTGCACAACCACTA CACCCAGAAGTCCCTGAGCCTGAGCCCCGG CAAG
SEQ ID NO: 92	LCDR1 (Combined)	SGDNLGTYYAH
SEQ ID NO: 93	LCDR2 (Combined)	SQSHRPS
SEQ ID NO: 94	LCDR3 (Combined)	GAWDAPSPELV
SEQ ID NO: 92	LCDR1 (Kabat)	SGDNLGTYYAH
SEQ ID NO: 93	LCDR2 (Kabat)	SQSHRPS
SEQ ID NO: 94	LCDR3 (Kabat)	GAWDAPSPELV
SEQ ID NO: 95	LCDR1 (Chothia)	DNLGTYY
SEQ ID NO: 96	LCDR2 (Chothia)	SQS
SEQ ID NO: 97	LCDR3 (Chothia)	WDAPSPEL

SEQ ID NO: 98	LCDR1 (IMGT)	NLGTYY
SEQ ID NO: 96	LCDR2 (IMGT)	SQS
SEQ ID NO: 94	LCDR3 (IMGT)	GAWDAPSPELV
SEQ ID NO: 99	VL	SYELTQPLSVSVALGQTARITCSGDNLGTYYAH WYQQKPGQAPVLVIYSQSHRPSGIPERFSGSN SGNTATLTISRAQAGDEADYYCGAWDAPSPEL VFGGGTKLTVL
SEQ ID NO: 100	DNA VL	AGCTATGAGCTGACACAGCCTCTGTCCGTGT CTGTGGCTCTGGGACAGACCGCCAGAATCA CCTGTAGCGGCGATAACCTGGGCACCTACTA CGCCCACTGGTATCAGCAGAAGCCTGGACA GGCTCCCGTGCTGGTCATCTACAGCCAGTCT CACAGACCCAGCGGCATCCCCGAGAGATTC AGCGGCAGCAATAGCGGCAATACCGCCACA CTGACCATCAGCAGAGCACAGGCTGGCGAC GAGGCCGATTACTATTGTGGCGCTTGGGAC GCCCCATCTCCTGAGCTTGTTTTTGGCGGAG GCACCAAGCTGACAGTGCTG
SEQ ID NO: 101	Light Chain	SYELTQPLSVSVALGQTARITCSGDNLGTYYAH WYQQKPGQAPVLVIYSQSHRPSGIPERFSGSN SGNTATLTISRAQAGDEADYYCGAWDAPSPEL VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
SEQ ID NO: 102	DNA Light Chain	AGCTATGAGCTGACACAGCCTCTGTCCGTGT CTGTGGCTCTGGGACAGACCGCCAGAATCA CCTGTAGCGGCGATAACCTGGGCACCTACTA CGCCCACTGGTATCAGCAGAAGCCTGGACA GGCTCCCGTGCTGGTCATCTACAGCCAGTCT CACAGACCCAGCGGCATCCCCGAGAGATTC AGCGGCAGCAATAGCGGCAATACCGCCACA CTGACCATCAGCAGAGCACAGGCTGGCGAC GAGGCCGATTACTATTGTGGCGCTTGGGAC GCCCCATCTCCTGAGCTTGTTTTTGGCGGAG GCACCAAGCTGACAGTGCTGGGACAGCCTA AGGCCGCTCCCTCCGTGACCCTGTTCCCCC CCAGCTCCGAGGAACTGCAGGCCAACAAGG CCACCCTGGTGTGCCTGATCAGCGACTTCTA CCCTGGCGCCGTGACCGTGGCCTGGAAGGC CGACAGCAGCCCCGTGAAGGCCGGCGTGGA GACAACCACCCCCAGCAAGCAGAGCAACAA CAAGTACGCCGCCAGCAGCTACCTGAGCCT GACCCCCGAGCAGTGGAAGAGCCACAGAAG CTACAGCTGCCAGGTCACCCACGAGGGCAG CACCGTGGAGAAAACCGTGGCCCCCACCGA GTGCAGC

Y010341 E152C_S375C		
SEQ ID NO: 103	HCDR1 (Combined)	GFTFSSYAMS
SEQ ID NO: 104	HCDR2 (Combined)	AISGSGGSTYYADSVKG
SEQ ID NO: 105	HCDR3 (Combined)	AFRLYWLDV
SEQ ID NO: 106	HCDR1 (Kabat)	SYAMS
SEQ ID NO: 104	HCDR2 (Kabat)	AISGSGGSTYYADSVKG
SEQ ID NO: 105	HCDR3 (Kabat)	AFRLYWLDV
SEQ ID NO: 107	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 108	HCDR2 (Chothia)	SGSGGS
SEQ ID NO: 105	HCDR3(Chothia)	AFRLYWLDV
SEQ ID NO: 109	HCDR1 (IMGT)	GFTFSSYA
SEQ ID NO: 110	HCDR2 (IMGT)	ISGSGGST
SEQ ID NO: 111	HCDR3 (IMGT)	ARAFRLYWLDV
SEQ ID NO: 112	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARAFRLYWLDVWGQGTLVTVSS
SEQ ID NO: 113	DNA VH	GAAGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTTAGCAG CTACGCCATGAGCTGGGTCCGACAGGCTCC TGGCAAAGGCCTTGAATGGGTGTCCGCCATC TCTGGCTCTGGCGGCAGCACATATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAG ATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTATTGTGCCAGAGCCTTCCGGCTGT ACTGGCTGGATGTTTGGGGACAGGGCACCC TGGTCACAGTGTCATCT
SEQ ID NO: 114	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARAFRLYWLDVWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPCPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH

		NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPCDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO: 115	DNA Heavy Chain	GAAGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTTAGCAG CTACGCCATGAGCTGGGTCCGACAGGCTCC TGGCAAAGGCCTTGAATGGGTGTCCGCCATC TCTGGCTCTGGCGGCAGCACATATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAG ATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTATTGTGCCAGAGCCTTCCGGCTGT ACTGGCTGGATGTTTGGGGACAGGGCACCC TGGTCACAGTGTCATCTGCTAGCACCAAGGG CCCAAGTGTGTTTCCCCTGGCCCCCAGCAG CAAGTCTACTTCCGGCGGAACTGCTGCCCTG GGTTGCCTGGTGAAGGACTACTTCCCCTGTC CCGTGACAGTGTCCTGGAACTCTGGGGCTCT GACTTCCGGCGTGCACACCTTCCCCGCCGT GCTGCAGAGCAGCGGCCTGTACAGCCTGAG CAGCGTGGTGACAGTGCCCTCCAGCTCTCT GGGAACCCAGACCTATATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAG AGAGTGGAGCCCAAGAGCTGCGACAAGACC CACACCTGCCCCCCCTGCCCAGCTCCAGAA CTGCTGGGAGGGCCTTCCGTGTTCCTGTTCC CCCCCAAGCCCAAGGACACCCTGATGATCA GCAGGACCCCCGAGGTGACCTGCGTGGTGG TGGACGTGTCCCACGAGGACCCAGAGGTGA AGTTCAACTGGTACGTGGACGGCGTGGAGG TGCACAACGCCAAGACCAAGCCCAGAGAGG AGCAGTACAACAGCACCTACAGGGTGGTGTC CGTGCTGACCGTGCTGCACCAGGACTGGCT GAACGGCAAAGAATACAAGTGCAAAGTCTCC AACAAGGCCCTGCCAGCCCCAATCGAAAAGA CAATCAGCAAGGCCAAGGGCCAGCCACGGG AGCCCCAGGTGTACACCCTGCCCCCCAGCC GGGAGGAGATGACCAAGAACCAGGTGTCCC TGACCTGTCTGGTGAAGGGCTTCTACCCCTG TGATATCGCCGTGGAGTGGGAGAGCAACGG CCAGCCCGAGAACAACTACAAGACCACCCC CCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGTCC AGGTGGCAGCAGGGCAACGTGTTCAGCTGC AGCGTGATGCACGAGGCCCTGCACAACCAC TACACCCAGAAGTCCCTGAGCCTGAGCCCC GGCAAG

SEQ ID NO: 116	LCDR1 (Combined)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Combined)	AASSLQS
SEQ ID NO: 117	LCDR3 (Combined)	QQVYSAPVT
SEQ ID NO: 116	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 117	LCDR3 (Kabat)	QQVYSAPVT
SEQ ID NO: 49	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 118	LCDR3 (Chothia)	VYSAPV
SEQ ID NO: 52	LCDR1 (IMGT)	QSISSY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 117	LCDR3 (IMGT)	QQVYSAPVT
SEQ ID NO: 119	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQVYSAPVTF GQGTKVEIK
SEQ ID NO: 120	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGGTCTA CAGCGCCCCTGTGACATTTGGCCAGGGCAC CAAGGTGGAAATCAAG
SEQ ID NO: 121	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQVYSAPVTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 122	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG

		GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGGTCTA CAGCGCCCCTGTGACATTTGGCCAGGGCAC CAAGGTGGAAATCAAGCGTACGGTGGCCGC TCCCAGCGTGTTCATCTTCCCCCCCAGCGAC GAGCAGCTGAAGAGTGGCACCGCCAGCGTG GTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGAGCGGCAACAGCCAGGAGAGCG TCACCGAGCAGGACAGCAAGGACTCCACCT ACAGCCTGAGCAGCACCCTGACCCTGAGCA AGGCCGACTACGAGAAGCATAAGGTGTACG CCTGCGAGGTGACCCACCAGGGCCTGTCCA GCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC
Y010355 E152C_S375C		
SEQ ID NO: 123	HCDR1 (Combined)	GFTFSNYWIS
SEQ ID NO: 124	HCDR2 (Combined)	RIKSKTYGGTTDYAEPVKG
SEQ ID NO: 125	HCDR3 (Combined)	TSRRSYAFDY
SEQ ID NO: 126	HCDR1 (Kabat)	NYWIS
SEQ ID NO: 124	HCDR2 (Kabat)	RIKSKTYGGTTDYAEPVKG
SEQ ID NO: 125	HCDR3 (Kabat)	TSRRSYAFDY
SEQ ID NO: 127	HCDR1 (Chothia)	GFTFSNY
SEQ ID NO: 128	HCDR2 (Chothia)	KSKTYGGT
SEQ ID NO: 125	HCDR3(Chothia)	TSRRSYAFDY
SEQ ID NO: 129	HCDR1 (IMGT)	GFTFSNYW
SEQ ID NO: 130	HCDR2 (IMGT)	IKSKTYGGTT
SEQ ID NO: 131	HCDR3 (IMGT)	ARTSRRSYAFDY
SEQ ID NO: 132	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNY WISWVRQAPGKGLEWVGRIKSKTYGGTTDYA EPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARTSRRSYAFDYWGQGTLVTVSS
SEQ ID NO: 133	DNA VH	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA

		CTACTGGATCAGCTGGGTCCGACAGGCCCC TGGCAAAGGACTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCTACGGCGGCACCACCGA TTATGCCGAGCCTGTGAAGGGCAGATTCACC ATCAGCCGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAACCA GCAGAAGAAGCTACGCCTTCGACTACTGGG GCCAGGGCACACTGGTTACCGTTAGCTCT
SEQ ID NO: 134	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNY WISWVRQAPGKGLEWVGRIKSKTYGGTTDYA EPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARTSRRSYAFDYWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPCPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPCDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
SEQ ID NO: 135	DNA Heavy Chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA CTACTGGATCAGCTGGGTCCGACAGGCCCC TGGCAAAGGACTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCTACGGCGGCACCACCGA TTATGCCGAGCCTGTGAAGGGCAGATTCACC ATCAGCCGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAACCA GCAGAAGAAGCTACGCCTTCGACTACTGGG GCCAGGGCACACTGGTTACCGTTAGCTCTGC TAGCACCAAGGGCCCAAGTGTGTTTCCCCTG GCCCCCAGCAGCAAGTCTACTTCCGGCGGA ACTGCTGCCCTGGGTTGCCTGGTGAAGGAC TACTTCCCCTGTCCCGTGACAGTGTCCTGGA ACTCTGGGGCTCTGACTTCCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCC TGTACAGCCTGAGCAGCGTGGTGACAGTGC CCTCCAGCTCTCTGGGAACCCAGACCTATAT CTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGC TGCGACAAGACCCACACCTGCCCCCCCTGC CCAGCTCCAGAACTGCTGGGAGGGCCTTCC GTGTTCCTGTTCCCCCCCAAGCCCAAGGACA CCCTGATGATCAGCAGGACCCCCGAGGTGA CCTGCGTGGTGGTGGACGTGTCCCACGAGG

		ACCCAGAGGTGAAGTTCAACTGGTACGTGGA CGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTA CAGGGTGGTGTCCGTGCTGACCGTGCTGCA CCAGGACTGGCTGAACGGCAAAGAATACAA GTGCAAAGTCTCCAACAAGGCCCTGCCAGC CCCAATCGAAAAGACAATCAGCAAGGCCAAG GGCCAGCCACGGGAGCCCCAGGTGTACACC CTGCCCCCCAGCCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGG GCTTCTACCCCTGTGATATCGCCGTGGAGTG GGAGAGCAACGGCCAGCCCGAGAACAACTA CAAGACCACCCCCCCAGTGCTGGACAGCGA CGGCAGCTTCTTCCTGTACAGCAAGCTGACC GTGGACAAGTCCAGGTGGCAGCAGGGCAAC GTGTTCAGCTGCAGCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGTCCCTGA GCCTGAGCCCCGGCAAG
SEQ ID NO: 136	LCDR1 (Combined)	RASQSISSWLA
SEQ ID NO: 137	LCDR2 (Combined)	DASSLES
SEQ ID NO: 138	LCDR3 (Combined)	QQITRYPVT
SEQ ID NO: 136	LCDR1 (Kabat)	RASQSISSWLA
SEQ ID NO: 137	LCDR2 (Kabat)	DASSLES
SEQ ID NO: 138	LCDR3 (Kabat)	QQITRYPVT
SEQ ID NO: 139	LCDR1 (Chothia)	SQSISSW
SEQ ID NO: 140	LCDR2 (Chothia)	DAS
SEQ ID NO: 141	LCDR3 (Chothia)	ITRYPV
SEQ ID NO: 142	LCDR1 (IMGT)	QSISSW
SEQ ID NO: 140	LCDR2 (IMGT)	DAS
SEQ ID NO: 138	LCDR3 (IMGT)	QQITRYPVT
SEQ ID NO: 143	VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQITRYPVTF GQGTKVEIK
SEQ ID NO: 144	DNA VL	GACATCCAGATGACACAGAGCCCCAGCACA CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCTCCT CTTGGCTGGCCTGGTATCAGCAGAAGCCTG

		GCAAGGCCCCTAAGCTGCTGATCTACGATGC CAGCAGCCTGGAAAGCGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGAGTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGATCAC AAGATACCCCGTGACCTTTGGCCAGGGCAC CAAGGTGGAAATCAAG
SEQ ID NO: 145	Light Chain	DIQMTQSPSTLSASVGDRVTITCRASQSISSWL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQITRYPVTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 146	DNA Light Chain	GACATCCAGATGACACAGAGCCCCAGCACA CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCTCCT CTTGGCTGGCCTGGTATCAGCAGAAGCCTG GCAAGGCCCCTAAGCTGCTGATCTACGATGC CAGCAGCCTGGAAAGCGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGAGTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGATCAC AAGATACCCCGTGACCTTTGGCCAGGGCAC CAAGGTGGAAATCAAGCGTACGGTGGCCGC TCCCAGCGTGTTCATCTTCCCCCCCAGCGAC GAGCAGCTGAAGAGTGGCACCGCCAGCGTG GTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGAGCGGCAACAGCCAGGAGAGCG TCACCGAGCAGGACAGCAAGGACTCCACCT ACAGCCTGAGCAGCACCCTGACCCTGAGCA AGGCCGACTACGAGAAGCATAAGGTGTACG CCTGCGAGGTGACCCACCAGGGCCTGTCCA GCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC
Y010356 E152C_S375C		
SEQ ID NO: 123	HCDR1 (Combined)	GFTFSNYWIS
SEQ ID NO: 124	HCDR2 (Combined)	RIKSKTYGGTTDYAEPVKG
SEQ ID NO: 147	HCDR3 (Combined)	VSGYYSHSGGFDV
SEQ ID NO: 126	HCDR1 (Kabat)	NYWIS
SEQ ID NO: 124	HCDR2 (Kabat)	RIKSKTYGGTTDYAEPVKG
SEQ ID NO: 147	HCDR3 (Kabat)	VSGYYSHSGGFDV

SEQ ID NO: 127	HCDR1 (Chothia)	GFTFSNY
SEQ ID NO: 128	HCDR2 (Chothia)	KSKTYGGT
SEQ ID NO: 147	HCDR3(Chothia)	VSGYYSHSGGFDV
SEQ ID NO: 129	HCDR1 (IMGT)	GFTFSNYW
SEQ ID NO: 130	HCDR2 (IMGT)	IKSKTYGGTT
SEQ ID NO: 148	HCDR3 (IMGT)	ARVSGYYSHSGGFDV
SEQ ID NO: 149	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNY WISWVRQAPGKGLEWVGRIKSKTYGGTTDYA EPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARVSGYYSHSGGFDVWGQGTLVTVSS
SEQ ID NO: 150	DNA VH	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA CTACTGGATCAGCTGGGTCCGACAGGCCCC TGGCAAAGGACTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCTACGGCGGCACCACCGA TTATGCCGAGCCTGTGAAGGGCAGATTCACC ATCAGCCGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAGTGTC TGGCTACTACTCTCACAGCGGCGGCTTTGAT GTGTGGGGCCAGGGAACACTGGTCACCGTT AGTTCT
SEQ ID NO: 151	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNY WISWVRQAPGKGLEWVGRIKSKTYGGTTDYA EPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARVSGYYSHSGGFDVWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPC PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPCDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
SEQ ID NO: 152	DNA Heavy Chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA CTACTGGATCAGCTGGGTCCGACAGGCCCC TGGCAAAGGACTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCTACGGCGGCACCACCGA

		TTATGCCGAGCCTGTGAAGGGCAGATTCACC ATCAGCCGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAGTGTC TGGCTACTACTCTCACAGCGGCGGCTTTGAT GTGTGGGGCCAGGGAACACTGGTCACCGTT AGTTCTGCTAGCACCAAGGGCCCAAGTGTGT TTCCCCTGGCCCCCAGCAGCAAGTCTACTTC CGGCGGAACTGCTGCCCTGGGTTGCCTGGT GAAGGACTACTTCCCCTGTCCCGTGACAGTG TCCTGGAACTCTGGGGCTCTGACTTCCGGC GTGCACACCTTCCCCGCCGTGCTGCAGAGC AGCGGCCTGTACAGCCTGAGCAGCGTGGTG ACAGTGCCCTCCAGCTCTCTGGGAACCCAGA CCTATATCTGCAACGTGAACCACAAGCCCAG CAACACCAAGGTGGACAAGAGAGTGGAGCC CAAGAGCTGCGACAAGACCCACACCTGCCC CCCCTGCCCAGCTCCAGAACTGCTGGGAGG GCCTTCCGTGTTCCTGTTCCCCCCCAAGCCC AAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGTCC CACGAGGACCCAGAGGTGAAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCACAACGCC AAGACCAAGCCCAGAGAGGAGCAGTACAAC AGCACCTACAGGGTGGTGTCCGTGCTGACC GTGCTGCACCAGGACTGGCTGAACGGCAAA GAATACAAGTGCAAAGTCTCCAACAAGGCCC TGCCAGCCCCAATCGAAAAGACAATCAGCAA GGCCAAGGGCCAGCCACGGGAGCCCCAGG TGTACACCCTGCCCCCCAGCCGGGAGGAGA TGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCCTGTGATATCGCC GTGGAGTGGGAGAGCAACGGCCAGCCCGAG AACAACTACAAGACCACCCCCCCAGTGCTGG ACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGTCCAGGTGGCAGCA GGGCAACGTGTTCAGCTGCAGCGTGATGCA CGAGGCCCTGCACAACCACTACACCCAGAA GTCCCTGAGCCTGAGCCCCGGCAAG
SEQ ID NO: 153	LCDR1 (Combined)	RASQGISNYLA
SEQ ID NO: 154	LCDR2 (Combined)	AASTLQS
SEQ ID NO: 155	LCDR3 (Combined)	QKTWRTPGT
SEQ ID NO: 153	LCDR1 (Kabat)	RASQGISNYLA
SEQ ID NO: 154	LCDR2 (Kabat)	AASTLQS

SEQ ID NO: 155	LCDR3 (Kabat)	QKTWRTPGT
SEQ ID NO: 156	LCDR1 (Chothia)	SQGISNY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 157	LCDR3 (Chothia)	TWRTPG
SEQ ID NO: 158	LCDR1 (IMGT)	QGISNY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 155	LCDR3 (IMGT)	QKTWRTPGT
SEQ ID NO: 159	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISNYL AWYQQKPGKVPKLLIYAASTLQSGVPSRFSGS GSGTDFTLTISSLQPEDVATYYCQKTWRTPGT FGQGTKVEIK
SEQ ID NO: 160	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGGGCATCAGC AACTACCTGGCCTGGTATCAGCAGAAACCCG GCAAGGTGCCCAAGCTGCTGATCTACGCTG CCAGCACACTGCAGAGCGGAGTGCCTAGCA GATTTTCTGGCAGCGGCTCCGGCACCGATTT CACCCTGACCATATCTAGCCTGCAGCCAGAG GACGTGGCCACCTACTACTGTCAGAAAACCT GGCGGACCCCTGGCACATTTGGCCAGGGAA CAAAGGTGGAAATCAAG
SEQ ID NO: 161	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQGISNYL AWYQQKPGKVPKLLIYAASTLQSGVPSRFSGS GSGTDFTLTISSLQPEDVATYYCQKTWRTPGT FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 162	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGGGCATCAGC AACTACCTGGCCTGGTATCAGCAGAAACCCG GCAAGGTGCCCAAGCTGCTGATCTACGCTG CCAGCACACTGCAGAGCGGAGTGCCTAGCA GATTTTCTGGCAGCGGCTCCGGCACCGATTT CACCCTGACCATATCTAGCCTGCAGCCAGAG GACGTGGCCACCTACTACTGTCAGAAAACCT GGCGGACCCCTGGCACATTTGGCCAGGGAA CAAAGGTGGAAATCAAGCGTACGGTGGCCG CTCCCAGCGTGTTCATCTTCCCCCCCAGCGA CGAGCAGCTGAAGAGTGGCACCGCCAGCGT GGTGTGCCTGCTGAACAACTTCTACCCCCGG

		GAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGC GTCACCGAGCAGGACAGCAAGGACTCCACC TACAGCCTGAGCAGCACCCTGACCCTGAGC AAGGCCGACTACGAGAAGCATAAGGTGTAC GCCTGCGAGGTGACCCACCAGGGCCTGTCC AGCCCCGTGACCAAGAGCTTCAACAGGGGC GAGTGC
Y010415 E152C_S375C		
SEQ ID NO: 103	HCDR1 (Combined)	GFTFSSYAMS
SEQ ID NO: 104	HCDR2 (Combined)	AISGSGGSTYYADSVKG
SEQ ID NO: 163	HCDR3 (Combined)	SRLIAPWLDY
SEQ ID NO: 106	HCDR1 (Kabat)	SYAMS
SEQ ID NO: 104	HCDR2 (Kabat)	AISGSGGSTYYADSVKG
SEQ ID NO: 163	HCDR3 (Kabat)	SRLIAPWLDY
SEQ ID NO: 107	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 108	HCDR2 (Chothia)	SGSGGS
SEQ ID NO: 163	HCDR3(Chothia)	SRLIAPWLDY
SEQ ID NO: 109	HCDR1 (IMGT)	GFTFSSYA
SEQ ID NO: 110	HCDR2 (IMGT)	ISGSGGST
SEQ ID NO: 164	HCDR3 (IMGT)	ARSRLIAPWLDY
SEQ ID NO: 165	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARSRLIAPWLDYWGQGTLVTVSS
SEQ ID NO: 166	DNA VH	GAAGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTTAGCAG CTACGCCATGAGCTGGGTCCGACAGGCTCC TGGCAAAGGCCTTGAATGGGTGTCCGCCATC TCTGGCTCTGGCGGCAGCACATATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAG ATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTACTGTGCCAGAAGCAGACTGATCG CCCCTTGGCTGGATTATTGGGGCCAGGGCA CACTGGTCACCGTGTCATCT

SEQ ID NO: 167	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARSRLIAPWLDYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPCPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPCDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO: 168	DNA Heavy Chain	GAAGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTTAGCAG CTACGCCATGAGCTGGGTCCGACAGGCTCC TGGCAAAGGCCTTGAATGGGTGTCCGCCATC TCTGGCTCTGGCGGCAGCACATATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAG ATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTACTGTGCCAGAAGCAGACTGATCG CCCCTTGGCTGGATTATTGGGGCCAGGGCA CACTGGTCACCGTGTCATCTGCTAGCACCAA GGGCCCAAGTGTGTTTCCCCTGGCCCCCAG CAGCAAGTCTACTTCCGGCGGAACTGCTGCC CTGGGTTGCCTGGTGAAGGACTACTTCCCCT GTCCCGTGACAGTGTCCTGGAACTCTGGGG CTCTGACTTCCGGCGTGCACACCTTCCCCGC CGTGCTGCAGAGCAGCGGCCTGTACAGCCT GAGCAGCGTGGTGACAGTGCCCTCCAGCTC TCTGGGAACCCAGACCTATATCTGCAACGTG AACCACAAGCCCAGCAACACCAAGGTGGAC AAGAGAGTGGAGCCCAAGAGCTGCGACAAG ACCCACACCTGCCCCCCCTGCCCAGCTCCA GAACTGCTGGGAGGGCCTTCCGTGTTCCTGT TCCCCCCCAAGCCCAAGGACACCCTGATGAT CAGCAGGACCCCCGAGGTGACCTGCGTGGT GGTGGACGTGTCCCACGAGGACCCAGAGGT GAAGTTCAACTGGTACGTGGACGGCGTGGA GGTGCACAACGCCAAGACCAAGCCCAGAGA GGAGCAGTACAACAGCACCTACAGGGTGGT GTCCGTGCTGACCGTGCTGCACCAGGACTG GCTGAACGGCAAAGAATACAAGTGCAAAGTC TCCAACAAGGCCCTGCCAGCCCCAATCGAAA AGACAATCAGCAAGGCCAAGGGCCAGCCAC GGGAGCCCCAGGTGTACACCCTGCCCCCCA GCCGGGAGGAGATGACCAAGAACCAGGTGT

		CCCTGACCTGTCTGGTGAAGGGCTTCTACCC CTGTGATATCGCCGTGGAGTGGGAGAGCAA CGGCCAGCCCGAGAACAACTACAAGACCAC CCCCCCAGTGCTGGACAGCGACGGCAGCTT CTTCCTGTACAGCAAGCTGACCGTGGACAAG TCCAGGTGGCAGCAGGGCAACGTGTTCAGC TGCAGCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGAGCCTGAGCC CCGGCAAG
SEQ ID NO: 116	LCDR1 (Combined)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Combined)	AASSLQS
SEQ ID NO: 169	LCDR3 (Combined)	QQVYGSPPT
SEQ ID NO: 116	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 169	LCDR3 (Kabat)	QQVYGSPPT
SEQ ID NO: 49	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 170	LCDR3 (Chothia)	VYGSPP
SEQ ID NO: 52	LCDR1 (IMGT)	QSISSY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 169	LCDR3 (IMGT)	QQVYGSPPT
SEQ ID NO: 171	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQVYGSPPTF GQGTKVEIK
SEQ ID NO: 172	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGGTCTA CGGCAGCCCTCCTACATTTGGCCAGGGCAC CAAGGTGGAAATCAAG
SEQ ID NO: 173	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS

		GSGTDFTLTISSLQPEDFATYYCQQVYGSPPTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 174	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGGTCTA CGGCAGCCCTCCTACATTTGGCCAGGGCAC CAAGGTGGAAATCAAGCGTACGGTGGCCGC TCCCAGCGTGTTCATCTTCCCCCCCAGCGAC GAGCAGCTGAAGAGTGGCACCGCCAGCGTG GTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGAGCGGCAACAGCCAGGAGAGCG TCACCGAGCAGGACAGCAAGGACTCCACCT ACAGCCTGAGCAGCACCCTGACCCTGAGCA AGGCCGACTACGAGAAGCATAAGGTGTACG CCTGCGAGGTGACCCACCAGGGCCTGTCCA GCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC
Y010417 E152C_S375C		
SEQ ID NO: 175	HCDR1 (Combined)	GYSFTSYWIG
SEQ ID NO: 176	HCDR2 (Combined)	IIYPGDSDTRYSPSFQG
SEQ ID NO: 177	HCDR3 (Combined)	GSSAASGLSGDL
SEQ ID NO: 178	HCDR1 (Kabat)	SYWIG
SEQ ID NO: 176	HCDR2 (Kabat)	IIYPGDSDTRYSPSFQG
SEQ ID NO: 177	HCDR3 (Kabat)	GSSAASGLSGDL
SEQ ID NO: 179	HCDR1 (Chothia)	GYSFTSY
SEQ ID NO: 180	HCDR2 (Chothia)	YPGDSD
SEQ ID NO: 177	HCDR3(Chothia)	GSSAASGLSGDL
SEQ ID NO: 181	HCDR1 (IMGT)	GYSFTSYW
SEQ ID NO: 182	HCDR2 (IMGT)	IYPGDSDT

SEQ ID NO: 183	HCDR3 (IMGT)	ARGSSAASGLSGDL
SEQ ID NO: 184	VH	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIYPGDSDTRYSPS FQGQVTISADKSISTAYLQWSSLKASDTAMYYC ARGSSAASGLSGDLWGQGTLVTVSS
SEQ ID NO: 185	DNA VH	GAAGTTCAGCTGGTGCAGTCTGGCGCCGAA GTGAAGAAGCCTGGCGAGAGCCTGAAGATC TCCTGCAAAGGCAGCGGCTACAGCTTCACCA GCTACTGGATCGGCTGGGTCCGACAGATGC CTGGCAAAGGCCTTGAGTGGATGGGCATCAT CTACCCCGGCGACAGCGACACCAGATACAG CCCTAGCTTTCAGGGCCAAGTGACCATCAGC GCCGACAAGAGCATCAGCACAGCCTACCTG CAGTGGTCCAGCCTGAAGGCCTCTGACACC GCCATGTACTACTGTGCCAGAGGAAGCTCTG CCGCCTCTGGACTGTCTGGCGATCTTTGGG GACAGGGCACACTGGTCACAGTGTCTAGT
SEQ ID NO: 186	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIYPGDSDTRYSPS FQGQVTISADKSISTAYLQWSSLKASDTAMYYC ARGSSAASGLSGDLWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPCPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPCDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
SEQ ID NO: 187	DNA Heavy Chain	GAAGTTCAGCTGGTGCAGTCTGGCGCCGAA GTGAAGAAGCCTGGCGAGAGCCTGAAGATC TCCTGCAAAGGCAGCGGCTACAGCTTCACCA GCTACTGGATCGGCTGGGTCCGACAGATGC CTGGCAAAGGCCTTGAGTGGATGGGCATCAT CTACCCCGGCGACAGCGACACCAGATACAG CCCTAGCTTTCAGGGCCAAGTGACCATCAGC GCCGACAAGAGCATCAGCACAGCCTACCTG CAGTGGTCCAGCCTGAAGGCCTCTGACACC GCCATGTACTACTGTGCCAGAGGAAGCTCTG CCGCCTCTGGACTGTCTGGCGATCTTTGGG GACAGGGCACACTGGTCACAGTGTCTAGTG CTAGCACCAAGGGCCCAAGTGTGTTTCCCCT GGCCCCCAGCAGCAAGTCTACTTCCGGCGG AACTGCTGCCCTGGGTTGCCTGGTGAAGGA CTACTTCCCCTGTCCCGTGACAGTGTCCTGG AACTCTGGGGCTCTGACTTCCGGCGTGCACA

		CCTTCCCCGCCGTGCTGCAGAGCAGCGGCC TGTACAGCCTGAGCAGCGTGGTGACAGTGC CCTCCAGCTCTCTGGGAACCCAGACCTATAT CTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGC TGCGACAAGACCCACACCTGCCCCCCCTGC CCAGCTCCAGAACTGCTGGGAGGGCCTTCC GTGTTCCTGTTCCCCCCCAAGCCCAAGGACA CCCTGATGATCAGCAGGACCCCCGAGGTGA CCTGCGTGGTGGTGGACGTGTCCCACGAGG ACCCAGAGGTGAAGTTCAACTGGTACGTGGA CGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTA CAGGGTGGTGTCCGTGCTGACCGTGCTGCA CCAGGACTGGCTGAACGGCAAAGAATACAA GTGCAAAGTCTCCAACAAGGCCCTGCCAGC CCCAATCGAAAAGACAATCAGCAAGGCCAAG GGCCAGCCACGGGAGCCCCAGGTGTACACC CTGCCCCCCAGCCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGG GCTTCTACCCCTGTGATATCGCCGTGGAGTG GGAGAGCAACGGCCAGCCCGAGAACAACTA CAAGACCACCCCCCCAGTGCTGGACAGCGA CGGCAGCTTCTTCCTGTACAGCAAGCTGACC GTGGACAAGTCCAGGTGGCAGCAGGGCAAC GTGTTCAGCTGCAGCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGTCCCTGA GCCTGAGCCCCGGCAAG
SEQ ID NO: 116	LCDR1 (Combined)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Combined)	AASSLQS
SEQ ID NO: 188	LCDR3 (Combined)	QQDYYSPFT
SEQ ID NO: 116	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 188	LCDR3 (Kabat)	QQDYYSPFT
SEQ ID NO: 49	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 189	LCDR3 (Chothia)	DYYSPF
SEQ ID NO: 52	LCDR1 (IMGT)	QSISSY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS

SEQ ID NO: 188	LCDR3 (IMGT)	QQDYYSPFT
SEQ ID NO: 190	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQDYYSPFTF GQGTKVEIK
SEQ ID NO: 191	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGGACTA CTACAGCCCCTTCACCTTTGGCCAGGGCACC AAGGTGGAAATCAAG
SEQ ID NO: 192	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQDYYSPFTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 193	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAGGACTA CTACAGCCCCTTCACCTTTGGCCAGGGCACC AAGGTGGAAATCAAGCGTACGGTGGCCGCT CCCAGCGTGTTCATCTTCCCCCCCAGCGACG AGCAGCTGAAGAGTGGCACCGCCAGCGTGG TGTGCCTGCTGAACAACTTCTACCCCCGGGA GGCCAAGGTGCAGTGGAAGGTGGACAACGC CCTGCAGAGCGGCAACAGCCAGGAGAGCGT CACCGAGCAGGACAGCAAGGACTCCACCTA CAGCCTGAGCAGCACCCTGACCCTGAGCAA GGCCGACTACGAGAAGCATAAGGTGTACGC CTGCGAGGTGACCCACCAGGGCCTGTCCAG CCCCGTGACCAAGAGCTTCAACAGGGGCGA GTGC
Y010429 E152C_S375C		
SEQ ID NO: 103	HCDR1 (Combined)	GFTFSSYAMS

SEQ ID NO: 104	HCDR2 (Combined)	AISGSGGSTYYADSVKG
SEQ ID NO: 194	HCDR3 (Combined)	AYKLSWLDL
SEQ ID NO: 106	HCDR1 (Kabat)	SYAMS
SEQ ID NO: 104	HCDR2 (Kabat)	AISGSGGSTYYADSVKG
SEQ ID NO: 194	HCDR3 (Kabat)	AYKLSWLDL
SEQ ID NO: 107	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 108	HCDR2 (Chothia)	SGSGGS
SEQ ID NO: 194	HCDR3(Chothia)	AYKLSWLDL
SEQ ID NO: 109	HCDR1 (IMGT)	GFTFSSYA
SEQ ID NO: 110	HCDR2 (IMGT)	ISGSGGST
SEQ ID NO: 195	HCDR3 (IMGT)	ARAYKLSWLDL
SEQ ID NO: 196	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARAYKLSWLDLWGQGTLVTVSS
SEQ ID NO: 197	DNA VH	GAAGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTTAGCAG CTACGCCATGAGCTGGGTCCGACAGGCTCC TGGCAAAGGCCTTGAATGGGTGTCCGCCATC TCTGGCTCTGGCGGCAGCACATATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAG ATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTATTGTGCCAGAGCCTACAAGCTGA GCTGGCTGGATCTTTGGGGCCAGGGCACAC TGGTCACAGTGTCATCT
SEQ ID NO: 198	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CARAYKLSWLDLWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPCPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPCDIAVEWES

		NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K
SEQ ID NO: 199	DNA Heavy Chain	GAAGTTCAGCTGCTGGAATCTGGCGGAGGA CTGGTTCAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCCAGCGGCTTCACCTTTAGCAG CTACGCCATGAGCTGGGTCCGACAGGCTCC TGGCAAAGGCCTTGAATGGGTGTCCGCCATC TCTGGCTCTGGCGGCAGCACATATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCAGCCG GGACAACAGCAAGAACACCCTGTACCTGCAG ATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTATTGTGCCAGAGCCTACAAGCTGA GCTGGCTGGATCTTTGGGGCCAGGGCACAC TGGTCACAGTGTCATCTGCTAGCACCAAGGG CCCAAGTGTGTTTCCCCTGGCCCCCAGCAG CAAGTCTACTTCCGGCGGAACTGCTGCCCTG GGTTGCCTGGTGAAGGACTACTTCCCCTGTC CCGTGACAGTGTCCTGGAACTCTGGGGCTCT GACTTCCGGCGTGCACACCTTCCCCGCCGT GCTGCAGAGCAGCGGCCTGTACAGCCTGAG CAGCGTGGTGACAGTGCCCTCCAGCTCTCT GGGAACCCAGACCTATATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAG AGAGTGGAGCCCAAGAGCTGCGACAAGACC CACACCTGCCCCCCCTGCCCAGCTCCAGAA CTGCTGGGAGGGCCTTCCGTGTTCCTGTTCC CCCCCAAGCCCAAGGACACCCTGATGATCA GCAGGACCCCCGAGGTGACCTGCGTGGTGG TGGACGTGTCCCACGAGGACCCAGAGGTGA AGTTCAACTGGTACGTGGACGGCGTGGAGG TGCACAACGCCAAGACCAAGCCCAGAGAGG AGCAGTACAACAGCACCTACAGGGTGGTGTC CGTGCTGACCGTGCTGCACCAGGACTGGCT GAACGGCAAAGAATACAAGTGCAAAGTCTCC AACAAGGCCCTGCCAGCCCCAATCGAAAAGA CAATCAGCAAGGCCAAGGGCCAGCCACGGG AGCCCCAGGTGTACACCCTGCCCCCCAGCC GGGAGGAGATGACCAAGAACCAGGTGTCCC TGACCTGTCTGGTGAAGGGCTTCTACCCCTG TGATATCGCCGTGGAGTGGGAGAGCAACGG CCAGCCCGAGAACAACTACAAGACCACCCC CCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGTCC AGGTGGCAGCAGGGCAACGTGTTCAGCTGC AGCGTGATGCACGAGGCCCTGCACAACCAC TACACCCAGAAGTCCCTGAGCCTGAGCCCC GGCAAG
SEQ ID NO: 116	LCDR1 (Combined)	RASQSISSYLN

SEQ ID NO: 47	LCDR2 (Combined)	AASSLQS
SEQ ID NO: 200	LCDR3 (Combined)	QQVWYAPVT
SEQ ID NO: 116	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 47	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 200	LCDR3 (Kabat)	QQVWYAPVT
SEQ ID NO: 49	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 201	LCDR3 (Chothia)	VWYAPV
SEQ ID NO: 52	LCDR1 (IMGT)	QSISSY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 200	LCDR3 (IMGT)	QQVWYAPVT
SEQ ID NO: 202	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQVWYAPVT FGQGTKVEIK
SEQ ID NO: 203	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAAGTTTG GTACGCCCCTGTGACCTTTGGCCAGGGCAC CAAGGTGGAAATCAAG
SEQ ID NO: 204	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQVWYAPVT FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 205	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCAGCA GCTACCTGAACTGGTATCAGCAGAAGCCCG GCAAGGCCCCTAAACTGCTGATCTATGCCGC CAGCTCTCTGCAGTCTGGCGTGCCAAGCAG

		ATTTTCTGGCAGCGGCTCTGGCACCGACTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTACTGCCAGCAAGTTTG GTACGCCCCTGTGACCTTTGGCCAGGGCAC CAAGGTGGAAATCAAGCGTACGGTGGCCGC TCCCAGCGTGTTCATCTTCCCCCCCAGCGAC GAGCAGCTGAAGAGTGGCACCGCCAGCGTG GTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGAGCGGCAACAGCCAGGAGAGCG TCACCGAGCAGGACAGCAAGGACTCCACCT ACAGCCTGAGCAGCACCCTGACCCTGAGCA AGGCCGACTACGAGAAGCATAAGGTGTACG CCTGCGAGGTGACCCACCAGGGCCTGTCCA GCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC
Y010900 E152C_S375C		
SEQ ID NO: 206	HCDR1 (Combined)	GFTFSNAWMS
SEQ ID NO: 207	HCDR2 (Combined)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 208	HCDR3 (Combined)	TIYPSAPSSSLDY
SEQ ID NO: 209	HCDR1 (Kabat)	NAWMS
SEQ ID NO: 207	HCDR2 (Kabat)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 208	HCDR3 (Kabat)	TIYPSAPSSSLDY
SEQ ID NO: 210	HCDR1 (Chothia)	GFTFSNA
SEQ ID NO: 211	HCDR2 (Chothia)	KSKTDAGT
SEQ ID NO: 208	HCDR3(Chothia)	TIYPSAPSSSLDY
SEQ ID NO: 212	HCDR1 (IMGT)	GFTFSNAW
SEQ ID NO: 213	HCDR2 (IMGT)	IKSKTDAGTT
SEQ ID NO: 214	HCDR3 (IMGT)	ARTIYPSAPSSSLDY
SEQ ID NO: 215	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDAGTTDYA APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARTIYPSAPSSSLDYWGQGTLVTVSS
SEQ ID NO: 216	DNA VH	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA TGCCTGGATGAGCTGGGTCCGACAGGCCCC TGGAAAAGGCCTTGAGTGGGTCGGACGGAT

		CAAGAGCAAGACCGATGCCGGCACCACCGA TTATGCTGCCCCTGTGAAGGGCAGATTCACC ATCAGCAGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAACAAT CTACCCCAGCGCTCCTAGCAGCAGCCTGGA TTATTGGGGCCAGGGCACACTGGTCACCGT GTCATCT
SEQ ID NO: 217	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDAGTTDYA APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARTIYPSAPSSSLDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPCP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPCDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
SEQ ID NO: 218	DNA Heavy Chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA TGCCTGGATGAGCTGGGTCCGACAGGCCCC TGGAAAAGGCCTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCGATGCCGGCACCACCGA TTATGCTGCCCCTGTGAAGGGCAGATTCACC ATCAGCAGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAACAAT CTACCCCAGCGCTCCTAGCAGCAGCCTGGA TTATTGGGGCCAGGGCACACTGGTCACCGT GTCATCTGCTAGCACCAAGGGCCCAAGTGTG TTTCCCCTGGCCCCCAGCAGCAAGTCTACTT CCGGCGGAACTGCTGCCCTGGGTTGCCTGG TGAAGGACTACTTCCCCTGTCCCGTGACAGT GTCCTGGAACTCTGGGGCTCTGACTTCCGG CGTGCACACCTTCCCCGCCGTGCTGCAGAG CAGCGGCCTGTACAGCCTGAGCAGCGTGGT GACAGTGCCCTCCAGCTCTCTGGGAACCCA GACCTATATCTGCAACGTGAACCACAAGCCC AGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGC CCCCCCTGCCCAGCTCCAGAACTGCTGGGA GGGCCTTCCGTGTTCCTGTTCCCCCCCAAGC CCAAGGACACCCTGATGATCAGCAGGACCC CCGAGGTGACCTGCGTGGTGGTGGACGTGT CCCACGAGGACCCAGAGGTGAAGTTCAACT

		GGTACGTGGACGGCGTGGAGGTGCACAACG CCAAGACCAAGCCCAGAGAGGAGCAGTACA ACAGCACCTACAGGGTGGTGTCCGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCA AAGAATACAAGTGCAAAGTCTCCAACAAGGC CCTGCCAGCCCCAATCGAAAAGACAATCAGC AAGGCCAAGGGCCAGCCACGGGAGCCCCAG GTGTACACCCTGCCCCCCAGCCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTC TGGTGAAGGGCTTCTACCCCTGTGATATCGC CGTGGAGTGGGAGAGCAACGGCCAGCCCGA GAACAACTACAAGACCACCCCCCCAGTGCTG GACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGTCCAGGTGGCAGC AGGGCAACGTGTTCAGCTGCAGCGTGATGC ACGAGGCCCTGCACAACCACTACACCCAGAA GTCCCTGAGCCTGAGCCCCGGCAAG
SEQ ID NO: 153	LCDR1 (Combined)	RASQGISNYLA
SEQ ID NO: 154	LCDR2 (Combined)	AASTLQS
SEQ ID NO: 219	LCDR3 (Combined)	QQLIFFPLT
SEQ ID NO: 153	LCDR1 (Kabat)	RASQGISNYLA
SEQ ID NO: 154	LCDR2 (Kabat)	AASTLQS
SEQ ID NO: 219	LCDR3 (Kabat)	QQLIFFPLT
SEQ ID NO: 156	LCDR1 (Chothia)	SQGISNY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 220	LCDR3 (Chothia)	LIFFPL
SEQ ID NO: 158	LCDR1 (IMGT)	QGISNY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 219	LCDR3 (IMGT)	QQLIFFPLT
SEQ ID NO: 221	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISNYL AWYQQKPGKVPKLLIYAASTLQSGVPSRFSGS GSGTDFTLTISSLQPEDVATYYCQQLIFFPLTFG QGTKVEIK
SEQ ID NO: 222	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGGGCATCAGC AACTACCTGGCCTGGTATCAGCAGAAACCCG GCAAGGTGCCCAAGCTGCTGATCTACGCTG

		CCAGCACACTGCAGAGCGGAGTGCCTAGCA GATTTTCTGGCAGCGGCTCCGGCACCGATTT CACCCTGACCATATCTAGCCTGCAGCCAGAG GACGTGGCCACCTACTATTGCCAGCAGCTGA TCTTCTTCCCTCTGACCTTTGGCCAGGGCAC CAAGGTGGAAATCAAG
SEQ ID NO: 223	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQGISNYL AWYQQKPGKVPKLLIYAASTLQSGVPSRFSGS GSGTDFTLTISSLQPEDVATYYCQQLIFFPLTFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC
SEQ ID NO: 224	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGGGCATCAGC AACTACCTGGCCTGGTATCAGCAGAAACCCG GCAAGGTGCCCAAGCTGCTGATCTACGCTG CCAGCACACTGCAGAGCGGAGTGCCTAGCA GATTTTCTGGCAGCGGCTCCGGCACCGATTT CACCCTGACCATATCTAGCCTGCAGCCAGAG GACGTGGCCACCTACTATTGCCAGCAGCTGA TCTTCTTCCCTCTGACCTTTGGCCAGGGCAC CAAGGTGGAAATCAAGCGTACGGTGGCCGC TCCCAGCGTGTTCATCTTCCCCCCCAGCGAC GAGCAGCTGAAGAGTGGCACCGCCAGCGTG GTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACG CCCTGCAGAGCGGCAACAGCCAGGAGAGCG TCACCGAGCAGGACAGCAAGGACTCCACCT ACAGCCTGAGCAGCACCCTGACCCTGAGCA AGGCCGACTACGAGAAGCATAAGGTGTACG CCTGCGAGGTGACCCACCAGGGCCTGTCCA GCCCCGTGACCAAGAGCTTCAACAGGGGCG AGTGC
Y010903 E152C_S375C		
SEQ ID NO: 206	HCDR1 (Combined)	GFTFSNAWMS
SEQ ID NO: 207	HCDR2 (Combined)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 225	HCDR3 (Combined)	ASHRLHSLFDV
SEQ ID NO: 209	HCDR1 (Kabat)	NAWMS
SEQ ID NO: 207	HCDR2 (Kabat)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 225	HCDR3 (Kabat)	ASHRLHSLFDV
SEQ ID NO: 210	HCDR1 (Chothia)	GFTFSNA

SEQ ID NO: 211	HCDR2 (Chothia)	KSKTDAGT
SEQ ID NO: 225	HCDR3(Chothia)	ASHRLHSLFDV
SEQ ID NO: 212	HCDR1 (IMGT)	GFTFSNAW
SEQ ID NO: 213	HCDR2 (IMGT)	IKSKTDAGTT
SEQ ID NO: 226	HCDR3 (IMGT)	ARASHRLHSLFDV
SEQ ID NO: 227	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKSKTDAGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARASHRLHSLFDVWGQGTLVTVSS
SEQ ID NO: 228	DNA VH	GAAGTGCAGCTGGTGGAATCTGGCGGCGGACTTGTGAAACCTGGCGGCTCTCTGAGACTGAGCTGTGCCGCTTCCGGCTTCACCTTCAGCAATGCCTGGATGAGCTGGGTCCGACAGGCCCCTGGAAAAGGCCTTGAGTGGGTCGGACGGATCAAGAGCAAGACCGATGCCGGCACCACCGATTATGCTGCCCCTGTGAAGGGCAGATTCACCATCAGCAGGGACGACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCGCCGTGTACTACTGTGCCAGAGCCTCTCACAGACTGCACAGCCTGTTTGACGTGTGGGGCCAGGGAACACTGGTCACCGTTAGTTCT
SEQ ID NO: 229	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKSKTDAGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARASHRLHSLFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPCPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPCDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 230	DNA Heavy Chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGACTTGTGAAACCTGGCGGCTCTCTGAGACTGAGCTGTGCCGCTTCCGGCTTCACCTTCAGCAATGCCTGGATGAGCTGGGTCCGACAGGCCCCTGGAAAAGGCCTTGAGTGGGTCGGACGGATCAAGAGCAAGACCGATGCCGGCACCACCGATTATGCTGCCCCTGTGAAGGGCAGATTCACCATCAGCAGGGACGACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGG

		ACACCGCCGTGTACTACTGTGCCAGAGCCTC TCACAGACTGCACAGCCTGTTTGACGTGTGG GGCCAGGGAACACTGGTCACCGTTAGTTCTG CTAGCACCAAGGGCCCAAGTGTGTTTCCCCT GGCCCCCAGCAGCAAGTCTACTTCCGGCGG AACTGCTGCCCTGGGTTGCCTGGTGAAGGA CTACTTCCCCTGTCCCGTGACAGTGTCCTGG AACTCTGGGGCTCTGACTTCCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCC TGTACAGCCTGAGCAGCGTGGTGACAGTGC CCTCCAGCTCTCTGGGAACCCAGACCTATAT CTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGC TGCGACAAGACCCACACCTGCCCCCCCTGC CCAGCTCCAGAACTGCTGGGAGGGCCTTCC GTGTTCCTGTTCCCCCCCAAGCCCAAGGACA CCCTGATGATCAGCAGGACCCCCGAGGTGA CCTGCGTGGTGGTGGACGTGTCCCACGAGG ACCCAGAGGTGAAGTTCAACTGGTACGTGGA CGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTA CAGGGTGGTGTCCGTGCTGACCGTGCTGCA CCAGGACTGGCTGAACGGCAAAGAATACAA GTGCAAAGTCTCCAACAAGGCCCTGCCAGC CCCAATCGAAAAGACAATCAGCAAGGCCAAG GGCCAGCCACGGGAGCCCCAGGTGTACACC CTGCCCCCCAGCCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGG GCTTCTACCCCTGTGATATCGCCGTGGAGTG GGAGAGCAACGGCCAGCCCGAGAACAACTA CAAGACCACCCCCCCAGTGCTGGACAGCGA CGGCAGCTTCTTCCTGTACAGCAAGCTGACC GTGGACAAGTCCAGGTGGCAGCAGGGCAAC GTGTTCAGCTGCAGCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGTCCCTGA GCCTGAGCCCCGGCAAG
SEQ ID NO: 136	LCDR1 (Combined)	RASQSISSWLA
SEQ ID NO: 137	LCDR2 (Combined)	DASSLES
SEQ ID NO: 231	LCDR3 (Combined)	QQGLFYPHT
SEQ ID NO: 136	LCDR1 (Kabat)	RASQSISSWLA
SEQ ID NO: 137	LCDR2 (Kabat)	DASSLES
SEQ ID NO: 231	LCDR3 (Kabat)	QQGLFYPHT
SEQ ID NO: 139	LCDR1 (Chothia)	SQSISSW

SEQ ID NO: 140	LCDR2 (Chothia)	DAS
SEQ ID NO: 232	LCDR3 (Chothia)	GLFYPH
SEQ ID NO: 142	LCDR1 (IMGT)	QSISSW
SEQ ID NO: 140	LCDR2 (IMGT)	DAS
SEQ ID NO: 231	LCDR3 (IMGT)	QQGLFYPHT
SEQ ID NO: 233	VL	DIQMTQSPSTLSASVGDRVTITCRASQSISSWL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQGLFYPHTF GQGTKVEIK
SEQ ID NO: 234	DNA VL	GACATCCAGATGACACAGAGCCCCAGCACA CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCTCCT CTTGGCTGGCCTGGTATCAGCAGAAGCCTG GCAAGGCCCCTAAGCTGCTGATCTACGATGC CAGCAGCCTGGAAAGCGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGAGTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTATTGTCAGCAGGGCCT GTTCTACCCTCACACCTTTGGCCAGGGCACC AAGGTGGAAATCAAG
SEQ ID NO: 235	Light Chain	DIQMTQSPSTLSASVGDRVTITCRASQSISSWL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQGLFYPHTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 236	DNA Light Chain	GACATCCAGATGACACAGAGCCCCAGCACA CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGAGCATCTCCT CTTGGCTGGCCTGGTATCAGCAGAAGCCTG GCAAGGCCCCTAAGCTGCTGATCTACGATGC CAGCAGCCTGGAAAGCGGCGTGCCAAGCAG ATTTTCTGGCAGCGGCTCTGGCACCGAGTTC ACCCTGACCATATCTAGCCTGCAGCCAGAGG ACTTCGCCACCTACTATTGTCAGCAGGGCCT GTTCTACCCTCACACCTTTGGCCAGGGCACC AAGGTGGAAATCAAGCGTACGGTGGCCGCT CCCAGCGTGTTCATCTTCCCCCCCAGCGACG AGCAGCTGAAGAGTGGCACCGCCAGCGTGG TGTGCCTGCTGAACAACTTCTACCCCCGGGA GGCCAAGGTGCAGTGGAAGGTGGACAACGC CCTGCAGAGCGGCAACAGCCAGGAGAGCGT CACCGAGCAGGACAGCAAGGACTCCACCTA CAGCCTGAGCAGCACCCTGACCCTGAGCAA

		GGCCGACTACGAGAAGCATAAGGTGTACGC CTGCGAGGTGACCCACCAGGGCCTGTCCAG CCCCGTGACCAAGAGCTTCAACAGGGGCGA GTGC
Y010906 E152C_S375C		
SEQ ID NO: 206	HCDR1 (Combined)	GFTFSNAWMS
SEQ ID NO: 207	HCDR2 (Combined)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 237	HCDR3 (Combined)	DEYPWGWFDV
SEQ ID NO: 209	HCDR1 (Kabat)	NAWMS
SEQ ID NO: 207	HCDR2 (Kabat)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 237	HCDR3 (Kabat)	DEYPWGWFDV
SEQ ID NO: 210	HCDR1 (Chothia)	GFTFSNA
SEQ ID NO: 211	HCDR2 (Chothia)	KSKTDAGT
SEQ ID NO: 237	HCDR3(Ch othia)	DEYPWGWFDV
SEQ ID NO: 212	HCDR1 (IMGT)	GFTFSNAW
SEQ ID NO: 213	HCDR2 (IMGT)	IKSKTDAGTT
SEQ ID NO: 238	HCDR3 (IMGT)	ARDEYPWGWFDV
SEQ ID NO: 239	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDAGTTDYA APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARDEYPWGWFDVWGQGTLVTVSS
SEQ ID NO: 240	DNA VH	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA TGCCTGGATGAGCTGGGTCCGACAGGCCCC TGGAAAAGGCCTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCGATGCCGGCACCACCGA TTATGCTGCCCCTGTGAAGGGCAGATTCACC ATCAGCAGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAGATGA GTACCCCTGGGGATGGTTCGATGTGTGGGG ACAGGGAACCCTGGTCACCGTTAGTTCT
SEQ ID NO: 241	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDAGTTDYA APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARDEYPWGWFDVWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPCPV

		TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPCDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
SEQ ID NO: 242	DNA Heavy Chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA TGCCTGGATGAGCTGGGTCCGACAGGCCCC TGGAAAAGGCCTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCGATGCCGGCACCACCGA TTATGCTGCCCCTGTGAAGGGCAGATTCACC ATCAGCAGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAGATGA GTACCCCTGGGGATGGTTCGATGTGTGGGG ACAGGGAACCCTGGTCACCGTTAGTTCTGCT AGCACCAAGGGCCCAAGTGTGTTTCCCCTG GCCCCCAGCAGCAAGTCTACTTCCGGCGGA ACTGCTGCCCTGGGTTGCCTGGTGAAGGAC TACTTCCCCTGTCCCGTGACAGTGTCCTGGA ACTCTGGGGCTCTGACTTCCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCC TGTACAGCCTGAGCAGCGTGGTGACAGTGC CCTCCAGCTCTCTGGGAACCCAGACCTATAT CTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGC TGCGACAAGACCCACACCTGCCCCCCCTGC CCAGCTCCAGAACTGCTGGGAGGGCCTTCC GTGTTCCTGTTCCCCCCCAAGCCCAAGGACA CCCTGATGATCAGCAGGACCCCCGAGGTGA CCTGCGTGGTGGTGGACGTGTCCCACGAGG ACCCAGAGGTGAAGTTCAACTGGTACGTGGA CGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTA CAGGGTGGTGTCCGTGCTGACCGTGCTGCA CCAGGACTGGCTGAACGGCAAAGAATACAA GTGCAAAGTCTCCAACAAGGCCCTGCCAGC CCCAATCGAAAAGACAATCAGCAAGGCCAAG GGCCAGCCACGGGAGCCCCAGGTGTACACC CTGCCCCCCAGCCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGG GCTTCTACCCCTGTGATATCGCCGTGGAGTG GGAGAGCAACGGCCAGCCCGAGAACAACTA CAAGACCACCCCCCCAGTGCTGGACAGCGA CGGCAGCTTCTTCCTGTACAGCAAGCTGACC

		GTGGACAAGTCCAGGTGGCAGCAGGGCAAC GTGTTCAGCTGCAGCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGTCCCTGA GCCTGAGCCCCGGCAAG
SEQ ID NO: 243	LCDR1 (Combined)	RASQGISSWLA
SEQ ID NO: 47	LCDR2 (Combined)	AASSLQS
SEQ ID NO: 244	LCDR3 (Combined)	QQYIFYPLT
SEQ ID NO: 243	LCDR1 (Kabat)	RASQGISSWLA
SEQ ID NO: 47	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 244	LCDR3 (Kabat)	QQYIFYPLT
SEQ ID NO: 245	LCDR1 (Chothia)	SQGISSW
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 246	LCDR3 (Chothia)	YIFYPL
SEQ ID NO: 247	LCDR1 (IMGT)	QGISSW
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 244	LCDR3 (IMGT)	QQYIFYPLT
SEQ ID NO: 248	VL	DIQMTQSPSSVSASVGDRVTITCRASQGISSWL AWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQYIFYPLTF GQGTKVEIK
SEQ ID NO: 249	DNA VL	GACATCCAGATGACACAGAGCCCTAGCTCCG TGTCTGCCAGCGTGGGAGACAGAGTGACCA TCACCTGTAGAGCCAGCCAGGGCATCTCTTC TTGGCTGGCCTGGTATCAGCAGAAGCCTGG CAAGGCCCCTAAGCTGCTGATCTATGCCGCT TCCAGTCTGCAGAGCGGCGTGCCAAGCAGA TTTTCTGGCAGCGGCTCTGGCACCGACTTCA CCCTGACCATATCTAGCCTGCAGCCAGAGGA CTTCGCCACCTACTACTGCCAGCAGTACATC TTCTACCCTCTGACCTTCGGCCAGGGCACCA AGGTGGAAATCAAG
SEQ ID NO: 250	Light Chain	DIQMTQSPSSVSASVGDRVTITCRASQGISSWL AWYQQKPGKAPKLLIYAASSLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQYIFYPLTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC

SEQ ID NO: 251	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCTCCG TGTCTGCCAGCGTGGGAGACAGAGTGACCA TCACCTGTAGAGCCAGCCAGGGCATCTCTTC TTGGCTGGCCTGGTATCAGCAGAAGCCTGG CAAGGCCCCTAAGCTGCTGATCTATGCCGCT TCCAGTCTGCAGAGCGGCGTGCCAAGCAGA TTTTCTGGCAGCGGCTCTGGCACCGACTTCA CCCTGACCATATCTAGCCTGCAGCCAGAGGA CTTCGCCACCTACTACTGCCAGCAGTACATC TTCTACCCTCTGACCTTCGGCCAGGGCACCA AGGTGGAAATCAAGCGTACGGTGGCCGCTC CCAGCGTGTTCATCTTCCCCCCCAGCGACGA GCAGCTGAAGAGTGGCACCGCCAGCGTGGT GTGCCTGCTGAACAACTTCTACCCCCGGGAG GCCAAGGTGCAGTGGAAGGTGGACAACGCC CTGCAGAGCGGCAACAGCCAGGAGAGCGTC ACCGAGCAGGACAGCAAGGACTCCACCTAC AGCCTGAGCAGCACCCTGACCCTGAGCAAG GCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCC CCGTGACCAAGAGCTTCAACAGGGGCGAGT GC
Y010910 E152C_S375C		
SEQ ID NO: 206	HCDR1 (Combined)	GFTFSNAWMS
SEQ ID NO: 207	HCDR2 (Combined)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 252	HCDR3 (Combined)	VASPSAPGGFDY
SEQ ID NO: 209	HCDR1 (Kabat)	NAWMS
SEQ ID NO: 207	HCDR2 (Kabat)	RIKSKTDAGTTDYAAPVKG
SEQ ID NO: 252	HCDR3 (Kabat)	VASPSAPGGFDY
SEQ ID NO: 210	HCDR1 (Chothia)	GFTFSNA
SEQ ID NO: 211	HCDR2 (Chothia)	KSKTDAGT
SEQ ID NO: 252	HCDR3(Chothia)	VASPSAPGGFDY
SEQ ID NO: 212	HCDR1 (IMGT)	GFTFSNAW
SEQ ID NO: 213	HCDR2 (IMGT)	IKSKTDAGTT
SEQ ID NO: 253	HCDR3 (IMGT)	ARVASPSAPGGFDY
SEQ ID NO: 254	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDAGTTDYA

		APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARVASPSAPGGFDYWGQGTLVTVSS
SEQ ID NO: 255	DNA VH	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA TGCCTGGATGAGCTGGGTCCGACAGGCCCC TGGAAAAGGCCTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCGATGCCGGCACCACCGA TTATGCTGCCCCTGTGAAGGGCAGATTCACC ATCAGCAGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAGTGG CTTCTCCTTCTGCTCCCGGCGGATTCGATTA TTGGGGCCAGGGAACACTGGTCACCGTGTC TAGT
SEQ ID NO: 256	Heavy Chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDAGTTDYA APVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCARVASPSAPGGFDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPCP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPCDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
SEQ ID NO: 257	DNA Heavy Chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGA GCTGTGCCGCTTCCGGCTTCACCTTCAGCAA TGCCTGGATGAGCTGGGTCCGACAGGCCCC TGGAAAAGGCCTTGAGTGGGTCGGACGGAT CAAGAGCAAGACCGATGCCGGCACCACCGA TTATGCTGCCCCTGTGAAGGGCAGATTCACC ATCAGCAGGGACGACAGCAAGAACACCCTG TACCTGCAGATGAACAGCCTGAAAACCGAGG ACACCGCCGTGTACTACTGCGCCAGAGTGG CTTCTCCTTCTGCTCCCGGCGGATTCGATTA TTGGGGCCAGGGAACACTGGTCACCGTGTC TAGTGCTAGCACCAAGGGCCCAAGTGTGTTT CCCCTGGCCCCCAGCAGCAAGTCTACTTCC GGCGGAACTGCTGCCCTGGGTTGCCTGGTG AAGGACTACTTCCCCTGTCCCGTGACAGTGT CCTGGAACTCTGGGGCTCTGACTTCCGGCG TGCACACCTTCCCCGCCGTGCTGCAGAGCA GCGGCCTGTACAGCCTGAGCAGCGTGGTGA CAGTGCCCTCCAGCTCTCTGGGAACCCAGA CCTATATCTGCAACGTGAACCACAAGCCCAG

		CAACACCAAGGTGGACAAGAGAGTGGAGCC CAAGAGCTGCGACAAGACCCACACCTGCCC CCCCTGCCCAGCTCCAGAACTGCTGGGAGG GCCTTCCGTGTTCCTGTTCCCCCCCAAGCCC AAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGTCC CACGAGGACCCAGAGGTGAAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCACAACGCC AAGACCAAGCCCAGAGAGGAGCAGTACAAC AGCACCTACAGGGTGGTGTCCGTGCTGACC GTGCTGCACCAGGACTGGCTGAACGGCAAA GAATACAAGTGCAAAGTCTCCAACAAGGCCC TGCCAGCCCCAATCGAAAAGACAATCAGCAA GGCCAAGGGCCAGCCACGGGAGCCCCAGG TGTACACCCTGCCCCCCAGCCGGGAGGAGA TGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCCTGTGATATCGCC GTGGAGTGGGAGAGCAACGGCCAGCCCGAG AACAACTACAAGACCACCCCCCCAGTGCTGG ACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGTCCAGGTGGCAGCA GGGCAACGTGTTCAGCTGCAGCGTGATGCA CGAGGCCCTGCACAACCACTACACCCAGAA GTCCCTGAGCCTGAGCCCCGGCAAG
SEQ ID NO: 153	LCDR1 (Combined)	RASQGISNYLA
SEQ ID NO: 154	LCDR2 (Combined)	AASTLQS
SEQ ID NO: 258	LCDR3 (Combined)	QQSLFAPFT
SEQ ID NO: 153	LCDR1 (Kabat)	RASQGISNYLA
SEQ ID NO: 154	LCDR2 (Kabat)	AASTLQS
SEQ ID NO: 258	LCDR3 (Kabat)	QQSLFAPFT
SEQ ID NO: 156	LCDR1 (Chothia)	SQGISNY
SEQ ID NO: 50	LCDR2 (Chothia)	AAS
SEQ ID NO: 259	LCDR3 (Chothia)	SLFAPF
SEQ ID NO: 158	LCDR1 (IMGT)	QGISNY
SEQ ID NO: 50	LCDR2 (IMGT)	AAS
SEQ ID NO: 258	LCDR3 (IMGT)	QQSLFAPFT
SEQ ID NO: 260	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISNYL AWYQQKPGKVPKLLIYAASTLQSGVPSRFSGS

		GSGTDFTLTISSLQPEDVATYYCQQSLFAPFTF GQGTKVEIK
SEQ ID NO: 261	DNA VL	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGGGCATCAGC AACTACCTGGCCTGGTATCAGCAGAAACCCG GCAAGGTGCCCAAGCTGCTGATCTACGCTG CCAGCACACTGCAGAGCGGAGTGCCTAGCA GATTTTCTGGCAGCGGCTCCGGCACCGATTT CACCCTGACCATATCTAGCCTGCAGCCAGAG GACGTGGCCACCTACTACTGTCAGCAGAGC CTGTTCGCCCCTTTCACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAG
SEQ ID NO: 262	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQGISNYL AWYQQKPGKVPKLLIYAASTLQSGVPSRFSGS GSGTDFTLTISSLQPEDVATYYCQQSLFAPFTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 263	DNA Light Chain	GACATCCAGATGACACAGAGCCCTAGCAGC CTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGGGCATCAGC AACTACCTGGCCTGGTATCAGCAGAAACCCG GCAAGGTGCCCAAGCTGCTGATCTACGCTG CCAGCACACTGCAGAGCGGAGTGCCTAGCA GATTTTCTGGCAGCGGCTCCGGCACCGATTT CACCCTGACCATATCTAGCCTGCAGCCAGAG GACGTGGCCACCTACTACTGTCAGCAGAGC CTGTTCGCCCCTTTCACCTTTGGCCAGGGCA CCAAGGTGGAAATCAAGCGTACGGTGGCCG CTCCCAGCGTGTTCATCTTCCCCCCCAGCGA CGAGCAGCTGAAGAGTGGCACCGCCAGCGT GGTGTGCCTGCTGAACAACTTCTACCCCCGG GAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGC GTCACCGAGCAGGACAGCAAGGACTCCACC TACAGCCTGAGCAGCACCCTGACCCTGAGC AAGGCCGACTACGAGAAGCATAAGGTGTAC GCCTGCGAGGTGACCCACCAGGGCCTGTCC AGCCCCGTGACCAAGAGCTTCAACAGGGGC GAGTGC

[00278] Other antibodies of the invention include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity to the sequences described in Table 2. In some embodiments, 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable

regions depicted in the sequence described in Table 2, while retaining substantially the same therapeutic activity as the antibodies listed in Table 2.

[00279] Since each of these antibodies can bind to PMEL17, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other PMEL17-binding antibodies of the invention. Such "mixed and matched" PMEL17-binding antibodies can be tested using the binding assays known in the art (*e.g.*, ELISAs, and other assays described in the Example section). When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise a full length light chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the invention provides an isolated monoclonal antibody or antigen binding region thereof having: a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 42, 64, 88, 112, 132, 149, 165, 184, 196, 215, 227, 239 or 254; and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 21, 25, 29, 53, 75, 99, 119, 143, 159, 171, 190, 202, 221, 233, 248 or 260; wherein the antibody specifically binds to PMEL17.

[00280] In another aspect, the invention provides (i) an isolated monoclonal antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian expression system selected from the group consisting of SEQ ID NOs: 12, 44, 66, 90, 114, 134, 151, 167, 186, 198, 217, 229, 241 or 256; and a full length light chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOs: 23, 27, 31, 55, 77, 101, 121, 145, 161, 173, 192, 204, 223, 235, 250 or 262; or (ii) a functional protein comprising an antigen binding portion thereof.

[00281] In another aspect, the present invention provides PMEL17-binding antibodies that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 2, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown, for example, in SEQ ID NOs: 1, 4, 5, 7, 33, 36, 37, 39, 57, 60, 79, 82, 83, 85, 103, 106, 107, 109, 123, 126, 127, 129, 175, 178, 179, 181, 206, 209, 210, and 212. The amino acid

sequences of the VH CDR2s of the antibodies and are shown, for example, in SEQ ID NOs: 2, 6, 8, 34, 38, 40, 58, 61, 62, 80, 84, 86, 104, 108, 110, 124, 128, 130, 176, 180, 182, 207, 211, and 213. The amino acid sequences of the VH CDR3s of the antibodies are shown, for example, in SEQ ID NOs: 3, 9, 35, 41, 59, 63, 81, 87, 105, 111, 125, 131, 147, 148, 163, 164, 177, 183, 194, 195, 208, 214, 225, 226, 237, 238, 252, and 253. The amino acid sequences of the VL CDR1s of the antibodies are shown, for example, in SEQ ID NOs: 14, 17, 20, 46, 49, 52, 68, 71, 74, 92, 95, 98, 116, 136, 139, 142, 153, 156, 158, 243, 245, and 247. The amino acid sequences of the VL CDR2s of the antibodies are shown, for example, in SEQ ID Nos: 15, 18, 47, 50, 69, 72, 93, 96, 137, 140, and 154. The amino acid sequences of the VL CDR3s of the antibodies are shown, for example, in SEQ ID NOs: 16, 19, 48, 51, 70, 73, 94, 97, 117, 118, 138, 141, 155, 157, 169, 170188, 189, 200, 201, 219, 220, 231, 232, 244, 246, 258, and 259.

[00282] Given that each of these antibodies can bind to PMEL17 and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, CDR2 and CDR3 sequences and VL CDR1, CDR2 and CDR3 sequences can be "mixed and matched" (*i.e.*, CDRs from different antibodies can be mixed and matched. Such "mixed and matched" PMEL17-binding antibodies can be tested using the binding assays known in the art and those described in the Examples (*e.g.*, ELISAs). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence(s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences shown herein for monoclonal antibodies of the present invention.

[00283] Accordingly, in some embodiments, the present invention provides an isolated monoclonal antibody or antigen binding region thereof comprising a heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 4, 5, 7, 33, 36, 37, 39, 57, 60, 79, 82, 83, 85, 103, 106, 107, 109, 123, 126, 127, 129, 175, 178, 179, 181, 206, 209, 210, and 212; a heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 34, 38, 40, 58, 61, 62, 80, 84, 86, 104, 108, 110, 124, 128, 130, 176, 180, 182, 207, 211, and 213; a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 35, 41, 59, 63, 81, 87, 105, 111, 125, 131, 147, 148, 163, 164, 177, 183, 194, 195, 208, 214, 225, 226, 237, 238, 252, and 253; a light chain CDR1 comprising an amino acid sequence selected from the

group consisting of SEQ ID NOs: 14, 17, 20, 46, 49, 52, 68, 71, 74, 92, 95, 98, 116, 136, 139, 142, 153, 156, 158, 243, 245, and 247; a light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 18, 47, 50, 69, 72, 93, 96, 137, 140, and 154; and a light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 19, 48, 51, 70, 73, 94, 97, 117, 118, 138, 141, 155, 157, 169, 170, 188, 189, 200, 201, 219, 220, 231, 232, 244, 246, 258, and 259; wherein the antibody specifically binds PMEL17.

[00284] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:1, 4, 5 or 7, a heavy chain CDR2 of SEQ ID NO:2, 6 or 8; a heavy chain CDR3 of SEQ ID NO:3 or 9; a light chain CDR1 of SEQ ID NO:14, 17 or 20; a light chain CDR2 of SEQ ID NO:15 or 18; and a light chain CDR3 of SEQ ID NO:16 or 19.

[00285] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:33, 36, 37 or 39, a heavy chain CDR2 of SEQ ID NO:34, 38 or 40; a heavy chain CDR3 of SEQ ID NO:35 or 41; a light chain CDR1 of SEQ ID NO:46, 49 or 52; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:48 or 51.

[00286] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:5, 7, 57 or 60, a heavy chain CDR2 of SEQ ID NO:58, 61 or 62; a heavy chain CDR3 of SEQ ID NO:59 or 63; a light chain CDR1 of SEQ ID NO:68, 71 or 74; a light chain CDR2 of SEQ ID NO:69 or 72; and a light chain CDR3 of SEQ ID NO:70 or 73.

[00287] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:79, 82, 83 or 85, a heavy chain CDR2 of SEQ ID NO:80, 84 or 86; a heavy chain CDR3 of SEQ ID NO:81 or 87; a light chain CDR1 of SEQ ID NO:92, 95 or 98; a light chain CDR2 of SEQ ID NO:93 or 96; and a light chain CDR3 of SEQ ID NO:94 or 97.

[00288] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO:104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:105 or 111; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:117 or 118.

[00289] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID

NO:123, 126, 127 or 129, a heavy chain CDR2 of SEQ ID NO:124, 128 or 130; a heavy chain CDR3 of SEQ ID NO:125 or 131; a light chain CDR1 of SEQ ID NO:136, 139 or 142; a light chain CDR2 of SEQ ID NO:137 or 140; and a light chain CDR3 of SEQ ID NO:138 or 141.

[00290] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:123, 126, 127 or 129, a heavy chain CDR2 of SEQ ID NO:124, 128 or 130; a heavy chain CDR3 of SEQ ID NO:147 or 148; a light chain CDR1 of SEQ ID NO:153, 156 or 158; a light chain CDR2 of SEQ ID NO:50 or 154; and a light chain CDR3 of SEQ ID NO:155 or 157.

[00291] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO:104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:163 or 164; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:169 or 170.

[00292] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:175, 178, 179 or 181, a heavy chain CDR2 of SEQ ID NO:176, 180 or 182; a heavy chain CDR3 of SEQ ID NO:177 or 183; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:188 or 189.

[00293] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO: 103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO: 104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:194 or 195; a light chain CDR1 of SEQ ID NO: 49, 52 or 116; a light chain CDR2 of SEQ ID NO: 47 or 50; and a light chain CDR3 of SEQ ID NO:200 or 201.

[00294] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO:206, 209, 210 or 212, a heavy chain CDR2 of SEQ ID NO:207, 211 or 213; a heavy chain CDR3 of SEQ ID NO:208 or 214; a light chain CDR1 of SEQ ID NO:153, 156 or 158; a light chain CDR2 of SEQ ID NO:50 or 154; and a light chain CDR3 of SEQ ID NO:219 or 220.

[00295] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain CDR1 of SEQ ID NO: 206, 209, 210 or 212, a heavy chain CDR2 of SEQ ID NO: 207, 211 or 213; a heavy chain CDR3 of SEQ ID NO:225 or 226; a light chain CDR1 of SEQ ID NO:136, 139 or 142; a light chain CDR2 of SEQ ID NO:137 or 140; and a light chain CDR3 of SEQ ID NO:231 or 232.

[00296] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, 209, 210 or 212, an HCDR2 of SEQ ID NO: 207, 211 or 213, and an HCDR3 of SEQ ID NO:237 or 238; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, 245 or 247, an LCDR2 of SEQ ID NO:47 or 50, and an LCDR3 of SEQ ID NO:244 or 246.

[00297] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, 209, 210 or 212, an HCDR2 of SEQ ID NO: 207, 211 or 213, and an HCDR3 of SEQ ID NO:252 or 253; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, 156 or 158, an LCDR2 of SEQ ID NO:50 or 154, and an LCDR3 of SEQ ID NO:258 or 259.

[00298] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO:1, , a heavy chain CDR2 of SEQ ID NO:2, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:14, a light chain CDR2 of SEQ ID NO:15, and a light chain CDR3 of SEQ ID NO:16;

b) a heavy chain CDR1 of SEQ ID NO: 4, a heavy chain CDR2 of SEQ ID NO:2, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:14, a light chain CDR2 of SEQ ID NO:15, and a light chain CDR3 of SEQ ID NO:16;

c) a heavy chain CDR1 of SEQ ID NO:5, a heavy chain CDR2 of SEQ ID NO:6, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:17, a light chain CDR2 of SEQ ID NO: 18, and a light chain CDR3 of SEQ ID NO: 19; or

d) a heavy chain CDR1 of SEQ ID NO:7, a heavy chain CDR2 of SEQ ID NO:8, a heavy chain CDR3 of SEQ ID NO:9, a light chain CDR1 of SEQ ID NO:20, a light chain CDR2 of SEQ ID NO:18, and a light chain CDR3 of SEQ ID NO:16.

[00299] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO:33, a heavy chain CDR2 of SEQ ID NO:34, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:46, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:48;

b) a heavy chain CDR1 of SEQ ID NO:36, a heavy chain CDR2 of SEQ ID NO:34, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:46, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:48;

c) a heavy chain CDR1 of SEQ ID NO:37, a heavy chain CDR2 of SEQ ID NO:38, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:51; or

d) a heavy chain CDR1 of SEQ ID NO: 39, a heavy chain CDR2 of SEQ ID NO:40, a heavy chain CDR3 of SEQ ID NO:41, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:48.

[00300] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO:57, a heavy chain CDR2 of SEQ ID NO:58, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:68, a light chain CDR2 of SEQ ID NO:69, and a light chain CDR3 of SEQ ID NO:70;

b) a heavy chain CDR1 of SEQ ID NO:60, a heavy chain CDR2 of SEQ ID NO:58, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:68, a light chain CDR2 of SEQ ID NO:69, and a light chain CDR3 of SEQ ID NO:70;

c) a heavy chain CDR1 of SEQ ID NO:5, a heavy chain CDR2 of SEQ ID NO:61, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:71, a light chain CDR2 of SEQ ID NO:72, and a light chain CDR3 of SEQ ID NO:73; or

d) a heavy chain CDR1 of SEQ ID NO:7, a heavy chain CDR2 of SEQ ID NO:62, a heavy chain CDR3 of SEQ ID NO:63, a light chain CDR1 of SEQ ID NO:74, a light chain CDR2 of SEQ ID NO:72, and a light chain CDR3 of SEQ ID NO:70.

[00301] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO:79, , a heavy chain CDR2 of SEQ ID NO:80, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:92, a light chain CDR2 of SEQ ID NO:93, and a light chain CDR3 of SEQ ID NO:94;

b) a heavy chain CDR1 of SEQ ID NO:82, a heavy chain CDR2 of SEQ ID NO:80, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:92, a light chain CDR2 of SEQ ID NO:93, and a light chain CDR3 of SEQ ID NO:94;

c) a heavy chain CDR1 of SEQ ID NO:83, a heavy chain CDR2 of SEQ ID NO:84, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:95, a light chain CDR2 of SEQ ID NO:96, and a light chain CDR3 of SEQ ID NO: 97; or

d) a heavy chain CDR1 of SEQ ID NO: 85, a heavy chain CDR2 of SEQ ID NO:86, a heavy chain CDR3 of SEQ ID NO:87, a light chain CDR1 of SEQ ID NO:98, a light chain CDR2 of SEQ ID NO:96, and a light chain CDR3 of SEQ ID NO:94.

[00302] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:
a) a heavy chain CDR1 of SEQ ID NO:103, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO: 116; a light chain CDR2 of SEQ ID NO:47; and a light chain CDR3 of SEQ ID NO:117;
b) a heavy chain CDR1 of SEQ ID NO:106, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:117;
c) a heavy chain CDR1 of SEQ ID NO:107, a heavy chain CDR2 of SEQ ID NO:108, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:118; or
d) a heavy chain CDR1 of SEQ ID NO:109, a heavy chain CDR2 of SEQ ID NO:110, a heavy chain CDR3 of SEQ ID NO:111, a light chain CDR1 of SEQ ID NO:52 a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:117.

[00303] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:
a) a heavy chain CDR1 of SEQ ID NO:123, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137,and a light chain CDR3 of SEQ ID NO:138;
b) a heavy chain CDR1 of SEQ ID NO:126, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137, and a light chain CDR3 of SEQ ID NO:138;
c) a heavy chain CDR1 of SEQ ID NO:127, a heavy chain CDR2 of SEQ ID NO:128, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:139, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO: 141; or
d) a heavy chain CDR1 of SEQ ID NO: 129, a heavy chain CDR2 of SEQ ID NO:130, a heavy chain CDR3 of SEQ ID NO:131, a light chain CDR1 of SEQ ID NO:142, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO:138.

[00304] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:
a) a heavy chain CDR1 of SEQ ID NO:123, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO:154, and a light chain CDR3 of SEQ ID NO:155;

b) a heavy chain CDR1 of SEQ ID NO:126, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO: 154, and a light chain CDR3 of SEQ ID NO:155;
c) a heavy chain CDR1 of SEQ ID NO:127, a heavy chain CDR2 of SEQ ID NO:128, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:156, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:157; or
d) a heavy chain CDR1 of SEQ ID NO: 129, a heavy chain CDR2 of SEQ ID NO:130, a heavy chain CDR3 of SEQ ID NO:148, a light chain CDR1 of SEQ ID NO:158, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:155.

[00305] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:
a) a heavy chain CDR1 of SEQ ID NO:103, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:169;
b) a heavy chain CDR1 of SEQ ID NO:106, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:169;
c) a heavy chain CDR1 of SEQ ID NO:107, a heavy chain CDR2 of SEQ ID NO:108, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:170; or
d) a heavy chain CDR1 of SEQ ID NO: 109, a heavy chain CDR2 of SEQ ID NO:110, a heavy chain CDR3 of SEQ ID NO:164, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:169.

[00306] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selection from:
a) a heavy chain CDR1 of SEQ ID NO:175, a heavy chain CDR2 of SEQ ID NO:176, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:188;
b) a heavy chain CDR1 of SEQ ID NO:178, a heavy chain CDR2 of SEQ ID NO:176, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:188;
c) a heavy chain CDR1 of SEQ ID NO:179, a heavy chain CDR2 of SEQ ID NO:180, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:189; or

d) a heavy chain CDR1 of SEQ ID NO: 181, a heavy chain CDR2 of SEQ ID NO:182; a heavy chain CDR3 of SEQ ID NO:183, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:188.

[00307] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO: 103, a heavy chain CDR2 of SEQ ID NO: 104, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO: 47, and a light chain CDR3 of SEQ ID NO:200;

b) a heavy chain CDR1 of SEQ ID NO: 106, a heavy chain CDR2 of SEQ ID NO: 104, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO: 47, and a light chain CDR3 of SEQ ID NO:200;

c) a heavy chain CDR1 of SEQ ID NO: 107, a heavy chain CDR2 of SEQ ID NO: 108, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 49, a light chain CDR2 of SEQ ID NO: 50, and a light chain CDR3 of SEQ ID NO: 201; or

d) a heavy chain CDR1 of SEQ ID NO: 109, a heavy chain CDR2 of SEQ ID NO: 110, a heavy chain CDR3 of SEQ ID NO:195, a light chain CDR1 of SEQ ID NO: 52, a light chain CDR2 of SEQ ID NO: 50, and a light chain CDR3 of SEQ ID NO:200.

[00308] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO:206, a heavy chain CDR2 of SEQ ID NO:207, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO:154, and a light chain CDR3 of SEQ ID NO:219;

b) a heavy chain CDR1 of SEQ ID NO:209, a heavy chain CDR2 of SEQ ID NO:207, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO: 154, and a light chain CDR3 of SEQ ID NO:219;

c) a heavy chain CDR1 of SEQ ID NO:210, a heavy chain CDR2 of SEQ ID NO:211, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:156, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:220; or

d) a heavy chain CDR1 of SEQ ID NO: 212, a heavy chain CDR2 of SEQ ID NO:213, a heavy chain CDR3 of SEQ ID NO:214, a light chain CDR1 of SEQ ID NO:158, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:219.

[00309] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:

a) a heavy chain CDR1 of SEQ ID NO: 206, a heavy chain CDR2 of SEQ ID NO: 207, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137,and a light chain CDR3 of SEQ ID NO:231;
b) a heavy chain CDR1 of SEQ ID NO: 209, a heavy chain CDR2 of SEQ ID NO: 207, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137, and a light chain CDR3 of SEQ ID NO:231;
c) a heavy chain CDR1 of SEQ ID NO: 210, a heavy chain CDR2 of SEQ ID NO: 211, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:139, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO: 232; or
d) a heavy chain CDR1 of SEQ ID NO: 212, a heavy chain CDR2 of SEQ ID NO: 213, a heavy chain CDR3 of SEQ ID NO: 226, a light chain CDR1 of SEQ ID NO:142; a light chain CDR2 of SEQ ID NO: 140; and a light chain CDR3 of SEQ ID NO:231.

[00310] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:
a) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:237, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, an LCDR2 of SEQ ID NO:47, and an LCDR3 of SEQ ID NO:244;
b) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 209, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:237, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, an LCDR2 of SEQ ID NO:47, and an LCDR3 of SEQ ID NO:244;
c) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 210, an HCDR2 of SEQ ID NO: 211, and an HCDR3 of SEQ ID NO:237, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:245, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:246; or
d) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 212, an HCDR2 of SEQ ID NO: 213, and an HCDR3 of SEQ ID NO:238; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:247, an LCDR2 of SEQ ID NO: 50, and an LCDR3 of SEQ ID NO:244.

[00311] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises CDR sequences selected from:
a) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that

comprises an LCDR1 of SEQ ID NO:153, an LCDR2 of SEQ ID NO: 154, and an LCDR3 of SEQ ID NO:258;

b) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 209, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, an LCDR2 of SEQ ID NO:154, and an LCDR3 of SEQ ID NO:258;

c) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 210, an HCDR2 of SEQ ID NO: 211, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:156, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:259; or

d) a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 212, an HCDR2 of SEQ ID NO: 213, and an HCDR3 of SEQ ID NO: 253; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:158, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:258.

[00312] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:21.

[00313] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:25.

[00314] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:29.

[00315] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:42, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:53.

[00316] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:64, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:75.

[00317] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:88, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:99.

[00318] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:112, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:119.

[00319] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:132, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:143.

[00320] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:149, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:159.

[00321] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:165, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:171.

[00322] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:184, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:190.

[00323] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:196, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:202.

[00324] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:215, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:221.

[00325] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH)

comprising the amino acid sequence of SEQ ID NO:227, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:233.

[00326] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:239, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:248.

[00327] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:254, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:260.

[00328] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:23.

[00329] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:27.

[00330] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:31.

[00331] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:44, and a light chain comprising the amino acid sequence of SEQ ID NO:55.

[00332] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:66, and a light chain comprising the amino acid sequence of SEQ ID NO:77.

[00333] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:90, and a light chain comprising the amino acid sequence of SEQ ID NO:101.

[00334] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:114, and a light chain comprising the amino acid sequence of SEQ ID NO:121.

[00335] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:134, and a light chain comprising the amino acid sequence of SEQ ID NO:145.

[00336] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:151, and a light chain comprising the amino acid sequence of SEQ ID NO:161.

[00337] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:167, and a light chain comprising the amino acid sequence of SEQ ID NO:173.

[00338] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:186, and a light chain comprising the amino acid sequence of SEQ ID NO:192.

[00339] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:198, and a light chain comprising the amino acid sequence of SEQ ID NO:204.

[00340] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:217, and a light chain comprising the amino acid sequence of SEQ ID NO:223.

[00341] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:229, and a light chain comprising the amino acid sequence of SEQ ID NO:235.

[00342] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino

acid sequence of SEQ ID NO:241, and a light chain comprising the amino acid sequence of SEQ ID NO:250.

[00343] In a specific embodiment, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to PMEL17 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:256, and a light chain comprising the amino acid sequence of SEQ ID NO:262.

[00344] In certain embodiments, an antibody that specifically binds to PMEL17 is an antibody or antibody fragment (*e.g.*, antigen binding fragment) that is described in Table 2.

1. Identification of Epitopes and Antibodies That Bind to the Same Epitope

[00345] The present invention also provides antibodies and antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to the same epitope as the anti-PMEL17 antibodies described in Table 2, or cross compete with the antibodies described in Table 2. Additional antibodies and antibody fragments (*e.g.*, antigen binding fragments) can therefore be identified based on their ability to cross-compete (*e.g.*, to competitively inhibit the binding of, in a statistically significant manner) with other antibodies of the invention in PMEL17 binding assays, for example, via BIACORE or assays known to persons skilled in the art for measuring binding. The ability of a test antibody to inhibit the binding of antibodies and antibody fragments (*e.g.*, antigen binding fragments) of the present invention to a PMEL17 (*e.g.*, human PMEL17) demonstrates that the test antibody can compete with that antibody or antibody fragment (*e.g.*, antigen binding fragments) for binding to PMEL17; such an antibody may, according to non-limiting theory, bind to the same or a related (*e.g.*, a structurally similar or spatially proximal or overlapping) epitope on the PMEL17 protein as the antibody or antibody fragment (*e.g.*, antigen binding fragments) with which it competes. In certain embodiments, the antibodies that bind to the same epitope on PMEL17 as the antibodies or antibody fragments (*e.g.*, antigen binding fragments) described in Table 2 are human or humanized monoclonal antibodies. Such human or humanized monoclonal antibodies can be prepared and isolated as described herein.

2. Further Alteration of the Framework of Fc Region

[00346] The immunoconjugates of the invention may comprise modified antibodies or antigen binding fragments thereof that further comprise modifications to framework residues within VH and/or VL, *e.g.* to improve the properties of the antibody. In some embodiments, the framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to “back-mutate” one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic

mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "back-mutated" to the germline sequence by, for example, site-directed mutagenesis. Such "back-mutated" antibodies are also intended to be encompassed by the invention.

[00347] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T-cell epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 20030153043 by Carr *et al.*

[00348] In addition or in the alternative to modifications made within the framework or CDR regions, antibodies of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity (ADCC). Furthermore, an antibody of the invention may be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these embodiments is described in further detail below.

[00349] In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, *e.g.*, increased or decreased. This approach is described further in U.S. Patent No. 5,677,425 by Bodmer *et al.* The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[00350] In some embodiments, the antibody or antibody fragment disclosed herein include modified or engineered amino acid residues, *e.g.*, one or more cysteine residues, as sites for conjugation to a drug moiety (Junutula JR, *et al.*, Nat Biotechnol 2008, 26:925-932). In one embodiment, the invention provides a modified antibody or antibody fragment comprising a substitution of one or more amino acids with cysteine at the positions described herein. Sites for cysteine substitution are in the constant regions of the antibody or antibody fragment and are thus applicable to a variety of antibody or antibody fragment, and the sites are selected to provide stable and homogeneous conjugates. A modified antibody or fragment can have one, two or more cysteine substitutions, and these substitutions can be used in combination with other modification and conjugation methods as described herein. Methods for inserting cysteine

at specific locations of an antibody are known in the art, *see, e.g.*, Lyons *et al.*, (1990) Protein Eng., 3:703-708, WO 2011/005481, WO2014/124316, WO 2015/138615. In certain embodiments, a modified antibody comprises a substitution of one or more amino acids with cysteine on its constant region selected from positions 117, 119, 121, 124, 139, 152, 153, 155, 157, 164, 169, 171, 174, 189, 191, 195, 197, 205, 207, 246, 258, 269, 274, 286, 288, 290, 292, 293, 320, 322, 326, 333, 334, 335, 337, 344, 355, 360, 375, 382, 390, 392, 398, 400 and 422 of a heavy chain of the antibody, and wherein the positions are numbered according to the EU system. In some embodiments a modified antibody or antibody fragment comprises a substitution of one or more amino acids with cysteine on its constant region selected from positions 107, 108, 109, 114, 129, 142, 143, 145, 152, 154, 156, 159, 161, 165, 168, 169, 170, 182, 183, 197, 199, and 203 of a light chain of the antibody or antibody fragment, wherein the positions are numbered according to the EU system, and wherein the light chain is a human kappa light chain. In certain embodiments a modified antibody or antibody fragment thereof comprises a combination of substitution of two or more amino acids with cysteine on its constant regions wherein the combinations comprise substitutions at positions 375 of an antibody heavy chain, position 152 of an antibody heavy chain, position 360 of an antibody heavy chain, or position 107 of an antibody light chain and wherein the positions are numbered according to the EU system. In certain embodiments a modified antibody or antibody fragment thereof comprises a substitution of one amino acid with cysteine on its constant regions wherein the substitution is position 375 of an antibody heavy chain, position 152 of an antibody heavy chain, position 360 of an antibody heavy chain, position 107 of an antibody light chain, position 165 of an antibody light chain or position 159 of an antibody light chain and wherein the positions are numbered according to the EU system, and wherein the light chain is a kappa chain. In particular embodiments a modified antibody or antibody fragment thereof comprises a combination of substitution of two amino acids with cysteine on its constant regions wherein the combinations comprise substitutions at positions 375 of an antibody heavy chain and position 152 of an antibody heavy chain, wherein the positions are numbered according to the EU system. In particular embodiments a modified antibody or antibody fragment thereof comprises a substitution of one amino acid with cysteine at position 360 of an antibody heavy chain, wherein the positions are numbered according to the EU system. In other particular embodiments a modified antibody or antibody fragment thereof comprises a substitution of one amino acid with cysteine at position 107 of an antibody light chain and wherein the positions are numbered according to the EU system, and wherein the light chain is a kappa chain.

[00351] In additional embodiments antibodies or antibody fragments (*e.g.*, antigen binding fragment) useful in immunoconjugates of the invention include modified or engineered antibodies, such as an antibody modified to introduce one or more other reactive amino acid (other than cysteine), including Pcl, pyrrolysine, peptide tags (such as S6, A1 and ybbR tags), and non-natural amino acids, in place of at least one amino acid of the native sequence, thus providing a reactive site on the antibody or antigen binding fragment for conjugation to a drug moiety or a linker-drug moiety with complementary reactivity. For example, the antibodies or antibody fragments can be modified to incorporate Pcl or pyrrolysine (W. Ou, *et al.*, (2011) PNAS 108 (26), 10437-10442; WO2014124258) or unnatural amino acids (J.Y. Axup, *et al.*, Proc Natl Acad Sci U S A, 109 (2012), pp. 16101–16106; for review, see C.C. Liu and P.G. Schultz (2010) Annu Rev Biochem 79, 413-444; C.H. Kim, *et al.*, (2013) Curr Opin Chem Biol. 17, 412-419) as sites for conjugation to a drug. Similarly, peptide tags for enzymatic conjugation methods can be introduced into an antibody (Strop P., *et al.*, Chem Biol. 2013, 20(2):161-7; Rabuka D., Curr Opin Chem Biol. 2010 Dec;14(6):790-6; Rabuka D, *et al.*, Nat Protoc. 2012, 7(6):1052-67). One other example is the use of 4'-phosphopantetheinyl transferases (PPTase) for the conjugation of Co-enzyme A analogs (WO2013184514), and (Grünewald *et al., (2015)* Bioconjugate Chem. 26 (12), 2554-62). Methods for conjugating such modified or engineered antibodies with payloads or linker-payload combinations are known in the art.

[00352] In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745 by Ward *et al.*

[00353] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in, *e.g.*, U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

[00354] In another embodiment, one or more amino acids selected from amino acid residues can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in, *e.g.*, U.S. Patent Nos. 6,194,551 by Idusogie *et al.*

[00355] In another embodiment, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described in, *e.g.*, the PCT Publication WO 94/29351 by Bodmer *et al.* Allotypic amino acid residues include, but are not limited to, constant region of a heavy chain of the IgG1, IgG2, and IgG3 subclasses as well as constant region of a light chain of the kappa isotype as described by Jefferis *et al.*, MAbs. 1:332-338 (2009).

[00356] Antibody fusion protein complexes containing such mutations mediate reduced or no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). In some embodiments, amino acid residues L234 and L235 of the IgG1 constant region are substituted to A234 and A235. In some embodiments, amino acid residue N267 of the IgG1 constant region is substituted to A267. In some embodiments, amino acid residues D265 and P329 of the IgG1 constant region are substituted to A265 and A329. Other antibody Fc silencing mutations may also be used.

[00357] In another embodiment, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described in, *e.g.*, the PCT Publication WO 94/29351 by Bodmer *et al.* In a specific embodiment, one or more amino acids of an antibody or antigen binding fragment thereof of the present invention are replaced by one or more allotypic amino acid residues. Allotypic amino acid residues also include, but are not limited to, the constant region of the heavy chain of the IgG1, IgG2, and IgG3 subclasses as well as the constant region of the light chain of the kappa isotype as described by Jefferis *et al.*, MAbs. 1:332-338 (2009).

[00358] In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for "antigen." Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in, *e.g.*, U.S. Patent Nos. 5,714,350 and 6,350,861 by Co *et al.*

[00359] In another embodiment, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half-life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta *et al.*

3. Production of the anti-PMEL17 Antibodies

[00360] Anti-PMEL17 antibodies and antibody fragments (*e.g.*, antigen binding fragments) thereof can be produced by any means known in the art, including but not limited to, recombinant expression, chemical synthesis, and enzymatic digestion of antibody tetramers, whereas full-length monoclonal antibodies can be obtained by, *e.g.*, hybridoma or recombinant production. Recombinant expression can be from any appropriate host cells known in the art, for example, mammalian host cells, bacterial host cells, yeast host cells, insect host cells, etc.

[00361] The invention further provides polynucleotides encoding the antibodies described herein, *e.g.*, polynucleotides encoding heavy or light chain variable regions or segments comprising the complementarity determining regions as described herein. In some embodiments, the polynucleotide encoding the heavy chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 11, 43, 65, 89, 113, 133, 150, 166, 185, 197, 216, 228, 240, and 255. In some embodiments, the polynucleotide encoding the light chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 22, 26, 30, 54, 76, 100, 120, 144, 160, 172, 191, 203, 222, 234, 249, and 261.

[00362] In some embodiments, the polynucleotide encoding the heavy chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 13, 45, 67, 91, 115, 135, 152, 168, 187, 199, 218, 230, 242, and 257. In some embodiments, the polynucleotide encoding the light chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 24, 28, 32, 56, 78, 102, 122, 146, 162, 174, 193, 205, 224, 236, 251, and 263.

[00363] The polynucleotides of the invention can encode only the variable region sequence of an anti-PMEL17 antibody. They can also encode both a variable region and a

constant region of the antibody. Some of the polynucleotide sequences encode a polypeptide that comprises variable regions of both the heavy chain and the light chain of one of the exemplified mouse anti-PMEL17 antibody. Some other polynucleotides encode two polypeptide segments that respectively are substantially identical to the variable regions of the heavy chain and the light chain of one of the mouse antibodies.

[00364] The polynucleotide sequences can be produced by *de novo* solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence (*e.g.*, sequences as described in the Examples below) encoding an anti-PMEL17 antibody or its binding fragment. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang *et al.*, Meth. Enzymol. 68:90, 1979; the phosphodiester method of Brown *et al.*, Meth. Enzymol. 68:109, 1979; the diethylphosphoramidite method of Beaucage *et al.*, Tetra. Lett., 22:1859, 1981; and the solid support method of U.S. Patent No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, *e.g.*, PCR Technology: Principles and Applications for DNA Amplification, H.A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis *et al.* (Ed.), Academic Press, San Diego, CA, 1990; Mattila *et al.*, Nucleic Acids Res. 19:967, 1991; and Eckert *et al.*, PCR Methods and Applications 1:17, 1991.

[00365] Also provided in the invention are expression vectors and host cells for producing the anti-PMEL17 antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the anti-PMEL17 antibody chains or binding fragments. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with an expression cassette for expressing a protein or RNA, and human artificial chromosomes (*see, e.g.*, Harrington *et al.*, Nat Genet 15:345, 1997). For example, nonviral vectors useful for expression of the anti-PMEL17 polynucleotides and polypeptides in mammalian (*e.g.*, human) cells include pThioHis A, B & C, pcDNA™3.1/His, pEBVHis A, B & C (Invitrogen, San Diego, CA), MPSV vectors, and numerous other vectors known in the art for expressing other proteins. Useful viral vectors include vectors based on retroviruses, adenoviruses, adenoassociated viruses, herpes viruses, vectors based on SV40, papilloma virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). *See* Brent *et al.*, *supra*; Smith, Annu. Rev. Microbiol. 49:807, 1995; and Rosenfeld *et al.*, Cell 68:143, 1992.

[00366] The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other

regulatory sequences (*e.g.*, enhancers) that are operably linked to the polynucleotides encoding an anti-PMEL17 antibody chain or fragment. In some embodiments, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, *e.g.*, arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under noninducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of an anti-PMEL17 antibody chain or fragment. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (*see, e.g.*, Scharf *et al.*, Results Probl. Cell Differ. 20:125, 1994; and Bittner *et al.*, Meth. Enzymol., 153:516, 1987). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

[00367] The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted anti-PMEL17 antibody sequences. More often, the inserted anti-PMEL17 antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding anti-PMEL17 antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

[00368] The host cells for harboring and expressing the anti-PMEL17 antibody chains can be either prokaryotic or eukaryotic. *E. coli* is one prokaryotic host useful for cloning and expressing the polynucleotides of the present invention. Other microbial hosts suitable for use include bacilli, such as Bacillus subtilis, and other enterobacteriaceae, such as Salmonella, Serratia, and various Pseudomonas species. In these prokaryotic hosts, one can also make expression vectors, which typically contain expression control sequences compatible with the host cell (*e.g.*, an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be employed to express anti-PMEL17

polypeptides of the invention. Insect cells in combination with baculovirus vectors can also be used.

[00369] In some preferred embodiments, mammalian host cells are used to express and produce the anti-PMEL17 polypeptides of the present invention. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (*e.g.*, the myeloma hybridoma clones as described in the Examples) or a mammalian cell line harboring an exogenous expression vector (*e.g.*, the SP2/0 myeloma cells exemplified below). These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed, including the CHO cell lines, various Cos cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, *e.g.*, Winnacker, From Genes to Clones, VCH Publishers, N.Y., N.Y., 1987. Expression vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (*see, e.g.*, Queen *et al.*, Immunol. Rev. 89:49-68, 1986), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP polIII promoter, the constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

[00370] Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts (*see generally* Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 4th ed.). Other methods include, *e.g.*, electroporation, calcium phosphate treatment, liposome-mediated transformation, injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, Cell 88:223, 1997), agent-enhanced uptake of DNA, and *ex vivo* transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example,

cell lines which stably express anti-PMEL17 antibody chains or binding fragments can be prepared using expression vectors of the invention which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

Therapeutic Uses

[00371] The antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates of the invention are useful in a variety of applications including, but not limited to, treatment or prevention of cancer, such as solid cancers or heme malignancies. In certain embodiments, the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates of the invention are useful for inhibiting tumor growth, inducing differentiation, reducing tumor volume, and/or reducing the tumorigenicity of a tumor. The methods of use can be *in vitro*, *ex vivo*, or *in vivo* methods.

[00372] In one aspect, the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates of the invention are useful for detecting the presence of PMEL17 in a biological sample. The term “detecting” as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue. In certain embodiments, such tissues include normal and/or cancerous tissues that express PMEL17 at higher levels relative to other tissues.

[00373] In one aspect, the invention provides a method of detecting the presence of PMEL17 in a biological sample. In certain embodiments, the method comprises contacting the biological sample with an anti-PMEL17 antibody under conditions permissive for binding of the antibody to the antigen, and detecting whether a complex is formed between the antibody and the antigen.

[00374] In one aspect, the invention provides a method of diagnosing a disorder associated with increased expression of PMEL17. In certain embodiments, the method comprises contacting a test cell with an anti-PMEL17 antibody; determining the level of expression (either quantitatively or qualitatively) of PMEL17 on the test cell by detecting binding of the anti-PMEL17 antibody to the PMEL17 antigen; and comparing the level of expression of PMEL17 in the test cell with the level of expression of PMEL17 on a control cell (*e.g.*, a normal cell of the same tissue origin as the test cell or a cell that expresses PMEL17 at levels

comparable to such a normal cell), wherein a higher level of expression of PMEL17 on the test cell as compared to the control cell indicates the presence of a disorder associated with increased expression of PMEL17. In certain embodiments, the test cell is obtained from an individual suspected of having a disorder associated with increased expression of PMEL17. In certain embodiments, the disorder is a cell proliferative disorder, such as a cancer or a tumor. In certain embodiments, the method comprises measuring the copy number of the PMEL17 gene in a test cell.

[00375] In certain embodiments, a method of diagnosis or detection, such as those described above, comprises detecting binding of an anti-PMEL17 antibody to PMEL17 expressed on the surface of a cell or in a membrane preparation obtained from a cell expressing PMEL17 on its surface. An exemplary assay for detecting binding of an anti-PMEL17 antibody to PMEL17 expressed on the surface of a cell is a "FACS" assay.

[00376] Certain other methods can be used to detect binding of anti-PMEL17 antibodies to PMEL17. Such methods include, but are not limited to, antigen-binding assays that are well known in the art, such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, fluorescent immunoassays, protein A immunoassays, and immunohistochemistry (IHC).

[00377] In certain embodiments, anti-PMEL17 antibodies are labeled. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, *e.g.*, through an enzymatic reaction or molecular interaction.

[00378] In certain embodiments, anti-PMEL17 antibodies are immobilized on an insoluble matrix. Immobilization entails separating the anti-PMEL17 antibody from any PMEL17 protein that remains free in solution. This conventionally is accomplished by either insolubilizing the anti-PMEL17 antibody before the assay procedure, as by adsorption to a water-insoluble matrix or surface (Bennich et al, U.S. Patent No. 3,720,760), or by covalent coupling (for example, using glutaraldehyde cross-linking), or by insolubilizing the anti-PMEL17 antibody after formation of a complex between the anti-PMEL17 antibody and PMEL17 protein, *e.g.*, by immunoprecipitation.

[00379] Any of the above embodiments of diagnosis or detection can be carried out using an immunoconjugate of the invention in place of or in addition to an anti-PMEL17 antibody.

[00380] In one embodiment, the invention provides a method of treating or preventing a disease comprising administering the antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention to a patient. The invention also provides use of the antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention to treat or prevent disease in a patient. In some embodiments, the invention provides antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention for use in the treatment or prevention of disease in a patient. In further embodiments, the invention provides use of the antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention in the manufacture of a medicament for treatment or prevention of disease in a patient.

[00381] In certain embodiments, the disease treated with the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates of the invention is a cancer. In certain embodiments, the cancer is characterized by PMEL17 expressing cells to which the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates of the invention binds. In certain embodiments, the cancer is characterized by an increase in expression of PMEL17 relative to a healthy patient. In some embodiments, the expression of PMEL17 may be measured by an increase in PMEL17 RNA. In other embodiments, the cancer is characterized by an increase in DNA copy number of PMEL17. Other methods of measuring or determining levels of PMEL17 expression are known to persons skilled in the art. In certain embodiments, the cancer is characterized by a mutation, e.g., an activating mutation affecting Q209 or R183, in the GNAQ and/or the GNA11 gene. Examples of diseases which can be treated and/or prevented include, but are not limited to, melanoma, uveal melanoma, hepatocellular carcinoma, and a metastatic cancer thereof.

[00382] The present invention provides for methods of treating or preventing cancer comprising administering a therapeutically effective amount of the antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention. In certain embodiments, the cancer is a solid cancer such as melanoma, uveal melanoma, uveal melanoma, hepatocellular carcinoma, or a metastatic cancer thereof. In certain embodiments, the subject is a human. In certain embodiments, the cancer is a resistant cancer and/or relapsed cancer.

[00383] In certain embodiments, the invention provides for methods of inhibiting tumor growth comprising administering to a subject a therapeutically effective amount of the antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention. In certain embodiments, the tumor is of a solid cancer such as melanoma, uveal

melanoma, hepatocellular carcinoma, or a metastatic cancer thereof. In certain embodiments, the subject is a human. In certain embodiments, the subject has a tumor or has had a tumor removed.

[00384] In certain embodiments, the tumor expresses the PMEL17 to which the anti-PMEL17 antibody binds. In certain embodiments, the tumor overexpresses the human PMEL17. In certain embodiments, the tumor has an increase copy number of the PMEL17 gene. In certain embodiments, the tumor is characterized by a mutation, e.g., an activating mutation affecting Q209 or R183, in the GNAQ and/or the GNA11 gene.

[00385] The present invention also provides for methods of selecting patients for treatment with antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the invention comprising administering a therapeutically effective amount of said antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates. In certain aspects of the invention the methods comprise selecting a patient by measuring for expression of PMEL17. In certain aspects of the invention the methods comprise selecting a patient by identifying a mutation, e.g., an activating mutation affecting Q209 or R183, in the GNAQ or the GNA11 gene. In certain embodiments, the methods comprise measuring the level of PMEL17 expression in the patient as well as detecting for the GNAQ and/or GNA11 gene.

[00386] For the treatment or prevention of the disease, the appropriate dosage of the antibodies, antibody fragments (*e.g.*, antigen binding fragments), or antibody drug conjugates of the present invention depends on various factors, such as the type of disease to be treated, the severity and course of the disease, the responsiveness of the disease, previous therapy, patient's clinical history, and so on. The antibody or agent can be administered one time or over a series of treatments lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved (*e.g.*, reduction in tumor size). Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient and will vary depending on the relative potency of an individual antibody, antibody fragment (*e.g.*, antigen binding fragment), or antibody drug conjugates. The treating physician can estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues.

Combination Therapy

[00387] In certain instances, an antibody, antibody fragment (*e.g.*, antigen binding fragment), or antibody drug conjugate of the present invention is combined with other therapeutic treatments, such as surgery and radiation therapy, therapeutic agents, such as

other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

[00388] In one embodiment, an antibody, antibody fragment (*e.g.*, antigen binding fragment), or antibody drug conjugate of the present invention is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second compound having anti-cancer properties. The second compound of the pharmaceutical combination formulation or dosing regimen can have complementary activities to the antibody or immunoconjugate of the combination such that they do not adversely affect each other. For example, an antibody, antibody fragment (*e.g.*, antigen binding fragment), or antibody drug conjugate of the present invention can be administered in combination with, but not limited to, a chemotherapeutic agent, immunomodulatory agents, a tyrosine kinase inhibitor, a GNAQ/GNA11 downstream signaling pathway inhibitor, IAP inhibitors, Bcl2 inhibitors, Mcl1 inhibitors, and other GNAQ/GNA11 inhibitors.

[00389] The term "pharmaceutical combination" as used herein refers to either a fixed combination in one dosage unit form, or non-fixed combination or a kit of parts for the combined administration where two or more therapeutic agents may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, *e.g.*, synergistic effect.

[00390] The term "combination therapy" refers to the administration of two or more therapeutic agents to treat or prevent a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (*e.g.*, capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating or preventing the conditions or disorders described herein.

[00391] The combination therapy can provide "synergy" and prove "synergistic", *i.e.*, the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect can be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate

formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect can be attained when the compounds are administered or delivered sequentially, *e.g.*, by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.*, serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

[00392] General Chemotherapeutic agents considered for use in combination therapies include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®), and pemetrexed.

[00393] In one aspect, the present invention provides a method of treating or preventing cancer by administering to a subject in need thereof an antibody drug conjugate of the present invention in combination with one or more MDM2 inhibitors, PKC inhibitors, PRC2 inhibitors, MAPK inhibitors, GPCR inhibitors, tyrosine kinase inhibitors, including but not limited to, BTK inhibitors, EGFR inhibitors, Her2 inhibitors, Her3 inhibitors, IGFR inhibitors, and Met inhibitors.

[00394] For example, MDM2 inhibitors include but are not limited to, RG7112 (RO5045337); RG7388 (RO5503781, Idasanutlin); MI-77301 (SAR405838); MK-8242 (SCH-900242); AMG232; CGM097; DS3032b; HDM201; and ALRN-6924.

[00395] For example, PKC inhibitors include but are not limited to, Balanol; Riluzole; Staurosporin; Enzastaurin; δV1-1 (KAI-9803 or Delcasertib); εV1-2 (KAI-1678); Aprinocarsen; Midostaurin (PKC412); UCN-01 (7-hydroxy-staurosporin); Rottlerin (5, 7, dihydroxy-2,2-dimethyl-6-(2,4,6-trihydroxy-3-methyl-5-acetlybenzyl)-8-cinnamoyl-1,2-chromene); and Bryostatin 1.

[00396] For example, PRC2 inhibitors include but are not limited to, EI1; EPZ011989; EPZ005687; Tetramethylpiperidinyl Benzamides; UNC1999; and GSK126.

[00397] For example, MAPK inhibitors include but are not limited to, Vemurafenib (Zelboraf);, dabrafenib (Tafinlar); encorafenib (Braftovi); trametinib (Mekinist); cobimetinib (Cotellic); binimetinib (Mektovi); and ulixertinib.

[00398] For example, tyrosine kinase inhibitors include but are not limited to, Ibrutinib (PCI-32765); Erlotinib hydrochloride (Tarceva®); Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea, also known as ABT 869, available from Genentech); Sunitinib malate (Sutent®); Bosutinib (4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile, also known as SKI-606, and described in US Patent No. 6,780,996); Dasatinib (Sprycel®); Pazopanib (Votrient®); Sorafenib (Nexavar®); Zactima (ZD6474); and Imatinib or Imatinib mesylate (Gilvec® and Gleevec®).

[00399] Epidermal growth factor receptor (EGFR) inhibitors include but are not limited to, Erlotinib hydrochloride (Tarceva®), Gefitinib (Iressa®); N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3"S")-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, Tovok®); Vandetanib (Caprelsa®); Lapatinib (Tykerb®); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); Canertinib dihydrochloride (CI-1033); 6-[4-[(4-Ethyl-1-piperazinyl)methyl]phenyl]-N-[(1R)-1-phenylethyl]- 7H-Pyrrolo[2,3-d]pyrimidin-4-amine (AEE788, CAS 497839-62-0); Mubritinib (TAK165); Pelitinib (EKB569); Afatinib (BIBW2992); Neratinib (HKI-272); N-[4-[[1-[(3-Fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3S)-3-morpholinylmethyl ester (BMS599626); N-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[c]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8); and 4-[4-[[(1R)-1-Phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol (PKI166, CAS 187724-61-4).

[00400] EGFR antibodies include but are not limited to, Cetuximab (Erbitux®); Panitumumab (Vectibix®); Matuzumab (EMD-72000); ; Nimotuzumab (hR3); Zalutumumab; TheraCIM h-R3; MDX0447 (CAS 339151-96-1); and ch806 (mAb-806, CAS 946414-09-1).

[00401] Human Epidermal Growth Factor Receptor 2 (Her2 receptor) (also known as Neu, ErbB-2, CD340, or p185) inhibitors include but are not limited to, Trastuzumab (Herceptin®); Pertuzumab (Omnitarg®); trastuzumab emtansine (Kadcyla®); Neratinib (HKI-272, (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide, and described PCT Publication No. WO 05/028443); Lapatinib or Lapatinib ditosylate (Tykerb®); (3R,4R)-4-amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); (2E)-N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-2-butenamide (BIBW-2992, CAS 850140-72-6); N-[4-[[1-[(3-Fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3S)-3-morpholinylmethyl ester (BMS 599626, CAS 714971-09-2); Canertinib dihydrochloride (PD183805 or CI-1033); and N-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[c]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8).

[00402] Her3 inhibitors include but are not limited to, LJM716, MM-121, AMG-888, RG7116, REGN-1400, AV-203, MP-RM-1, MM-111, and MEHD-7945A.

[00403] MET inhibitors include but are not limited to, Cabozantinib (XL184, CAS 849217-68-1); Foretinib (GSK1363089, formerly XL880, CAS 849217-64-7); Tivantinib (ARQ197, CAS 1000873-98-2); 1-(2-Hydroxy-2-methylpropyl)-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (AMG 458); Cryzotinib (Xalkori®, PF-02341066); (3Z)-5-(2,3-Dihydro-1H-indol-1-ylsulfonyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-1,3-dihydro-2H-indol-2-one (SU11271); (3Z)-N-(3-Chlorophenyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-N-methyl-2-oxoindoline-5-sulfonamide (SU11274); (3Z)-N-(3-Chlorophenyl)-3-{[3,5-dimethyl-4-(3-morpholin-4-ylpropyl)-1H-pyrrol-2-yl]methylene}-N-methyl-2-oxoindoline-5-sulfonamide (SU11606); 6-[Difluoro[6-(1-methyl-1H-pyrazol-4-yl)-1,2,4-triazolo[4,3-b]pyridazin-3-yl]methyl]-quinoline (JNJ38877605, CAS 943540-75-8); 2-[4-[1-(Quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl]-1H-pyrazol-1-yl]ethanol (PF04217903, CAS 956905-27-4); N-((2R)-1,4-Dioxan-2-ylmethyl)-N-methyl-N'-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]sulfamide (MK2461, CAS 917879-39-1); 6-[[6-(1-Methyl-1H-pyrazol-4-yl)-1,2,4-triazolo[4,3-b]pyridazin-3-yl]thio]-quinoline

(SGX523, CAS 1022150-57-7); and (3Z)-5-[[(2,6-Dichlorophenyl)methyl]sulfonyl]-3-[[3,5-dimethyl-4-[[(2R)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl]-1H-pyrrol-2-yl]methylene]-1,3-dihydro-2H-indol-2-one (PHA665752, CAS 477575-56-7).

[00404] IGF1R inhibitors include but are not limited to, BMS-754807, XL-228, OSI-906, GSK0904529A, A-928605, AXL1717, KW-2450, MK0646, AMG479, IMCA12, MEDI-573, and BI836845. See *e.g.*, Yee, JNCI, 104; 975 (2012) for review.

[00405] In another aspect, the present invention provides a method of treating or preventing cancer by administering to a subject in need thereof an antibody drug conjugate of the present invention in combination with one or more GNAQ/GNA11 downstream signaling pathway inhibitors, including but not limited to, β-arrestin inhibitors, GRK inhibitors, MAPK inhibitors, PI3K inhibitors, JAK inhibitors, etc.

[00406] For example, phosphoinositide 3-kinase (PI3K) inhibitors include but are not limited to, Idelalisib (Zydelig, GS-1101, Cal-101), 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730); 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806); 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine (also known as BKM120 or NVP-BKM120, and described in PCT Publication No. WO2007/084786); Tozasertib (VX680 or MK-0457, CAS 639089-54-6); (5Z)-5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidinedione (GSK1059615, CAS 958852-01-2); (1E,4S,4aR,5R,6aS,9aR)-5-(Acetyloxy)-1-[(di-2-propenylamino)methylene]-4,4a,5,6,6a,8,9,9a-octahydro-11-hydroxy-4-(methoxymethyl)-4a,6a-dimethyl-cyclopenta[5,6]naphtho[1,2-c]pyran-2,7,10(1H)-trione (PX866, CAS 502632-66-8); and 8-Phenyl-2-(morpholin-4-yl)-chromen-4-one (LY294002, CAS 154447-36-6).

[00407] In yet another aspect, the present invention provides a method of treating or preventing cancer by administering to a subject in need thereof an antibody drug conjugate of the present invention in combination with one or more pro-apoptosis, including but not limited to, IAP inhibitors, Bcl2 inhibitors, MCl1 inhibitors, Trail agents, Chk inhibitors.

[00408] For examples, IAP inhibitors include but are not limited to, LCL161, GDC-0917, AEG-35156, AT406, and TL32711. Other examples of IAP inhibitors include but are not limited to those disclosed in WO04/005284, WO 04/007529, WO05/097791, WO 05/069894, WO 05/069888, WO 05/094818, US2006/0014700, US2006/0025347, WO 06/069063, WO

06/010118, WO 06/017295, and WO08/134679, all of which are incorporated herein by reference.

[00409] BCL-2 inhibitors include but are not limited to, Venetoclax (also known as GDC-0199, ABT-199, RG7601); 4-[4-[[2-(4-Chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (also known as ABT-263 and described in PCT Publication No. WO 09/155386); Tetrocarcin A; Antimycin; Gossypol ((-)BL-193); Obatoclax; Ethyl-2-amino-6-cyclopentyl-4-(1-cyano-2-ethoxy-2-oxoethyl)-4Hchromone-3-carboxylate (HA14 – 1); Oblimersen (G3139, Genasense®); Bak BH3 peptide; (-)-Gossypol acetic acid (AT-101); 4-[4-[(4'-Chloro[1,1'-biphenyl]-2-yl)methyl]-1-piperazinyl]-**N**-[[4-[[(1**R**)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl]amino]-3-nitrophenyl]sulfonyl]-benzamide (ABT-737, CAS 852808-04-9); and Navitoclax (ABT-263, CAS 923564-51-6).

[00410] Proapoptotic receptor agonists (PARAs) including DR4 (TRAILR1) and DR5 (TRAILR2), including but are not limited to, Dulanermin (AMG-951, RhApo2L/TRAIL); Mapatumumab (HRS-ETR1, CAS 658052-09-6); Lexatumumab (HGS-ETR2, CAS 845816-02-6); Apomab (Apomab®); Conatumumab (AMG655, CAS 896731-82-1); and Tigatuzumab (CS1008, CAS 946415-34-5, available from Daiichi Sankyo).

[00411] Checkpoint Kinase (CHK) inhibitors include but are not limited to, 7-Hydroxystaurosporine (UCN-01); 6-Bromo-3-(1-methyl-1*H*-pyrazol-4-yl)-5-(3*R*)-3-piperidinyl-pyrazolo[1,5-*a*]pyrimidin-7-amine (SCH900776, CAS 891494-63-6); 5-(3-Fluorophenyl)-3-ureidothiophene-2-carboxylic acid N-[(S)-piperidin-3-yl]amide (AZD7762, CAS 860352-01-8); 4-[((3S)-1-Azabicyclo[2.2.2]oct-3-yl)amino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one (CHIR 124, CAS 405168-58-3); 7-Aminodactinomycin (7-AAD), Isogranulatimide, debromohymenialdisine; N-[5-Bromo-4-methyl-2-[(2S)-2-morpholinylmethoxy]-phenyl]-N'-(5-methyl-2-pyrazinyl)urea (LY2603618, CAS 911222-45-2); Sulforaphane (CAS 4478-93-7, 4-Methylsulfinylbutyl isothiocyanate); 9,10,11,12-Tetrahydro- 9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocine-1,3(2*H*)-dione (SB-218078, CAS 135897-06-2); and TAT-S216A (YGRKKRRQRRRLYRSPAMPENL (SEQ ID NO: 282)), and CBP501 ((d-Bpa)sws(d-Phe-F5)(d-Cha)rrrqrr).

[00412] In a further embodiment, the present invention provides a method of treating or preventing cancer by administering to a subject in need thereof an antibody drug conjugate of the present invention in combination with one or more immunomodulators (*e.g.*, one or more of: an activator of a costimulatory molecule or an inhibitor of an immune checkpoint molecule).

[00413] In certain embodiments, the immunomodulator is an activator of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, STING, or CD83 ligand.

[00414] In certain embodiments, the immunomodulator is an inhibitor of an immune checkpoint molecule. In one embodiment, the immunomodulator is an inhibitor of PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta. In one embodiment, the inhibitor of an immune checkpoint molecule inhibits PD-1, PD-L1, LAG-3, TIM-3 or CTLA4, or any combination thereof. The term "inhibition" or "inhibitor" includes a reduction in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, an immune checkpoint inhibitor. For example, inhibition of an activity, *e.g.*, a PD-1 or PD-L1 activity, of at least 5%, 10%, 20%, 30%, 40%, 50% or more is included by this term. Thus, inhibition need not be 100%.

[00415] Inhibition of an inhibitory molecule can be performed at the DNA, RNA or protein level. In some embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is a polypeptide *e.g.*, a soluble ligand (*e.g.*, PD-1-Ig or CTLA-4 Ig), or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule; *e.g.*, an antibody or fragment thereof (also referred to herein as "an antibody molecule") that binds to PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta, or a combination thereof.

[00416] In one embodiment, the antibody molecule is a full antibody or fragment thereof (*e.g.*, a Fab, $F(ab')_2$, Fv, or a single chain Fv fragment (scFv)). In yet other embodiments, the antibody molecule has a heavy chain constant region (Fc) chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4, more particularly, the heavy chain constant region of IgG1 or IgG4 (*e.g.*, human IgG1 or IgG4). In one embodiment, the heavy chain constant region is human IgG1 or human IgG4. In one embodiment, the constant region is altered, *e.g.,* mutated, to modify the properties of the antibody molecule (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

[00417] In certain embodiments, the antibody molecule is in the form of a bispecific or multispecific antibody molecule. In one embodiment, the bispecific antibody molecule has a first binding specificity to PD-1 or PD-L1 and a second binding specificity, *e.g.*, a second binding specificity to TIM-3, LAG-3, or PD-L2. In one embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and TIM-3. In another embodiment, the bispecific antibody molecule binds to PD-1 or PD-L1 and LAG-3. In another embodiment, the bispecific antibody molecule binds to PD-1 and PD-L1. In yet another embodiment, the bispecific antibody molecule binds to PD-1 and PD-L2. In another embodiment, the bispecific antibody molecule binds to TIM-3 and LAG-3. Any combination of the aforesaid molecules can be made in a multispecific antibody molecule, *e.g.*, a trispecific antibody that includes a first binding specificity to PD-1 or PD-1, and a second and third binding specificities to two or more of: TIM-3, LAG-3, or PD-L2.

[00418] In certain embodiments, the immunomodulator is an inhibitor of PD-1, *e.g.*, human PD-1. In another embodiment, the immunomodulator is an inhibitor of PD-L1, *e.g.*, human PD-L1. In one embodiment, the inhibitor of PD-1 or PD-L1 is an antibody molecule to PD-1 or PD-L1. The PD-1 or PD-L1 inhibitor can be administered alone, or in combination with other immunomodulators, *e.g.*, in combination with an inhibitor of LAG-3, TIM-3 or CTLA4. In an exemplary embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a LAG-3 inhibitor, *e.g.*, an anti-LAG-3 antibody molecule. In another embodiment, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 or PD-L1 antibody molecule, is administered in combination with a TIM-3 inhibitor, *e.g.*, an anti-TIM-3 antibody molecule. In yet other embodiments, the inhibitor of PD-1 or PD-L1, *e.g.*, the anti-PD-1 antibody molecule, is administered in combination with a LAG-3 inhibitor, *e.g.*, an anti-LAG-3 antibody molecule, and a TIM-3 inhibitor, *e.g.*, an anti-TIM-3 antibody molecule. Other combinations of immunomodulators with a PD-1 inhibitor (e.g., one or more of PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR) are also within the present invention. Any of the antibody molecules known in the art or disclosed herein can be used in the aforesaid combinations of inhibitors of checkpoint molecule.

[00419] In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody chosen from Nivolumab, Pembrolizumab or Pidilizumab. In some embodiments, the anti-PD-1 antibody is Nivolumab. Alternative names for Nivolumab include MDX- 1106, MDX-1106-04, ONO-4538, or BMS-936558. In some embodiments, the anti-PD- 1 antibody is Nivolumab (CAS Registry Number: 946414-94-4). Nivolumab is a fully human IgG4 monoclonal antibody which specifically blocks PD1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD1 are disclosed in US Pat No. 8,008,449 and PCT Publication No. WO2006/121168.

[00420] In other embodiments, the anti-PD-1 antibody is Pembrolizumab. Pembrolizumab (Trade name KEYTRUDA formerly Lambrolizumab,-also known as Merck 3745, MK-3475 or SCH-900475) is a humanized IgG4 monoclonal antibody that binds to PD1. Pembrolizumab is disclosed, *e.g.*, in Hamid, O. *et al*. (2013) *New England Journal of Medicine* 369 (2): 134–44, PCT Publication No. WO2009/114335, and US Patent No. 8,354,509.

[00421] In some embodiments, the anti-PD-1 antibody is Pidilizumab. Pidilizumab (CT-011; Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in PCT Publication No. WO2009/101611. Other anti-PD1 antibodies are disclosed in US Patent No. 8,609,089, US Publication No. 2010028330, and/or US Publication No. 20120114649. Other anti-PD1 antibodies include AMP 514 (Amplimmune).

[00422] In some embodiments, the PD-1 inhibitor is PDR001, also known as spartalizumab, or any other anti-PD-1 antibody disclosed in WO2015/112900.

[00423] In some embodiments, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-LI or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 inhibitor is AMP-224.

[00424] In some embodiments, the PD-LI inhibitor is anti-PD-LI antibody. In some embodiments, the anti-PD-LI inhibitor is chosen from YW243.55.S70, MPDL3280A, MEDI-4736, or MDX-1105MSB-0010718C (also referred to as A09-246-2) disclosed in, *e.g.*, WO 2013/0179174, and having a sequence disclosed herein (or a sequence substantially identical or similar thereto, *e.g.*, a sequence at least 85%, 90%, 95% identical or higher to the sequence specified).

[00425] In one embodiment, the PD-L1 inhibitor is MDX-1105. MDX-1105, also known as BMS-936559, is an anti-PD-LI antibody described in PCT Publication No. WO2007/005874.

[00426] In one embodiment, the PD-L1 inhibitor is YW243.55.S70. The YW243.55.S70 antibody is an anti-PD-LI described in PCT Publication No. WO 2010/077634 (heavy and light chain variable region sequences shown in SEQ ID Nos. 20 and 21, respectively).

[00427] In one embodiment, the PD-L1 inhibitor is MDPL3280A (Genentech / Roche). MDPL3280A is a human Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 20120039906.

[00428] In other embodiments, the PD-L2 inhibitor is AMP-224. AMP-224 is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD1 and B7-H1 (B7-DCIg; Amplimmune; *e.g.*, disclosed in PCT Publication Nos. WO2010/027827 and WO2011/066342).

[00429] In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule. In one embodiment, the LAG-3 inhibitor is BMS-986016. In one embodiment, the LAG-3 inhibitor is LAG525 or any anti-LAG3 antibody disclosed in WO2015/138920.

[00430] In one embodiment, the TIM-3 inhibitor is an anti-TIM3 antibody molecule. In one embodiment, the TIM-3 inhibitor is MBG453 or any anti-TIM3 antibody disclosed in WO2015/117002.

Pharmaceutical Compositions

[00431] To prepare pharmaceutical or sterile compositions including immunoconjugates, the immunoconjugates of the invention are mixed with a pharmaceutically acceptable carrier or excipient. The compositions can additionally contain one or more other therapeutic agents that are suitable for treating or preventing a PMEL17 expressing cancer (including, but not limited to subcutaneous melanoma, uveal melanoma, hepatocellular carcinoma, and a metastatic cancer thereof).

[00432] Formulations of therapeutic and diagnostic agents can be prepared by mixing with physiologically acceptable carriers, excipients, or stabilizers in the form of, *e.g.*, lyophilized powders, slurries, aqueous solutions, lotions, or suspensions (*see, e.g.*, Hardman *et al.*, Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y., 2001; Gennaro, Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y., 2000; Avis, *et al.* (eds.), Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY, 1993; Lieberman, *et al.* (eds.), Pharmaceutical Dosage Forms: tablets, Marcel Dekker, NY, 1990; Lieberman, *et al.* (eds.) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY, 1990; Weiner and Kotkoskie, Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y., 2000).

[00433] Selecting an administration regimen for a therapeutic depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells in the biological matrix. In certain embodiments, an administration regimen maximizes the amount of therapeutic delivered to the patient consistent with an acceptable level of side effects. Accordingly, the amount of biologic delivered depends in part on the particular entity and the severity of the condition being treated. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules

are available (*see, e.g.*, Wawrzynczak, Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK, 1996; Kresina (ed.), Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, N.Y., 1991; Bach (ed.), Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, N.Y., 1993; Baert *et al.*, New Engl. J. Med. 348:601-608, 2003; Milgrom *et al.*, New Engl. J. Med. 341:1966-1973, 1999; Slamon *et al.*, New Engl. J. Med. 344:783-792, 2001; Beniaminovitz *et al.*, New Engl. J. Med. 342:613-619, 2000; Ghosh *et al.*, New Engl. J. Med. 348:24-32, 2003; Lipsky *et al.*, New Engl. J. Med. 343:1594-1602, 2000).

[00434] Determination of the appropriate dose is made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment or prevention or predicted to affect treatment or prevention. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, *e.g.*, the inflammation or level of inflammatory cytokines produced.

[00435] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors known in the medical arts.

[00436] Compositions comprising antibodies or fragments thereof of the invention can be provided by continuous infusion, or by doses at intervals of, *e.g.*, one day, one week, or 1-7 times per week, once every other week, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once very eight weeks. Doses may be provided intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, or by inhalation. A specific dose protocol is one involving the maximal dose or dose frequency that avoids significant undesirable side effects.

[00437] For the immunoconjugates of the invention, the dosage administered to a patient may be 0.0001 mg/kg to 100 mg/kg of the patient's body weight. The dosage may be between 0.0001 mg/kg and 30 mg/kg, 0.0001 mg/kg and 20 mg/kg, 0.0001 mg/kg and 10 mg/kg, 0.0001 mg/kg and 5 mg/kg, 0.0001 and 2 mg/kg, 0.0001 and 1 mg/kg, 0.0001 mg/kg and 0.75 mg/kg, 0.0001 mg/kg and 0.5 mg/kg, 0.0001 mg/kg to 0.25 mg/kg, 0.0001 to 0.15 mg/kg, 0.0001 to 0.10 mg/kg, 0.001 to 0.5 mg/kg, 0.01 to 0.25 mg/kg or 0.01 to 0.10 mg/kg of the patient's body weight. The dosage of the antibodies or fragments thereof of the invention may be calculated using the patient's weight in kilograms (kg) multiplied by the dose to be administered in mg/kg.

[00438] Doses of the immunoconjugates the invention may be repeated and the administrations may be separated by less than 1 day, at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, 4 months, 5 months, or at least 6 months. In some embodiments, the immunoconjugates of the invention may be given twice weekly, once weekly, once every two weeks, once every three weeks, once every four weeks, or less frequently. In a specific embodiment, doses of the immunoconjugates of the invention are repeated every 2 weeks.

[00439] An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method, route and dose of administration and the severity of side effects (*see, e.g.*, Maynard *et al.*, A Handbook of SOPs for Good Clinical Practice, Interpharm Press, Boca Raton, Fla., 1996; Dent, Good Laboratory and Good Clinical Practice, Urch Publ., London, UK, 2001).

[00440] The route of administration may be by, *e.g.*, topical or cutaneous application, injection or infusion by subcutaneous, intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intracerebrospinal, intralesional administration, or by sustained release systems or an implant (*see, e.g.*, Sidman *et al.*, Biopolymers 22:547-556, 1983; Langer *et al.*, J. Biomed. Mater. Res. 15:167-277, 1981; Langer, Chem. Tech. 12:98-105, 1982; Epstein *et al.*, Proc. Natl. Acad. Sci. USA 82:3688-3692, 1985; Hwang *et al.*, Proc. Natl. Acad. Sci. USA 77:4030-4034, 1980; U.S. Pat. Nos. 6,350,466 and 6,316,024). Where necessary, the composition may also include a solubilizing agent or a local anesthetic such as lidocaine to ease pain at the site of the injection, or both. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. *See, e.g.*, U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO

97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety.

[00441] A composition of the present invention may also be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Selected routes of administration for the immunoconjugates of the invention include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. Parenteral administration may represent modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. Alternatively, a composition of the invention can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. In one embodiment, the immunoconjugates of the invention is administered by infusion. In another embodiment, the immunoconjugates of the invention is administered subcutaneously.

[00442] If the immunoconjugates of the invention are administered in a controlled release or sustained release system, a pump may be used to achieve controlled or sustained release (*see* Langer, *supra*; Sefton, CRC Crit. Ref Biomed. Eng. 14:20, 1987; Buchwald *et al.*, Surgery 88:507, 1980; Saudek *et al.*, N. Engl. J. Med. 321:574, 1989). Polymeric materials can be used to achieve controlled or sustained release of the therapies of the invention (*see, e.g.*, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla., 1974; Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York, 1984; Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61, 1983; see also Levy *et al.*, Science 228:190, 1985; During *et al.*, Ann. Neurol. 25:351, 1989; Howard *et al.*, J. Neurosurg. 7 1:105, 1989; U.S. Pat. No. 5,679,377; U.S. Pat. No. 5,916,597; U.S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-

glycolides) (PLGA), and polyorthoesters. In one embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. A controlled or sustained release system can be placed in proximity of the prophylactic or therapeutic 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).

[00443] Controlled release systems are discussed in the review by Langer, Science 249:1527-1533, 1990). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more immunoconjugates of the invention. *See, e.g.*, U.S. Pat. No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.*, Radiotherapy & Oncology 39:179-189, 1996; Song *et al.*, PDA Journal of Pharmaceutical Science & Technology 50:372-397, 1995; Cleek *et al.*, Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, 1997; and Lam *et al.*, Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, 1997, each of which is incorporated herein by reference in their entirety.

[00444] If the immunoconjugates of the invention are administered topically, they can be formulated in the form of an ointment, cream, transdermal patch, lotion, gel, spray, aerosol, solution, emulsion, or other form well-known to one of skill in the art. *See, e.g.*, Remington's Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms, 19th ed., Mack Pub. Co., Easton, Pa. (1995). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity, in some instances, greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (*e.g.*, preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, in some instances, in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (*e.g.*, a gaseous propellant, such as freon) or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well-known in the art.

[00445] If the compositions comprising the immunoconjugates are administered intranasally, it can be formulated in an aerosol form, spray, mist or in the form of drops. In particular, prophylactic or therapeutic agents for use according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a

nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges (composed of, *e.g.*, gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00446] Methods for co-administration or treatment with a second therapeutic agent, *e.g.*, a cytokine, steroid, chemotherapeutic agent, antibiotic, or radiation, are known in the art (*see, e.g.*, Hardman *et al.*, (eds.) (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill, New York, N.Y.; Poole and Peterson (eds.) (2001) Pharmacotherapeutics for Advanced Practice:A Practical Approach, Lippincott, Williams & Wilkins, Phila., Pa.; Chabner and Longo (eds.) (2001) Cancer Chemotherapy and Biotherapy, Lippincott, Williams & Wilkins, Phila., Pa.). An effective amount of therapeutic may decrease the symptoms by at least 10%; by at least 20%; at least about 30%; at least 40%, or at least 50%.

[00447] Additional therapies (*e.g.*, prophylactic or therapeutic agents), which can be administered in combination with the immunoconjugates of the invention may be administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart from the immunoconjugates of the invention. The two or more therapies may be administered within one same patient visit.

[00448] In certain embodiments, the immunoconjugates of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, *see, e.g.*, U.S. Pat. Nos. 4,522,811; 5,374,548; and

5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (*see, e.g.*, Ranade, (1989) J. Clin. Pharmacol. 29:685). Exemplary targeting moieties include folate or biotin (*see, e.g.*, U.S. Pat. No. 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) Biochem. Biophys. Res. Commun. 153:1038); antibodies (Bloeman *et al.*, (1995) FEBS Lett. 357:140; Owais *et al.*, (1995) Antimicrob. Agents Chemother. 39:180); surfactant protein A receptor (Briscoe *et al.*, (1995) Am. J. Physiol. 1233:134); p 120 (Schreier *et al.*, (1994) J. Biol. Chem. 269:9090); *see also* K. Keinanen; M. L. Laukkanen (1994) FEBS Lett. 346:123; J. J. Killion; I. J. Fidler (1994) Immunomethods 4:273.

[00449] The invention provides protocols for the administration of pharmaceutical composition comprising immunoconjugates of the invention alone or in combination with other therapies to a subject in need thereof. The therapies (*e.g.*, prophylactic or therapeutic agents) of the combination therapies of the present invention can be administered concomitantly or sequentially to a subject. The therapy (*e.g.*, prophylactic or therapeutic agents) of the combination therapies of the present invention can also be cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agent) for a period of time and repeating this sequential administration, *i.e.*, the cycle, in order to reduce the development of resistance to one of the therapies (*e.g.*, agents) to avoid or reduce the side effects of one of the therapies (*e.g.*, agents), and/or to improve, the efficacy of the therapies.

[00450] The therapies (*e.g.*, prophylactic or therapeutic agents) of the combination therapies of the invention can be administered to a subject concurrently.

[00451] The term “concurrently” is not limited to the administration of therapies (*e.g.*, prophylactic or therapeutic agents) at exactly the same time, but rather it is meant that a pharmaceutical composition comprising antibodies or fragments thereof the invention are administered to a subject in a sequence and within a time interval such that the antibody drug conjugates of the invention can act together with the other therapy(ies) to provide an increased benefit than if they were administered otherwise. For example, each therapy may be administered to a subject at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each therapy can be administered to a subject separately, in any appropriate form and by any suitable route. In

various embodiments, the therapies (*e.g.*, prophylactic or therapeutic agents) are administered to a subject less than 5 minutes apart, less than 15 minutes apart, less than 30 minutes apart, less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, 24 hours apart, 48 hours apart, 72 hours apart, or 1 week apart. In other embodiments, two or more therapies (*e.g.*, prophylactic or therapeutic agents) are administered to a within the same patient visit.

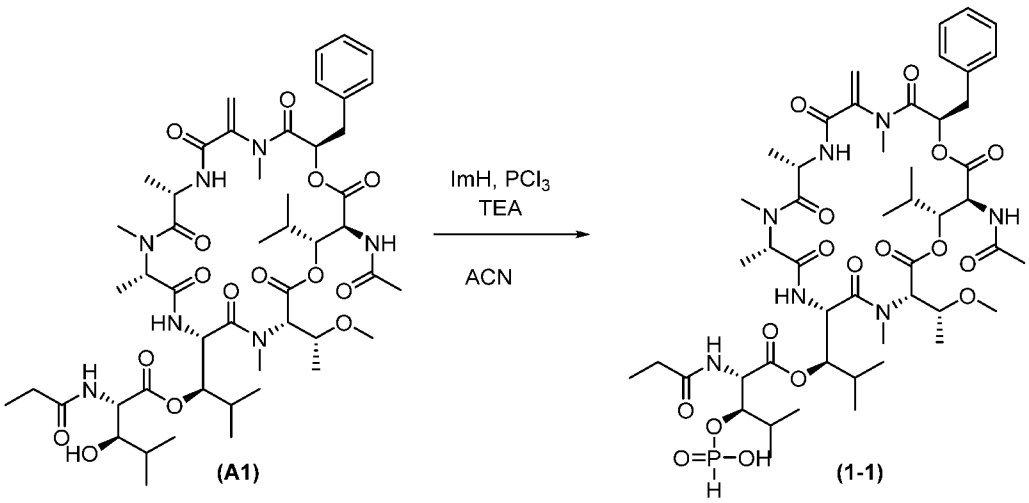
[00452] The prophylactic or therapeutic agents of the combination therapies can be administered to a subject in the same pharmaceutical composition. Alternatively, the prophylactic or therapeutic agents of the combination therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The prophylactic or therapeutic agents may be administered to a subject by the same or different routes of administration. The prophylactic or therapeutic agents of the combination therapies can be administered to a subject in the same pharmaceutical composition. Alternatively, the prophylactic or therapeutic agents of the combination therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The prophylactic or therapeutic agents may be administered to a subject by the same or different routes of administration.

EXAMPLES

Example 1: Synthesis of Exemplary Linker-Drug Compounds

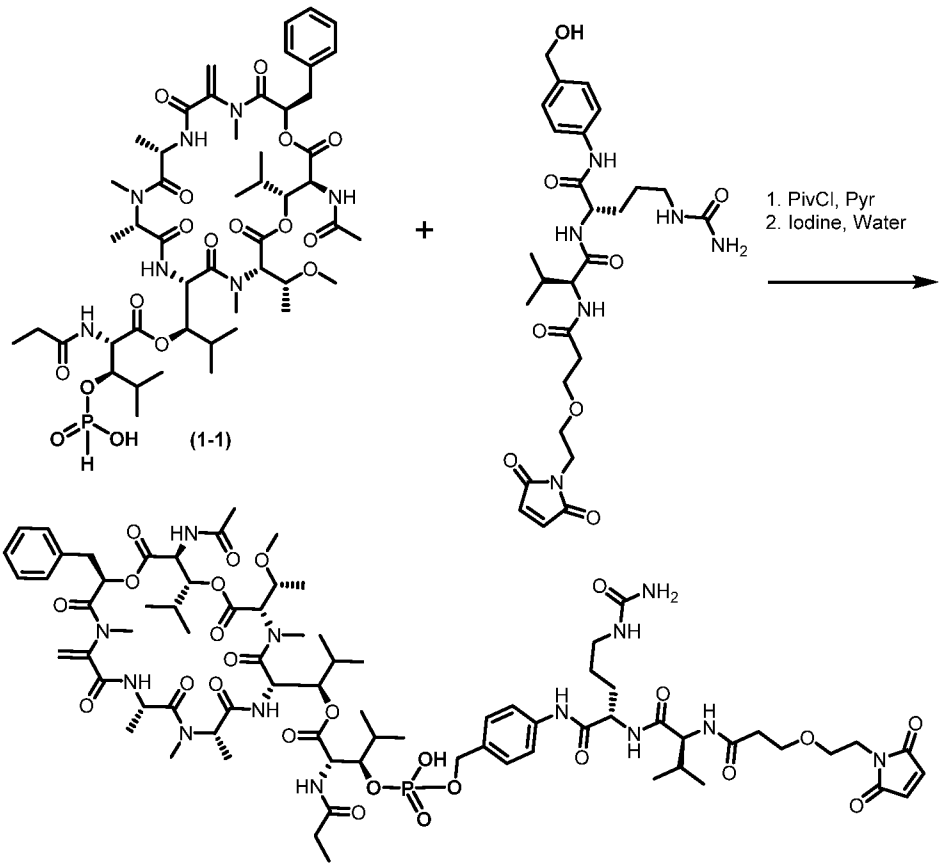
Example 1-1: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(B1)**

Step 1: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((hydroxyhydrophosphoryl)oxy)-4-methyl-2-propionamidopentanoate (1-1):



[00453] Imidazole (102 mg, 1.49 mmol, 15 equiv.) was dissolved in acetonitrile (ACN) (1.4 mL) and cooled in an ice-bath (crashing of ImH is observed and the mixture was raised from the ice-bath to solubilize ImH) while still cold. Then, phosphorus trichloride (1.0 M in ACN) (499 µl, 0.499 mmol, 5 equiv.) was added dropwise (which results in a white suspension) and the mixture was agitiated for 10 min. Then triethylamine (250 µl, 1.796 mmol, 18 equiv.) was added and the mixture agitated for 40 min after which (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-hydroxy-4-methyl-2-propionamidopentanoate **(A1)** (100 mg, 0.100 mmol, 1.0 equiv., compound (A1) was obtained using the method described in Example 3-1) in ACN (1.7 mL) was added. The yellowish-orange heterogenous mixture was warmed to room temperature and agitiated for a total of 60 minutes. The mixture was treated with water (0.2 mL) and the material purified by reverse-phase flash chromatography (0-100% ACN/Water, 40 gram C18 column, neutral mobile phase) and the product fractions collected and lyophillized to afford the H-phosphonate **(1-1)** as a yellowish-white amorphous powder. LCMS: MH+ = 1066.3, 0.78 min (Acquity UPLC BEH C18 1.7um Column, 2-98% 2min run with Water/MeCN +0.1% NH_4OH, basic method).

Step 2: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate (B1):

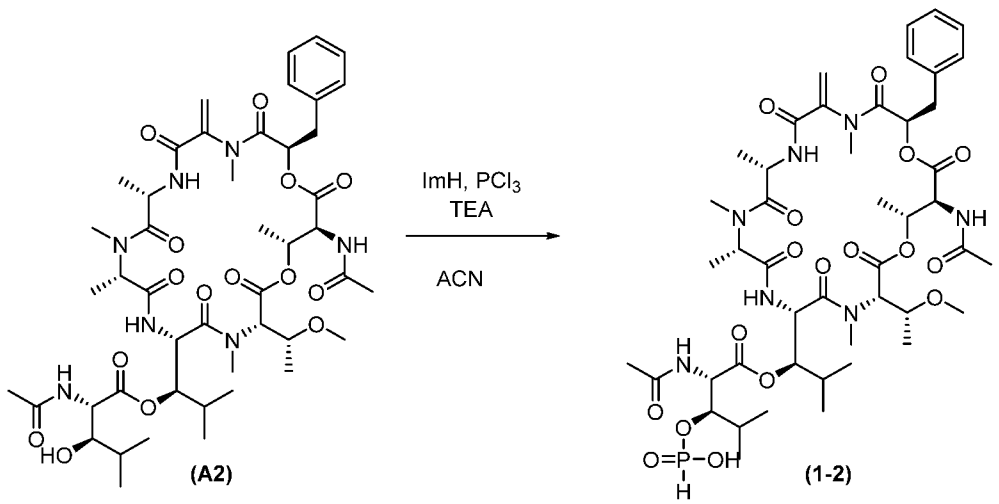


[00454] (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((hydroxyhydrophosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(1-1)** (100 mg, 0.094 mmol, 1.0 equiv.) and (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (108 mg, 0.188 mmol, 2.0 equiv., CAS# is 2055041-37-5) (both lyophilized powders were transferred into a 10 mL vial) and dissolved in pyridine (4 mL). Then, pivaloyl chloride (0.058 mL, 0.469 mmol, 5 equiv.) was added dropwise to give a faint yellow solution. The mixture was agitiated at room temperature for 10 minutes and then 1.0 equiv. additoinal pivaloyl chloride was added. A freshly prepared solution of iodine (47.6 mg, 0.188 mmol, 2.0 equiv.) in pyridine-water (14:1, 750 uL) was added to give a dark-brown clear solution. The mixture was agitated for 25 minutes and directly purified by reverse-phase flash chromatography (40 g C-18 column, 0%Ac/MeCN 3 minutes, then 0-60% ACN/Water over 15 minutes, neutral method) to afford (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-

2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(B-1)**. HRMS; MH+ = 1638.7700, 2.84 min.

Example 1-2: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methylpentanoate **(B2)**

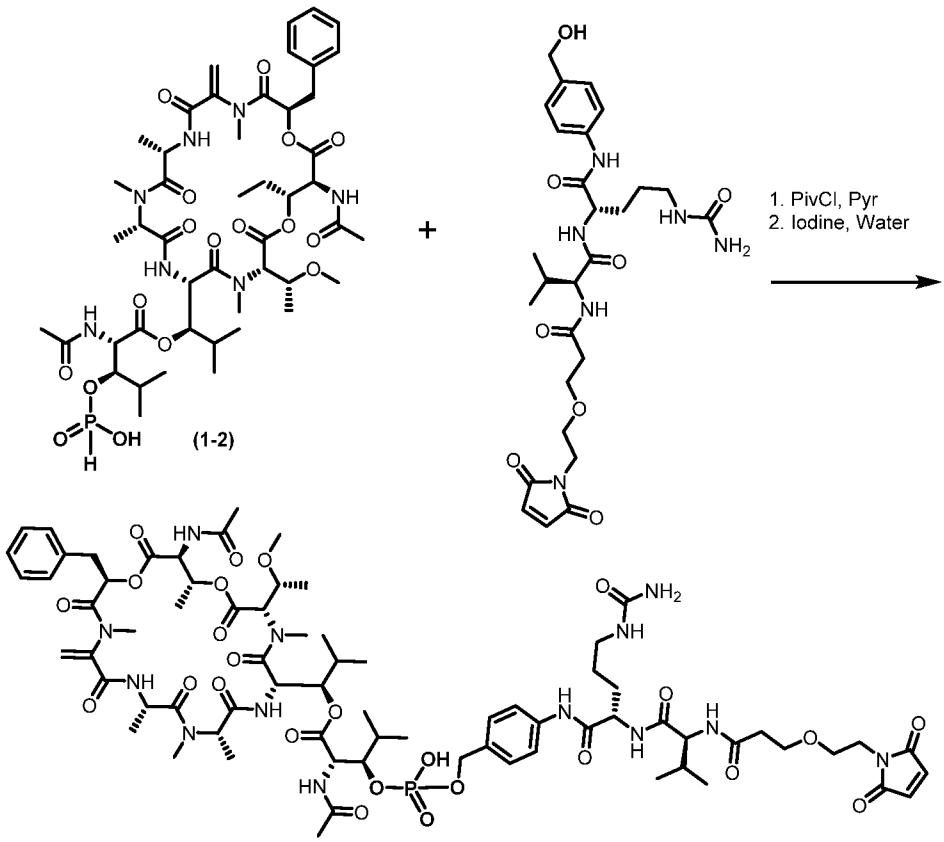
Step 1: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((hydroxyhydrophosphoryl)oxy)-4-methylpentanoate (1-2):



[00455] Imidazole (85 mg, 1.25 mmol, 15 equiv.) was dissolved in acetonitrile (ACN) (2.5 mL) and cooled in an ice-bath (crashing of ImH is observed and the mixture was raised from the ice-bath to solubilize ImH) while still cold. Then, phosphorus trichloride (36.4 µl dissolved in 0.5 mL MeCN, 0.417 mmol, 5 equiv.) was added dropwise (which results in a white suspension) and the mixture was agitiated for 10 min. Then triethylamine (174 µl, 1.25 mmol, 15 equiv.) was added and the mixture agitated for 40 min after which (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-

acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-hydroxy-4-methylpentanoate **(A2)** (80 mg, 0.084 mmol, 1.0 equiv., compound (A2) was obtained using the method described in Example 3-2) in ACN (1.7 mL) was added. The yellowish-orange heterogenous mixture was warmed to room temperature and agitiated for a total of 30 minutes. The mixture was treated with water (1 mL) and the material purified by reverse-phase flash chromatography (0-100% ACN/Water, 40 gram C18 column, neutral mobile phase) and the product fractions collected and lyophillized to afford the H-phosphonate **(1-2)** as a yellowish-white amorphous powder. LCMS: MH+ = 1024.3, 0.78 min (Acquity UPLC BEH C18 1.7um Column, 2-98% 2min run with Water/MeCN +0.1% NH_4OH, basic method).

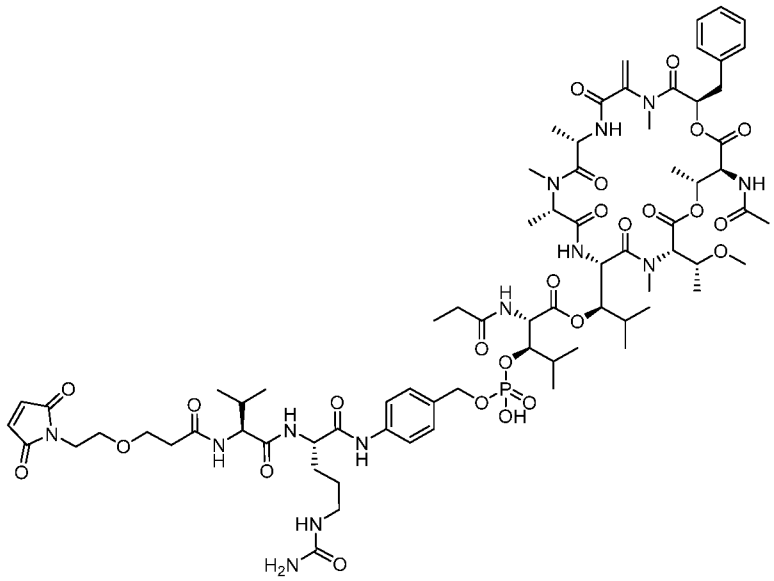
Step 2: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methylpentanoate:



[00456] (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((hydroxyhydrophosphoryl)oxy)-4-methylpentanoate **(1-2)** (50 mg, 0.049 mmol, 1.0 equiv.) and (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# 2055041-37-5) (33.7 mg, 0.059 mmol, 1.2 equiv.) (both lyophilized powders were transferred into a 10 mL vial) and dissolved in pyridine (1 mL). Then, pivaloyl chloride (0.042 mL, 0.342 mmol, 7 equiv.) was added dropwise to give a faint yellow solution. The mixture was agitiated at room temperature for 30 minutes. A freshly prepared solution of iodine (49.6 mg, 0.195 mmol, 4 equiv.) in pyridine-water (20:1, 500 uL) was added to give a dark-brown clear solution. The mixture was agitated for 30 minutes and directly purified by reverse-phase flash chromatography (40 g C-18 column, 0%Ac/MeCN 3 minutes, then 0-70% ACN/Water over 15 minutes, neutral method) to afford (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-

(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(B2)**. HRMS; MH+ = 1595.7200, 2.25 min.

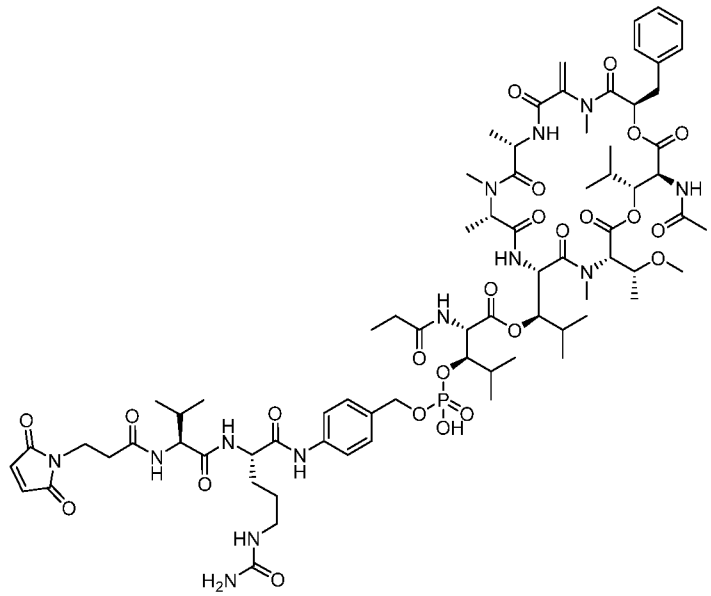
Example 1-3: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(B3)**



(B3)

[00457] Compound (B3) can be obtained using procedures similar to the methods described in Example 1-1, except in step 1 where compound (A3) (from Example 3-3) is used in place of compound (A1).

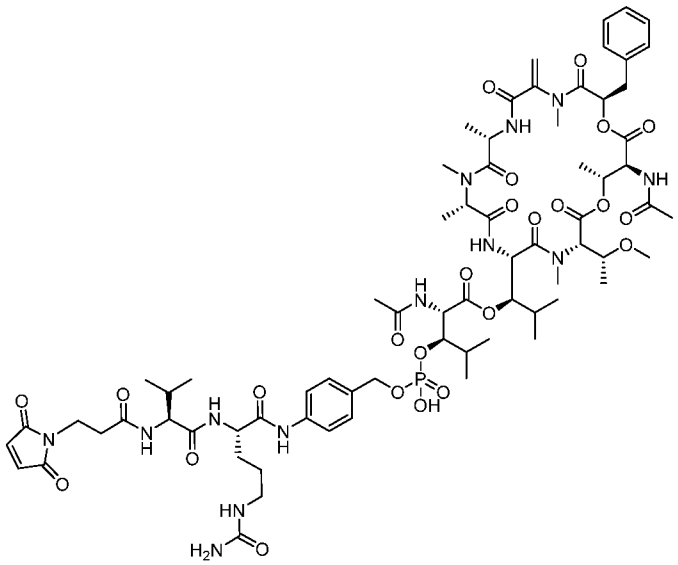
Example 1-4: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(B4)**



(B4)

[00458] Compound (B4) was obtained using procedures similar to the methods described in Example 1-1, except in step 2 where (S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# 1949793-46-7) was used in place of (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# is 2055041-37-5). HRMS; MH+ = 1594.5400, 2.88 min.

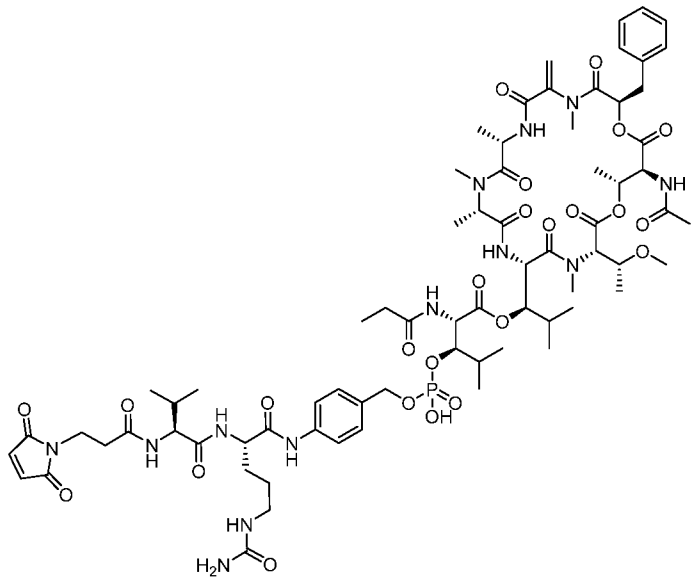
Example 1-5: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methylpentanoate **(B5)**



(B5)

[00459] Compound (B5) can be obtained using procedures similar to the methods described in Example 1-1, except in step 1 where compound (A2) (from Example 3-2) was used in place of compound (A1), and in step 2 where (S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# 1949793-46-7) is used in place of (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# is 2055041-37-5).

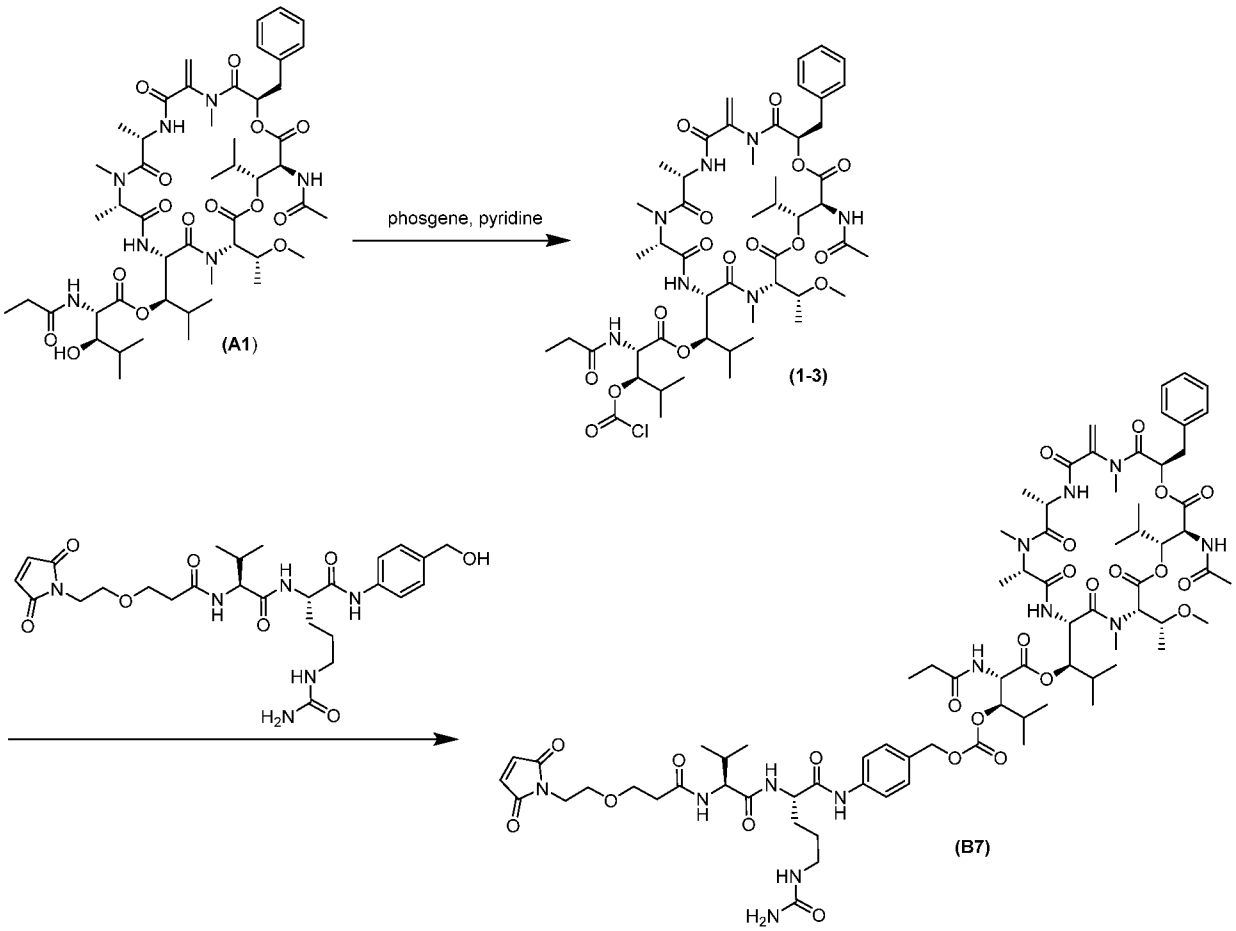
Example 1-6: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)(hydroxy)phosphoryl)oxy)-4-methyl-2-propionamidopentanoate **(B6)**



(B6)

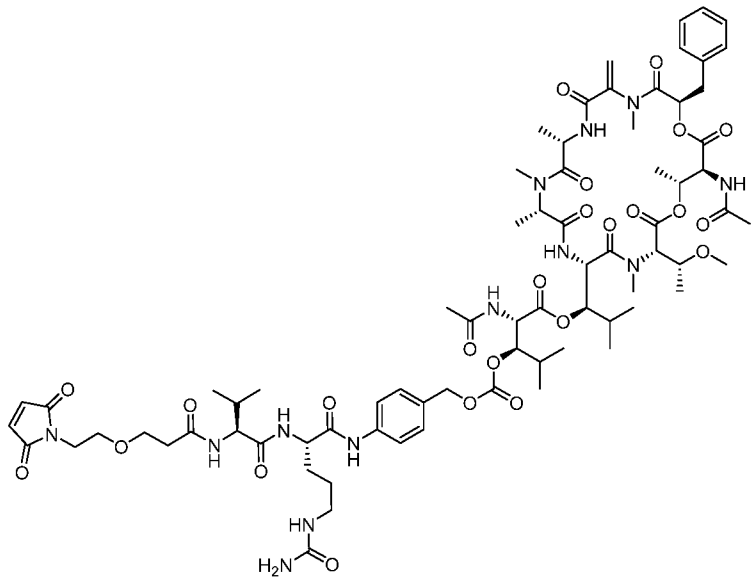
[00460] Compound (B6) can be obtained using procedures similar to the methods described in Example 1-1, except in step 1 where compound (A3) (from Example 3-3) was used in place of compound (A1), and in step 2 where (S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# 1949793-46-7) is used in place of (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# is 2055041-37-5).

Example 1-7: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)oxy)-4-methyl-2-propionamidopentanoate **(B7)**



[00461] Compound (B7) may be obtained by reacting chloroformate (1-3) with (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# is 2055041-37-5). Chloroformate (1-3) may be obtained by reacting Compound (A1) with phosgene.

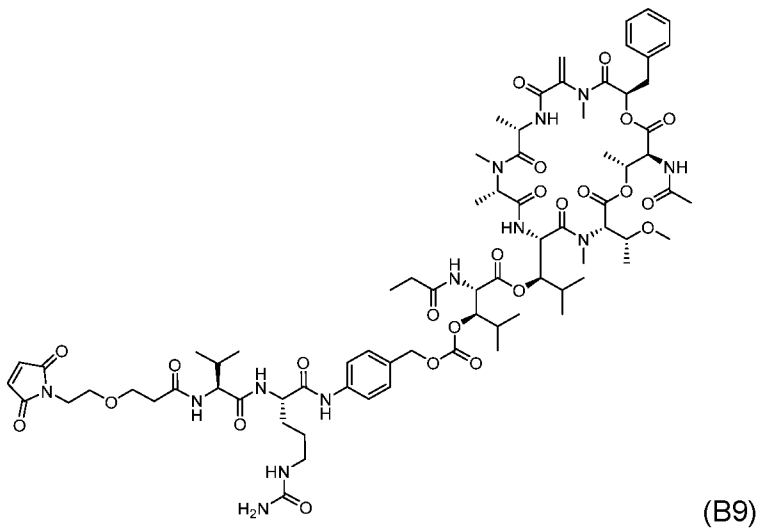
Example 1-8: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)oxy)-4-methylpentanoate **(B8)**



(B8)

[00462] Compound (B8) may be obtained using the method described in Example 1-7, except Compound (A2) is used in place of Compound (A1).

Example 1-9: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)oxy)-4-methyl-2-propionamidopentanoate (**B9)**

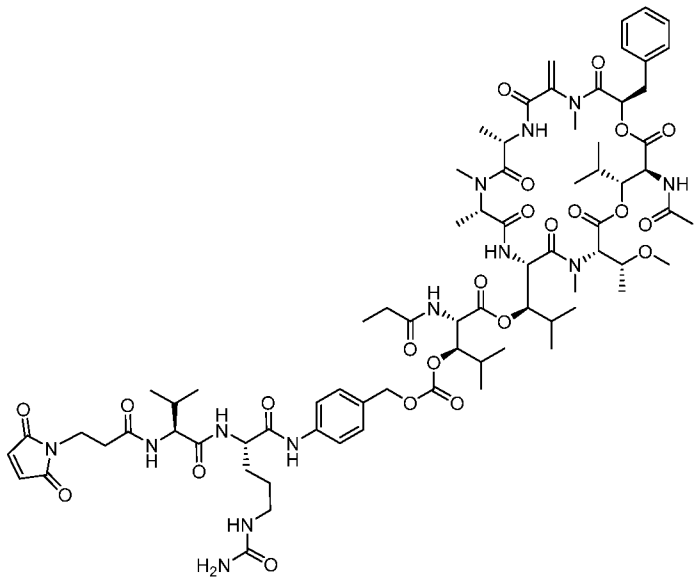


(B9)

[00463] Compound (B9) may be obtained using the method described in Example 1-7, except Compound (A3) is used in place of Compound (A1).

Example 1-10: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-

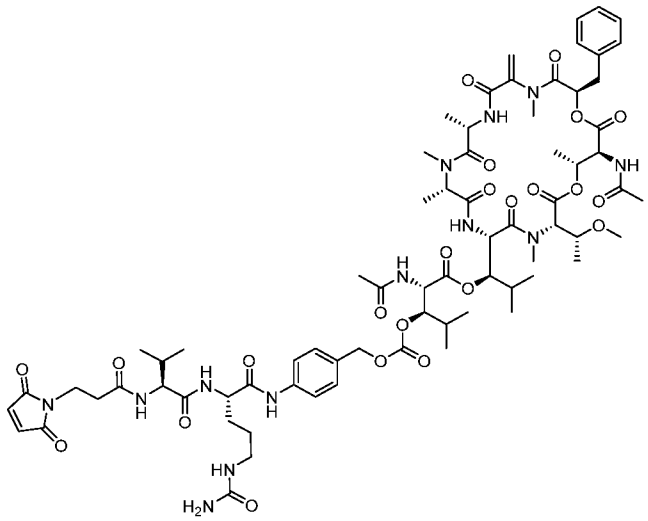
((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)oxy)-4-methyl-2-propionamidopentanoate (**B10)**



(B10)

[00464] Compound (B10) may be obtained using the method described in Example 1-7, except (S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# 1949793-46-7) is used in place of (S)-2-((S)-2-(3-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)propanamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide (CAS# is 2055041-37-5).

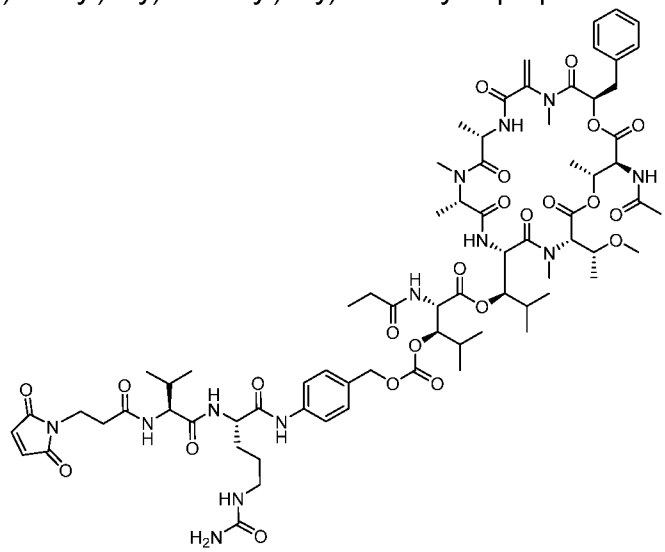
Example 1-11: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)oxy)-4-methylpentanoate (**B11)**



(B11)

[00465] Compound (B11) may be obtained using the method described in Example 1-10, except Compound (A2) is used in place of Compound (A1).

Example 1-12: Synthesis of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-((((4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl)oxy)carbonyl)oxy)-4-methyl-2-propionamidopentanoate (**B12)**



(B12)

[00466] Compound (B12) may be obtained using the method described in Example 1-10, except Compound (A3) is used in place of Compound (A1).

Example 2: Generation of Anti-PMEL17 Antibodies

Example 2-1: Preparation of cell lines expressing PMEL17

[00467] Full length human, cyno and rat PMEL17 genes were synthesized based on amino acid sequences from the GenBank or Uniprot databases. All synthesized DNA fragments were cloned into appropriate expression vectors.

[00468] Engineered stable PMEL17-expressing cell lines were generated and cultured under appropriate selection conditions to produce stable PMEL17-expressing cell lines.

Example 2-2: Whole cell panning against PMEL17

[00469] The phagemid libraries are based on the HuCAL PLATINUM® (Knappik et al., 2000) and Ylanthia concepts (Tiller et al., 2013) and employ the CysDisplayTM technology for displaying the Fab on the phage surface (Lohning, 2001).

[00470] For each panning, about $4x10^{13}$ HuCAL PLATINUM® or about $1x10^{14}$ Ylanthia® phage-antibodies phage-antibodies were blocked in PBS/5% FCS. In parallel, 0.5 - 1.0 x 10^7 target cells expressing antigen PMEL17 and 0.5 - 1.0 x 10^7 adsorption cells without expression of antigen PMEL17 per phage pool were resuspended in 1 ml PBS/5% FCS for blocking on ice. The blocked target cells were spun down, resuspended in the pre-blocked phage particles and incubated for 2 h at 4°C on a rotator. The phage-cell complexes were washed three times in PBS/5% FCS. Elution of specifically bound phage from target cells was performed by 10 min acidic elution with 0.1 M glycine-HCl/0.5 M NaCl, pH 2.2. After centrifugation, the supernatant (eluate) was neutralized by adding 2 M unbuffered Tris. For removal of phage binding to cell surface molecules other than the target antigen, post-adsorption was performed three times with 0.5 - 1.0 x 10^7 adsorption cells each. The final supernatant was used for infection of 14 ml E. coli TG1 culture grown to an OD600 of 0.6 - 0.8. The culture was incubated for 45 min in a water bath at 37°C for phage infection. The bacterial pellets were resuspended in 2xYT medium, plated on LB/Cam agar plates and incubated o/n at 30°C. Colonies were scraped off the plates and were used for phage rescue and phage amplification. Amplified phage were used for the next panning round. The second and third round of the whole cell panning was performed according to the protocol of the first round.

Example 2-3: Subcloning, expression and screening of Fab fragments

[00471] To facilitate rapid expression of soluble Fab, the Fab encoding inserts of the selected HuCAL PLATINUM® phage were subcloned from pMORPH®30 display vector into pMORPH®x11_FH expression vector. Subcloning was performed by triple digest via EcoRI, XbaI and BmtI. After transformation of E. coli TG1-F- single clone expression and preparation of

periplasmic extracts containing HuCAL®-Fab fragments were performed as described previously (Rauchenberger et al., 2003).

[00472] The Fab encoding inserts of the selected Ylanthia® phage were subcloned from pYPdis10 display vector into pYBex10_Fab_FH expression vector. Subcloning was performed by triple digest via XbaI, EcoRI-HF and PstI-HF. After transformation of E. coli TG1-F- single clone expression and preparation of periplasmic extracts containing Ylanthia®-Fab fragments were performed as described previously (Rauchenberger et al., 2003).

[00473] Expression of Fab fragments encoded by pMORPH®x11_Fab_FH and pYBex10_Fab_FH in *E. coli* TG1 F^- cells was carried out in shake flask cultures using 500 ml of 2xYT medium supplemented with 0.1% glucose and 34 µg/ml chloramphenicol. Cultures were shaken at 30°C until the OD_{600} reached a value of 0.5. Fab expression was induced by addition IPTG (isopropyl-ß-D-thiogalactopyranoside) at a final concentration of 0.75 mM and further cultivation for 20 h at 30°C. Cells were harvested and disrupted using lysozyme. His_6-tagged (SEQ ID NO: 267) Fab fragments were isolated via IMAC (Bio-Rad, Germany) and eluted using imidazole. Buffer exchange to 1x Dulbecco´s PBS (pH 7.2) was performed using PD10 columns (GE Healthcare, Germany). Samples were sterile filtered (0.2 µm). Protein concentrations were determined by UV-spectrophotometry. The purity of the samples was analyzed in denaturing, reducing 15% SDS-PAGE. The homogeneity of Fab preparations was determined in native state by size exclusion chromatography (HP-SEC) with calibration standards.

[00474] In FACS screening, purified Fabs were titrated on a variety of PMEL17 expressing and PMEL17 non expressing cell lines (for control). Cells were harvested using Accutase, adjusted to ~ $4x10^6$ cells/ml into FACS buffer (PBS, 3%FCS and 0,02% Na-Azide) and kept on ice to avoid internalization. 15 µl of cell suspension/well were transferred into 384 well V-bottom plates (Greiner, Cat# 781280) and incubated with 15 µl of Fab at different concentrations (most commonly from 200 to $3,5x10^{-3}$nm) for 1 hour at 4°C, gently shaking. Following incubation, cells were washed three times with FACS buffer. After each washing step, cells were centrifuged (250xg, 4 min, 4°C) and carefully resuspended. 15 µl of detection antibody conjugated to PE (PE-conjugated goat anti-human IgG, F(ab`)2 fragment specific, 1:150 in FACS buffer; Jackson Immuno Research, #109-116-097) or Alexa Fluor (Alexa Fluor-conjugated goat anti-human IgG, F(ab`)2 fragment specific, 1:150 in FACS buffer; Jackson Immuno Research, #109-606-097) were added and samples were incubated for 45 minutes to 1 hour on ice in the dark, gently shaking. After 3 washing steps, cells were resuspended in 30 µl of FACS buffer and samples were measured using the IntelliCyt HTFC device.

[00475] In order additionally verify the specificity of the identified antibodies, the antigen was immuno-captured from cell lysate and used as coating material for ELISA based screenings. PMEL17 expressing and PMEL17 non expressing cells (used as negative control) were centrifugated (250g, 5min) and resuspended in lysis buffer (MSD Tris Lysis Buffer, Meso Scale Discovery, R60TX-2) containing protease inhibitors (Complete EDTA free Protease Inhibitor Cocktail, Roche, 11 873 580 001) at $1x10^7$ to $1x10^8$ cells/mL and incubated 30 min at 4°C. Lysate was spinned down at 13000rpm for 5 minutes to discard cell debris and the supernatant was aliquotted and stored at -80°C. Preliminary testing demonstrated that the lysate could be freezed and thawed 3 times without major loss of signal in ELISA.

[00476] So as to perform the screening ELISA anti-His IgGs were coated overnight on a maxisorb 384 wells plate (R&D systems, MAB050, 10 µg/ml, 20 µl per well). Plates were blocked with 3% BSA and 20 µl of purified Fab were transferred at different concentrations (most commonly from 400 to 0,2nM) to each well for 1 hour. The plate was washed 3 times and 20 µl PMEL17 containing cell lysate was added at a concentration of 2x105 lysed cells/well for 1 hour. After 3 additional washing, the presence of PMEL17 was revealed using the tool antibody PMEL17 biotinylated (5 µg/ml, 20 µl per well) and streptavidin-ECL (Dianova, 13MSA37, 1:1500, 20 µl per well). 20 µl per well of MSD read buffer 1X (Meso Scale Discovery, R92TC-2) were added to the plate and signals were detected via the MSD Sector Imager 6000.

Example 2-4: Conversion into IgG

[00477] Conversion of selected Fabs into IgGs was achieved by a PCR-based method in 96-well format. The Fab bacterial expression vectors pMORPH®x11_FH and pYBex10_Fab_FH were converted into the IgG mammalian expression vector pMORPH®4 and pYMex10 (for HuCAL and Ylanthia clones, respectively).

[00478] pMORPHx11_FH plasmid DNA was first amplified by PCR using a biotinylated primer specific to the phoA leader region and a non biotinylated primer specific to the bacterial CL domain. The amplified product was captured on streptavidin beads, digested with BsiWI or HpaI (for VLkappa or VLlambda clones, respectively), washed and then digested again with MfeI. This procedure resulted in the release of the purified vector backbone into the supernatant, now lacking the bacterial constant light chain region (CL) and the phoA heavy chain leader. A kappa or lambda specific mammalian pIN expression cassette was then cloned into the vector backbone carrying the mammalian CL, polyA site, CMV promotor and mammalian heavy chain leader sequence. In a second PCR step, the newly generated Fab insert was amplified again using a biotinylated primer specific to the CH1 region and a non-biotinylated primer binding within the

bacterial ompA leader. The PCR product was captured on streptavidin beads, digested with EcoRV, washed and digested with BlpI resulting in the release of the purified insert into the supernatant. Inserts were finally cloned into the Fab_Cys acceptor vector for expression in mammalian cells.

[00479] pYBex10_Fab_FH plasmid DNA was first amplified by PCR using a biotinylated primer specific to the phoA leader region and a non biotinylated primer specific to the bacterial CL domain. The amplified product was captured on streptavidin beads, digested with NheI, washed and then digested again with KpnI. This procedure resulted in the release of the purified vector backbone into the supernatant, now lacking the bacterial constant light chain region (CL) and the phoA heavy chain leader. A kappa or lambda specific mammalian pIN expression cassette was then cloned into the vector backbone carrying the mammalian CL, polyA site, CMV promotor and mammalian heavy chain leader sequence. In a second PCR step, the newly generated Fab insert was amplified again using a biotinylated primer specific to the CH1 region and a non-biotinylated primer binding within the bacterial ompA leader. The PCR product was captured on streptavidin beads, digested with XhoI, washed and digested with NdeI resulting in the release of the purified insert into the supernatant. Inserts were finally cloned into the Fab_Cys acceptor vector for expression in mammalian cells.

[00480] After transformation of E. coli XL-1 blue cells, single clones were controlled via colony PCR and sequencing of the whole insert region.

Example 2-5: Confirmatory screening of human IgG

[00481] DNA preparations of single colonies were prepared by using an appropriate DNA preparation kit in combination with the BioRobot®8000 device. Individual DNA concentrations were determined by UV-spectrophotometry. Eukaryotic HEK293 c18 cells (ATCC #CRL-10852) were used in a 96-well expression system for the generation of conditioned cell culture supernatants containing full-length IgG. Eukaryotic HEK293 c18 cells were seeded in a 96-well flat-bottom plate to a density of ~4x10^{4}cells/50µl/well the day before and transfected with equal amounts of Ig expression vector DNA. After incubation for 40-50 h at 37°C and 6% CO2 the culture supernatants were transferred to a 96-well U-bottom plate and cleared by centrifugation. The resulting Ig supernatants were tested by an anti-Fd capture ELISA for calculation of Ig concentration in reference to known standards and stored at -20°C for later use in specificity and/or functional screening assays.

[00482] DNA of clones of interest were subjected to sequencing with primer CMV_HC_for (CTC TAG CGC CAC CAT GAA ACA (SEQ ID NO: 264)) for VH domain and IgG_const_for (AGC

CCA GCA ACA CCA AGG (SEQ ID NO: 265)) for Fc domain followed by light chain sequencing with T7 promoter primer (TAA TAC GAC TCA CTA TAG GG (SEQ ID NO: 266)) to obtain complete IgG sequence information.

[00483] FACS screening was performed in the 384-well plate format using the HTFC screening platform from IntelliCyt. Cells were harvested using Accutase, adjusted to ~ $4x10^6$ cells/ml into FACS buffer (PBS, 3%FCS and 0,02% Na-Azide) and kept on ice to avoid internalization. 15 µl of cell suspension/well were transferred into 384 well V-bottom plates (Greiner, Cat# 781280) and incubated with 15 µl of IgG containing supernatant (or diluted purified control antibodies) for 1 hour at 4°C, gently shaking. Following incubation, cells were washed three times with FACS buffer. After each washing step, cells were centrifuged (250xg, 4 min, 4°C) and carefully resuspended. 15 µl of detection antibody conjugated to PE (PE-conjugated goat anti-human IgG, F(ab`)2 fragment specific, 1:150 in FACS buffer; Jackson Immuno Research, #109-116-097) were added and samples were incubated for 45 minutes to 1 hour on ice in the dark, gently shaking. After 3 washing steps, cells were resuspended in 30 µl of FACS buffer and samples were measured using the IntelliCyt HTFC device.

Example 2-6: Production of human IgG and human Fab_Cys

[00484] Eukaryotic HKB11 cells were transfected with pMORPH®4 or pYMex10 expression vector DNA encoding both heavy and light chains of IgGs. Cell culture supernatant was harvested on day 3 or 7 post transfection. The cell culture supernatant was subjected to standard Protein A affinity chromatography (MabSelect SURE, GE Healthcare) and Capture Select IgG-CH1 (BAC) for human IgG and human Fab_Cys, respectively. If not stated otherwise, buffer exchange was performed to 1x Dulbcecco´s PBS (pH 7.2, Invitrogen) and samples were sterile filtered (0.2 µm pore size). Purity of IgG was analyzed under denaturing, reducing and non-reducing conditions using a Labchip System (GXII, Perkin Elmer, USA) or on SDS-PAGE. Protein concentrations were determined by UV-spectrophotometry and HP-SEC was performed to analyze IgG preparations in native state.

Example 2-7: Production of anti-PMEL17 G1 and G4 antibodies

[00485] For the first panning round, about $4x10^{13}$ HuCAL PLATINUM® phage were blocked with PBS/5% FBS. In parallel, 1.0 x 10^7 target cells expressing antigen PMEL17 and 1.5-3.0 x 10^7 adsorption cells without expression of antigen PMEL17 per phage pool were resuspended in 1 ml PBS/5% FCS for blocking on ice. To preclear non-specific binding, phage were incubated with 0.5 x 10^7 adsorption cells without expression of antigen PMEL17 per phage pool for 30 minutes on ice. After incubation, the cells were pelleted by centrifugation and the supernatant

was added to a fresh sample of with 0.5 x 10^7 adsorption cells without expression of antigen PMEL17. The same incubation conditions were applied and pre-absorption was again applied to a fresh sample of 0.5 x 10^7 adsorption cells without expression of antigen PMEL17 for a total of three pre-absorption rounds. After the final pre-absorption, the supernatant was added to 1.0 x 10^7 target cells expressing antigen PMEL17 and incubated on ice for 2 hours with occasional mixing. The phage-cell complexes were washed three times in PBS/5% FCS. Elution of specifically bound phage from target cells was performed by 10 minute acidic elution with 0.1 M glycine-HCl/0.5 M NaCl, pH 2.5. After centrifugation, the supernatant (eluate) was neutralized by adding 2 M unbuffered Tris and this eluate was used to infect 14 ml *E. coli* TG1 F' culture grown to an OD_{600} of 0.6 - 0.8. The culture was incubated for 20 minutes at 37°C and then an addition 25 minutes at 37°C with shaking at 200 rpm for phage infection. The bacterial pellets were resuspended in 2xYT medium, plated on LB/Chloroamphenicol agar plates and incubated overnight at 30°C. Colonies were scraped off the plates and were used for phage rescue and phage amplification. Amplified phage were used for the next panning round. The second and third rounds of panning were performed similarly except that only about $1x10^{12}$ HuCAL phage was used to reduce background and improve the effectiveness of preclearing. After the final round of panning, plasmid DNA was prepared from each phage output and the Fab-containing inserts were cloned into a bacterial expression vector. After ligation and transformation, individual colonies were picked into 2XT/chloramphenicol and cultured. Fab expression was induced by addition of 0.25 mM IPTG in cultures grown overnight in 96 well microtiter plates at 25°C. Cell pellets were lysed with 0.1% lysozyme in PBS and then blocked by the addition of BSA to a final concentration of 1%. FACS staining was performed on PMEL17-expressing and control cells.

Example 2-8: Apparent affinities of anti-PMEL17 antibodies

[00486] Purified IgGs were titrated on a variety of PMEL17 expressing and PMEL17 non expressing cell lines (for control) to determine EC50 values. Cells were harvested using Accutase, adjusted to ~ 4x106 cells/ml into FACS buffer (PBS, 3%FCS and 0,02% Na-Azide) and kept on ice to avoid internalization. 15 µl of cell suspension/well were transferred into 384 well V-bottom plates (Greiner, Cat# 781280) and incubated with 15 µl of IgGs at different concentrations (most commonly from 200 to 3,5x10-3 nM) for 1 hour at 4°C, gently shaking. Following incubation, cells were washed three times with FACS buffer. After each washing step, cells were centrifuged (250xg, 5 min, 4°C) and carefully resuspended. 15 µl of detection antibody conjugated to PE (PE-conjugated goat anti-human IgG, F(ab`)2 fragment specific, 1:150 in FACS buffer; Jackson Immuno Research, #109-116-097) or Alexa Fluor (Alexa Fluor-conjugated goat anti-human IgG,

F(ab`)2 fragment specific, 1:150 in FACS buffer; Jackson Immuno Research, #109-606-097) were added and samples were incubated for 45 minutes to 1 hour on ice in the dark, gently shaking. After 3 washing steps, cells were resuspended in 30 µl of FACS buffer and samples were measured using the IntelliCyt HTFC device. EC50 values were calculated using the Graphpad Prism software. G-361 melanoma cell line expresses human PMEL17 at a lower level compared to the HKB11-human PMEL17 overexpressing cell line, and therefore allows a more precise ranking of the clones depending on their apparent affinity on cells. As illustrated in Table 3, a variety of EC50 ranging from ~200 pM to ~70nM was reached.

Table 3. Apparent affinities (FACS EC50 (nM)) and cross-reactivity of anti-PMEL17 antibodies.

	G-361 (PE)	G-361 (Alexa Fluor)	HKB11-cyno (Alexa Fluor)	HKB11-rat (Alexa Fluor)	B16-F10 (mouse) (Alexa Fluor)	UACC-62 (PE)	Cross spe profile (based on C14 detection ab)
Y101341	0.4		2.6	1.8	1.2	Negative	h/c/r/m
Y010906	-	2.0	2.0	21.7	139.8	Negative	h/c/r/m
Y010900	-	1.3	1.2	9.3	>100	Negative	h/c/r/m
Y010355	0.5		3.9	0.8	0.8	Negative	h/c/r/m
Y010356	1.6		4.5	1.4	1.4	Negative	h/c/r/m
Y010429	2.5		10.7	1.5	60.2	Negative	h/c/r
MOR024354	-	1.7	2.1	2.4	>100	Negative	h/c/r
Y010415	0.3		5.4	0.4	>100	Negative	h/c/r
Y010903	-	3.2	2.0	5.6	927.5	Negative	h/c/(m)
Y010910	-	10.0	3.5	13.7	41.1	Negative	h/c/(m)
MOR024353	-	62.8	1.6	7.5	>100	Negative	h/c
Y010417	2.8		6.3	>100	>100	Negative	h/c

Example 2-9: Cross-reactivity of anti-PMEL17 antibodies

[00487] The cross-specificity of the IgGs was evaluated in does response FACS on G-361 (human melanoma), HKB11-cyno-PMEL17, HKB11-rat PMEL17 and B16-F10 (mouse PMEL17 expressing melanoma) (Table 3). Testing on G-361 was performed using a detection antibody labelled to PE. In contrast, an Alexa-Fluor labelled detection antibody had to be used for testing the candidates on the other cell lines so as to reach detectable signals.

[00488] IgGs were classified into several epitope groups according to their cross-specificity profiles. The various cross-reactive profiles of the IgGs nevertheless suggest that their target at least 4 epitopes (human/cyno/rat/mouse, human/cyno/rat, human/cyno/mouse and human/cyno).

Example 2-10: ADC assays

[00489] IgGs were tested in dose response for their ability to internalize and induce the killing of various PMEL17 expressing cells in both piggyback ADC assay and after direct conjugation.

[00490] For piggyback ADC assay, the Fab-ZAP (goat anti-hu-mAb-saporin-coupled; ATS Biotechnology, Cat# IT-51) compound was used which specifically binds to human Fc and is coupled to a cytotoxin element, the saporin. Cells were harvested using Accutase and adjusted to $5x10^4$ cells/ml. 50 µl of the cell suspension were transferred per well into a 96-well flat clear bottom white plate (Corning, 3610) and incubated overnight at 37°C, 5% CO2. On the following day, antibody candidates were incubated at different concentrations (most commonly from 44 to 7×10^{-3} nM) with the Fab-ZAP compound at 8 nM for 30 minutes at 37°C. 50 µl per well of the IgG – Fab-ZAP complexes were then added to the target cells. For controls, wells with cells only, cells only incubated with candidate IgGs (=100% viability control) and cells only incubated with Fab-ZAP (to check for unspecific killing of the secondary reagent) were prepared. Final concentration of IgGs were 22 to $3,5 \times 10^{-3}$ nM and Fab-ZAP 4 nM. Plates were incubated for 72 h at 37°C and 5% CO2. The amount of viable cells was evaluated using CellTiter-Glo (Promega #G7571) and the luminescence detected with the Tecan Infinite 500. Viability was then normalized to the cells + IgG only control.

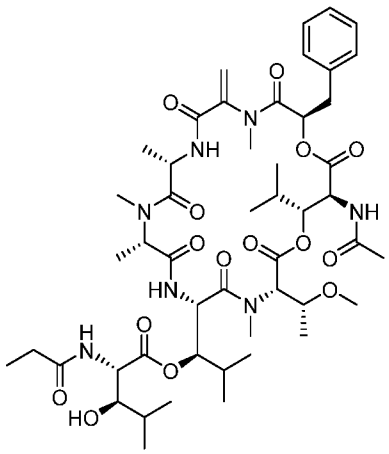
[00491] Almost all IgGs could efficiently kill G-361 melanoma (>80% maximum killing) and showed limited killing on the non PMEL17 expressing 293T cells (<30% maximum killing). G-361 killing was also achieved with a range of EC50s which may be affinity or epitope related. Cross-specificity could also be confirmed for most of the IgGs reactive to human/cyno/rat/mouse, human/cyno/rat and human/cyno/mouse, i.e. IgGs specific to mouse PMEL17 could also kill B16-F10 (mouse melanoma).

Example 2-11: Engineering of Anti-PMEL17 antibodies

[00492] Generally, all engineering processes, were performed using PCR-based strategies. Engineering processes involved the following aspects: Germlining, Removal of PTM sites, pI engineering, and Codon optimization.After synthesis and assembly by overlap extension PCR the re-engineered VH and VL fragments were subcloned into the appropriate vector backbones for subsequent IgG expressions.

Example 3: Synthesis of Compounds A1-A3

Example 3-1: Isolation process of (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-22-isopropyl-3-((R)-1-methoxyethyl)-4,9,10,12,16-pentamethyl-15-methylene-2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-hydroxy-4-methyl-2-propionamidopentanoate (A1) from dried leaves of Ardisia crenata



(A1)

[00493] Compound A1 was isolated based on methods described in Japanese Patent Publication No. JP62283999. Step 1: Extraction: 25 kg dried leaves of Ardisia crenata were milled into fine powder and extracted with 500 L methanol. After filtration the extract was evaporated to dryness. The residue was dissolved in 100 L ethyl acetate and extracted five times with 100 L deionized water (sodium chloride was added in order to improve phase separation. The organic layer was evaporated to dryness. The residue was dissolved in 50 L acetonitrile/water (9/1) and extracted with 50 L heptane. The acetonitrile/water layer was evaporated until only water was left. This was then extracted with 50 L ethyl acetate. The ethyl acetate layer was evaporated to dryness yielding 109 g of crude extract.

[00494] Step 2: Defatting: The crude extract was dissolved in 25 L acetonitrile/water (9/1) and extracted three times with 25 L heptane. The acetonitrile/water layer was evaporated until

only water was left. This was then extracted with 25 L ethyl acetate. The ethyl acetate layer was evaporated to dryness yielding 40 g of crude extract.

[00495] Step 3: Flash chromatography: The crude extract was dissolved in acetone/methanol (1/1), adsorbed onto 100 g Isolute (diatomaceous earth) and evaporated to dryness. Flash chromatography on silica gel with a ternary solvent system with cyclohexane (eluent A), ethyl acetate (eluent B) and methanol (eluent C) was performed (experimental details: column: RediSep Rf 120 g; flow rate: 85 mL/min; gradient: 0 min: 75 % A, 25 % B, 0 % C; 3 min: 75 % A, 25 % B, 0 % C; 10 min: 0 % A, 100 % B, 0 % C; 17.5 min: 0% A, 90% B 10 % C; 25 min: 0 % A, 50 % B, 50 % C; 30 min: 0 % A, 50 % B, 50 % C; the different segments of the gradient are connected by linear changes over time). Four runs with 10 g extract each were performed. Time based fractionation was applied and the collected fractions were analyzed by UPLC-UV-MS for presence of Compound (A1). Fractions containing Compound (A1) were pooled and evaporated to dryness resulting in a fraction of 25 g.

[00496] Step 4: Size-exclusion chromatography (SEC): The 25 g fraction was dissolved in 400 mL methanol and further fractionated by SEC on a column (length 25 cm, diameter 12.5 cm) packed with Sephadex LH20 and methanol as eluent. Fractions of 200 mL each were collected and the collected fractions were analyzed by UPLC-UV-MS for presence of Compound (A1). Fractions containing Compound (A1) were pooled and evaporated to dryness resulting in an enriched fraction of 6.2 g.

[00497] Step 5: 1st preparative HPLC: The enriched fraction of 6.2 g was dissolved in 12 mL methanol/dimethylsulfoxide (1/1) and further fractionated by preparative HPLC (experimental details: column: Sunfire C18, 30 x 150mm, 5µm particle size; eluent A: deionized water with 0.1 % formic acid, eluent B: methanol with 0.1 % formic acid; flow rate 60 mL/min; gradient: 0 min: 35 % A, 65 % B; 0.5 min: 35 % A, 65 % B; 17 min: 15 % A, 85 % B; 15.0 min: 0 % A, 100 % B; 19 min: 0 % A, 100 % B; 19.1 min: 35 % A, 65 % B; 20 min: 35 % A, 65 % B; the different segments of the gradient are connected by linear changes over time). Fractionation was triggered by mass spectrometry. 15 runs with 410 mg enriched fraction each were performed. Fractions containing Compound (A1) were pooled and evaporated to dryness resulting in a semi-pure fraction of 488 mg with an estimated content of 70 % Compound (A1).

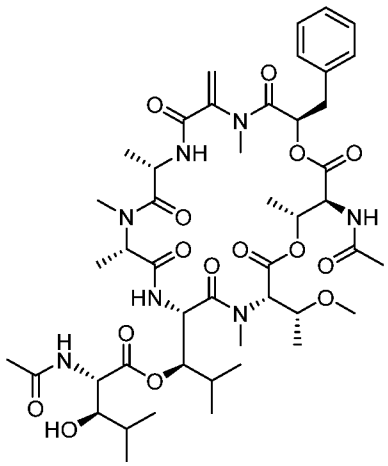
[00498] Step 6: 2nd preparative HPLC: The semi-pure fraction of 488 mg was dissolved in 4 mL methanol and further fractionated by preparative HPLC (experimental details: column: X-Select PFP, 19 x 250mm, 5µm particle size; eluent A: deionized water with 0.1 % formic acid,

eluent B: acetonitrile with 0.1 % formic acid; flow rate 30 mL/min; gradient: 0 min: 45 % A, 55 % B; 0.5 min: 45 % A, 55 % B; 24 min: 25 % A, 75 % B; 24.0 min: 0 % A, 100 % B; 27.5 min: 0 % A, 100 % B; 27.6 min: 45 % A, 55 % B; 30.5 min: 45 % A, 55 % B; the different segments of the gradient are connected by linear changes over time). Fractionation was triggered by mass spectrometry. Five runs witch 98 mg semi-pure fraction each were performed. Fractions containing Compound (A1) were pooled and evaporated to dryness resulting in 287 mg Compound (A1) with a purity > 95 %.

[00499] Compound (A1): Retention time: 4.73 min, molecular formula [M+H]+: C49H76N7O15+, calculated monoisotopic mass [M+H]+: 1002.5394 Da, observed mass: 1002.5391 Da. Experimental details: column: ACQUITY UPLC BEH C18, 2.1 x 100mm, 1.7µm particle size; eluent A: deionized water with 0.1 % formic acid, eluent B: acetonitrile with 0.1 % formic acid; flow rate 0.9 mL/min; linear gradient: 0 min: 95 % A, 5 % B to 6.4 min: 0 % A, 100 % B. ^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 8.36 (d, J = 9.4 Hz, 1H), 7.50 (d, J = 10.0 Hz, 1H), 7.38 – 7.22 (m, 6H), 6.94 (d, J = 4.4 Hz, 1H), 6.77 (d, J = 9.9 Hz, 1H), 5.39 (d, J = 9.8 Hz, 1H), 5.34 (dd, J = 8.8, 3.8 Hz, 1H), 5.31 – 5.25 (m, 2H), 5.21 – 5.15 (m, 2H), 5.11 (dd, J = 9.9, 1.9 Hz, 1H), 4.90 – 4.84 (m, 1H), 4.70 (q, J = 6.9 Hz, 1H), 4.39 (dd, J = 7.7, 2.1 Hz, 1H), 4.10 (d, J = 9.8 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.60 (ddd, J = 9.8, 4.4, 2.0 Hz, 1H), 3.38 (s, 3H), 3.23 (s, 3H), 3.16 – 3.11 (m, 1H), 2.94 – 2.85 (m, 1H), 2.84 (s, 3H), 2.66 (s, 3H), 2.55 – 2.43 (m, 2H), 2.16 (s, 3H), 1.96 – 1.90 (m, 1H), 1.89 – 1.74 (m, 2H), 1.37 (d, J = 7.0 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.12 (d, J = 7.7 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H).

Example 3-2: Generation process for (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-

2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-2-acetamido-3-hydroxy-4-methylpentanoate **(A2)**

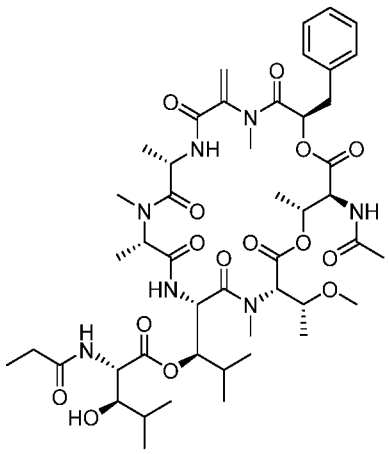


(A2)

Compound (A2) was obtained using the methods described in [M. Taniguchi et al., *Tetrahedron* 59 (2003) 4533-4538]. Isolation was performed using the methods described for Compound (A1) in Example 3-1 The material was then characterized by UPLC-UV-HRMS, 1D-NMR- and 2D-NMR-experiments. Compound (A2): Retention time: 4.20 min, molecular formula [M+H]+: C46H70N7O15+, calculated monoisotopic mass [M+H]+: 960.4924 Da, observed mass: 960.4914 Da. ^{1}H NMR (600 MHz, $_{1,4}$-Dioxane-d_8) δ 8.36 (d, *J* = 9.2 Hz, 1H), 7.37 (d, *J* = 10.0 Hz, 1H), 7.31 – 7.21 (m, 4H), 7.21 – 7.16 (m, 2H), 6.79 – 6.72 (m, 2H), 5.40 – 5.37 (m, 1H), 5.36 – 5.33 (m, 1H), 5.30 – 5.28 (m, 2H), 5.20 (dd, *J* = 9.0, 3.7 Hz, 1H), 5.13 (d, *J* = 1.9 Hz, 1H), 5.04 (dd, *J* = 9.9, 1.4 Hz, 1H), 4.89 – 4.82 (m, 1H), 4.73 (q, *J* = 6.9 Hz, 1H), 4.39 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.04 (d, *J* = 9.9 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.65 (ddd, *J* = 9.8, 4.3, 1.9 Hz, 1H), 3.37 (s, 3H), 3.21 (s, 3H), 3.11 (dd, *J* = 14.7, 3.7 Hz, 1H), 2.89 (dd, *J* = 14.7, 8.9 Hz, 1H), 2.84 (s, 3H), 2.62 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 1.99 – 1.90 (m, 1H), 1.75 – 1.69 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.18 – 1.14 (m, 6H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 4H).

Example 3-3: Generation process for (R)-1-((3S,6S,9S,12S,18R,21S,22R)-21-acetamido-18-benzyl-3-((R)-1-methoxyethyl)-4,9,10,12,16,22-hexamethyl-15-methylene-

2,5,8,11,14,17,20-heptaoxo-1,19-dioxa-4,7,10,13,16-pentaazacyclodocosan-6-yl)-2-methylpropyl (2S,3R)-3-hydroxy-4-methyl-2-propionamidopentanoate **(A3)**



(A3)

Compound (A3) was obtained using the methods described in [M. Taniguchi et al. Tetrahedron 59 (2003) 4533-4538]. Isolation was performed using the methods described for Compound (A1) in Example 3-1. The material was then characterized by UPLC-UV-HRMS, 1D-NMR- and 2D-NMR-experiments. Compound (A3): Retention time: 4.42 min, molecular formula [M+H]+: C47H72N7O15+, calculated monoisotopic mass [M+H]+: 974.5081 Da, observed mass: 974.5098 Da. ^{1}H NMR (600 MHz, $_{1,4}$-Dioxane-d_8) δ 8.37 (d, *J* = 9.1 Hz, 1H), 7.38 (d, *J* = 9.9 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.22 – 7.16 (m, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.78 – 6.72 (m, 2H), 5.41 – 5.33 (m, 2H), 5.32 – 5.26 (m, 2H), 5.20 (dd, *J* = 8.8, 3.7 Hz, 1H), 5.12 (d, *J* = 2.2 Hz, 1H), 5.04 (dd, *J* = 9.9, 1.7 Hz, 1H), 4.89 – 4.81 (m, 1H), 4.72 (q, *J* = 7.0 Hz, 1H), 4.40 (dd, *J* = 7.8, 2.1 Hz, 1H), 4.04 (d, *J* = 9.8 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.68 – 3.64 (m, 1H), 3.38 (s, 3H), 3.21 (s, 3H), 3.11 (dd, *J* = 14.6, 3.7 Hz, 1H), 2.89 (dd, *J* = 14.7, 8.9 Hz, 1H), 2.83 (s, 3H), 2.62 (s, 3H), 2.51 – 2.41 (m, 2H), 2.14 (s, 3H), 1.99 – 1.89 (m, 1H), 1.78 – 1.68 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.18 – 1.14 (m, 6H), 1.13 – 1.08 (m, 6H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H).

Example 4: Process for the production of anti-PMEL17 antibody drug conjugates

[00500] Antibody was incubated with RMP Protein A resin (GE) at a ratio of 10 mg Ab to 1 ml resin in PBS for 15 minutes with mixing in an appropriately sized disposable column. Cysteine HCl was added to a final concentration of 20 mM and incubated with agitation for 30 min at room temperature to allow the reactive cysteines to be deblocked. The resin was quickly washed with 50 column volumes PBS on a vacuum manifold. The resin was then resuspeneded in an equal volume PBS containing 250 nM $CuCl_2$. Reformation of antibody interchain disulfides was monitored by taking time points. At each time point, 25 µL of resin slurry was removed, 1 µL of 20 mM of Compound (B1) or Compound (B2) was added, and the

tube flicked several times. The resin was spun down, supernatant removed, and then eluted with 50 µL Antibody elution buffer (Thermo). The resin was pelleted and the supernatant analyzed by reverse phase chromatography using an Agilent PLRP-S 4000A 5um, 4.6x50mm column (Buffer A is water, 0.1% TFA, Buffer B Acetonitrile, 0.1% TFA, column held at 80 C, Flowrate 1.5 ml/min).

[00501] Once it was determined that the antibody has reformed its interchain disulfide bonds, the resin was washed with 10 column volumes PBS and the resin was resuspended in an equal volume PBS and 8 equivalents of linker-payload (20 mM) in DMSO was added and then incubated at room temperature for 2 hours. The resin was then washed with 50 column volumes PBS. The ADC was eluted from the protein A resin with Antibody elution buffer and neutralized with 1/10 volume 1 M Tris pH 9.0. The ADC was then buffer exchanged into PBS or other suitable buffer and preparative size exclusion chromatography to remove aggregates was performed (S200 Increase; GE), if needed. The following analyses were performed - analytical SEC to determine percent monomer, mass spectroscopy to determine DAR, LAL test to determine endotoxin load and protein concentration was determined by A280 utilizing extinction coefficient and molecular weight of antibody.

Example 5: In vitro anti-uveal melanoma activity of GNAQ/11 inhibitors Compound (A1) and Compound (A2)

[00502] 92.1 uveal melanoma and MIAPACA pancreatic ductal adenocarcinoma cells were seeded at low cell density in 96-well plates and treated with increasing concentrations of Compound (A1) or Compound (A2) as indicated. Following drug treatment for 96 or 120 hours, cell viability and proliferation were determined using a resazurin-based viability assay. Briefly, cells were incubated with a resazurin-based solution and color change was detected by absorbance with a spectrophotometer and used as a readout of cell viability. Data presented as mean of 3 independent replicates and relative to PBS-treated cells (control). Table 4 shows the growth inhibition 50% (GI_{50}) for Compound (A2) and Compound (A1). Compound (A2) and Compound (A1) displayed potent target-dependent anti-UM activity (Fig. 1).

Table 4. Growth inhibitory activity of Compound (A1) and Compound (A2) in UM cells

Cell line	Mutation	Compound (A1) GI_{50} nM	Compound (A2) GI_{50} nM
92.1	$GNAQ^{Q209L}$	0.18	7.7

MIAPACA	WT	> 10 μM	> 10 μM

Example 6: Compound (A1) and Compound (A2) induce apoptosis in uveal melanoma cells

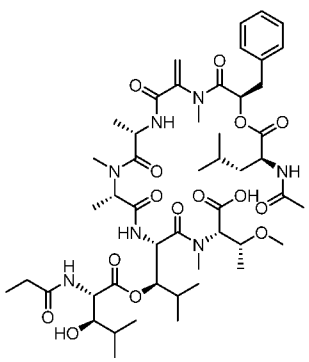
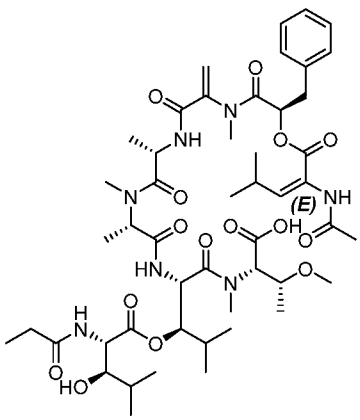
[00503] 92.1 and MIAPACA cells were seeded in 96-well plates (5000 cells per well) and treated with increasing concentrations of Compound (A1), Compound (A2), and a fixed dose of Staurosporine (100 nM, positive control) as indicated. Following drug treatment for 96, cells were subjected to fluorescence-activated flow cytometry using an Annexin V antibody conjugated to a fluorescent dye. Data presented as mean of 3 independent replicates. Compound (A2) and Compound (A1) induced apoptosis in UM cells in GNAQ/11 dependent manner (Fig. 2).

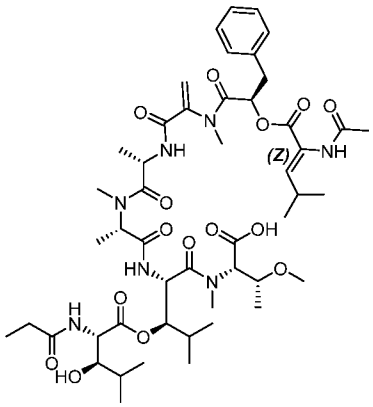
Example 7: Analysis of GNAQ/11 inhibition by Compound (A1) and Compound (A2) in uveal melanoma cells

[00504] 92.1 uveal melanoma were treated with increasing concentrations of Compound (A1) or Compound (A2) as indicated. Following drug treatment overnight, cells were processed for determination of IP1 levels using TR-FRET (time-resolved fluorescent resonance energy transfer) or protein levels by western-blotting. Fig. 3A shows IP1 levels (nM) in 92.1 cells treated with DMSO (control), Compound (A2) or Compound (A1). Fig. 3B shows correlation between IP1 levels and relative proliferation in Compound (A1)-treated 92.1 cells. Fig. 3C shows immunoblots of 92.1 cells treated with Compound (A1) and Compound (A2) to determine the effect on ERK signaling.

Example 8: Metabolic stability and PK properties of Compound (A1)

[00505] The plasma stability of Compound (A1) was investigated in mouse, rat, monkey and human plasma and compared to buffer. Both disappearance of Compound (A1) (Fig. 4A) as well as appearance of the ring-opened form of Compound (A1) having the structure of

Compound (A4)  , Compound (A6)  , or



Compound (A8) , (Fig. 4B) were monitored over 24h. The transformation seem to be slightly faster in human plasma when compared to the other species. With the exception of the rat, adding the % remaining Compound (A1) and % formed Compound (A8) shows stoichiometry over 24h, indicating that no other transformation seem to play a significant role (Fig. 4C).

[00506] The PK of Compound (A1) after intravenous dosing in mouse was characterized by a very high clearance and moderate to high volume of distribution. A slightly over-proportional increase of exposure with dose was observed in the range of 0.2-0.8 mg/kg (Fig. 4D). Table 5 summarizing all PK values is shown below.

Table 5. PK properties of Compound (A1)

	Dose (mg/kg)		
	0.2	**0.4**	**0.8**
Cmax (nM)	31	83	240
Cmax/D (nM/(mg/kg))	156	208	300
AUCinf (nM*h)	16	47	137
AUCinf/D (nM*h/(mg/kg))	82	118	171
C0 (nM)	43	108	380
C0/D (nM/(mg/kg))	217	270	475
CL [mL/min/kg]	204	141	97

Vss [L/kg]	8.6	4.9	4.6

Example 9: Metabolic stability and PK properties of Compound (A2)

[00507] In vitro stability of Compound (A2) was tested in plasma and blood from different species (Fig. 5A). Compound (A2) showed good chemical stability in three different systems (Fig. 5B). PK of Compound (A2) in female balb/c mice showed high clearance and a short elimination half-life (Fig. 5C). Table 6 summarizes some PK values. Compound (A2) showed high intrinsic clearance in liver microsomes from mouse, rat and human, but low clearance in hepatocytes, probably due to limited membrane permeability (Table 7). Incubations of Compound (A2) in hepatic S9 fraction and in plasma showed similar half-lives. Compound (A2) and Compound (A1) were stable in buffer at pH 5.6 and in lysosomes over 4h (Fig. 5D).

Table 6. PK properties of Compound (A2) in female balb/c mice (1 mg/kg iv)

CL ($mL \cdot min^{-1} \cdot kg^{-1}$)	175 ± 29
$t_{1/2}$ (h)	0.4 ± 0.01
AUC i.v. d.n. (nM·h)	101 ± 16

Table 7. Stability of Compound (A2)

	mouse	rat	human
Hepatic microsomes (ul/min/kg)	107	33	44
Hepatocytes (ul/min/10^6 cells)	-	8	<4
Hepatic S9 (+/- NADPH) t1/2 (h)	1.9 / >2	>2 / >2	1.9 / >2
Plasma t1/2 (h)	2.1	4.1	2.0

Example 10: In vitro anti-uveal melanoma activity of anti-PMEL17-(B1) ADCs

[00508] Parental and non-targeting control (NT)- or PMEL17-shRNA transduced 92.1 cells were seeded at low cell density in 96-well plates and treated with increasing concentrations of 3207-(B1) (Isotype control), G4-(B1), and G1-(B1) in the presence or absence of doxycycline as indicated. Following drug treatment for 96 or 120 hours, cell viability and proliferation were determined using a resazurin-based viability assay. Briefly, cells were incubated with a resazurin-based solution and color change was detected by absorbance with a spectrophotometer and used as a readout of cell viability. Data presented as mean of 3

independent replicates and relative to PBS-treated cells (control) (Fig. 6). Anti-PMEL17-(B1) ADCs inhibit the proliferation of uveal melanoma cells in a PMEL17- and dose-dependent manner.

Example 11: anti-PMEL17-(B1) ADCs induce apoptosis in uveal melanoma cells

[00509] 92.1 cells were seeded in 96-well plates (5000 cells per well) and treated with increasing concentrations of Compound (A1), 3207-(B1) (Isotype control), G4-(B1), and G1-(B1) as indicated. Following drug treatment for 96, cells were subjected to fluorescence-activated flow cytometry using an Annexin V antibody conjugated to a fluorescent dye. Data presented as mean of 3 independent replicates. Both G4-(B1) and G1-(B1) induced apoptosis in 92.1 cells in a dose-dependent manner (Fig. 7).

Example 12: In vitro anti-uveal melanoma activity of anti-PMEL17-(B2) ADCs and anti-PMEL17 mAbs

[00510] 92.1 uveal melanoma cells were seeded at low cell density in 96-well plates and treated with increasing concentrations of 3207-(B2) (Isotype control), G4-(B2), and G1-(B2), and anti-PMEL17-B1 and –G4 mAbs as indicated. Following drug treatment for 96 or 120 hours, cell viability and proliferation were determined using a resazurin-based viability assay. Data presented as mean of 3 independent replicates and relative to PBS-treated cells (control) (Fig. 8). Anti-PMEL17-(B2) ADCs and anti-PMEL17 mAbs exhibit minimal anti-proliferative effect in uveal melanoma cells.

Example 13: Analysis of GNAQ/11 inhibition by anti-PMEL17-(B1) and anti-PMEL17-(B2) ADCs in uveal melanoma cells

[00511] 92.1 uveal melanoma were treated with DMSO, Compound (A1) (8 nM) and increasing concentrations of Isotype-(B1), anti-PMEL17-(B1) and anti-PMEL17-(B2) ADCs as indicated. Following drug treatment for 2 days, cells were processed for determination of IP1 levels using TR-FRET (time-resolved fluorescent resonance energy transfer). IP1 levels (nM) are presented as mean of 3 independent replicates. As indicated by reduced levels of IP1, both G1-(B1) and G1-(B2) inhibit mutant GNAQ and GNA11 in a dose-dependent manner (Fig. 9).

Example 14: Binding analysis of anti-PMEL17 antibodies to intact platelets and uveal melanoma cells

[00512] The uveal melanoma cell line 92.1 and platelets isolated from Human Platelet Rich Plasma (PRP from 3 human donors) were subjected to fluorescence-activated flow cytometry using anti-PMEL17 antibodies G1 (black line) and G4 (grey line), and anti-human IgG secondary antibody conjugated to a fluorescent dye, or the conjugated secondary antibody only

(light grey line) (Fig. 10). In contrast to 92.1 uveal melanoma cells, human platelets do not show cell surface expression of PMEL17.

Example 15: Impact of Compound (A1) and anti-PMEL17-(B1) ADCs on human platelet aggregation

[00513] Human Platelet Rich Plasma (PRP) was incubated with ADC 17A9-(B1), an anti-PMEL Ab conjugated to B1,or Compound (A1) (0.1, 1, and 150nM) for 4, 16 or 24h. Platelet aggregation was then measured following treatment with Thrombin Receptor Activating Peptide 6 (TRAP6) at 32uM. While Compound (A1) induced platelet aggregation, anti-PMEL17-(B1) did not induce platelet aggregation up to 24 hours (Fig. 11).

Example 16: anti-PMEL17-(B1) ADCs inhibit tumor growth in mouse model

[00514] Female nude mice bearing 92.1-luciferase subcutaneous xenografts were treated with a single i.v. injection of 3207-(B1), G1-(B1) or vehicle at the indicated doses. Treatment (single dose i.v. injection) was performed 17 days post tumor inoculation. Values are mean ± SEM; sample size, (n=5-12 mice per group). Initial tumor volume at day 0 was approximately 200-250 mm^3. G1-(B1) inhibited tumor growth in a dose-dependent manner (Fig. 12A).

[00515] Body weight change of female naive nude mice after treatment with G1-(B1) was monitored at the indicated doses. Treatments (single dose i.v. injection) were performed at day 0. Values are mean ± SEM; sample size, (n=4 mice per group). Initial body weight at day 0 was approximately 24 g. Body weight was measured every day for 14 days following drug treatment. No body weight loss was observed for up to 14 days after treatment (Fig. 12B).

[00516] Immunohistochemical analysis of tumour tissue from 92.1-luciferase subcutaneous xenografts treated with vehicle, 3207-(B1) (7.5 mg/kg body weight), or G1-(B1) (7.5 mg/kg body weight) was performed. Tumors were fixed in 10% (vol/vol) neutral buffered formalin for 24 h at room temperature, then rinsed in PBS, processed for dehydration, cleared, and embedded in paraffin. 3 µm sections were prepared and processed for hematoxylin and eosin (H&E) staining and for immunohistochemistry. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections using a Bond-RX (Leica) fully automated system for anti-hIgG (ThermoFischer) and anti-gp100 (PMEL17) (clone EP4863; Abcam) staining, and a Discovery XT (Ventana Medical System) fully automated system for anti-Ki67 (clone Sp6; NeoMarkers), anti-pERK1/2 (clone D13.14.4E; Cell Signaling), anti-MITF (Sigma) and anti-cleaved Caspase-3 (Cell Signaling) staining. Briefly, G1-(B1) treatment resulted in GNAQ signaling inhibition and inhibition of tumor cell proliferation as indicated by reduced levels of pERK and Ki67, respectively (Fig. 12C). In addition, G1-(B1) induced cell

apoptosis compared to vehicle- and 3207-(B1)-treated mice, which correlated with tumor cell accumulation of G1-(B1) ADC as detected by IgG staining (Fig. 12C). No changes were observed in MITF and PMEL17 levels following G1-(A1) treatment (Fig. 12C).

[00517] Whole blood platelet aggregation of naive mice treated with vehicle, G1-(B1) (20 mg/kg body weight), or Compound (A1) (0.01, 0.03, 0.1, and 0.3 mg/kg body weight) was tested. Animals were euthanized 5 min post single i.v. dosing and blood was collected via vena cava. After 1h, whole blood aggregation was measured following platelet activation with ADP at 6.5uM (Fig. 12D). In contrast to Compound (A1) G1-(B1) did not have any significant effect on ADP-induced platelet aggregation in vivo.

[00518] Whole blood platelet aggregation of naive mice treated with vehicle and G1-(B1) (7.5 and 30 mg/kg body weight) at 24 h or 7 d post dosing was measured. Mice were euthanized 24 h or 7 d post single i.v. dosing and blood was collected via vena cava. After 1h, whole blood aggregation was measured following platelet activation with ADP at 6.5uM. No platelet aggregation inhibition was observed in G1-(B1) treated mice for up to 7 days (Fig. 12E).

Example 17: Effect of G1-(B1) on a liver and lung metastasis mouse model of uveal melanoma

[00519] Female NOD-Scid mice were intravenously injected with 92.1-luciferase cells (approximately 2 million cells per animal) and bioluminescence was measured twice a week to evaluate tumor formation. After 45 days all injected mice developed liver and lung metastases as detected by bioluminescence signal (BLI) (Figs. 13A and 13B). Tumor bearing mice were treated with a single i.v. injection of G1-(B1) (20 mg/kg body weight) and bioluminescence was monitored over time as a readout of tumor progression. Individual pictures from each mice are presented at day 45 following i.v. injection of 92.1-luciferase cells (just before the initiation of treatment) and 12 days post treatment (Figs. 13A and 13B); sample size, (n=6 mice per group). Initial BLI for liver metastasis at day 0 was approximately $2.8 * 10^9$ p/sec/cm^2. Lung tumors (bioluminescence signal) in Fig. 13B are indicated by a black arrow. As indicated by reduced in vivo and ex vivo bioluminescence, G1-(B1) induced regression of liver and lung metastases following a single i.v. dose of 20 mg/kg.

[00520] Corresponding body weight modulation (% vs day 15) was assessed 2-3 times per week prior and post treatment with G1-(B1) 20 mg/kg (grey circles). Values are mean ± SEM; sample size, (n=5-6 mice per group). Initial body weight at day 15 was approximately 21 g. G1-(B1) treatment resulted in body weight restoration in a liver and lung metastasis model of uveal melanoma.

Example 18: PK properties of G1-(B1) ADCs.

[00521] The pharmacokinetic profile of G1-(B1) showed a slightly over-proportional increase of exposure with dose between 7.5 and 30 mg/kg in nude mice (Fig. 14A). Clearance, volume of distribution and half-life are in the typical range for ADCs. Table 8 summarizes some PK values.

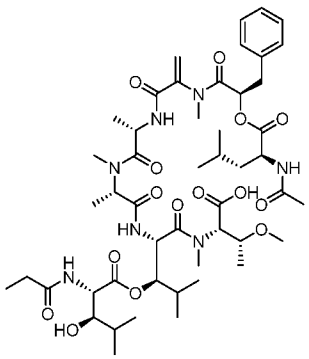
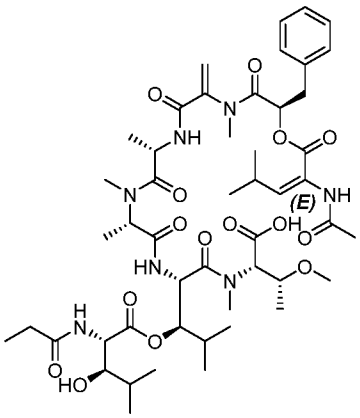
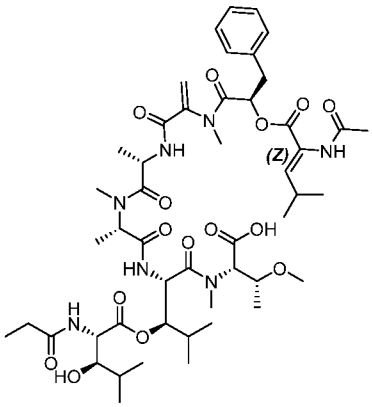
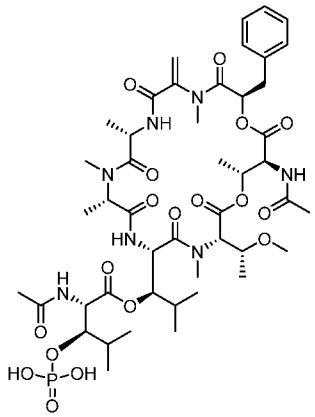
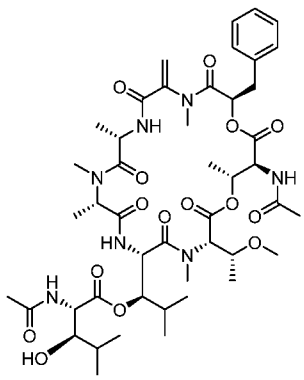
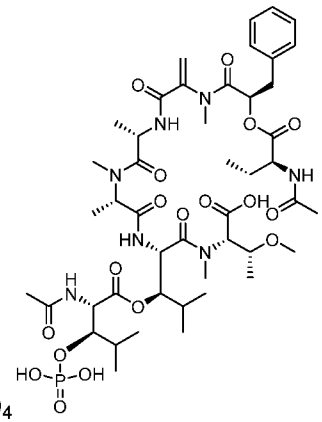
[00522] In tumor bearing mice, free payload concentrations were measured after dosing either target binding G1-(B1) or isotype control 3207-(B1). A clear (>4-fold) increase in tumor delivery of Compound (A1) payload could be observed using the targeted ADC (Fig. 14B). The conversion of Compound (A1) (open circles) into its ring-opened form of Compound (A1) having the structure of Compound (A4)  , Compound (A6)  , or Compound (A8)  , (filled circles) while being conjugated to the antibody was shown in vivo in mice (Fig. 14C). The exposures in an in vivo efficacy study, comparing two different DAR2 formats with the DAR4 format of G1-(B1) and with the DAR4 Fc-silent format, showed lowest clearance for the DAR2 (E152C) and the DAR4 Fc-silent ADCs, whereas the DAR2 (S375C) exposure decreases faster (Fig. 14D). From comparing the PK of the non-targeted 3207-ADCs (Fig. 14E) one can deduce that the Fc-silencing has a significant effect on lowering the clearance of the DAR4 format.

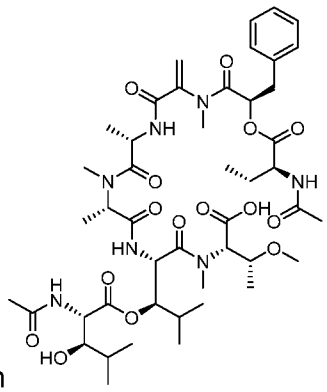
Table 8. PK properties of G1-(B1) ADCs

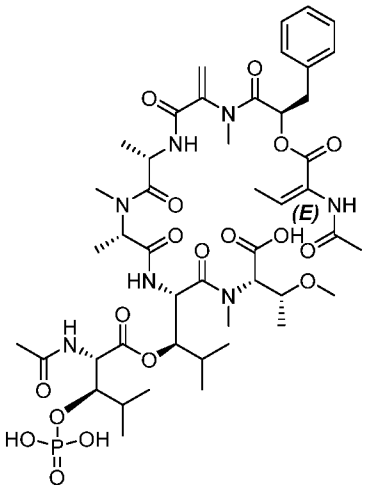
Nude mice - dose (mg/kg)	**7.5**	**30**
AUC_{last} (ug/mL*h)	6`779 ± 1`061	45`346 ± 3`785
AUC_{last} (ug/mL*h) dose normaliz.	904	1`511
AUC_{inf} (ug/mL*h)	9`211 ± 2`337	73`680 ± 9`867
AUC extrap (%)	25 ± 9	38 ± 3
CL (mL/h/kg)	0.9 ± 0.3	0.4 ± 0.05
Vz (L/kg)	0.21 ± 0.01	0.15 ± 0.01
app. t_{elim} (h)	176 ± 37	259 ± 25

Example 19: In vitro stability of anti-PMEL17-GNAQ/11i ADCs in buffer, mouse, rat, and human plasma and in vivo stability of anti-PMEL17-GNAQ/11i ADCs in mouse

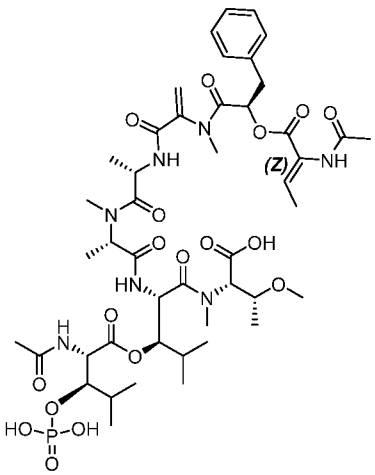
[00523] Anti-PMEL17G1_E152C_S375C_(B2) (G1-(B2)) was spiked at 100 µg/mL into respective matrix and incubated at 37 ºC. Samples were collected at 0, 1, 2, and 4 h by flash freezing at -70 ºC. Aliquots of each sample were immuno-precipitated using Capture Select FcXL beads and were incubated with buffer containing papain to release the payload from the bead captured ADC. Released payload was then analyzed by HPLC MS to determine relative levels of Compound (A2)-PO_4 (i.e.  from  see Example 1.2), and ring opened Compound (A2)-PO_4 having the structure of Compound (A5)-



PO_4 (i.e. Compound (A5)-PO_4 from ),



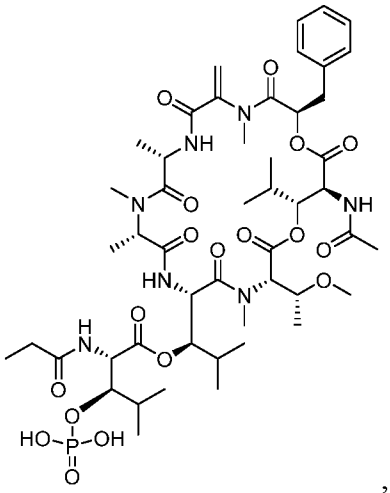
Compound (A7)-PO_4, or Compound (A9)-PO_4,



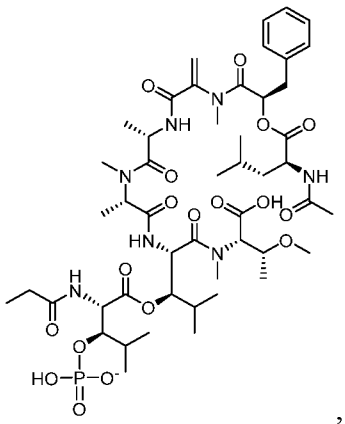
, (where ring opened Compound (A2)-PO_4 – inactive payload). Graph depicts the percent of released payload that was present as Compound (A2)-PO_4 over the time course of the experiment (Fig. 15A).

[00524] Anti-PMEL17G1_E152C_S375C_(B1) (G1-(B1)), Anti-PMEL17G1_E152C_(B1) (G1-E152C-DAR2-(B1)), Anti-PMEL17G1_S375C_(B1) (G1-S375C-DAR2-(B1)), and Fc-silent Anti-PMEL17G1_E152C_S375C_(B1) (Fc-silent G1-(B1)) were spiked at 100 µg/mL into

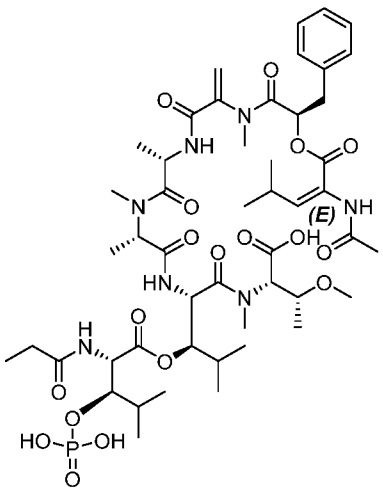
respective matrix and incubated at 37 ºC. Samples were collected at 0, 2, 4, and 6 h by flash freezing at -70 ºC. Aliquots of each sample were immuno-precipitated using Capture Select FcXL beads and were incubated with buffer containing papain to release the payload from the bead captured ADC. Released payloads were then analyzed by HPLC MS to determine relative

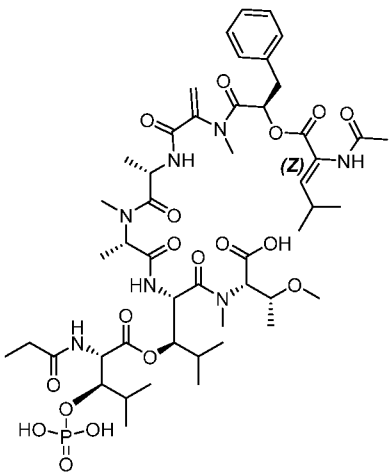


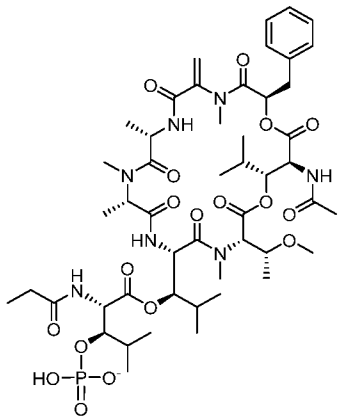
levels of Compound (A1)-PO_4, , and ring opened Compound (A1)-



PO_4 having the structure of Compound (A4)-PO_4, , Compound (A6)-

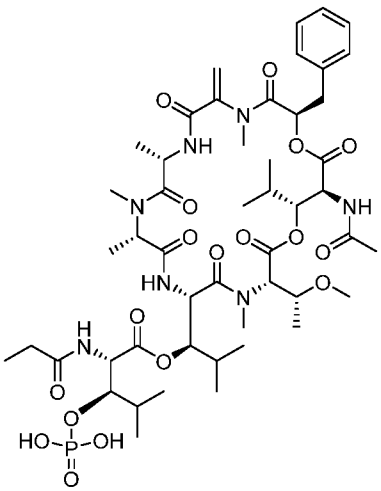


PO_4, , or Compound (A8)-PO_4,  ,

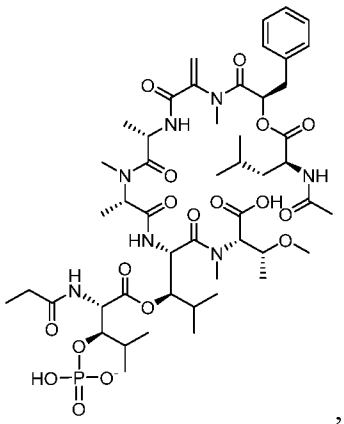


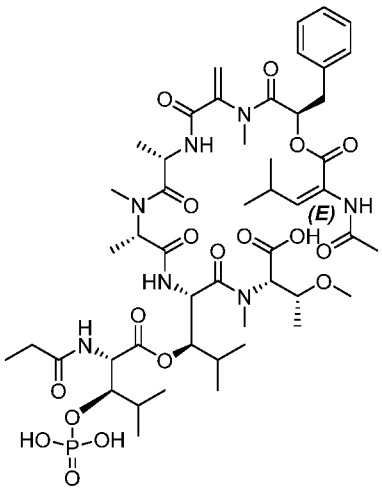
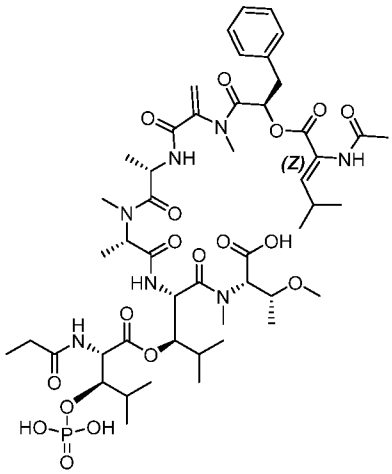
(where ring opened compounds of Compound (A1)-PO_4, , are – inactive payload). Graph depicts the percent of released payload that was present as Compound (A1)-PO_4 over the time course of the experiment for each of the different ADC constructs (Fig. 15B).

[00525] Anti-PMEL17G1_E152C_S375C_(B1) (G1-(B1)), Anti-PMEL17G1_E152C_(B1) (G1-E152C-DAR2-(B1)), Anti-PMEL17G1_S375C_(B1) (G1-S375C-DAR2-(B1)), and Fc-silent Anti-PMEL17G1_E152C_S375C_(B1) (Fc-silent G1- (B1)) were each intravenously injected in nude mice at 20 mg/kg (body weight). Nine mice were dosed with each of the ADC constructs described above. Three animals per group (ADC construct) were terminally bled to collect serum samples for analysis at 24 h, day 7, and day 14 post dose. Aliquots of each sample were immuno-precipitated using Capture Select FcXL beads and were incubated with buffer containing papain to release the payload from the bead captured ADC. Released payloads were then analyzed by HPLC MS to determine relative levels of Compound (A1)-PO_4,



, and ring opened Compound (A1)-PO_4 having the structure of

Compound (A4)-PO_4,  , Compound (A6)-PO_4,

 , or Compound (A8)-PO_4,  , (where ring opened compounds of Compound (A1)-PO_4 – are inactive payload). Graph shows the percent of payload present on the ADCs in the active form of Compound (A1)-PO_4 (assuming Compound (A1)-PO_4 + Compound (A8)-PO_4 = 100%) (Fig. 15C). Initial values were estimated based on in vitro experimental results.

Example 20: In vivo efficacy of G1-E152C-DAR2-(B1), G1-S375C-DAR2-(B1), Fc-silent G1-(B1) in a xenograft model of uveal melanoma

[00526] Female nude mice bearing 92.1-luciferase subcutaneous xenografts were treated with 3207-E152C_S375C-DAR4-(B1), G1-E152C_S375C-DAR4-(B1), G1-E152C-DAR2-(B1), G1-S375C-DAR2-(B1), Fc-silent 3207-(B1), and Fc-silent G1-DAR4 at 7.5 mg/kg. Treatments (single dose i.v. injection) were performed 17 days post tumor inoculation. Values represent mean ± SEM; sample size, (n=5-6 mice per group). Initial tumor volume at day 0 was approximately 300-325 mm^3. (Fig. 16). G1-E152C-DAR2-(B1), Fc-silent G1-DAR4, and G1-E152C_S375C-DAR4-(B1) exhibit comparable antitumor activity in the 92.1 xenograft model of uveal melanoma, while G1-S375C-DAR2-(B1) and non-targeted 3207-ADCs have no effect on tumor growth.

Example 21: In vitro activity of G1-3J-DAR4-(B1), G1-3R-DAR4-(B1), G1-DAR4-(B1), G1-3J-DAR2 (E152C)-(B1), Fc Silent G1-3J -DAR2 (E152C)-(B1), 3207-DAR2 (E152C)-(B1), and G1-DAR2 (E152C)-(B1)

[00527] In Fig. 17A, 92.1 (left panel) and MP41 (right panel) cells were seeded at low cell density in 96-well plates and treated with increasing concentrations of G1-3J-DAR4-(B1), G1-3R-DAR4-(B1), G1-DAR4-(B1) as indicated. Following drug treatment for 96 or 120 hours, cell viability and proliferation were determined using a resazurin-based viability assay. Briefly, cells were incubated with a resazurin-based solution and color change was detected by absorbance with a spectrophotometer and used as a readout of cell viability. Data presented as mean of 3 independent replicates and relative to PBS-treated cells (control). GI50 (is the concentration for 50% of maximal inhibition of cell proliferation) value for each ADC and cell line is depicted in Table 9. Anti-PMEL17-(B1) ADCs inhibit the proliferation of uveal melanoma cells in a PMEL17- and dose-dependent manner.

Table 9. Growth inhibitory activity of G1-3J-DAR4-(B1), G1-3R-DAR4-(B1), G1-DAR4-(B1) in UM cells

Cell line	G1-3J-DAR4-(B1) GI_{50} nM	G1-3R-DAR4-(B1) GI_{50} nM	G1-DAR4-(B1) GI_{50} nM
92.1	0.850	0.811	0.722
MP41	0.582	0.654	0.563

[00528] Fig. 17B depicts results of a cell proliferation assay in 92.1 cell line with G1-3J-DAR2 (E152C)-(B1), Fc Silent G1-3J-DAR2 (E152C)-(B1), 3207-DAR2 (E152C)-(B1), and G1-DAR2 (E152C)-(B1) as described in Fig. 17A. GI50 is depicted in Table 10.

Table 10. Growth inhibitory activity of G1-3J-DAR2 (E152C)-(B1), Fc Silent G1-3J -DAR2 (E152C)-(B1), 3207-DAR2 (E152C)-(B1), and G1-DAR2 (E152C)-(B1) in UM cells

Cell line	G1-3J-DAR2 (E152C)-(B1) GI_{50} nM	Fc Silent G1-3J -DAR2 (E152C)-(B1) GI_{50} nM	3207-DAR2 (E152C)-(B1) GI_{50} nM	G1-DAR2 (E152C)-(B1) GI_{50} nM
92.1	0.309	0.278	>150	0.365

Example 22: Anti-PMEL17-(B1) ADCs inhibit tumor growth in mouse model

[00529] Female nude mice bearing 92.1-luciferase subcutaneous xenografts were treated with a single i.v. injection of 3207-(B1), G1-3J(E152C), G1-3J-DAR2 (E152C)-(B1), Fc Silent G1-3J-DAR2 (E152C)-(B1), G1-DAR2 (E152C)-(B1) or vehicle at the indicated doses. Treatment (single dose i.v. injection) was performed 14-17 days post tumor inoculation. Values are mean ± SEM; sample size, (n=5-12 mice per group). Initial tumor volume at day 0 was approximately 200-250 mm3. G1-3J-DAR2 (E152C)-(B1) and Fc Silent G1-3J-DAR2 (E152C)-(B1) inhibited tumor growth in a dose-dependent manner (Fig. 18).

Example 23: Immunohistochemical analysis of tumor biopsies from metastatic uveal melanoma patients

[00530] Tumours were fixed in 10% (vol/vol) neutral buffered formalin for 24 h at room temperature, then rinsed in PBS, processed for dehydration, cleared, and embedded in paraffin. 3 µm sections were prepared and processed for immunohistochemistry. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections using a Bond-RX (Leica) fully automated system for anti-gp100 (PMEL17) (mouse monoclonal HMB45) staining. Metastatic uveal melanoma samples exhibit high and relatively homogenous expression of PMEL17 (Fig. 19A). Quantification of PMEL17 expression levels and proportion of PMEL17 positive cells in metastatic uveal melanoma patient samples (Fig. 19B, Fig. 19C).

Example 24: Competitive Binding Assay

[00531] SPR was used to assess epitope binning for anti-PMEL antibodies on a T200 Biacore instrument (catalog #28975001, GE Healthcare Life Sciences).

[00532] Surface Plasmon Resonance (SPR) is a technique to measure bimolecular interactions in real-time in a label free environment. Molecules are immobilized on a sensor surface over which a sample solution flows. The interaction between the immobilized molecule and the flowing sample causes a refractive index change. The refractive index change is an altering of the angle at which reduced intensity polarized light is reflected from the supporting glass plane. This angle change is caused by binding or dissociation of molecules from the sensor surface and is proportional to the mass of bound material and is recorded by the instrument in a sensorgram. The sensorgram shows increasing response as molecules interact, the response remains constant if the interaction reaches equilibrium, and the response decreases as the sample is replaced by buffer and the interaction partners dissociate. From the association and dissociation event responses, an association rate (ka), a dissociation rate (kd) and an overall affinity (KD) are determined. For epitope binning, KDs are not determined.

[00533] In the first step, G1 LC 3J and 17A9 antibodies were directly immobilized onto a CM5 chip surface via Amine Coupling to achieve approximately 2000RU respectively on Fc2 and Fc3. Flow cell 1 did not have an antibody immobilized onto it and served as the reference Fc. The immobilized antibodies on Fc2 and Fc3 are the base antibodies in the experiment

[00534] After immobilization, human PMEL flowed over in the second step at 20nM over all flow cells for 60 seconds at 30ul/min.

[00535] The third and final step has the G1 LC 3J antibody alone or G1 LC 3J antibody plus 17A9 antibody flowing over Fc2 or the 17A9 antibody alone or 17A9 antibody plus G1 LC 3J antibody flowing over Fc3 (FIG. 20A). The antibodies flowed over at 500nM total concentration over both flow cells for 120 seconds at 30ul/min for association followed by a dissociation phase of 120 seconds at 30ul/min with running buffer.

[00536] As expected, when G1 LC 3J was the base antibody, no binging signal was observed when G13J flowed over. 100RU binding was observed when 17A9 was flowed over, suggestive it binds to a different epitope than G1 LC 3J (FIG. 20B). Similar trends observed when 17A9 was the base antibody. In step 3, no binding observed with itself but binding observed when G1 LC 3J flowed over (FIG. 20C). This indicated that G1 LC 3J and 17A9 bind to different epitopes.

[00537] Regeneration was performed at the end of each cycle on all flow cells. The regeneration buffer was Glycine 2.0 which flowed at 30µl/min for 30 seconds.

[00538] The data was analyzed using the Biacore T200 Evaluation Software version 3.0.

[00539] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

We claim:

1. An antibody or antigen binding fragment thereof that binds PMEL17 comprising:

   a. a heavy chain variable region that comprises a heavy chain CDR1 (Complementarity Determining Region 1) of SEQ ID NO:1, 4, 5 or 7, a heavy chain CDR2 (Complementarity Determining Region 2) of SEQ ID NO:2, 6 or 8, and a heavy chain CDR3 (Complementarity Determining Region 3) of SEQ ID NO:3 or 9; and a light chain variable region that comprises a light chain CDR1 (Complementarity Determining Region 1) of SEQ ID NO:14, 17 or 20, a light chain CDR2 (Complementarity Determining Region 2) of SEQ ID NO:15 or 18, and a light chain CDR3 (Complementarity Determining Region 3) of SEQ ID NO:16 or 19;

   b. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:33, 36, 37 or 39, a heavy chain CDR2 of SEQ ID NO:34, 38 or 40; a heavy chain CDR3 of SEQ ID NO:35 or 41; a light chain CDR1 of SEQ ID NO:46, 49 or 52; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:48 or 51;

   c. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:5, 7, 57 or 60, a heavy chain CDR2 of SEQ ID NO:58, 61 or 62; a heavy chain CDR3 of SEQ ID NO:59 or 63; a light chain CDR1 of SEQ ID NO:68, 71 or 74; a light chain CDR2 of SEQ ID NO:69 or 72; and a light chain CDR3 of SEQ ID NO:70 or 73;

   d. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:79, 82, 83 or 85, a heavy chain CDR2 of SEQ ID NO:80, 84 or 86; a heavy chain CDR3 of SEQ ID NO:81 or 87; a light chain CDR1 of SEQ ID NO:92, 95 or 98; a light chain CDR2 of SEQ ID NO:93 or 96; and a light chain CDR3 of SEQ ID NO:94 or 97;

   e. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO:104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:105 or 111; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:117 or 118;

f. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:123, 126, 127 or 129, a heavy chain CDR2 of SEQ ID NO:124, 128 or 130; a heavy chain CDR3 of SEQ ID NO:125 or 131; a light chain CDR1 of SEQ ID NO:136, 139 or 142; a light chain CDR2 of SEQ ID NO:137 or 140; and a light chain CDR3 of SEQ ID NO:138 or 141;

g. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:123, 126, 127 or 129, a heavy chain CDR2 of SEQ ID NO:124, 128 or 130; a heavy chain CDR3 of SEQ ID NO:147 or 148; a light chain CDR1 of SEQ ID NO:153, 156 or 158; a light chain CDR2 of SEQ ID NO:50 or 154; and a light chain CDR3 of SEQ ID NO:155 or 157;

h. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO:104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:163 or 164; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:169 or 170;

i. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:175, 178, 179 or 181, a heavy chain CDR2 of SEQ ID NO:176, 180 or 182; a heavy chain CDR3 of SEQ ID NO:177 or 183; a light chain CDR1 of SEQ ID NO:49, 52 or 116; a light chain CDR2 of SEQ ID NO:47 or 50; and a light chain CDR3 of SEQ ID NO:188 or 189;

j. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO: 103, 106, 107 or 109, a heavy chain CDR2 of SEQ ID NO: 104, 108 or 110; a heavy chain CDR3 of SEQ ID NO:194 or 195; a light chain CDR1 of SEQ ID NO: 49, 52 or 116; a light chain CDR2 of SEQ ID NO: 47 or 50; and a light chain CDR3 of SEQ ID NO:200 or 201;

k. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO:206, 209, 210 or 212, a heavy chain CDR2 of SEQ ID NO:207, 211 or 213; a heavy chain CDR3 of SEQ ID NO:208 or 214; a light chain CDR1 of SEQ ID NO:153, 156 or 158; a light chain CDR2 of SEQ ID NO:50 or 154; and a light chain CDR3 of SEQ ID NO:219 or 220;

l. a heavy chain variable region that comprises a heavy chain CDR1 of SEQ ID NO: 206, 209, 210 or 212, a heavy chain CDR2 of SEQ ID NO: 207, 211 or 213; a heavy chain CDR3 of SEQ ID NO:225 or 226; a light chain CDR1 of SEQ ID NO:136, 139 or 142; a light chain CDR2 of SEQ ID NO:137 or 140; and a light chain CDR3 of SEQ ID NO:231 or 232;

m. a heavy chain variable region that comprises a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, 209, 210 or 212, an HCDR2 of SEQ ID NO: 207, 211 or 213, and an HCDR3 of SEQ ID NO:237 or 238; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, 245 or 247, an LCDR2 of SEQ ID NO:47 or 50, and an LCDR3 of SEQ ID NO:244 or 246;

n. a heavy chain variable region that comprises a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, 209, 210 or 212, an HCDR2 of SEQ ID NO: 207, 211 or 213, and an HCDR3 of SEQ ID NO:252 or 253; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, 156 or 158, an LCDR2 of SEQ ID NO:50 or 154, and an LCDR3 of SEQ ID NO:258 or 259;

o. a heavy chain CDR1 of SEQ ID NO:1, a heavy chain CDR2 of SEQ ID NO:2, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:14, a light chain CDR2 of SEQ ID NO:15, and a light chain CDR3 of SEQ ID NO:16;

p. a heavy chain CDR1 of SEQ ID NO: 4, a heavy chain CDR2 of SEQ ID NO:2, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:14, a light chain CDR2 of SEQ ID NO:15, and a light chain CDR3 of SEQ ID NO:16;

q. a heavy chain CDR1 of SEQ ID NO:5, a heavy chain CDR2 of SEQ ID NO:6, a heavy chain CDR3 of SEQ ID NO:3, a light chain CDR1 of SEQ ID NO:17, a light chain CDR2 of SEQ ID NO: 18, and a light chain CDR3 of SEQ ID NO: 19;

r. a heavy chain CDR1 of SEQ ID NO:7, a heavy chain CDR2 of SEQ ID NO:8, a heavy chain CDR3 of SEQ ID NO:9, a light chain CDR1 of SEQ ID NO:20, a light chain CDR2 of SEQ ID NO:18, and a light chain CDR3 of SEQ ID NO:16;

s. a heavy chain CDR1 of SEQ ID NO:33, a heavy chain CDR2 of SEQ ID NO:34, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:46, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:48;

t. a heavy chain CDR1 of SEQ ID NO:36, a heavy chain CDR2 of SEQ ID NO:34, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:46, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:48;

u. a heavy chain CDR1 of SEQ ID NO:37, a heavy chain CDR2 of SEQ ID NO:38, a heavy chain CDR3 of SEQ ID NO:35, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:51;

v. a heavy chain CDR1 of SEQ ID NO: 39, a heavy chain CDR2 of SEQ ID NO:40, a heavy chain CDR3 of SEQ ID NO:41, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:48;

w. a heavy chain CDR1 of SEQ ID NO:57, a heavy chain CDR2 of SEQ ID NO:58, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:68, a light chain CDR2 of SEQ ID NO:69, and a light chain CDR3 of SEQ ID NO:70;

x. a heavy chain CDR1 of SEQ ID NO:60, a heavy chain CDR2 of SEQ ID NO:58, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:68, a light chain CDR2 of SEQ ID NO:69, and a light chain CDR3 of SEQ ID NO:70;

y. a heavy chain CDR1 of SEQ ID NO:5, a heavy chain CDR2 of SEQ ID NO:61, a heavy chain CDR3 of SEQ ID NO:59, a light chain CDR1 of SEQ ID NO:71, a light chain CDR2 of SEQ ID NO:72, and a light chain CDR3 of SEQ ID NO:73;

z. a heavy chain CDR1 of SEQ ID NO:7, a heavy chain CDR2 of SEQ ID NO:62, a heavy chain CDR3 of SEQ ID NO:63, a light chain CDR1 of SEQ ID NO:74, a light chain CDR2 of SEQ ID NO:72, and a light chain CDR3 of SEQ ID NO:70;

aa. a heavy chain CDR1 of SEQ ID NO:79, , a heavy chain CDR2 of SEQ ID NO:80, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:92, a light chain CDR2 of SEQ ID NO:93, and a light chain CDR3 of SEQ ID NO:94;

bb. a heavy chain CDR1 of SEQ ID NO:82, a heavy chain CDR2 of SEQ ID NO:80, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:92, a light chain CDR2 of SEQ ID NO:93, and a light chain CDR3 of SEQ ID NO:94;

cc. a heavy chain CDR1 of SEQ ID NO:83, a heavy chain CDR2 of SEQ ID NO:84, a heavy chain CDR3 of SEQ ID NO:81, a light chain CDR1 of SEQ ID NO:95, a light chain CDR2 of SEQ ID NO:96, and a light chain CDR3 of SEQ ID NO: 97;

dd. a heavy chain CDR1 of SEQ ID NO: 85, a heavy chain CDR2 of SEQ ID NO:86, a heavy chain CDR3 of SEQ ID NO:87, a light chain CDR1 of SEQ ID NO:98, a light chain CDR2 of SEQ ID NO:96, and a light chain CDR3 of SEQ ID NO:94;

ee. a heavy chain CDR1 of SEQ ID NO:103, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO: 116; a light chain CDR2 of SEQ ID NO:47; and a light chain CDR3 of SEQ ID NO:117;

ff. a heavy chain CDR1 of SEQ ID NO:106, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:117;

gg. a heavy chain CDR1 of SEQ ID NO:107, a heavy chain CDR2 of SEQ ID NO:108, a heavy chain CDR3 of SEQ ID NO:105, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:118;

hh. a heavy chain CDR1 of SEQ ID NO:109, a heavy chain CDR2 of SEQ ID NO:110, a heavy chain CDR3 of SEQ ID NO:111, a light chain CDR1 of SEQ ID NO:52 a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:117;

ii. a heavy chain CDR1 of SEQ ID NO:123, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137,and a light chain CDR3 of SEQ ID NO:138;

jj. a heavy chain CDR1 of SEQ ID NO:126, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137, and a light chain CDR3 of SEQ ID NO:138;

kk. a heavy chain CDR1 of SEQ ID NO:127, a heavy chain CDR2 of SEQ ID NO:128, a heavy chain CDR3 of SEQ ID NO:125, a light chain CDR1 of SEQ ID NO:139, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO: 141;

ll. a heavy chain CDR1 of SEQ ID NO: 129, a heavy chain CDR2 of SEQ ID NO:130, a heavy chain CDR3 of SEQ ID NO:131, a light chain CDR1 of SEQ ID NO:142, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO:138;

mm. a heavy chain CDR1 of SEQ ID NO:123, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO:154, and a light chain CDR3 of SEQ ID NO:155;

nn. a heavy chain CDR1 of SEQ ID NO:126, a heavy chain CDR2 of SEQ ID NO:124, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO: 154, and a light chain CDR3 of SEQ ID NO:155;

oo. a heavy chain CDR1 of SEQ ID NO:127, a heavy chain CDR2 of SEQ ID NO:128, a heavy chain CDR3 of SEQ ID NO:147, a light chain CDR1 of SEQ ID NO:156, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:157;

pp. a heavy chain CDR1 of SEQ ID NO: 129, a heavy chain CDR2 of SEQ ID NO:130, a heavy chain CDR3 of SEQ ID NO:148, a light chain CDR1 of SEQ ID NO:158, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:155;

qq. a heavy chain CDR1 of SEQ ID NO:103, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:169;

rr. a heavy chain CDR1 of SEQ ID NO:106, a heavy chain CDR2 of SEQ ID NO:104, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID

NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:169;

ss. a heavy chain CDR1 of SEQ ID NO:107, a heavy chain CDR2 of SEQ ID NO:108, a heavy chain CDR3 of SEQ ID NO:163, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:170;

tt. a heavy chain CDR1 of SEQ ID NO: 109, a heavy chain CDR2 of SEQ ID NO:110, a heavy chain CDR3 of SEQ ID NO:164, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:169;

uu. a heavy chain CDR1 of SEQ ID NO:175, a heavy chain CDR2 of SEQ ID NO:176, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:188;

vv. a heavy chain CDR1 of SEQ ID NO:178, a heavy chain CDR2 of SEQ ID NO:176, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:116, a light chain CDR2 of SEQ ID NO:47, and a light chain CDR3 of SEQ ID NO:188;

ww. a heavy chain CDR1 of SEQ ID NO:179, a heavy chain CDR2 of SEQ ID NO:180, a heavy chain CDR3 of SEQ ID NO:177, a light chain CDR1 of SEQ ID NO:49, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:189;

xx. a heavy chain CDR1 of SEQ ID NO: 181, a heavy chain CDR2 of SEQ ID NO:182; a heavy chain CDR3 of SEQ ID NO:183, a light chain CDR1 of SEQ ID NO:52, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:188;

yy. a heavy chain CDR1 of SEQ ID NO: 103, a heavy chain CDR2 of SEQ ID NO: 104, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO: 47, and a light chain CDR3 of SEQ ID NO:200;

zz. a heavy chain CDR1 of SEQ ID NO: 106, a heavy chain CDR2 of SEQ ID NO: 104, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 116, a light chain CDR2 of SEQ ID NO: 47, and a light chain CDR3 of SEQ ID NO:200;

aaa. a heavy chain CDR1 of SEQ ID NO: 107, a heavy chain CDR2 of SEQ ID NO: 108, a heavy chain CDR3 of SEQ ID NO:194, a light chain CDR1 of SEQ ID NO: 49, a light chain CDR2 of SEQ ID NO: 50, and a light chain CDR3 of SEQ ID NO: 201;

bbb. a heavy chain CDR1 of SEQ ID NO: 109, a heavy chain CDR2 of SEQ ID NO: 110, a heavy chain CDR3 of SEQ ID NO:195, a light chain CDR1 of SEQ ID NO: 52, a light chain CDR2 of SEQ ID NO: 50, and a light chain CDR3 of SEQ ID NO:200;

ccc. a heavy chain CDR1 of SEQ ID NO:206, a heavy chain CDR2 of SEQ ID NO:207, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO:154, and a light chain CDR3 of SEQ ID NO:219;

ddd. a heavy chain CDR1 of SEQ ID NO:209, a heavy chain CDR2 of SEQ ID NO:207, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:153, a light chain CDR2 of SEQ ID NO: 154, and a light chain CDR3 of SEQ ID NO:219;

eee. a heavy chain CDR1 of SEQ ID NO:210, a heavy chain CDR2 of SEQ ID NO:211, a heavy chain CDR3 of SEQ ID NO:208, a light chain CDR1 of SEQ ID NO:156, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:220;

fff. a heavy chain CDR1 of SEQ ID NO: 212, a heavy chain CDR2 of SEQ ID NO:213, a heavy chain CDR3 of SEQ ID NO:214, a light chain CDR1 of SEQ ID NO:158, a light chain CDR2 of SEQ ID NO:50, and a light chain CDR3 of SEQ ID NO:219;

ggg. a heavy chain CDR1 of SEQ ID NO: 206, a heavy chain CDR2 of SEQ ID NO: 207, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID

NO:136, a light chain CDR2 of SEQ ID NO:137,and a light chain CDR3 of SEQ ID NO:231;

hhh. a heavy chain CDR1 of SEQ ID NO: 209, a heavy chain CDR2 of SEQ ID NO: 207, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:136, a light chain CDR2 of SEQ ID NO:137, and a light chain CDR3 of SEQ ID NO:231;

iii. a heavy chain CDR1 of SEQ ID NO: 210, a heavy chain CDR2 of SEQ ID NO: 211, a heavy chain CDR3 of SEQ ID NO:225, a light chain CDR1 of SEQ ID NO:139, a light chain CDR2 of SEQ ID NO:140, and a light chain CDR3 of SEQ ID NO: 232;

jjj. a heavy chain CDR1 of SEQ ID NO: 212, a heavy chain CDR2 of SEQ ID NO: 213, a heavy chain CDR3 of SEQ ID NO: 226, a light chain CDR1 of SEQ ID NO:142; a light chain CDR2 of SEQ ID NO: 140; and a light chain CDR3 of SEQ ID NO:231;

kkk. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:237,and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, an LCDR2 of SEQ ID NO:47, and an LCDR3 of SEQ ID NO:244;

lll. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 209, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:237, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:243, an LCDR2 of SEQ ID NO:47, and an LCDR3 of SEQ ID NO:244;

mmm. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 210, an HCDR2 of SEQ ID NO: 211, and an HCDR3 of SEQ ID NO:237, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:245, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:246;

nnn. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 212, an HCDR2 of SEQ ID NO: 213, and an HCDR3 of SEQ ID NO:238; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:247, an LCDR2 of SEQ ID NO: 50, and an LCDR3 of SEQ ID NO:244;

ooo. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 206, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:252,and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, an LCDR2 of SEQ ID NO: 154, and an LCDR3 of SEQ ID NO:258;

ppp. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 209, an HCDR2 of SEQ ID NO: 207, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:153, an LCDR2 of SEQ ID NO:154, and an LCDR3 of SEQ ID NO:258;

qqq. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 210, an HCDR2 of SEQ ID NO: 211, and an HCDR3 of SEQ ID NO:252, and a light chain variable region that comprises an LCDR1 of SEQ ID NO:156, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:259; or

rrr. a heavy chain variable region that comprises an HCDR1 of SEQ ID NO: 212, an HCDR2 of SEQ ID NO: 213, and an HCDR3 of SEQ ID NO: 253; and a light chain variable region that comprises an LCDR1 of SEQ ID NO:158, an LCDR2 of SEQ ID NO:50, and an LCDR3 of SEQ ID NO:258.

2. An antibody or antigen binding fragment thereof that binds PMEL17 comprising:

a. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:21;

b. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:25;

c. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:10, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:29;

d. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:42, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:53;

e. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:64, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:75;

f. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:88, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:99;

g. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:112, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:119;

h. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:132, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:143;

i. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:149, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:159;

j. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:165, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:171;

k. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:184, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:190;

l. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:196, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:202;

m. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:215, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:221;

n. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:227, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:233;

o. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:239, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:248; or

p. A heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:254, and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:260.

3. An antibody or antigen binding fragment thereof that binds PMEL17 comprising:

a. A heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:23;

b. A heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:27;

c. A heavy chain comprising the amino acid sequence of SEQ ID NO:12, and a light chain comprising the amino acid sequence of SEQ ID NO:31;

d. A heavy chain comprising the amino acid sequence of SEQ ID NO:44, and a light chain comprising the amino acid sequence of SEQ ID NO:55;

e. A heavy chain comprising the amino acid sequence of SEQ ID NO:66, and a light chain comprising the amino acid sequence of SEQ ID NO:77;

f. A heavy chain comprising the amino acid sequence of SEQ ID NO:90, and a light chain comprising the amino acid sequence of SEQ ID NO:101;

g. A heavy chain comprising the amino acid sequence of SEQ ID NO:114, and a light chain comprising the amino acid sequence of SEQ ID NO:121.;

h. A heavy chain comprising the amino acid sequence of SEQ ID NO:134, and a light chain comprising the amino acid sequence of SEQ ID NO:145;

i. A heavy chain comprising the amino acid sequence of SEQ ID NO:151, and a light chain comprising the amino acid sequence of SEQ ID NO:161;

j. A heavy chain comprising the amino acid sequence of SEQ ID NO:167, and a light chain comprising the amino acid sequence of SEQ ID NO:173;

k. A heavy chain comprising the amino acid sequence of SEQ ID NO:186, and a light chain comprising the amino acid sequence of SEQ ID NO:192;

l. A heavy chain comprising the amino acid sequence of SEQ ID NO:198, and a light chain comprising the amino acid sequence of SEQ ID NO:204;

m. A heavy chain comprising the amino acid sequence of SEQ ID NO:217, and a light chain comprising the amino acid sequence of SEQ ID NO:223;

n. A heavy chain comprising the amino acid sequence of SEQ ID NO:229, and a light chain comprising the amino acid sequence of SEQ ID NO:235;

o. A heavy chain comprising the amino acid sequence of SEQ ID NO:241, and a light chain comprising the amino acid sequence of SEQ ID NO:250; or

p. A heavy chain comprising the amino acid sequence of SEQ ID NO:256, and a light chain comprising the amino acid sequence of SEQ ID NO:262.

4. The antibody of any one of claims 1-3, wherein the antibody or antigen binding fragment thereof comprises one or more cysteine substitutions.

5. The antibody of claim 4, wherein the antibody or antigen binding fragment thereof comprises one or more cysteine substitutions selected from S152C, S375C, or both S152C and S375C of the heavy chain of the antibody or antigen binding fragment thereof, wherein the position is numbered according to the EU system.

6. The antibody of any one of claims 1-5, wherein said antibody is a monoclonal antibody.

7. An antibody drug conjugate comprising the formula (C)

$$Ab\text{-}(L_A\text{-}(D)_n)_y \qquad (C)$$

wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

L_A is a linker;

n is 1, 2, 3 or 4, and

y is 1, 2, 3 or 4.

8. The antibody drug conjugate of claim 7, wherein said n is 1.

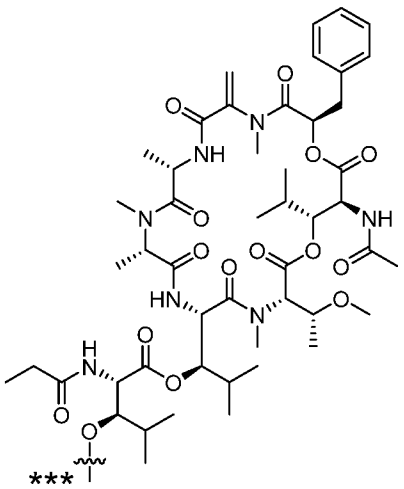
9. The antibody drug conjugate of any one of claims 7 or 8, wherein said y is about 1 to about 4.

10. The antibody drug conjugate of any one of claims 7-9, wherein said linker is a cleavable linker or a non-cleavable linker.

11. The antibody drug conjugate of claim 10, wherein the linker comprises a ValCit peptide linker.

12. The antibody drug conjugate of any one of claims 7-11, wherein said drug moiety is an inhibitor of GNAQ and GNA11.

13. The antibody drug conjugate of any one of claims 7-11, wherein the D is



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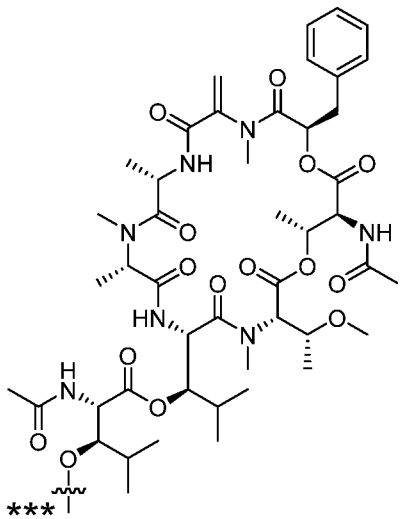
14. The antibody drug conjugate of any one of claims 7-11, wherein D is



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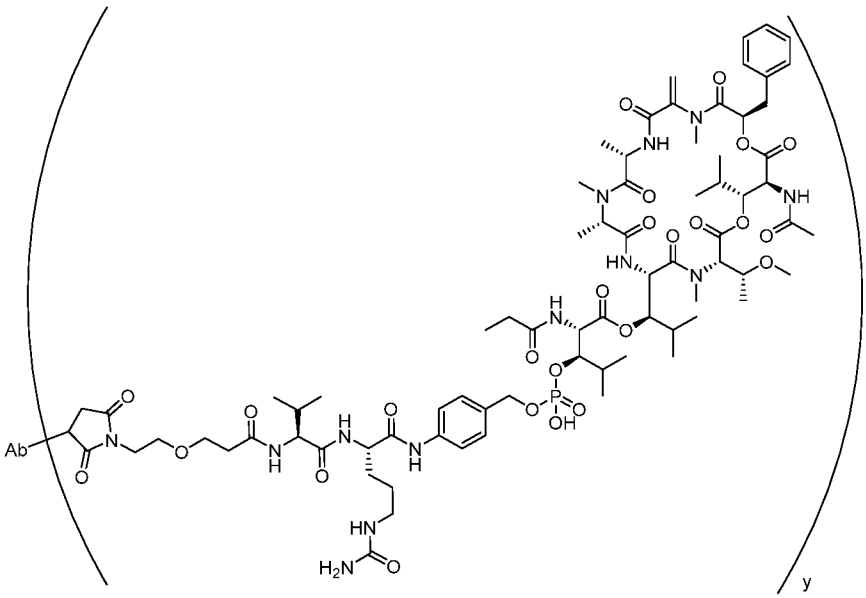
15. The antibody drug conjugate of any one of claims 7-14 having the following structure,



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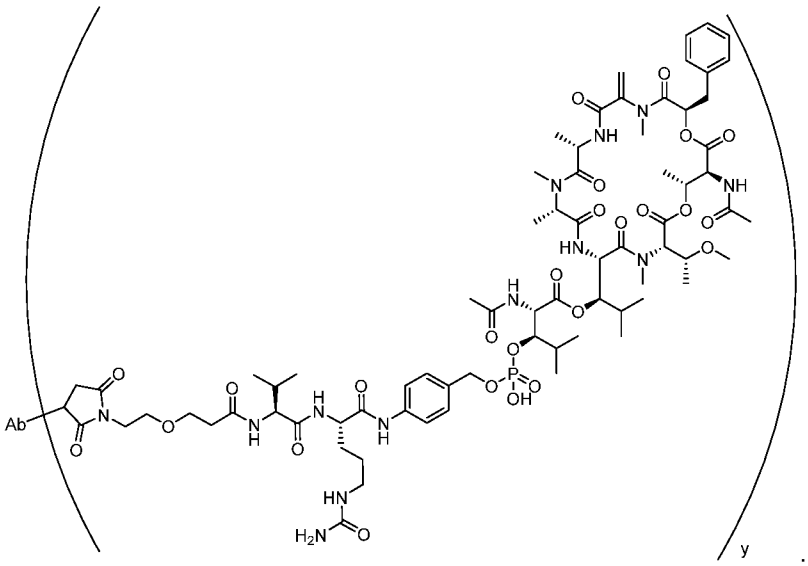
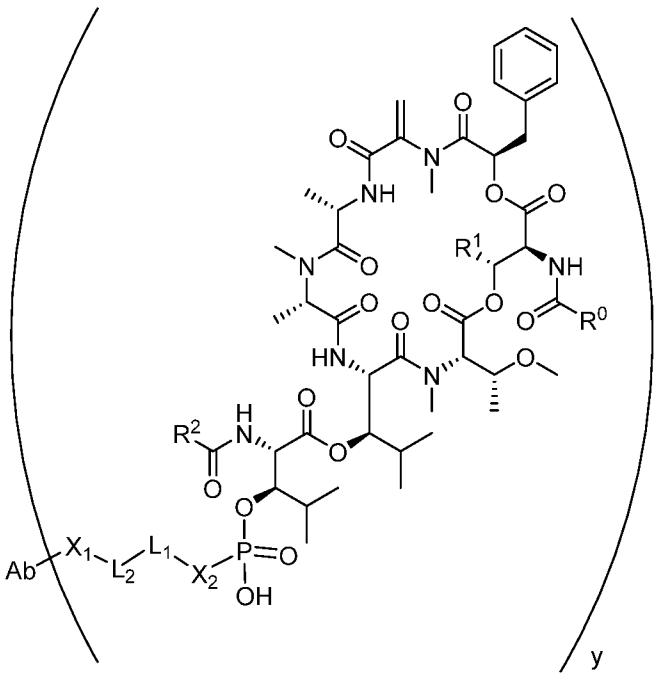
16. The antibody drug conjugate of any one of claims 7-14 having the following structure,



17. An antibody drug conjugate having the following Formula (C-2):



(C-2),

wherein:

R^0 is methyl or ethyl;

R^1 is methyl or isopropyl;

R^2 is methyl or ethyl;

Ab is an antibody or antigen binding fragment thereof that binds to human PMEL17 protein;

X_1 is a bivalent coupling group;
X_2 is a self-immolative spacer;
L_1 is a bivalent peptide linker;
L_2 is a bond or a linker, and
y is 1, 2, 3 or 4.

18. A pharmaceutical composition comprising the antibody, or antigen binding fragment thereof, of any one of claims 1-6 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising the antibody drug conjugate of any one of claims 7-17 and a pharmaceutically acceptable carrier.

20. A method of treating or preventing cancer in a patient in need thereof, comprising administering to said patient the antibody drug conjugate of any one of claims 7-17, or the pharmaceutical composition of any one of claims 18 or 19, wherein the cancer expresses PMEL17, contains a mutation of the GNAQ or GNA11 gene, or the cancer expresses PMEL17 and contains a mutation of GNAQ, GNA11, or both.

21. The method of claim 20, wherein the antibody drug conjugate or pharmaceutical composition are administered to the patient in combination with one or more additional therapeutic compounds.

22. The method of claim 21, wherein the one or more additional therapeutic compounds is selected from a standard of care chemotherapeutic, an MDM2 inhibitor, an MRC2 inhibitor, a PKC inhibitor, a MAPK inhibitor, a costimulatory molecule, or a checkpoint inhibitor.

23. The method of claim 22, wherein the costimulatory molecule is selected from an agonist of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, STING, or CD83 ligand.

24. The method of claim 22, wherein the checkpoint inhibitor is selected from an inhibitor of PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta.

25. The antibody drug conjugate of any one of claims 7-17, or the pharmaceutical composition of any one of claims 18 or 19, for use as a medicament.

26. The antibody drug conjugate of any one of claims 7-17, or the pharmaceutical composition of any one of claims 18 or 19, for use in the treatment or prevention of a PMEL17 expressing cancer or a cancer that contains a mutation of the GNAQ or GNA11 gene in a patient in need thereof.

27. Use of the antibody or antigen binding fragment thereof of any one of claims 1-6, the antibody drug conjugate of any one of claims 7-17, or the pharmaceutical composition of any one of claims 18 or 19, to treat or prevent a PMEL17 expressing cancer or a cancer that contains a mutation of the GNAQ or GNA11 gene in a patient in need thereof.

28. Use of the antibody or antigen binding fragment thereof of any one of claims 1-6, the antibody drug conjugate of any one of claims 7-17, or the pharmaceutical composition of any one of claims 18 or 19 in the manufacture of a medicament.

29. The method of any one of claims 20-24, the antibody drug conjugate of any one of claims 25-26, or the use of any one of claims 27-28, wherein the cancer expresses PMEL17 or contains a mutation of the GNAQ or GNA11 gene.

30. The method, antibody drug conjugate, or use of claim 28, wherein the cancer is uveal melanoma, subcutaneous melanoma, hepatocellular carcinoma, or a metastatic cancer thereof.

31. A nucleic acid that encodes the antibody or antigen binding fragment of any one of claims 1-6.

32. The nucleic acid of claim 31, wherein the nucleic acid comprises the nucleotide sequence of SEQ ID NOs: 13, 24, 28, 32, 45, 56, 67, 78, 91, 102, 115, 122, 135, 146, 152, 162, 168, 174, 187, 193, 199, 205, 218, 224, 230, 236, 242, 251, 257, or 263.

33. A vector comprising the nucleic acid of claim 31 or 32.

34. A host cell comprising the vector according to claim 33, or the nucleic acid according to claim 31 or 32.

35. A process for producing an antibody or antigen binding fragment comprising cultivating the host cell of claim 34 and recovering the antibody from cell culture.

36. The process of claim 35 wherein recovering the antibody from cell culture comprises the steps of:

a) removing cells and filtering the culture;

b) purifying the culture by affinity chromatography ;

c) inactivating any viruses in the culture by adjusting the pH to 3.4-3.6, then readjusting the pH to 5.8-6.2 and filtering the culture;

d) purifying the culture by cation exchange chromatography and performing on-column reduction of the culture;

e) performing anion exchange chromatography on the culture;

f) removing viruses by nanofiltration;

g) filtering the culture containing the antibody; and

h) obtaining purified antibody.

37. A process for producing an anti-PMEL17 antibody drug conjugate comprising:

(a) pre-forming a linker-drug moiety of the following Formula (B):

$$R^8\text{-}L_B\text{-}(D)_n \qquad (B)$$

wherein:

D is a GNAQ inhibitor, a GNA11 inhibitor or an inhibitor of GNAQ and GNA11;

R^8 is a reactive group;

L_B is a cleavable or non-cleavable linker, and

n is 1, 2, 3 or 4;

(b) conjugating said linker-drug moiety to the antibody recovered from the cell culture of claim 35 to produce an antibody drug conjugate; and

(c) purifying the antibody drug conjugate.

38. A diagnostic reagent comprising the antibody or antigen binding fragment thereof of any one of claims 1-6.

39. The diagnostic reagent of claim 38, wherein the antibody or antigen binding fragment thereof is labeled with a radiolabel, a fluorophore, a chromophore, an imaging agent, or a metal ion.

FIG. 1A

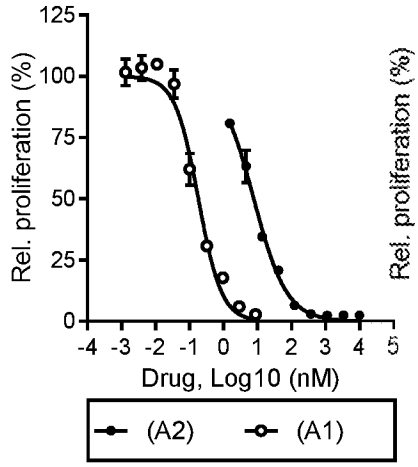


FIG. 1B

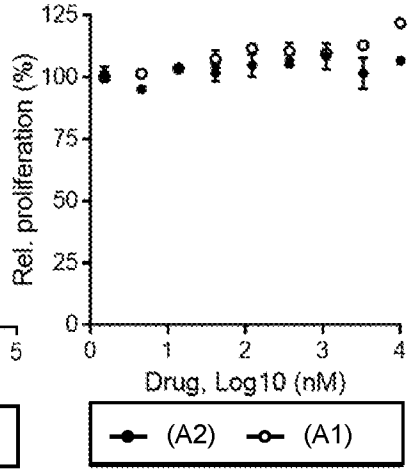


FIGURE 1

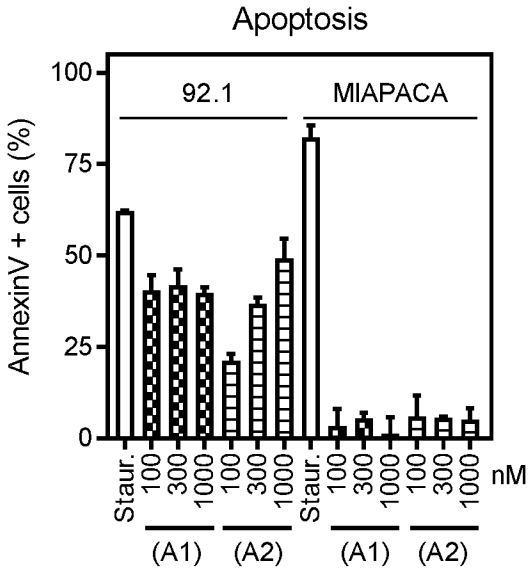


FIGURE 2

FIG. 3A

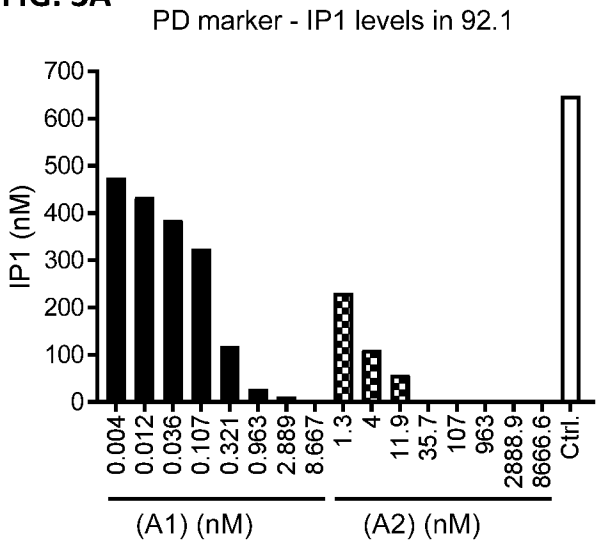


FIG. 3B

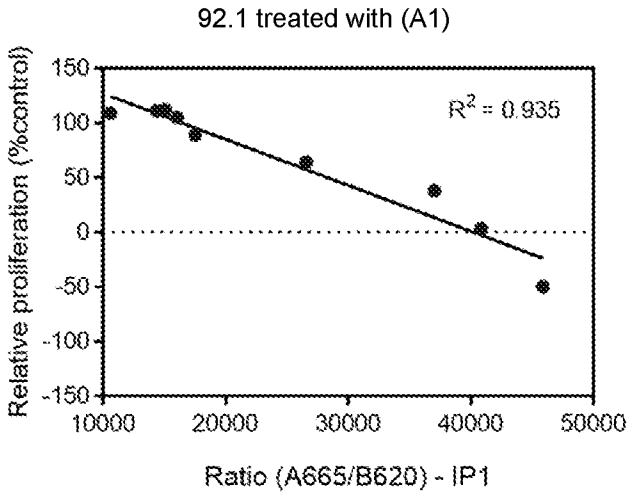


FIG. 3C

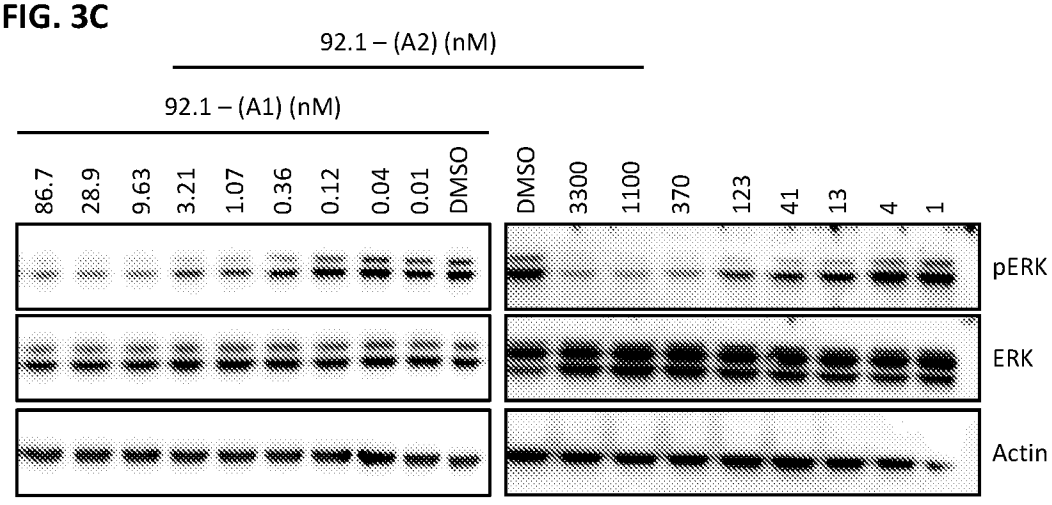


FIGURE 3

FIG. 4A

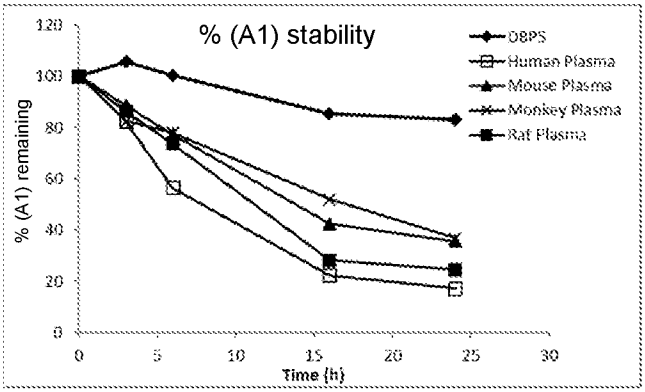
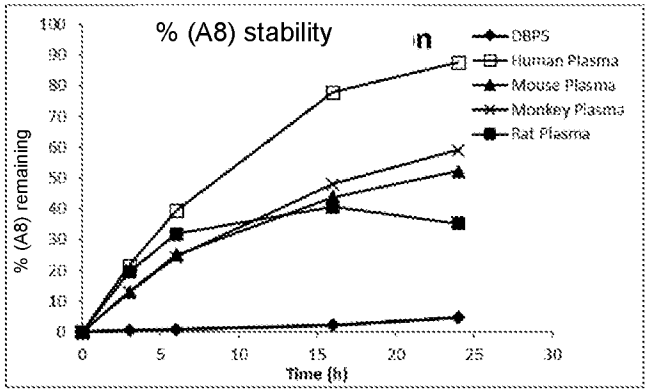


FIG. 4B



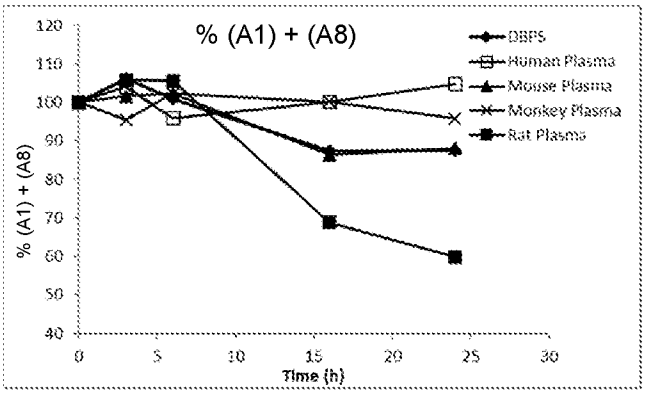


FIG. 4C

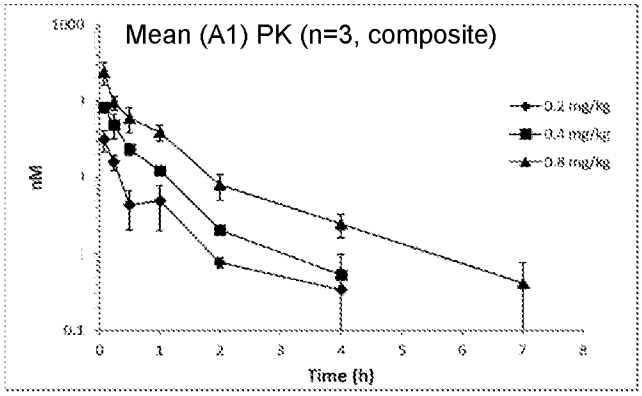


FIG. 4D

FIGURE 4

FIG. 5A

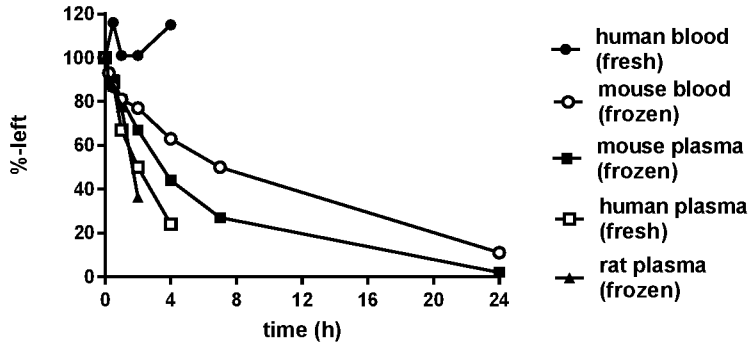


FIG. 5B

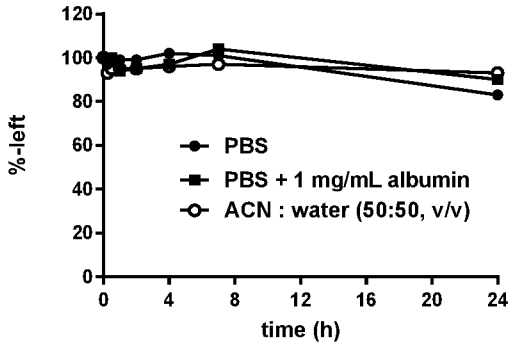


FIG. 5C

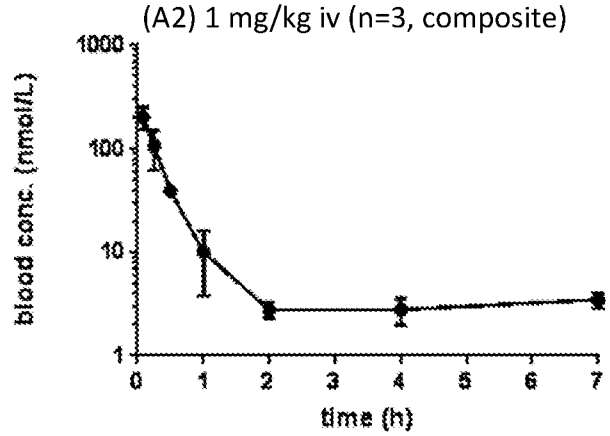


FIG. 5D

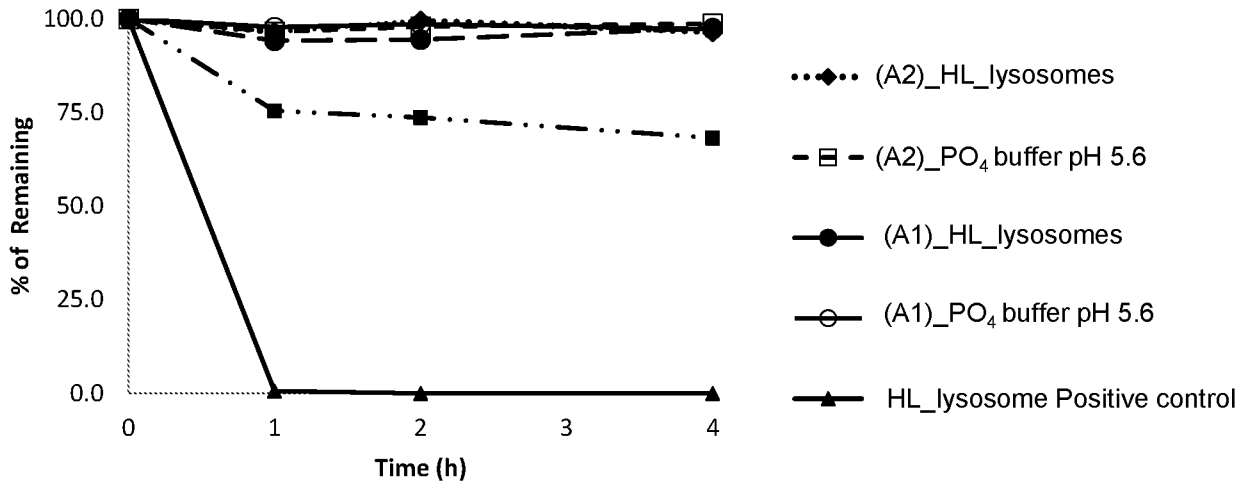


FIGURE 5

FIG. 6A

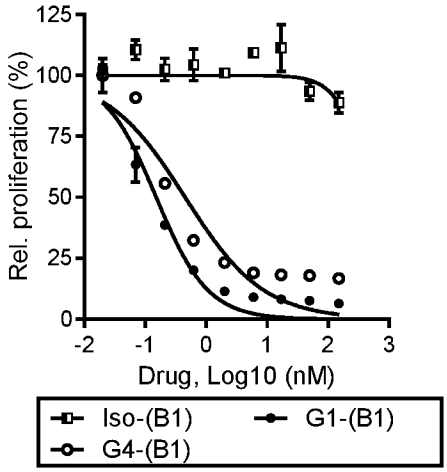


FIG. 6B

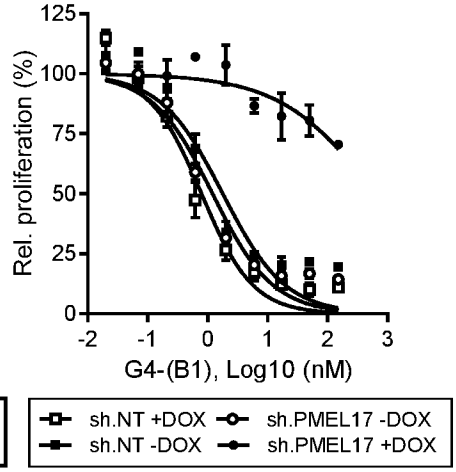


FIGURE 6

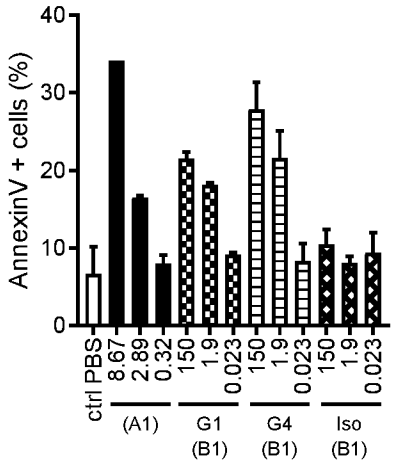


FIGURE 7

FIG. 8A

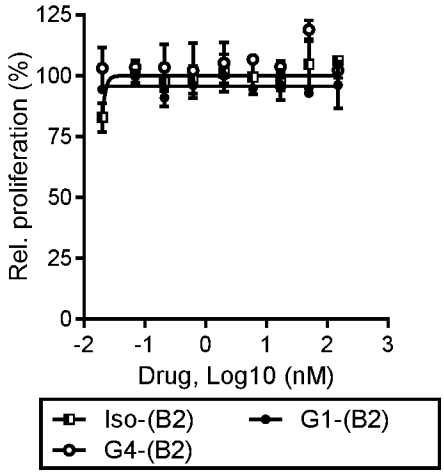


FIG. 8B

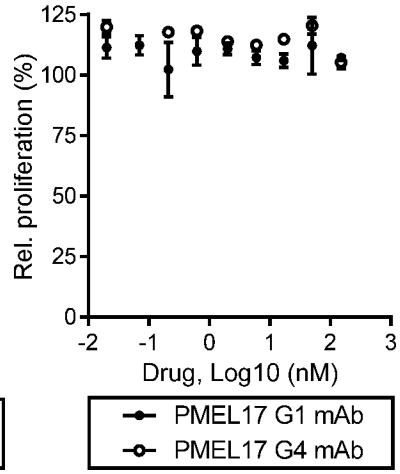


FIGURE 8

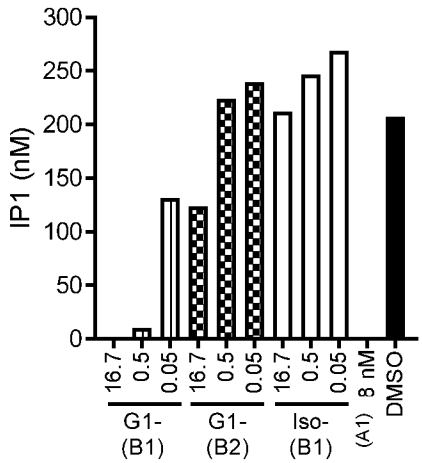


FIGURE 9

FIG. 10A 92.1 UM cells

FIG. 10B Platelets Donor #1

FIG. 10C Platelets Donor #2

FIG. 10D Platelets Donor #3

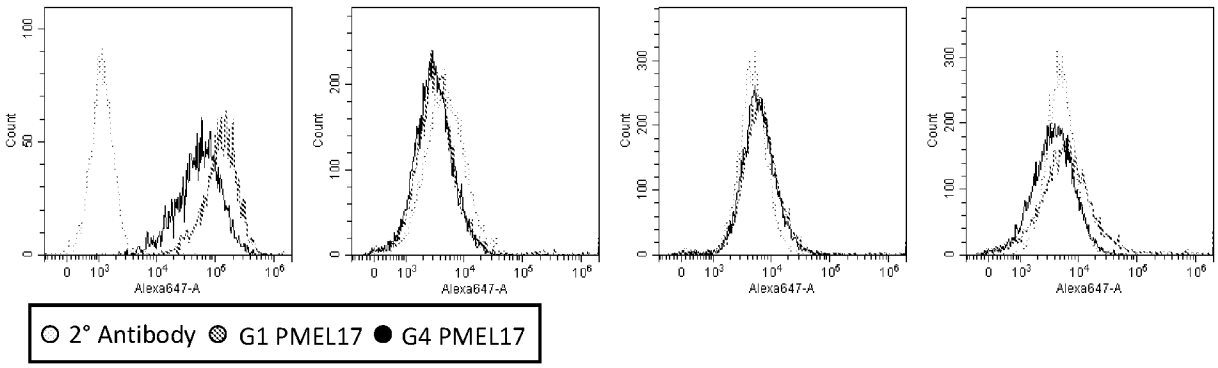


FIGURE 10

FIG. 11A

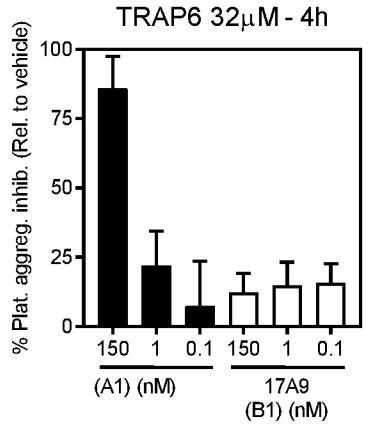


FIG. 11B

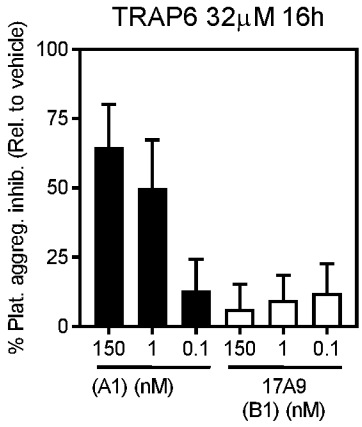


FIG. 11C

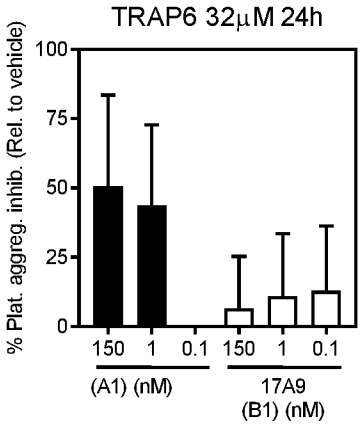


FIGURE 11

FIG.12A

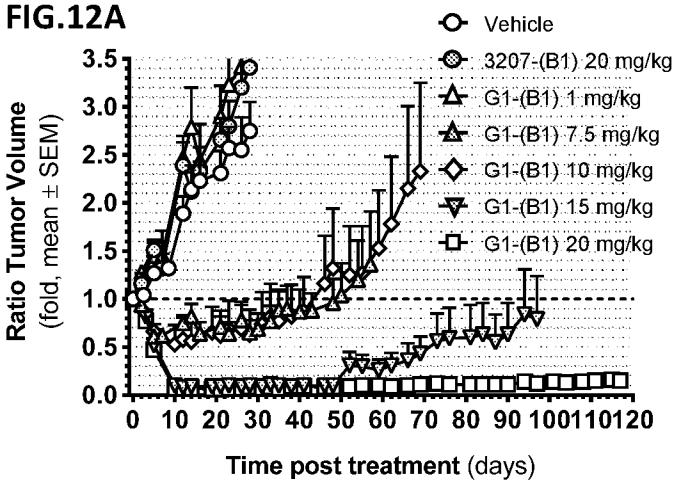


FIG. 12B

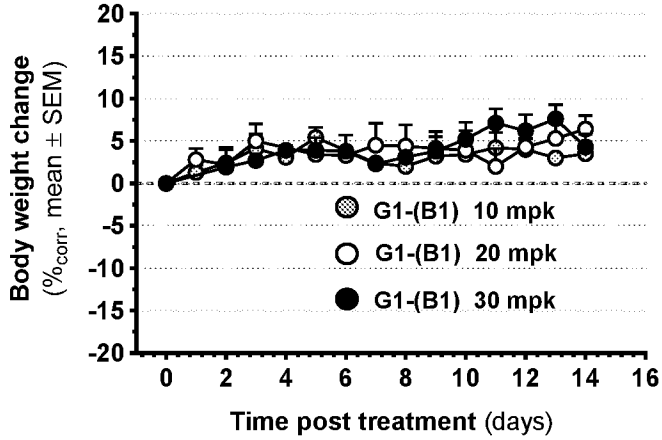


FIG. 12C

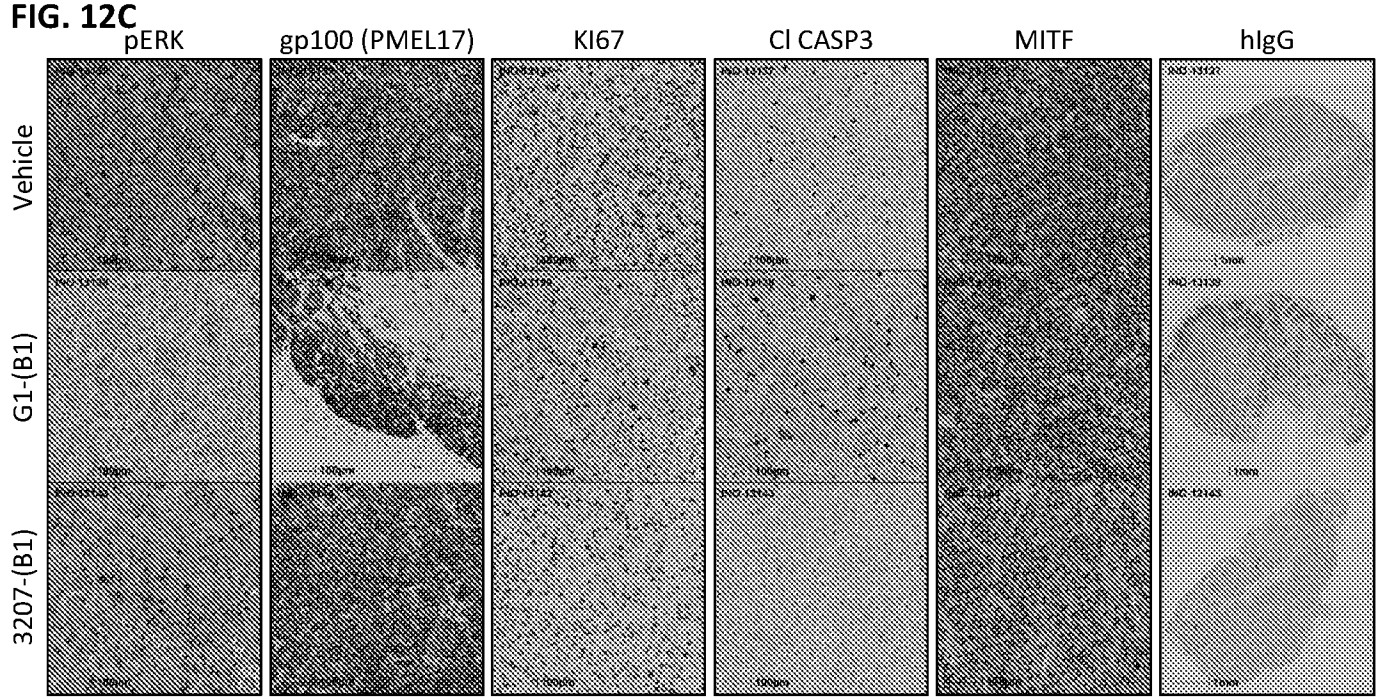


FIG. 12D

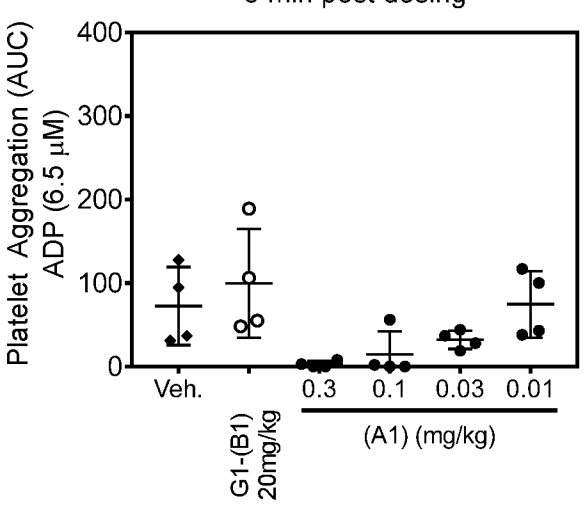


FIG. 12E

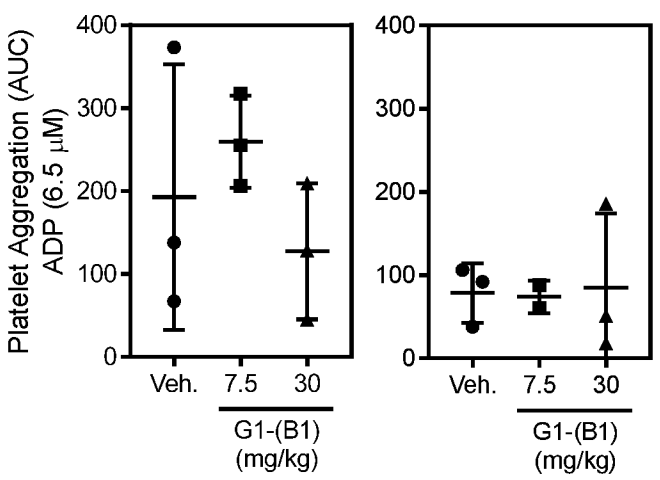
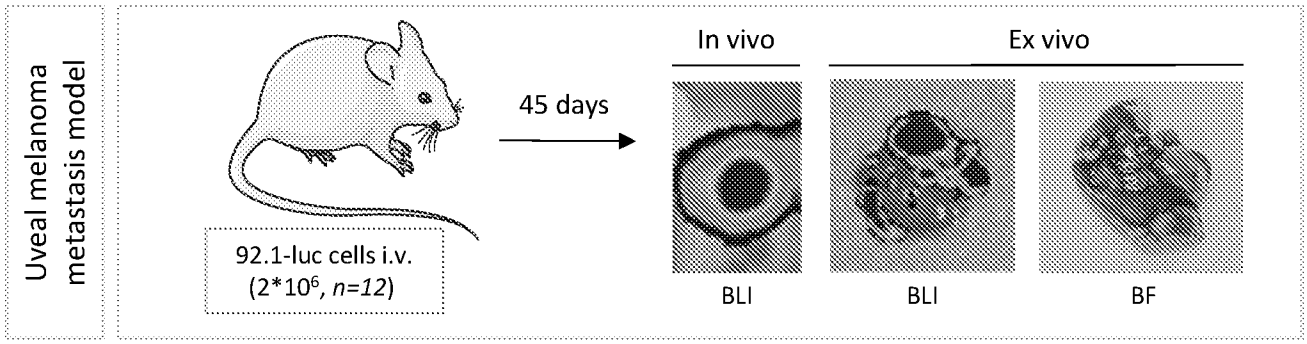


FIGURE 12

FIG. 13A



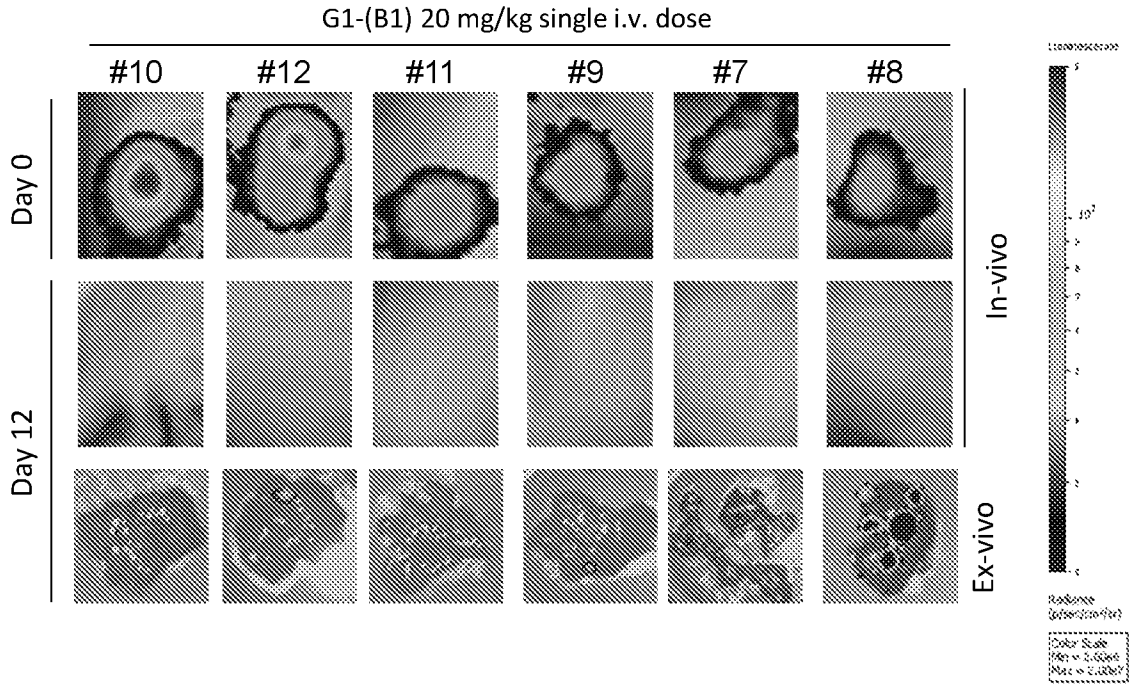


FIG. 13B

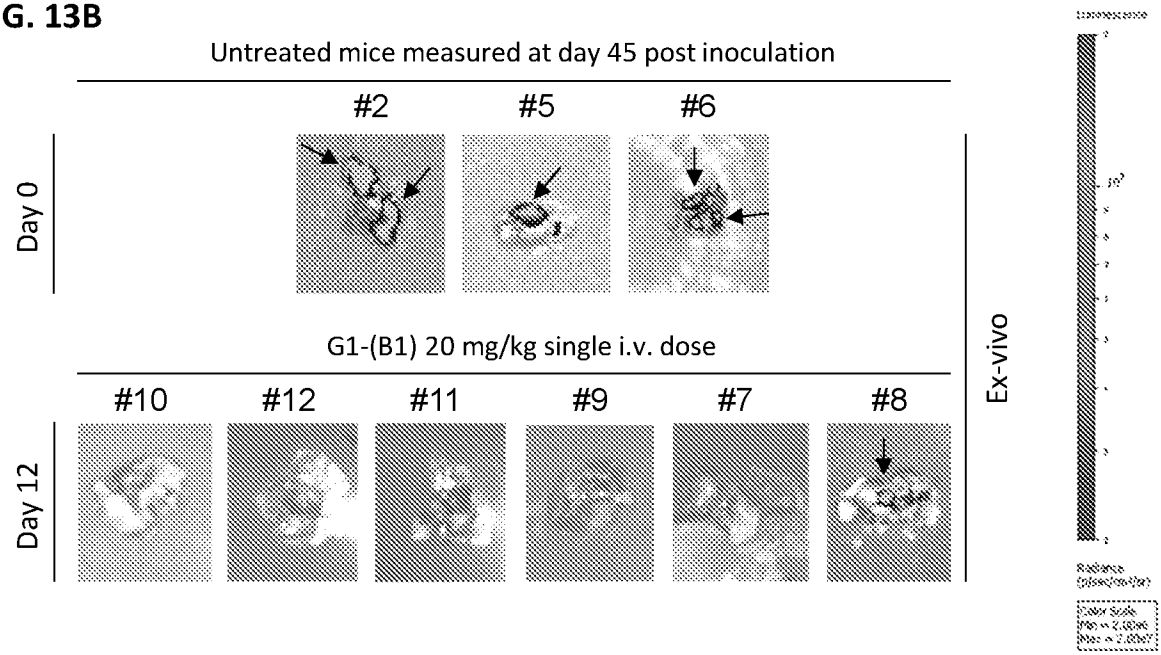


FIGURE 13

FIG. 13C

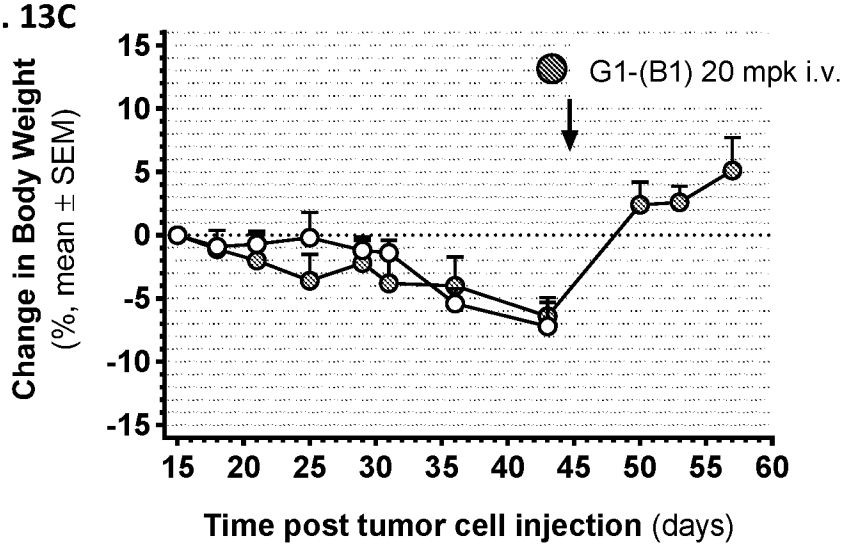


FIGURE 13

FIG. 14A

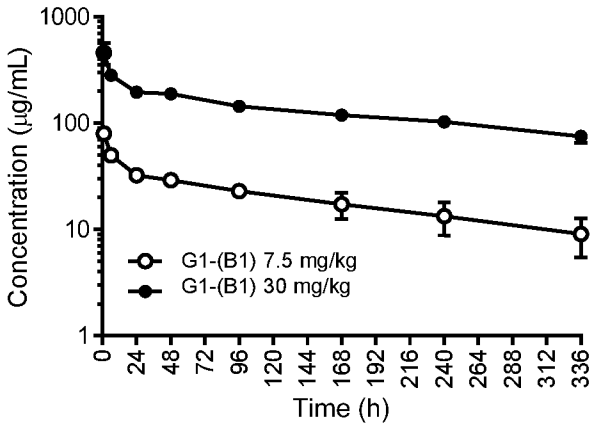
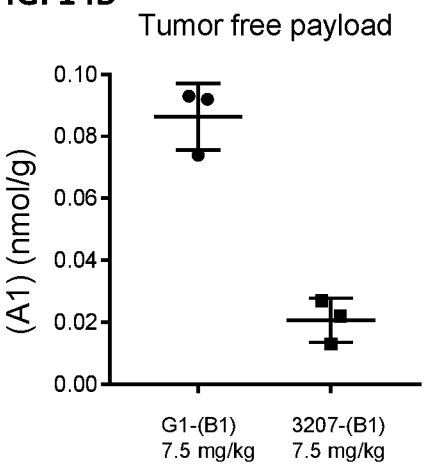


FIG. 14B



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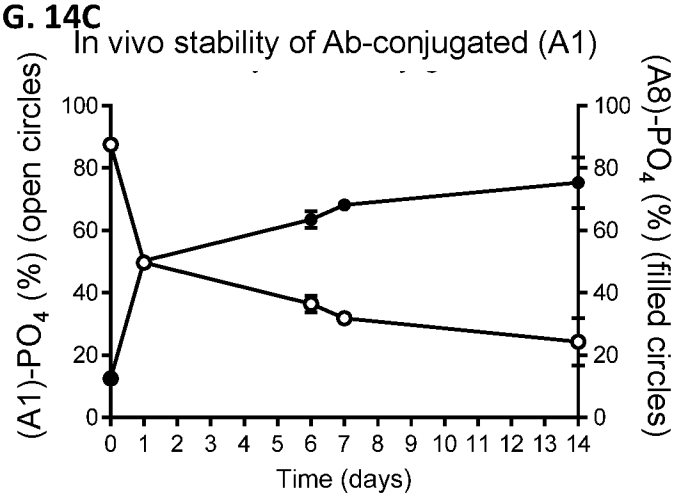


FIG. 14D

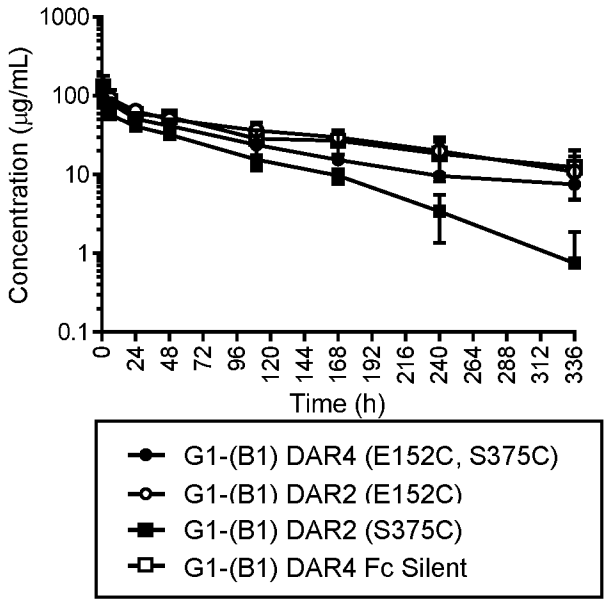


FIG. 14E

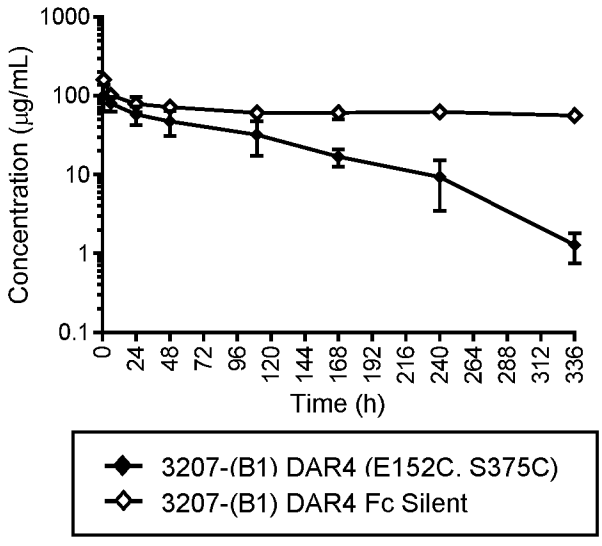


FIGURE 14

FIG. 15A

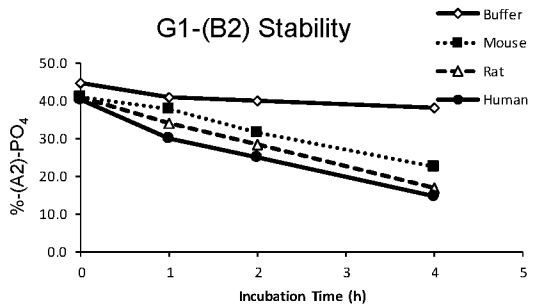


FIG. 15B

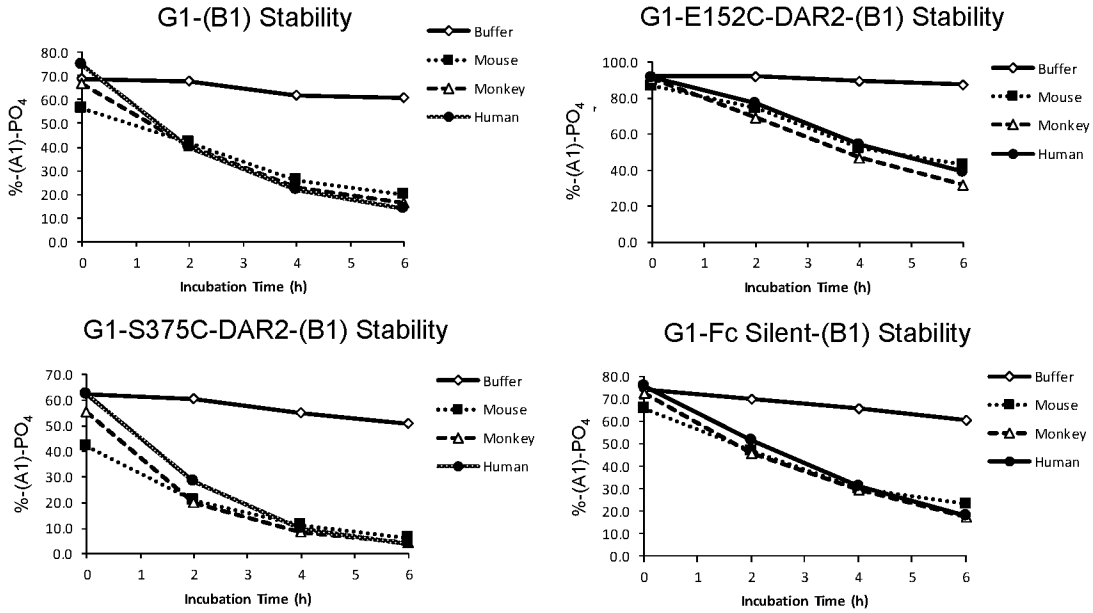
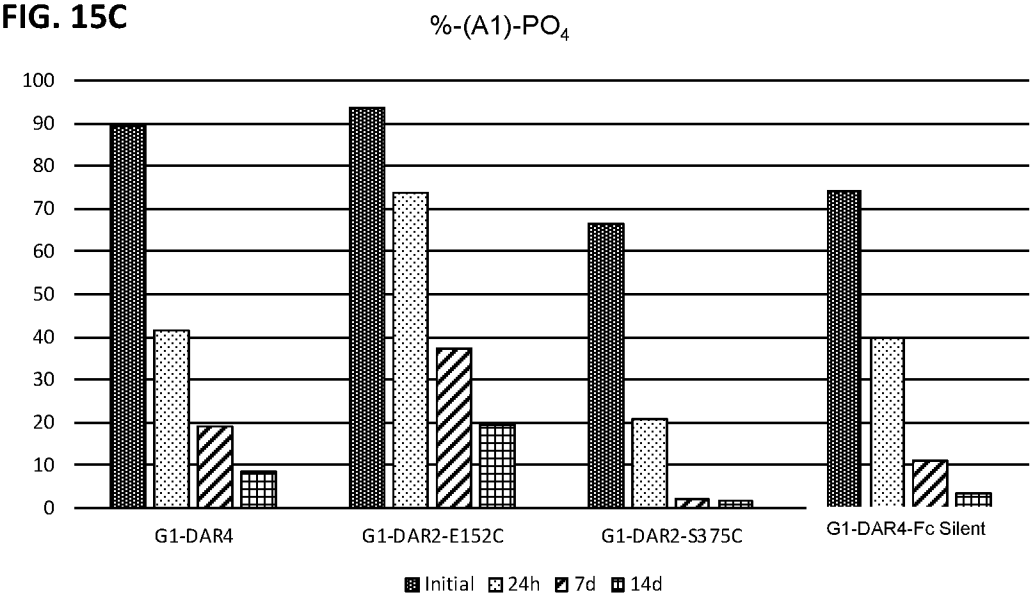


FIG. 15C



Initial values estimated based on in vitro experimental results

FIGURE 15

FIG. 16A

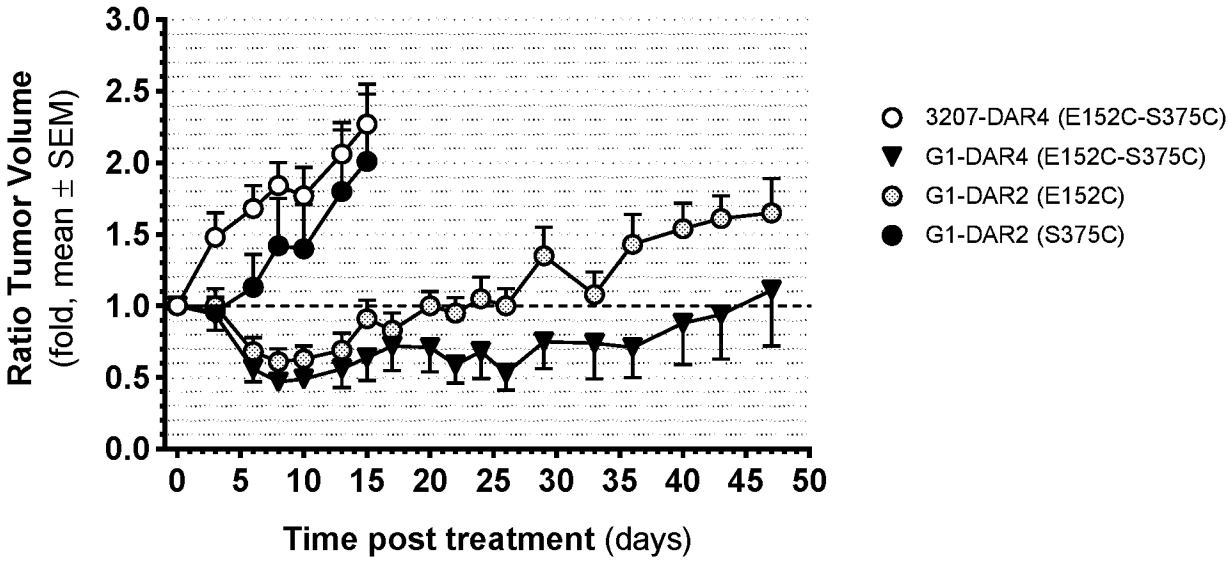


FIG. 16B

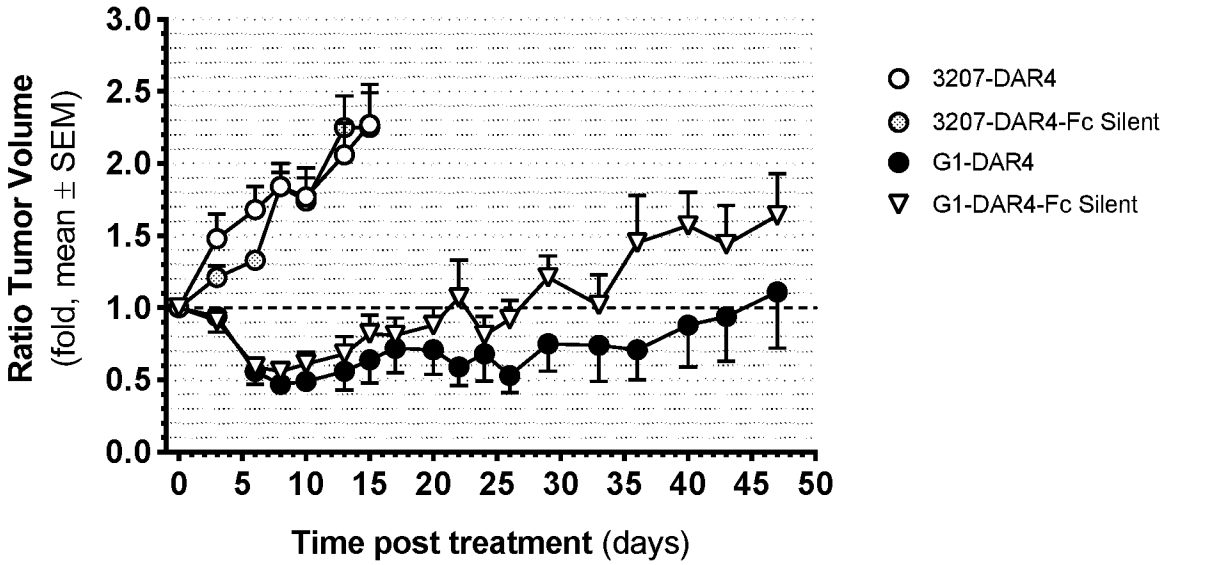


FIGURE 16

FIG. 17A

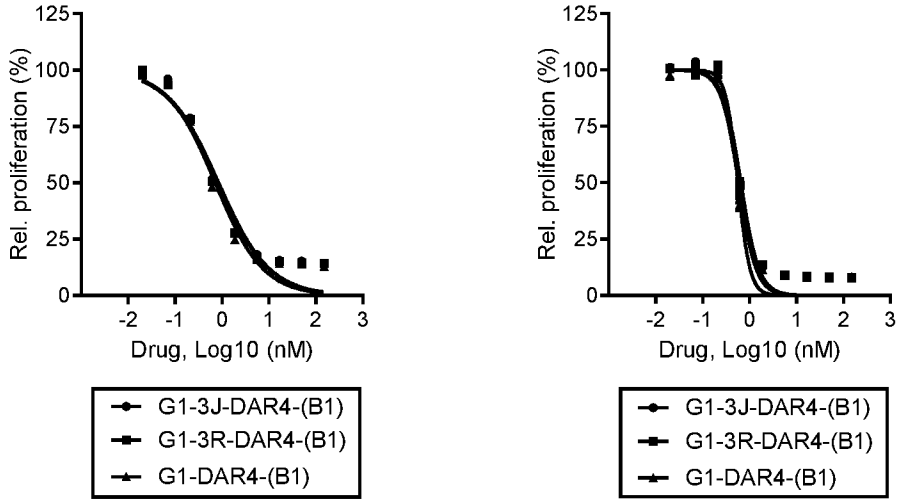


FIG. 17B

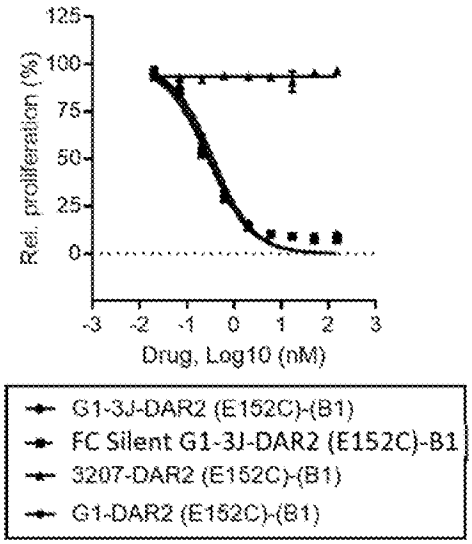


FIGURE 17

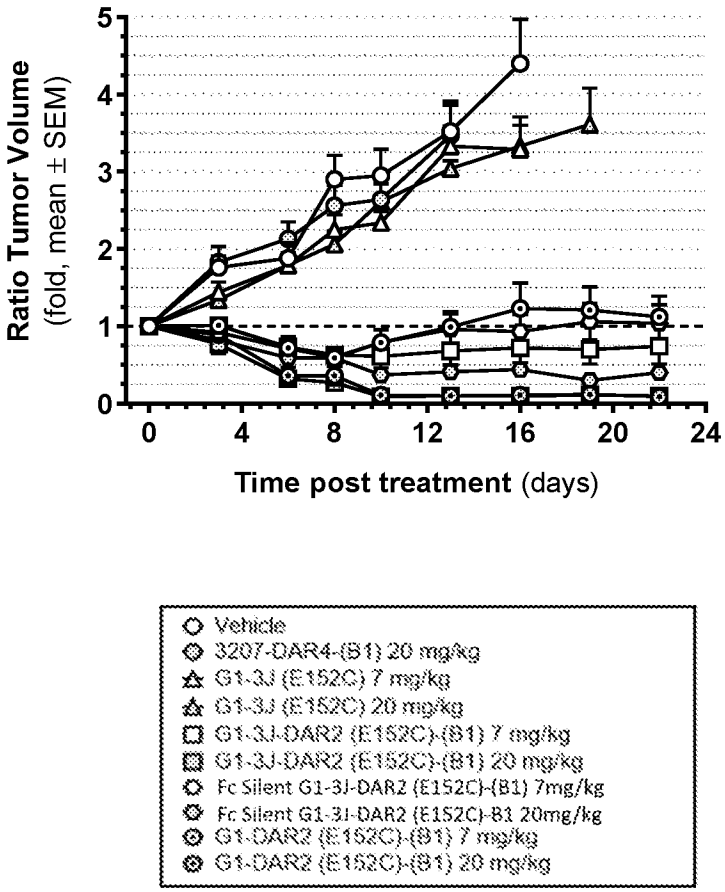

Ratio Tumor Volume
(fold, mean ± SEM)
5
4
3
2
1
0
0
4
8
12
16
20
24
Time post treatment (days)
Vehicle
3207-DAR4-(B1) 20 mg/kg
G1-3J (E152C) 7 mg/kg
G1-3J (E152C) 20 mg/kg
G1-3J-DAR2 (E152C)-(B1) 7 mg/kg
G1-3J-DAR2 (E152C)-(B1) 20 mg/kg
Fc Silent G1-3J-DAR2 (E152C)-(B1) 7mg/kg
Fc Silent G1-3J-DAR2 (E152C)-B1 20mg/kg
G1-DAR2 (E152C)-(B1) 7 mg/kg
G1-DAR2 (E152C)-(B1) 20 mg/kg

FIGURE 18

FIG. 19A

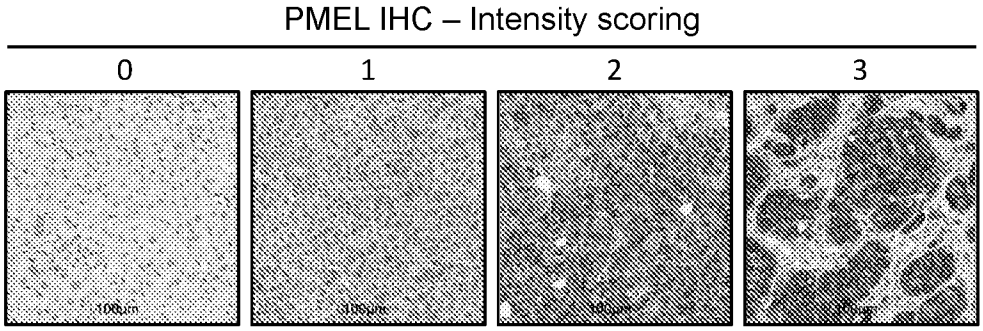
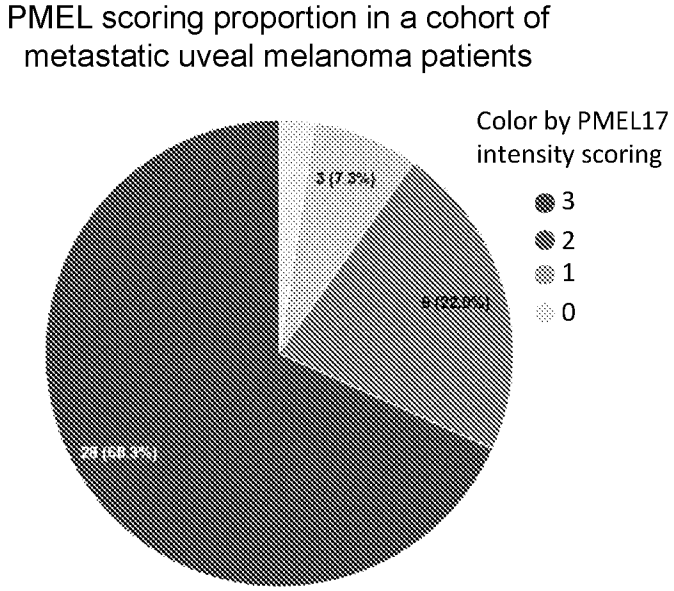


FIG. 19B



C

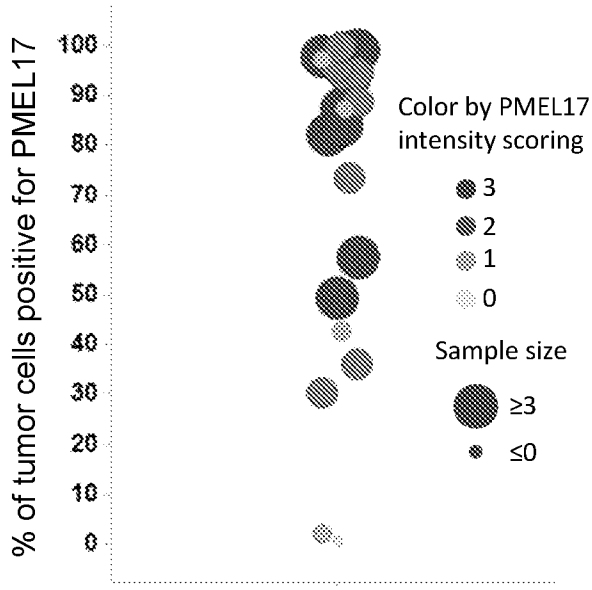


FIGURE 19

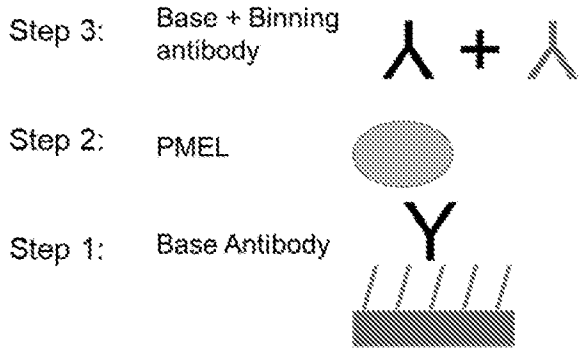


FIG. 20A

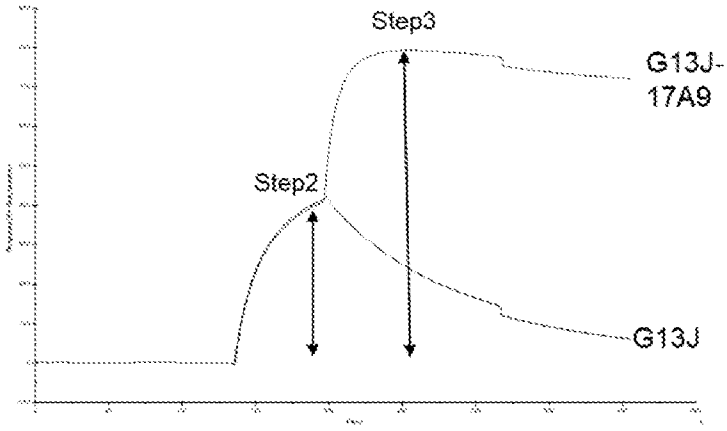


FIG. 20B

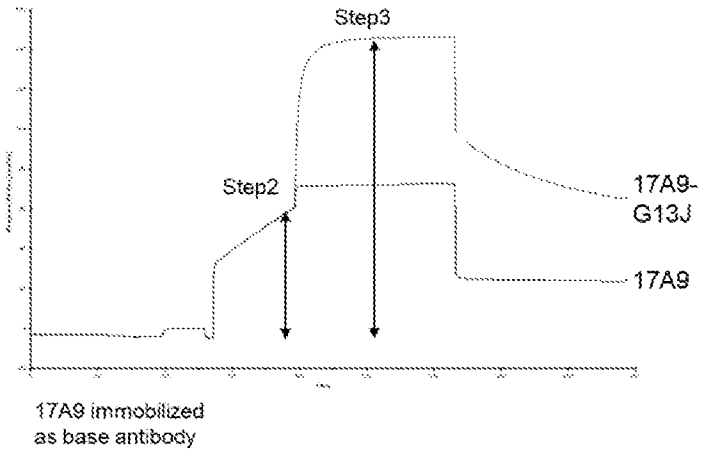


FIG. 20C

FIGURE 20

SEQUENCE LISTING

<110> NOVARTIS AG

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<130> PAT058359-WO-PCT

<140>
<141>

<150> 62/803,110
<151> 2019-02-08

<150> 62/783,565
<151> 2018-12-21

<160> 282

<170> PatentIn version 3.5

<210> 1
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<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1
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1 5 10

<210> 2
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 2
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 3
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 3
Glu Gly Gly Leu Leu Thr Asp Ile Ser Tyr Ser Arg Tyr Trp Phe Ala
1 5 10 15

Tyr

<210> 4
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 4
Asp Tyr Ala Ile Thr
1 5

<210> 5
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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peptide"

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

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

<220>
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peptide"

<400> 6
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1 5

<210> 7
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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peptide"

<400> 7
Gly Gly Thr Phe Ser Asp Tyr Ala
1 5

<210> 8
<211> 8
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 8
Ile Ile Pro Ile Phe Gly Thr Ala
1 5

<210> 9
<211> 19
<212> PRT
<213> Artificial Sequence

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

<400> 9
Ala Arg Glu Gly Gly Leu Leu Thr Asp Ile Ser Tyr Ser Arg Tyr Trp
1 5 10 15

Phe Ala Tyr

<210> 10
<211> 126
<212> PRT
<213> Artificial Sequence

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

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

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

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

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu Gly Gly Leu Leu Thr Asp Ile Ser Tyr Ser Arg Tyr Trp
100 105 110

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 11
<211> 378
<212> DNA
<213> Artificial Sequence

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

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agctgcaaag catccggagg gacgttttct gactacgcta tcacttgggt gcgccaggcc 120

ccgggccagg gcctcgagtg gatgggcggt atcatcccga tcttcggcac tgcgaactac 180

gcccagaaat ttcagggccg ggtgaccatt accgccgatg aaagcaccag caccgcctat 240

atggaactga gcagcctgcg cagcgaagat acggccgtgt attattgcgc gcgtgaaggt 300

ggtctgctga ctgacatctc ttactctcgt tactggttcg cttactgggg ccaaggcacc 360

ctggtgactg ttagctca 378

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<211> 456
<212> PRT
<213> Artificial Sequence

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

<400> 12
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

```
Ala Arg Glu Gly Gly Leu Leu Thr Asp Ile Ser Tyr Ser Arg Tyr Trp
            100                 105                 110

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145                 150                 155                 160

Cys Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
                165                 170                 175

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
            180                 185                 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
        195                 200                 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
    210                 215                 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225                 230                 235                 240

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
                245                 250                 255

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            260                 265                 270

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        275                 280                 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    290                 295                 300
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Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305                 310                 315                 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                325                 330                 335

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            340                 345                 350

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        355                 360                 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys
    370                 375                 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385                 390                 395                 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                405                 410                 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            420                 425                 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        435                 440                 445

Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455


<210> 13
<211> 1368
<212> DNA
<213> Artificial Sequence

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

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agctgcaaag catccggagg gacgttttct gactacgcta tcacttgggt gcgccaggcc      120
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ccgggccagg gcctcgagtg gatgggcggt atcatcccga tcttcggcac tgcgaactac 180

gcccagaaat ttcagggccg ggtgaccatt accgccgatg aaagcaccag caccgcctat 240

atggaactga gcagcctgcg cagcgaagat acggccgtgt attattgcgc gcgtgaaggt 300

ggtctgctga ctgacatctc ttactctcgt tactggttcg cttactgggg ccaaggcacc 360

ctggtgactg ttagctcagc tagcaccaag ggcccaagtg tgtttccccc ggcccccagc 420

agcaagtcta cttccggcgg aactgctgcc ctgggttgcc tggtgaagga ctacttcccc 480

tgtcccgtga cagtgtcctg gaactctggg gctctgactt ccggcgtgca caccttcccc 540

gccgtgctgc agagcagcgg cctgtacagc ctgagcagcg tggtgacagt gccctccagc 600

tctctgggaa cccagaccta tatctgcaac gtgaaccaca agcccagcaa caccaaggtg 660

gacaagagag tggagcccaa gagctgcgac aagacccaca cctgcccccc ctgcccagct 720

ccagaactgc tgggagggcc ttccgtgttc ctgttccccc ccaagcccaa ggacaccctg 780

atgatcagca ggacccccga ggtgacctgc gtggtggtgg acgtgtccca cgaggaccca 840

gaggtgaagt tcaactggta cgtggacggc gtggaggtgc acaacgccaa gaccaagccc 900

agagaggagc agtacaacag cacctacagg gtggtgtccg tgctgaccgt gctgcaccag 960

gactggctga acggcaaaga atacaagtgc aaagtctcca acaaggccct gccagcccca 1020

atcgaaaaga caatcagcaa ggccaagggc cagccacggg agccccaggt gtacaccctg 1080

ccccccagcc gggaggagat gaccaagaac caggtgtccc tgacctgtct ggtgaagggc 1140

ttctaccccct gtgatatcgc cgtggagtgg gagagcaacg gccagcccga gaacaactac 1200

aagaccaccc ccccagtgct ggacagcgac ggcagcttct tcctgtacag caagctgacc 1260

gtggacaagt ccaggtggca gcagggcaac gtgttcagct gcagcgtgat gcacgaggcc 1320

ctgcacaacc actacaccca gaagtccctg agcctgagcc ccggcaag 1368

<210> 14
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 14
Ser Gly Asp Ala Leu Arg Asp Lys Phe Val Tyr
1   5   10

<210> 15
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 15
Asp Asp Asn Asn Arg Pro Ser
1   5

<210> 16
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 16
Gln Ser Trp Asp His Ser Tyr Ser Leu Val Val
1   5   10

<210> 17
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 17
Asp Ala Leu Arg Asp Lys Phe
1   5

<210> 18
<211> 3
<212> PRT
<213> Artificial Sequence

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

<400> 18
Asp Asp Asn
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<210> 19
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 19
Trp Asp His Ser Tyr Ser Leu Val
1 5

<210> 20
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<400> 20
Ala Leu Arg Asp Lys Phe
1 5

<210> 21
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 21
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

```
Thr Ala Ser Ile Thr Cys Ser Gly Asp Ala Leu Arg Asp Lys Phe Val
            20                  25                  30

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

Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp His Ser Tyr Ser Leu
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> 22
<211> 324
<212> DNA
<213> Artificial Sequence

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

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acctgtagcg gcgatgctct gcgtgacaaa ttcgtttact ggtaccagca gaaaccgggc      120

caggcgccgg tgctggtgat ctacgacgac aacaaccgtc cgagcggcat cccggaacgt      180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa      240

gacgaagcgg attattactg ccagtcttgg gaccattctt actctctggt tgtgtttggc      300

ggcggcacga agttaactgt cctg                                             324


<210> 23
<211> 214
<212> PRT
<213> Artificial Sequence
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 23
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

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

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

Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp His Ser Tyr Ser Leu
85 90 95

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

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 24
<211> 642
<212> DNA
<213> Artificial Sequence

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

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acctgtagcg gcgatgctct gcgtgacaaa ttcgtttact ggtaccagca gaaaccgggc 120

caggcgccgg tgctggtgat ctacgacgac aacaaccgtc cgagcggcat cccggaacgt 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac ccaggcggaa 240

gacgaagcgg attattactg ccagtcttgg gaccattctt actctctggt tgtgtttggc 300

ggcggcacga agttaactgt cctgggacaa cctaaggccg ctccctccgt gaccctgttc 360

ccccccagct ccgaggaact gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccctg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacaa ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac agaagctaca gctgccaggt cacccacgag 600

ggcagcaccg tggagaaaac cgtggccccc accgagtgca gc 642

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

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

<400> 25

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

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

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

Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp His Ser Tyr Ser Leu
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 26
<211> 324
<212> DNA
<213> Artificial Sequence

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

<400> 26
agctacgagc tgacccagcc gctgtcggtg tcagtcgccc tgggacaaac tgccaggatc 60

acttgttccg gggacgcatt gcgggacaag ttcgtgtact ggtaccagca gaagccgggt 120

caagccccag tgctcgtgat ctacgacgac aacaaccggc cttccggtat ccccgaacgc 180

ttctccggat ccaatagcgg aaacaccgcc accctgacca tttcgagagc tcaggccggg 240

gatgaagcgg actactactg ccagtcatgg gatcactcgt actccctcgt cgtgtttgga 300

ggcggcacga agcttactgt gctg 324

<210> 27
<211> 214

<212> PRT
<213> Artificial Sequence

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

<400> 27
Ser Tyr Glu Leu Thr Gln Pro Leu Ser Val Ser Val Ala Leu Gly Gln
1 5 10 15

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

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

Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp His Ser Tyr Ser Leu
85 90 95

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

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser

180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 28
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 28
agctacgagc tgacccagcc gctgtcggtg tcagtcgccc tgggacaaac tgccaggatc 60

acttgttccg gggacgcatt gcgggacaag ttcgtgtact ggtaccagca gaagccgggt 120

caagccccag tgctcgtgat ctacgacgac aacaaccggc cttccggtat ccccgaacgc 180

ttctccggat ccaatagcgg aaacaccgcc accctgacca tttcgagagc tcaggccggg 240

gatgaagcgg actactactg ccagtcatgg gatcactcgt actccctcgt cgtgtttgga 300

ggcggcacga agcttactgt gctgggccag cctaaggccg ctccctccgt gaccctgttc 360

ccccccagct ccgaggaact gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccctg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacaa ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac agaagctaca gctgccaggt cacccacgag 600

ggcagcaccg tggagaaaac cgtggccccc accgagtgca gc 642

<210> 29
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 29
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1   5   10   15

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

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

Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp His Ser Tyr Ser Leu
                85   90   95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105

<210> 30
<211> 324
<212> DNA
<213> Artificial Sequence

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

<400> 30
tcgtacgagc tcactcaacc gccttctgtg tccgtgtcac ccgggcagac tgcctccatt 60

acctgttcgg gagatgccct gcgcgacaag tttgtgtact ggtaccagca gaagcccgga 120

cagtcgccag tgctcgtcat ctatgacgac aacaacagac cttccggtat cccggaacgg 180

ttcagcggaa gcaattccgg caacaccgct accctgacca ttagcggcac tcaggccatg 240

gacgaagcgg attactactg ccaatcctgg gaccactcat actcccttgt ggtgttcggt 300

ggcggaacga agctgaccgt cctg   324

<210> 31
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 31
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

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

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

Asp Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp His Ser Tyr Ser Leu
85 90 95

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

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 32
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 32
tcgtacgagc tcactcaacc gccttctgtg tccgtgtcac ccgggcagac tgcctccatt 60

acctgttcgg gagatgccct gcgcgacaag tttgtgtact ggtaccagca gaagcccgga 120

cagtcgccag tgctcgtcat ctatgacgac aacaacagac cttccggtat cccggaacgg 180

ttcagcggaa gcaattccgg caacaccgct accctgacca ttagcggcac tcaggccatg 240

gacgaagcgg attactactg ccaatcctgg gaccactcat actcccttgt ggtgttcggt 300

ggcggaacga agctgaccgt cctgggccag cctaaggccg ctccctccgt gaccctgttc 360

ccccccagct ccgaggaact gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccctg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacaa ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac agaagctaca gctgccaggt cacccacgag 600

ggcagcaccg tggagaaaac cgtggccccc accgagtgca gc 642

<210> 33
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 33
Gly Gly Thr Phe Ser Thr Tyr Ala Ile Ser
1 5 10

<210> 34
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 34
Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 35
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 35
Glu Val Arg Met Ile Phe Asp Tyr
1 5

<210> 36
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 36
Thr Tyr Ala Ile Ser

1 5

<210> 37
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 37
Gly Gly Thr Phe Ser Thr Tyr
1 5

<210> 38
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 38
Ile Pro Ile Leu Gly Ile
1 5

<210> 39
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 39
Gly Gly Thr Phe Ser Thr Tyr Ala
1 5

<210> 40
<211> 8
<212> PRT
<213> Artificial Sequence

<220>

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

<400> 40
Ile Ile Pro Ile Leu Gly Ile Ala
1 5

<210> 41
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 41
Ala Arg Glu Val Arg Met Ile Phe Asp Tyr
1 5 10

<210> 42
<211> 117
<212> PRT
<213> Artificial Sequence

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

<400> 42
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu Val Arg Met Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 43
<211> 351
<212> DNA
<213> Artificial Sequence

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

<400> 43
caggtgcaat tggtgcagag cggtgccgaa gtgaaaaaac cgggcagcag cgtgaaagtt 60

agctgcaaag catccggagg gacgttttct acttacgcta tctcttgggt gcgccaggcc 120

ccgggccagg gcctcgagtg gatgggccgt atcatcccga tcctgggcat cgcgaactac 180

gcccagaaat ttcagggccg ggtgaccatt accgccgatg aaagcaccag caccgcctat 240

atggaactga gcagcctgcg cagcgaagat acggccgtgt attattgcgc gcgtgaagtt 300

cgtatgatct tcgattactg gggccaaggc accctggtga ctgttagctc a 351

<210> 44
<211> 447
<212> PRT
<213> Artificial Sequence

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

<400> 44
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

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

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

Ala Arg Glu Val Arg Met Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240
```

```
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> 45
<211> 1341

<212> DNA
<213> Artificial Sequence

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

<400> 45
caggtgcaat tggtgcagag cggtgccgaa gtgaaaaaac cgggcagcag cgtgaaagtt 60

agctgcaaag catccggagg gacgttttct acttacgcta tctcttgggt gcgccaggcc 120

ccgggccagg gcctcgagtg gatgggccgt atcatcccga tcctgggcat cgcgaactac 180

gcccagaaat ttcagggccg ggtgaccatt accgccgatg aaagcaccag caccgcctat 240

atggaactga gcagcctgcg cagcgaagat acggccgtgt attattgcgc gcgtgaagtt 300

cgtatgatct tcgattactg gggccaaggc accctggtga ctgttagctc agcctctacg 360

aaaggcccaa gcgtatttcc cctggctcct tctagtaaat caacctcagg tggtacagca 420

gcccttggct gcctggtcaa agactatttc ccctgtccgg tgaccgtctc atggaactca 480

ggtgctttga catctggtgt gcatacattc ccagctgtgc tgcaaagtag tggactgtac 540

agcctttcca gcgtggtcac ggtgccaagt agctccttgg gtactcagac ttatatctgc 600

aatgtgaacc acaagccctc taacacgaag gtggacaagc gcgtggagcc caaatcttgc 660

gataagacgc atacttgtcc cccatgccct gctcctgagc tgttgggagg cccgtcagtg 720

ttcttgttcc ctccgaagcc taaggacact ttgatgataa gtaggacacc agaggtgact 780

tgcgtggtgg ttgatgtgtc ccatgaagat cccgaggtca aatttaattg gtacgtagat 840

ggtgtcgaag ttcacaatgc taagactaag ccaagggaag agcagtacaa cagtacatat 900

agggtagtct ccgtgctgac agtcctccac caggactggt tgaacggcaa ggaatacaaa 960

tgtaaggtgt caaacaaagc tctgcctgct cccattgaga aaacaatctc taaagccaaa 1020

ggccagccga gagagcccca agtctacact ttgccccga gcagggagga aatgaccaag 1080

aatcaggtga gtctgacgtg cctcgtcaaa ggattttatc catgcgatat tgcagttgaa 1140

tgggagagca atggccagcc agagaacaac tataaaacca caccacccgt gctcgactct 1200

gatggcagct tcttcctcta tagcaagctg acagtcgata aatctcgctg gcagcaaggc 1260

aatgtgttct cctgctccgt catgcacgag gctttgcata accattatac tcaaaaatct 1320

ctgtccctgt cacctggtaa a 1341

<210> 46
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 46
Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Ala
1 5 10

<210> 47
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 47
Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 48
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 48
Gln Gln Ser Tyr Asp Tyr Tyr Thr
1 5

<210> 49
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 49
Ser Gln Ser Ile Ser Ser Tyr
1 5

<210> 50
<211> 3
<212> PRT
<213> Artificial Sequence

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

<400> 50
Ala Ala Ser
1

<210> 51
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 51
Ser Tyr Asp Tyr Tyr
1 5

<210> 52
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 52
Gln Ser Ile Ser Ser Tyr
1 5

<210> 53

<211> 106
<212> PRT
<213> Artificial Sequence

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

<400> 53
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 54
<211> 318
<212> DNA
<213> Artificial Sequence

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

<400> 54
gatatccaga tgacccagag cccgagcagc ctgagcgcca gcgtgggcga tcgcgtgacc 60

attacctgca gagccagcca gtctatttct tcttacctgg cttggtacca gcagaaaccg 120

ggcaaagcgc cgaaactatt aatctacgct gcttcttctc tgcaaagcgg cgtgccgagc 180

cgctttagcg gcagcggatc cggcaccgat ttcaccctga ccattagctc tctgcaaccg 240

gaagactttg cgacctatta ttgccagcag tcttacgact actacacctt tggccagggc 300

acgaaagttg aaattaaa 318

<210> 55
<211> 213
<212> PRT
<213> Artificial Sequence

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

<400> 55
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

```
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160


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


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205


Asn Arg Gly Glu Cys
    210
```

<210> 56
<211> 639
<212> DNA
<213> Artificial Sequence

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

<400> 56

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gatatccaga tgacccagag cccgagcagc ctgagcgcca gcgtgggcga tcgcgtgacc       60

attacctgca gagccagcca gtctatttct tcttacctgg cttggtacca gcagaaaccg      120

ggcaaagcgc cgaaactatt aatctacgct gcttcttctc tgcaaagcgg cgtgccgagc      180

cgctttagcg gcagcggatc cggcaccgat ttcaccctga ccattagctc tctgcaaccg      240

gaagactttg cgacctatta ttgccagcag tcttacgact actacacctt tggccagggc      300

acgaaagttg aaattaaacg tacggtggca gctccgtctg ttttcatctt tccacctagc      360

gacgagcaac tcaaaagtgg tacagcatcc gtggtttgtc tgctgaacaa tttttacccc      420

agggaggcta aggtccagtg gaaagtcgat aacgctcttc agtctggcaa cagtcaggag      480

agcgtcacag agcaggactc taaggatagc acttatagtc tgtcctccac gctgacactg      540

tctaaagcgg attatgagaa gcacaaggtt tacgcctgtg aggtaacgca ccaaggactc      600

tcctccccag ttaccaaatc tttcaacaga ggagaatgt                              639
```

<210> 57
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 57
Gly Gly Thr Phe Ser Asp Tyr Ala Ile Ser
1 5 10

<210> 58
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 58
Gly Ile Ile Pro Ile Phe Gly Asp Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 59
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 59
Glu Gly Ser Ser Tyr Phe Tyr Met Ala Tyr
1 5 10

<210> 60
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 60
Asp Tyr Ala Ile Ser
1 5

<210> 61
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 61
Ile Pro Ile Phe Gly Asp
1 5

<210> 62
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 62
Ile Ile Pro Ile Phe Gly Asp Ala
1 5

<210> 63
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 63
Ala Arg Glu Gly Ser Ser Tyr Phe Tyr Met Ala Tyr
1 5 10

<210> 64
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 64
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

Gly Gly Ile Ile Pro Ile Phe Gly Asp Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu Gly Ser Ser Tyr Phe Tyr Met Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 65
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 65
caggttcagc tggtgcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg 60

tcctgcaaag caagcggcgg caccttcagc gattacgcca tctcttgggt ccgacaggcc 120

cctggacaag gcttggaatg gatgggcggc atcatcccca tcttcggcga cgccaattac 180

gcccagaaat tccagggcag agtgaccatc accgccgacg agtctacaag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc cagagagggc 300

agcagctact tctacatggc ctattggggc cagggcaccc tggtcacagt tagctct 357

<210> 66
<211> 449
<212> PRT
<213> Artificial Sequence

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

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

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

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

Gly Gly Ile Ile Pro Ile Phe Gly Asp Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu Gly Ser Ser Tyr Phe Tyr Met Ala Tyr Trp Gly Gln Gly
100 105 110

```
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335
```

```
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
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<210> 67
<211> 1347
<212> DNA
<213> Artificial Sequence

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

<400> 67

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caggttcagc tggtgcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg       60

tcctgcaaag caagcggcgg caccttcagc gattacgcca tctcttgggt ccgacaggcc      120

cctggacaag gcttggaatg gatgggcggc atcatcccca tcttcggcga cgccaattac      180

gcccagaaat tccagggcag agtgaccatc accgccgacg agtctacaag caccgcctac      240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc cagagagggc      300
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agcagctact tctacatggc ctattggggc cagggcaccc tggtcacagt tagctctgct 360

agcaccaagg gcccaagtgt gtttcccctg gcccccagca gcaagtctac ttccggcgga 420

actgctgccc tgggttgcct ggtgaaggac tacttcccct gtcccgtgac agtgtcctgg 480

aactctgggg ctctgacttc cggcgtgcac accttccccg ccgtgctgca gagcagcggc 540

ctgtacagcc tgagcagcgt ggtgacagtg ccctccagct ctctgggaac ccagacctat 600

atctgcaacg tgaaccacaa gcccagcaac accaaggtgg acaagagagt ggagcccaag 660

agctgcgaca agacccacac ctgcccccc tgcccagctc cagaactgct gggagggcct 720

tccgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag gacccccgag 780

gtgacctgcg tggtggtgga cgtgtcccac gaggacccag aggtgaagtt caactggtac 840

gtggacggcg tggaggtgca caacgccaag accaagccca gagaggagca gtacaacagc 900

acctacaggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaagaa 960

tacaagtgca aagtctccaa caaggccctg ccagccccaa tcgaaaagac aatcagcaag 1020

gccaagggcc agccacggga gccccaggtg tacaccctgc cccccagccg ggaggagatg 1080

accaagaacc aggtgtccct gacctgtctg gtgaagggct tctacccctg tgatatcgcc 1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc cccagtgctg 1200

gacagcgacg gcagcttctt cctgtacagc aagctgaccg tggacaagtc caggtggcag 1260

cagggcaacg tgttcagctg cagcgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagccc cggcaag 1347

<210> 68
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 68
Ser Gly Asp Asn Ile Gly Ser Lys Leu Ala Ser
1 5 10

<210> 69

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

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

<400> 69
Asp Asp Ser Asn Arg Pro Ser
1 5

<210> 70
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 70
Ala Ala Thr Ala Gly Asp Arg Trp Ala Tyr Val
1 5 10

<210> 71
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 71
Asp Asn Ile Gly Ser Lys Leu
1 5

<210> 72
<211> 3
<212> PRT
<213> Artificial Sequence

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

<400> 72
Asp Asp Ser
1

<210> 73
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 73
Thr Ala Gly Asp Arg Trp Ala Tyr
1 5

<210> 74
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 74
Asn Ile Gly Ser Lys Leu
1 5

<210> 75
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 75
Ser Tyr Glu Leu Thr Gln Pro Leu Ser Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Asn Ile Gly Ser Lys Leu Ala
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Thr Ala Gly Asp Arg Trp Ala
85 90 95

Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 76
<211> 324
<212> DNA
<213> Artificial Sequence

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

<400> 76
agctatgagc tgacacagcc tctgtccgtg tctgtggctc tgggacagac cgccagaatc 60

acctgtagcg gcgacaacat cggcagcaag ctggcctctt ggtatcagca gaagcctgga 120

caggcccctg tgctggtcat ctacgacgac agcaatagac ccagcggcat ccccgagaga 180

ttcagcggca gcaatagcgg caataccgcc acactgacca tcagcagagc acaggctggc 240

gacgaggccg attactattg tgctgccaca gccggcgaca gatgggccta tgtttttggc 300

ggcggaacaa agctgaccgt gctg 324

<210> 77
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 77
Ser Tyr Glu Leu Thr Gln Pro Leu Ser Val Ser Val Ala Leu Gly Gln
1   5   10   15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Asn Ile Gly Ser Lys Leu Ala
            20   25   30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Thr Ala Gly Asp Arg Trp Ala
                85   90   95

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

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115   120   125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130   135   140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145   150   155   160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165   170   175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180   185   190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195   200   205

Ala Pro Thr Glu Cys Ser

210

<210> 78
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 78
agctatgagc tgacacagcc tctgtccgtg tctgtggctc tgggacagac cgccagaatc 60

acctgtagcg gcgacaacat cggcagcaag ctggcctctt ggtatcagca gaagcctgga 120

caggcccctg tgctggtcat ctacgacgac agcaatagac ccagcggcat ccccgagaga 180

ttcagcggca gcaatagcgg caataccgcc acactgacca tcagcagagc acaggctggc 240

gacgaggccg attactattg tgctgccaca gccggcgaca gatgggccta tgtttttggc 300

ggcggaacaa agctgaccgt gctgggacag cctaaggccg ctccctccgt gaccctgttc 360

ccccccagct ccgaggaact gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccctg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacaa ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac agaagctaca gctgccaggt cacccacgag 600

ggcagcaccg tggagaaaac cgtggccccc accgagtgca gc 642

<210> 79
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 79
Gly Phe Thr Phe Ser Ser Phe Gly Met Ser
1 5 10

<210> 80
<211> 17

<212> PRT
<213> Artificial Sequence

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

<400> 80
Ala Ile Ser Tyr Ser Gly Ser Asp Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 81
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 81
Asp Val Gly Val Met Asp Tyr
1 5

<210> 82
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 82
Ser Phe Gly Met Ser
1 5

<210> 83
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 83
Gly Phe Thr Phe Ser Ser Phe
1 5

<210> 84
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 84
Ser Tyr Ser Gly Ser Asp
1 5

<210> 85
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 85
Gly Phe Thr Phe Ser Ser Phe Gly
1 5

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

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

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

<210> 87

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

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

<400> 87
Ala Arg Asp Val Gly Val Met Asp Tyr
1 5

<210> 88
<211> 116
<212> PRT
<213> Artificial Sequence

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

<400> 88
Gln 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 Phe
20 25 30

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

Ser Ala Ile Ser Tyr Ser Gly Ser Asp 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 Arg Asp Val Gly Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser

115

<210> 89
<211> 348
<212> DNA
<213> Artificial Sequence

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

<400> 89
caggttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg 60

tcttgtgccg ccagcggctt caccttcagc agctttggca tgagctgggt ccgacaggcc 120

cctggcaaag gacttgaatg ggtgtccgcc atcagctaca gcggcagcga tacctactac 180

gccgacagcg tgaagggcag attcaccatc tccagagaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc cagagatgtg 300

ggcgtgatgg actattgggg ccagggcaca ctggtcaccg ttagctct 348

<210> 90
<211> 446
<212> PRT
<213> Artificial Sequence

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

<400> 90
Gln 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 Phe
20 25 30

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

Ser Ala Ile Ser Tyr Ser Gly Ser Asp 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 Arg Asp Val Gly Val Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285
```

```
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> 91
<211> 1338
<212> DNA
<213> Artificial Sequence

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

<400> 91
caggttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg       60
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tcttgtgccg ccagcggctt caccttcagc agctttggca tgagctgggt ccgacaggcc 120

cctggcaaag gacttgaatg ggtgtccgcc atcagctaca gcggcagcga tacctactac 180

gccgacagcg tgaagggcag attcaccatc tccagagaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc cagagatgtg 300

ggcgtgatgg actattgggg ccagggcaca ctggtcaccg ttagctctgc tagcaccaag 360

ggcccaagtg tgtttcccct ggcccccagc agcaagtcta cttccggcgg aactgctgcc 420

ctgggttgcc tggtgaagga ctacttcccc tgtcccgtga cagtgtcctg gaactctggg 480

gctctgactt ccggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgagcagcg tggtgacagt gccctccagc tctctgggaa cccagaccta tatctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgcccagct ccagaactgc tgggagggcc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgtccca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaagtctcca acaaggccct gccagcccca atcgaaaaga caatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg ccccccagcc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctaccct gtgatatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaagt ccaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagtccctg 1320

agcctgagcc ccggcaag 1338

<210> 92
<211> 11
<212> PRT
<213> Artificial Sequence

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

peptide"

<400> 92
Ser Gly Asp Asn Leu Gly Thr Tyr Tyr Ala His
1 5 10

<210> 93
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 93
Ser Gln Ser His Arg Pro Ser
1 5

<210> 94
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 94
Gly Ala Trp Asp Ala Pro Ser Pro Glu Leu Val
1 5 10

<210> 95
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 95
Asp Asn Leu Gly Thr Tyr Tyr
1 5

<210> 96
<211> 3

<212> PRT
<213> Artificial Sequence

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

<400> 96
Ser Gln Ser
1

<210> 97
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 97
Trp Asp Ala Pro Ser Pro Glu Leu
1 5

<210> 98
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 98
Asn Leu Gly Thr Tyr Tyr
1 5

<210> 99
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 99

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


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


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


Ser Gln Ser His Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Trp Asp Ala Pro Ser Pro Glu
                85                  90                  95


Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
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<210> 100
<211> 324
<212> DNA
<213> Artificial Sequence

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

<400> 100
agctatgagc tgacacagcc tctgtccgtg tctgtggctc tgggacagac cgccagaatc 60

acctgtagcg gcgataacct gggcacctac tacgcccact ggtatcagca gaagcctgga 120

caggctcccg tgctggtcat ctacagccag tctcacagac ccagcggcat ccccgagaga 180

ttcagcggca gcaatagcgg caataccgcc acactgacca tcagcagagc acaggctggc 240

gacgaggccg attactattg tggcgcttgg gacgccccat ctcctgagct tgtttttggc 300

ggaggcacca agctgacagt gctg 324

<210> 101
<211> 214

<212> PRT
<213> Artificial Sequence

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

<400> 101
Ser Tyr Glu Leu Thr Gln Pro Leu Ser Val Ser Val Ala Leu Gly Gln
1 5 10 15

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

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

Ser Gln Ser His Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Trp Asp Ala Pro Ser Pro Glu
85 90 95

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

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser

180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 102
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 102
agctatgagc tgacacagcc tctgtccgtg tctgtggctc tgggacagac cgccagaatc 60

acctgtagcg gcgataacct gggcacctac tacgcccact ggtatcagca gaagcctgga 120

caggctcccg tgctggtcat ctacagccag tctcacagac ccagcggcat ccccgagaga 180

ttcagcggca gcaatagcgg caataccgcc acactgacca tcagcagagc acaggctggc 240

gacgaggccg attactattg tggcgcttgg gacgccccat ctcctgagct tgtttttggc 300

ggaggcacca agctgacagt gctgggacag cctaaggccg ctccctccgt gaccctgttc 360

ccccccagct ccgaggaact gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccctg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacaa ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac agaagctaca gctgccaggt cacccacgag 600

ggcagcaccg tggagaaaac cgtggccccc accgagtgca gc 642

<210> 103
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 103
Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1   5   10

<210> 104
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 104
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 105
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 105
Ala Phe Arg Leu Tyr Trp Leu Asp Val
1   5

<210> 106
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 106
Ser Tyr Ala Met Ser
1   5

<210> 107
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 107
Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> 108
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 108
Ser Gly Ser Gly Gly Ser
1 5

<210> 109
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 109
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 110
<211> 8
<212> PRT
<213> Artificial Sequence

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

peptide"

<400> 110
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 111
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 111
Ala Arg Ala Phe Arg Leu Tyr Trp Leu Asp Val
1 5 10

<210> 112
<211> 118
<212> PRT
<213> Artificial Sequence

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

<400> 112
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 Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

85 90 95

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

Leu Val Thr Val Ser Ser
115

<210> 113
<211> 354
<212> DNA
<213> Artificial Sequence

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

<400> 113
gaagttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg 60

tcttgtgccg ccagcggctt cacctttagc agctacgcca tgagctgggt ccgacaggct 120

cctggcaaag gccttgaatg ggtgtccgcc atctctggct ctggcggcag cacatattac 180

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagccttc 300

cggctgtact ggctggatgt ttggggacag ggcaccctgg tcacagtgtc atct 354

<210> 114
<211> 448
<212> PRT
<213> Artificial Sequence

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

<400> 114
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 Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

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

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255
```

```
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> 115
<211> 1344
<212> DNA
<213> Artificial Sequence

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

<400> 115
gaagttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg 60

tcttgtgccg ccagcggctt cacctttagc agctacgcca tgagctgggt ccgacaggct 120

cctggcaaag gccttgaatg ggtgtccgcc atctctggct ctggcggcag cacatattac 180

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagccttc 300

cggctgtact ggctggatgt ttggggacag ggcaccctgg tcacagtgtc atctgctagc 360

accaagggcc caagtgtgtt tcccctggcc cccagcagca agtctacttc cggcggaact 420

gctgccctgg gttgcctggt gaaggactac ttcccctgtc ccgtgacagt gtcctggaac 480

tctggggctc tgacttccgg cgtgcacacc ttccccgccg tgctgcagag cagcggcctg 540

tacagcctga gcagcgtggt gacagtgccc tccagctctc tgggaaccca gacctatatc 600

tgcaacgtga accacaagcc cagcaacacc aaggtggaca agagagtgga gcccaagagc 660

tgcgacaaga cccacacctg ccccccctgc ccagctccag aactgctggg agggccttcc 720

gtgttcctgt tcccccccaa gcccaaggac accctgatga tcagcaggac ccccgaggtg 780

acctgcgtgg tggtggacgt gtcccacgag gacccagagg tgaagttcaa ctggtacgtg 840

gacggcgtgg aggtgcacaa cgccaagacc aagcccagag aggagcagta caacagcacc 900

tacagggtgg tgtccgtgct gaccgtgctg caccaggact ggctgaacgg caaagaatac 960

aagtgcaaag tctccaacaa ggccctgcca gccccaatcg aaaagacaat cagcaaggcc 1020

aagggccagc cacgggagcc ccaggtgtac accctgcccc ccagccggga ggagatgacc 1080

aagaaccagg tgtccctgac ctgtctggtg aagggcttct acccctgtga tatcgccgtg 1140

gagtgggaga gcaacggcca gcccgagaac aactacaaga ccacccccc agtgctggac 1200

agcgacggca gcttcttcct gtacagcaag ctgaccgtgg acaagtccag gtggcagcag 1260

ggcaacgtgt tcagctgcag cgtgatgcac gaggccctgc acaaccacta cacccagaag 1320

tccctgagcc tgagccccgg caag 1344

<210> 116
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 116
Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 117
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 117
Gln Gln Val Tyr Ser Ala Pro Val Thr
1 5

<210> 118
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 118
Val Tyr Ser Ala Pro Val
1 5

<210> 119
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 119
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

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

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

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

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

<210> 120
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 120
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc   60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc   120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc   180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca   240

gaggacttcg ccacctacta ctgccagcag gtctacagcg cccctgtgac atttggccag   300

ggcaccaagg tggaaatcaa g   321

<210> 121
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 121
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 122
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 122
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag gtctacagcg cccctgtgac atttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttcccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 123
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 123
Gly Phe Thr Phe Ser Asn Tyr Trp Ile Ser
1 5 10

<210> 124
<211> 19
<212> PRT
<213> Artificial Sequence

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

<400> 124
Arg Ile Lys Ser Lys Thr Tyr Gly Gly Thr Thr Asp Tyr Ala Glu Pro
1 5 10 15

Val Lys Gly

<210> 125
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 125
Thr Ser Arg Arg Ser Tyr Ala Phe Asp Tyr
1 5 10

<210> 126
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 126
Asn Tyr Trp Ile Ser

1 5

<210> 127
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 127
Gly Phe Thr Phe Ser Asn Tyr
1 5

<210> 128
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 128
Lys Ser Lys Thr Tyr Gly Gly Thr
1 5

<210> 129
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 129
Gly Phe Thr Phe Ser Asn Tyr Trp
1 5

<210> 130
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

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

<400> 130
Ile Lys Ser Lys Thr Tyr Gly Gly Thr Thr
1 5 10

<210> 131
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 131
Ala Arg Thr Ser Arg Arg Ser Tyr Ala Phe Asp Tyr
1 5 10

<210> 132
<211> 121
<212> PRT
<213> Artificial Sequence

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

<400> 132
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 Asn Tyr
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Tyr Gly Gly Thr Thr Asp Tyr Ala Glu
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

```
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Ala Arg Thr Ser Arg Arg Ser Tyr Ala Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 133
<211> 363
<212> DNA
<213> Artificial Sequence

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

<400> 133
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg       60

agctgtgccg cttccggctt caccttcagc aactactgga tcagctgggt ccgacaggcc      120

cctggcaaag gacttgagtg ggtcggacgg atcaagagca agacctacgg cggcaccacc      180

gattatgccg agcctgtgaa gggcagattc accatcagcc gggacgacag caagaacacc      240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga      300

accagcagaa gaagctacgc cttcgactac tggggccagg gcacactggt taccgttagc      360

tct                                                                    363


<210> 134
<211> 451
<212> PRT
<213> Artificial Sequence

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

<400> 134
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 Asn Tyr
            20                  25                  30

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

Gly Arg Ile Lys Ser Lys Thr Tyr Gly Gly Thr Thr Asp Tyr Ala Glu
    50                  55                  60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

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

Tyr Cys Ala Arg Thr Ser Arg Arg Ser Tyr Ala Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240
```

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
```

Pro Gly Lys
    450

<210> 135
<211> 1353
<212> DNA
<213> Artificial Sequence

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

<400> 135
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aactactgga tcagctgggt ccgacaggcc 120

cctggcaaag gacttgagtg ggtcggacgg atcaagagca agacctacgg cggcaccacc 180

gattatgccg agcctgtgaa gggcagattc accatcagcc gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

accagcagaa gaagctacgc cttcgactac tggggccagg gcacactggt taccgttagc 360

tctgctagca ccaagggccc aagtgtgttt cccctggccc ccagcagcaa gtctacttcc 420

ggcggaactg ctgccctggg ttgcctggtg aaggactact tccctgtcc cgtgacagtg 480

tcctggaact ctggggctct gacttccggc gtgcacacct tccccgccgt gctgcagagc 540

agcggcctgt acagcctgag cagcgtggtg acagtgccct ccagctctct gggaacccag 600

acctatatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa gagagtggag 660

cccaagagct gcgacaagac ccacacctgc ccccccctgcc cagctccaga actgctggga 720

gggccttccg tgttcctgtt ccccccccaag cccaaggaca ccctgatgat cagcaggacc 780

cccgaggtga cctgcgtggt ggtggacgtg tcccacgagg acccagaggt gaagttcaac 840

tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agcccagaga ggagcagtac 900

aacagcacct acagggtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 960

aaagaataca agtgcaaagt ctccaacaag gccctgccag ccccaatcga aaagacaatc 1020

agcaaggcca agggccagcc acgggagccc caggtgtaca ccctgccccc cagccgggag 1080

gagatgacca agaaccaggt gtccctgacc tgtctggtga agggcttcta cccctgtgat 1140

atcgccgtgg agtgggagag caacggccag cccgagaaca actacaagac cacccccca 1200

gtgctggaca gcgacggcag cttcttcctg tacagcaagc tgaccgtgga caagtccagg 1260

tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac 1320

acccagaagt ccctgagcct gagccccggc aag 1353

<210> 136
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 136
Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> 137
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 137
Asp Ala Ser Ser Leu Glu Ser
1 5

<210> 138
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 138
Gln Gln Ile Thr Arg Tyr Pro Val Thr
1 5

<210> 139

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

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

<400> 139
Ser Gln Ser Ile Ser Ser Trp
1 5

<210> 140
<211> 3
<212> PRT
<213> Artificial Sequence

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

<400> 140
Asp Ala Ser
1

<210> 141
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 141
Ile Thr Arg Tyr Pro Val
1 5

<210> 142
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 142
Gln Ser Ile Ser Ser Trp
1   5

<210> 143
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 143
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 Asp 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

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

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

<210> 144
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 144
gacatccaga tgacacagag ccccagcaca ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatctcc tcttggctgg cctggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gatctacgat gccagcagcc tggaaagcgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgag ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag atcacaagat accccgtgac ctttggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 145
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 145
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 Asp 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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

```
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 146
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 146
gacatccaga tgacacagag ccccagcaca ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatctcc tcttggctgg cctggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gatctacgat gccagcagcc tggaaagcgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgag ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag atcacaagat accccgtgac ctttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 147
<211> 13
<212> PRT
<213> Artificial Sequence

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

<400> 147
Val Ser Gly Tyr Tyr Ser His Ser Gly Gly Phe Asp Val
1 5 10

<210> 148
<211> 15
<212> PRT
<213> Artificial Sequence

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

<400> 148
Ala Arg Val Ser Gly Tyr Tyr Ser His Ser Gly Gly Phe Asp Val
1 5 10 15

<210> 149
<211> 124
<212> PRT
<213> Artificial Sequence

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

<400> 149
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 Asn Tyr
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Tyr Gly Gly Thr Thr Asp Tyr Ala Glu
    50                  55                  60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

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

Tyr Cys Ala Arg Val Ser Gly Tyr Tyr Ser His Ser Gly Gly Phe Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 150
<211> 372
<212> DNA
<213> Artificial Sequence

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

<400> 150
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aactactgga tcagctgggt ccgacaggcc 120

cctggcaaag gacttgagtg ggtcggacgg atcaagagca agacctacgg cggcaccacc 180

gattatgccg agcctgtgaa gggcagattc accatcagcc gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtgtctggct actactctca cagcggcggc tttgatgtgt ggggccaggg aacactggtc 360

accgttagtt ct 372

<210> 151
<211> 454

<212> PRT
<213> Artificial Sequence

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

<400> 151
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 Asn Tyr
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Tyr Gly Gly Thr Thr Asp Tyr Ala Glu
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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

Tyr Cys Ala Arg Val Ser Gly Tyr Tyr Ser His Ser Gly Gly Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val

```
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro
    210                 215                 220

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    290                 295                 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                325                 330                 335

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
        355                 360                 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile
    370                 375                 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400
```

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly Lys
450

<210> 152
<211> 1362
<212> DNA
<213> Artificial Sequence

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

<400> 152
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aactactgga tcagctgggt ccgacaggcc 120

cctggcaaag gacttgagtg ggtcggacgg atcaagagca agacctacgg cggcaccacc 180

gattatgccg agcctgtgaa gggcagattc accatcagcc gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtgtctggct actactctca cagcggcggc tttgatgtgt ggggccaggg aacactggtc 360

accgttagtt ctgctagcac caagggccca agtgtgtttc ccctggcccc cagcagcaag 420

tctacttccg gcggaactgc tgccctgggt tgcctggtga aggactactt cccctgtccc 480

gtgacagtgt cctggaactc tggggctctg acttccggcg tgcacacctt ccccgccgtg 540

ctgcagagca gcggcctgta cagcctgagc agcgtggtga cagtgccctc cagctctctg 600

ggaacccaga cctatatctg caacgtgaac cacaagccca gcaacaccaa ggtggacaag 660

agagtggagc ccaagagctg cgacaagacc cacacctgcc ccccctgccc agctccagaa 720

ctgctgggag ggccttccgt gttcctgttc cccccaagc ccaaggacac cctgatgatc 780

agcaggaccc ccgaggtgac ctgcgtggtg gtggacgtgt cccacgagga cccagaggtg 840

aagttcaact ggtacgtgga cggcgtggag gtgcacaacg ccaagaccaa gcccagagag 900

gagcagtaca acagcaccta cagggtggtg tccgtgctga ccgtgctgca ccaggactgg 960

ctgaacggca aagaatacaa gtgcaaagtc tccaacaagg ccctgccagc cccaatcgaa 1020

aagacaatca gcaaggccaa gggccagcca cgggagcccc aggtgtacac cctgcccccc 1080

agccgggagg agatgaccaa gaaccaggtg tccctgacct gtctggtgaa gggcttctac 1140

ccctgtgata tcgccgtgga gtgggagagc aacggccagc ccgagaacaa ctacaagacc 1200

acccccccag tgctggacag cgacggcagc ttcttcctgt acagcaagct gaccgtggac 1260

aagtccaggt ggcagcaggg caacgtgttc agctgcagcg tgatgcacga ggccctgcac 1320

aaccactaca cccagaagtc cctgagcctg agccccggca ag 1362

<210> 153
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 153
Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 154
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 154
Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 155
<211> 9
<212> PRT

<213> Artificial Sequence

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

<400> 155
Gln Lys Thr Trp Arg Thr Pro Gly Thr
1 5

<210> 156
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 156
Ser Gln Gly Ile Ser Asn Tyr
1 5

<210> 157
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 157
Thr Trp Arg Thr Pro Gly
1 5

<210> 158
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 158
Gln Gly Ile Ser Asn Tyr

1 5

<210> 159
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 159
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Thr 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 Val Ala Thr Tyr Tyr Cys Gln Lys Thr Trp Arg Thr Pro Gly
85 90 95

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

<210> 160
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 160
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatcagc aactacctgg cctggtatca gcagaaaccc 120

ggcaaggtgc ccaagctgct gatctacgct gccagcacac tgcagagcgg agtgcctagc 180

agattttctg gcagcggctc cggcaccgat ttcaccctga ccatatctag cctgcagcca 240

gaggacgtgg ccacctacta ctgtcagaaa acctggcgga cccctggcac atttggccag 300

ggaacaaagg tggaaatcaa g 321

<210> 161
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 161
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Thr 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 Val Ala Thr Tyr Tyr Cys Gln Lys Thr Trp Arg Thr Pro Gly
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

```
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 162
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 162
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatcagc aactacctgg cctggtatca gcagaaaccc 120

ggcaaggtgc ccaagctgct gatctacgct gccagcacac tgcagagcgg agtgcctagc 180

agattttctg gcagcggctc cggcaccgat ttcaccctga ccatatctag cctgcagcca 240

gaggacgtgg ccacctacta ctgtcagaaa acctggcgga cccctggcac atttggccag 300

ggaacaaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 163
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 163
Ser Arg Leu Ile Ala Pro Trp Leu Asp Tyr
1 5 10

<210> 164
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 164
Ala Arg Ser Arg Leu Ile Ala Pro Trp Leu Asp Tyr
1 5 10

<210> 165
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 165
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 Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


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


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


Thr Leu Val Thr Val Ser Ser
        115


<210> 166
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 166
gaagttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg       60

tcttgtgccg ccagcggctt cacctttagc agctacgcca tgagctgggt ccgacaggct      120

cctggcaaag gccttgaatg ggtgtccgcc atctctggct ctggcggcag cacatattac      180

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac      240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc cagaagcaga      300

ctgatcgccc cttggctgga ttattggggc cagggcacac tggtcaccgt gtcatct         357


<210> 167
<211> 449
<212> PRT
<213> Artificial Sequence

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

<400> 167
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 Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

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

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

```
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415
```

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 168
<211> 1347
<212> DNA
<213> Artificial Sequence

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

<400> 168
gaagttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg 60

tcttgtgccg ccagcggctt cacctttagc agctacgcca tgagctgggt ccgacaggct 120

cctggcaaag gccttgaatg ggtgtccgcc atctctggct ctggcggcag cacatattac 180

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc cagaagcaga 300

ctgatcgccc cttggctgga ttattggggc cagggcacac tggtcaccgt gtcatctgct 360

agcaccaagg gcccaagtgt gtttcccctg gcccccagca gcaagtctac ttccggcgga 420

actgctgccc tgggttgcct ggtgaaggac tacttccccc gtcccgtgac agtgtcctgg 480

aactctgggg ctctgacttc cggcgtgcac accttccccg ccgtgctgca gagcagcggc 540

ctgtacagcc tgagcagcgt ggtgacagtg ccctccagct ctctgggaac ccagacctat 600

atctgcaacg tgaaccacaa gcccagcaac accaaggtgg acaagagagt ggagcccaag 660

agctgcgaca agacccacac ctgccccccc tgcccagctc cagaactgct gggagggcct 720

tccgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag gacccccgag 780

gtgacctgcg tggtggtgga cgtgtcccac gaggacccag aggtgaagtt caactggtac 840

gtggacggcg tggaggtgca caacgccaag accaagccca gagaggagca gtacaacagc 900

acctacaggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaagaa 960

tacaagtgca aagtctccaa caaggccctg ccagccccaa tcgaaaagac aatcagcaag 1020

gccaagggcc agccacggga gccccaggtg tacaccctgc cccccagccg ggaggagatg 1080

accaagaacc aggtgtccct gacctgtctg gtgaagggct tctacccctg tgatatcgcc 1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc cccagtgctg 1200

gacagcgacg gcagcttctt cctgtacagc aagctgaccg tggacaagtc caggtggcag 1260

cagggcaacg tgttcagctg cagcgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagccc cggcaag 1347

<210> 169
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 169
Gln Gln Val Tyr Gly Ser Pro Pro Thr
1 5

<210> 170
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 170
Val Tyr Gly Ser Pro Pro
1 5

<210> 171
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 171
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 172
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 172
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag gtctacggca gccctcctac atttggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 173
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 173
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 174
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 174
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag gtctacggca gccctcctac atttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 175
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 175
Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly
1 5 10

<210> 176
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 176
Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 177
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 177
Gly Ser Ser Ala Ala Ser Gly Leu Ser Gly Asp Leu
1 5 10

<210> 178
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 178
Ser Tyr Trp Ile Gly
1   5

<210> 179
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 179
Gly Tyr Ser Phe Thr Ser Tyr
1   5

<210> 180
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 180
Tyr Pro Gly Asp Ser Asp
1   5

<210> 181
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 181
Gly Tyr Ser Phe Thr Ser Tyr Trp
1   5

<210> 182
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 182
Ile Tyr Pro Gly Asp Ser Asp Thr
1 5

<210> 183
<211> 14
<212> PRT
<213> Artificial Sequence

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

<400> 183
Ala Arg Gly Ser Ser Ala Ala Ser Gly Leu Ser Gly Asp Leu
1 5 10

<210> 184
<211> 121
<212> PRT
<213> Artificial Sequence

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

<400> 184
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

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

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Ser Ala Ala Ser Gly Leu Ser Gly Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 185
<211> 363
<212> DNA
<213> Artificial Sequence

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

<400> 185
gaagttcagc tggtgcagtc tggcgccgaa gtgaagaagc ctggcgagag cctgaagatc 60

tcctgcaaag gcagcggcta cagcttcacc agctactgga tcggctgggt ccgacagatg 120

cctggcaaag gccttgagtg gatgggcatc atctaccccg gcgacagcga caccagatac 180

agccctagct ttcagggcca agtgaccatc agcgccgaca agagcatcag cacagcctac 240

ctgcagtggt ccagcctgaa ggcctctgac accgccatgt actactgtgc cagaggaagc 300

tctgccgcct ctggactgtc tggcgatctt tggggacagg gcacactggt cacagtgtct 360

agt 363

<210> 186
<211> 451
<212> PRT
<213> Artificial Sequence

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

<400> 186
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

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Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

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

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

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Ser Ser Ala Ala Ser Gly Leu Ser Gly Asp Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220
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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
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Pro Gly Lys
    450

<210> 187
<211> 1353
<212> DNA
<213> Artificial Sequence

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

<400> 187
gaagttcagc tggtgcagtc tggcgccgaa gtgaagaagc ctggcgagag cctgaagatc 60

tcctgcaaag gcagcggcta cagcttcacc agctactgga tcggctgggt ccgacagatg 120

cctggcaaag gccttgagtg gatgggcatc atctaccccg gcgacagcga caccagatac 180

agccctagct ttcagggcca agtgaccatc agcgccgaca agagcatcag cacagcctac 240

ctgcagtggt ccagcctgaa ggcctctgac accgccatgt actactgtgc cagaggaagc 300

tctgccgcct ctggactgtc tggcgatctt tggggacagg gcacactggt cacagtgtct 360

agtgctagca ccaagggccc aagtgtgttt cccctggccc ccagcagcaa gtctacttcc 420

ggcggaactg ctgccctggg ttgcctggtg aaggactact tccctgtcc cgtgacagtg 480

tcctggaact ctggggctct gacttccggc gtgcacacct tccccgccgt gctgcagagc 540

agcggcctgt acagcctgag cagcgtggtg acagtgccct ccagctctct gggaacccag 600

acctatatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa gagagtggag 660

cccaagagct gcgacaagac ccacacctgc ccccccctgcc cagctccaga actgctggga 720

gggccttccg tgttcctgtt ccccccccaag cccaaggaca ccctgatgat cagcaggacc 780

cccgaggtga cctgcgtggt ggtggacgtg tcccacgagg acccagaggt gaagttcaac 840

tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agcccagaga ggagcagtac 900

aacagcacct acagggtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 960

aaagaataca agtgcaaagt ctccaacaag gccctgccag ccccaatcga aaagacaatc 1020

agcaaggcca agggccagcc acgggagccc caggtgtaca ccctgccccc cagccgggag 1080

gagatgacca agaaccaggt gtccctgacc tgtctggtga agggcttcta cccctgtgat 1140

atcgccgtgg agtgggagag caacggccag cccgagaaca actacaagac cacccccca 1200

gtgctggaca gcgacggcag cttcttcctg tacagcaagc tgaccgtgga caagtccagg 1260

tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac 1320

acccagaagt ccctgagcct gagccccggc aag 1353

<210> 188
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 188
Gln Gln Asp Tyr Tyr Ser Pro Phe Thr
1 5

<210> 189
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 189
Asp Tyr Tyr Ser Pro Phe
1 5

<210> 190
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 190
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 191
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 191
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag gactactaca gccccttcac ctttggccag 300

ggcaccaagg tggaaatcaa g   321

<210> 192
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 192
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 193
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 193
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag gactactaca gccccttcac ctttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttcccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 194
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 194
Ala Tyr Lys Leu Ser Trp Leu Asp Leu

1 5

<210> 195
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 195
Ala Arg Ala Tyr Lys Leu Ser Trp Leu Asp Leu
1 5 10

<210> 196
<211> 118
<212> PRT
<213> Artificial Sequence

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

<400> 196
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 Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Ala Tyr Lys Leu Ser Trp Leu Asp Leu Trp Gly Gln Gly Thr

100 105 110

Leu Val Thr Val Ser Ser
115

<210> 197
<211> 354
<212> DNA
<213> Artificial Sequence

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

<400> 197
gaagttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg 60

tcttgtgccg ccagcggctt cacctttagc agctacgcca tgagctgggt ccgacaggct 120

cctggcaaag gccttgaatg ggtgtccgcc atctctggct ctggcggcag cacatattac 180

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagcctac 300

aagctgagct ggctggatct ttggggccag ggcacactgg tcacagtgtc atct 354

<210> 198
<211> 448
<212> PRT
<213> Artificial Sequence

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

<400> 198
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

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

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

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

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

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270
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Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> 199
<211> 1344
<212> DNA
<213> Artificial Sequence

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

<400> 199
gaagttcagc tgctggaatc tggcggagga ctggttcaac ctggcggctc tctgagactg 60

tcttgtgccg ccagcggctt cacctttagc agctacgcca tgagctgggt ccgacaggct 120

cctggcaaag gccttgaatg ggtgtccgcc atctctggct ctggcggcag cacatattac 180

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagcctac 300

aagctgagct ggctggatct ttggggccag ggcacactgg tcacagtgtc atctgctagc 360

accaagggcc caagtgtgtt tcccctggcc cccagcagca agtctacttc cggcggaact 420

gctgccctgg gttgcctggt gaaggactac ttccccctgtc ccgtgacagt gtcctggaac 480

tctggggctc tgacttccgg cgtgcacacc ttccccgccg tgctgcagag cagcggcctg 540

tacagcctga gcagcgtggt gacagtgccc tccagctctc tgggaaccca gacctatatc 600

tgcaacgtga accacaagcc cagcaacacc aaggtggaca agagagtgga gcccaagagc 660

tgcgacaaga cccacacctg ccccccctgc ccagctccag aactgctggg agggccttcc 720

gtgttcctgt tcccccccaa gcccaaggac accctgatga tcagcaggac ccccgaggtg 780

acctgcgtgg tggtggacgt gtcccacgag gacccagagg tgaagttcaa ctggtacgtg 840

gacggcgtgg aggtgcacaa cgccaagacc aagcccagag aggagcagta caacagcacc 900

tacagggtgg tgtccgtgct gaccgtgctg caccaggact ggctgaacgg caaagaatac 960

aagtgcaaag tctccaacaa ggccctgcca gccccaatcg aaaagacaat cagcaaggcc 1020

aagggccagc cacgggagcc ccaggtgtac accctgcccc ccagccggga ggagatgacc 1080

aagaaccagg tgtccctgac ctgtctggtg aagggcttct acccctgtga tatcgccgtg 1140

gagtgggaga gcaacggcca gcccgagaac aactacaaga ccacccccc agtgctggac 1200

agcgacggca gcttcttcct gtacagcaag ctgaccgtgg acaagtccag gtggcagcag 1260

ggcaacgtgt tcagctgcag cgtgatgcac gaggccctgc acaaccacta cacccagaag 1320

tccctgagcc tgagccccgg caag 1344

<210> 200
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 200
Gln Gln Val Trp Tyr Ala Pro Val Thr
1 5

<210> 201
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 201
Val Trp Tyr Ala Pro Val
1 5

<210> 202
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 202
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

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

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

<210> 203
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 203
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcaa gtttggtacg cccctgtgac ctttggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 204
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 204
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
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<210> 205
<211> 642
<212> DNA
<213> Artificial Sequence

<220>

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

<400> 205
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatcagc agctacctga actggtatca gcagaagccc 120

ggcaaggccc ctaaactgct gatctatgcc gccagctctc tgcagtctgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcaa gtttggtacg cccctgtgac ctttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttcccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 206
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 206
Gly Phe Thr Phe Ser Asn Ala Trp Met Ser
1 5 10

<210> 207
<211> 19
<212> PRT
<213> Artificial Sequence

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

<400> 207

Arg Ile Lys Ser Lys Thr Asp Ala Gly Thr Thr Asp Tyr Ala Ala Pro
1   5   10   15

Val Lys Gly

<210> 208
<211> 13
<212> PRT
<213> Artificial Sequence

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

<400> 208
Thr Ile Tyr Pro Ser Ala Pro Ser Ser Ser Leu Asp Tyr
1   5   10

<210> 209
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 209
Asn Ala Trp Met Ser
1   5

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

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

<400> 210
Gly Phe Thr Phe Ser Asn Ala
1   5

<210> 211

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

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

<400> 211
Lys Ser Lys Thr Asp Ala Gly Thr
1 5

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

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

<400> 212
Gly Phe Thr Phe Ser Asn Ala Trp
1 5

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

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

<400> 213
Ile Lys Ser Lys Thr Asp Ala Gly Thr Thr
1 5 10

<210> 214
<211> 15
<212> PRT
<213> Artificial Sequence

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

<400> 214
Ala Arg Thr Ile Tyr Pro Ser Ala Pro Ser Ser Ser Leu Asp Tyr
1   5   10   15

<210> 215
<211> 124
<212> PRT
<213> Artificial Sequence

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

<400> 215
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 Asn Ala
            20   25   30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65   70   75   80

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

Tyr Cys Ala Arg Thr Ile Tyr Pro Ser Ala Pro Ser Ser Ser Leu Asp
            100   105   110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 216
<211> 372
<212> DNA
<213> Artificial Sequence

<220>

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

<400> 216
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

acaatctacc ccagcgctcc tagcagcagc ctggattatt ggggccaggg cacactggtc 360

accgtgtcat ct 372

<210> 217
<211> 454
<212> PRT
<213> Artificial Sequence

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

<400> 217
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 Asn Ala
20 25 30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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

```
Tyr Cys Ala Arg Thr Ile Tyr Pro Ser Ala Pro Ser Ser Ser Leu Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
    130                 135                 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro
    210                 215                 220

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    290                 295                 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
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305 310 315 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
325 330 335

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
340 345 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly Lys
450

<210> 218
<211> 1362
<212> DNA
<213> Artificial Sequence

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

<400> 218
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

acaatctacc ccagcgctcc tagcagcagc ctggattatt ggggccaggg cacactggtc 360

accgtgtcat ctgctagcac caagggccca agtgtgtttc ccctggcccc cagcagcaag 420

tctacttccg gcggaactgc tgccctgggt tgcctggtga aggactactt cccctgtccc 480

gtgacagtgt cctggaactc tggggctctg acttccggcg tgcacacctt ccccgccgtg 540

ctgcagagca gcggcctgta cagcctgagc agcgtggtga cagtgccctc cagctctctg 600

ggaacccaga cctatatctg caacgtgaac cacaagccca gcaacaccaa ggtggacaag 660

agagtggagc ccaagagctg cgacaagacc cacacctgcc ccccctgccc agctccagaa 720

ctgctgggag ggccttccgt gttcctgttc ccccccaagc ccaaggacac cctgatgatc 780

agcaggaccc ccgaggtgac ctgcgtggtg gtggacgtgt cccacgagga cccagaggtg 840

aagttcaact ggtacgtgga cggcgtggag gtgcacaacg ccaagaccaa gcccagagag 900

gagcagtaca acagcaccta cagggtggtg tccgtgctga ccgtgctgca ccaggactgg 960

ctgaacggca aagaatacaa gtgcaaagtc tccaacaagg ccctgccagc cccaatcgaa 1020

aagacaatca gcaaggccaa gggccagcca cgggagcccc aggtgtacac cctgcccccc 1080

agccgggagg agatgaccaa gaaccaggtg tccctgacct gtctggtgaa gggcttctac 1140

ccctgtgata tcgccgtgga gtgggagagc aacggccagc ccgagaacaa ctacaagacc 1200

acccccccag tgctggacag cgacggcagc ttcttcctgt acagcaagct gaccgtggac 1260

aagtccaggt ggcagcaggg caacgtgttc agctgcagcg tgatgcacga ggccctgcac 1320

aaccactaca cccagaagtc cctgagcctg agccccggca ag 1362

<210> 219
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 219

Gln Gln Leu Ile Phe Phe Pro Leu Thr
1   5

<210> 220
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 220
Leu Ile Phe Phe Pro Leu
1   5

<210> 221
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 221
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

Tyr Ala Ala Ser Thr 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 Val Ala Thr Tyr Tyr Cys Gln Gln Leu Ile Phe Phe Pro Leu
                85   90   95

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

<210> 222
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 222
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatcagc aactacctgg cctggtatca gcagaaaccc 120

ggcaaggtgc ccaagctgct gatctacgct gccagcacac tgcagagcgg agtgcctagc 180

agattttctg gcagcggctc cggcaccgat ttcaccctga ccatatctag cctgcagcca 240

gaggacgtgg ccacctacta ttgccagcag ctgatcttct tccctctgac ctttggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 223
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 223
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Thr 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 Val Ala Thr Tyr Tyr Cys Gln Gln Leu Ile Phe Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 224
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 224
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatcagc aactacctgg cctggtatca gcagaaaccc 120

ggcaaggtgc ccaagctgct gatctacgct gccagcacac tgcagagcgg agtgcctagc 180

agattttctg gcagcggctc cggcaccgat ttcaccctga ccatatctag cctgcagcca 240

gaggacgtgg ccacctacta ttgccagcag ctgatcttct tccctctgac ctttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 225
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 225
Ala Ser His Arg Leu His Ser Leu Phe Asp Val
1 5 10

<210> 226
<211> 13
<212> PRT
<213> Artificial Sequence

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

<400> 226
Ala Arg Ala Ser His Arg Leu His Ser Leu Phe Asp Val
1 5 10

<210> 227
<211> 122
<212> PRT

<213> Artificial Sequence

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

<400> 227
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 Asn Ala
20 25 30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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

Tyr Cys Ala Arg Ala Ser His Arg Leu His Ser Leu Phe Asp Val Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 228
<211> 366
<212> DNA
<213> Artificial Sequence

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

<400> 228
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgccaga 300

gcctctcaca gactgcacag cctgtttgac gtgtggggcc agggaacact ggtcaccgtt 360

agttct 366

<210> 229
<211> 452
<212> PRT
<213> Artificial Sequence

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

<400> 229
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 Asn Ala
20 25 30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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

Tyr Cys Ala Arg Ala Ser His Arg Leu His Ser Leu Phe Asp Val Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

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Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
```

```
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly Lys
    450
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<210> 230
<211> 1356
<212> DNA
<213> Artificial Sequence

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

<400> 230
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgccaga 300

gcctctcaca gactgcacag cctgtttgac gtgtggggcc agggaacact ggtcaccgtt 360

agttctgcta gcaccaaggg cccaagtgtg tttcccctgg cccccagcag caagtctact 420

tccggcggaa ctgctgccct gggttgcctg gtgaaggact acttcccctg tcccgtgaca 480

gtgtcctgga actctggggc tctgacttcc ggcgtgcaca ccttccccgc cgtgctgcag 540

agcagcggcc tgtacagcct gagcagcgtg gtgacagtgc cctccagctc tctgggaacc 600

cagacctata tctgcaacgt gaaccacaag cccagcaaca ccaaggtgga caagagagtg 660

gagcccaaga gctgcgacaa gacccacacc tgccccccct gcccagctcc agaactgctg 720

ggagggcctt ccgtgttcct gttccccccc aagcccaagg acaccctgat gatcagcagg 780

acccccgagg tgacctgcgt ggtggtggac gtgtcccacg aggacccaga ggtgaagttc 840

aactggtacg tggacggcgt ggaggtgcac aacgccaaga ccaagcccag agaggagcag 900

tacaacagca cctacagggt ggtgtccgtg ctgaccgtgc tgcaccagga ctggctgaac 960

ggcaaagaat acaagtgcaa agtctccaac aaggccctgc cagccccaat cgaaaagaca 1020

atcagcaagg ccaagggcca gccacgggag ccccaggtgt acaccctgcc ccccagccgg 1080

gaggagatga ccaagaacca ggtgtccctg acctgtctgg tgaagggctt ctacccctgt 1140

gatatcgccg tggagtggga gagcaacggc cagcccgaga acaactacaa gaccaccccc 1200

ccagtgctgg acagcgacgg cagcttcttc ctgtacagca agctgaccgt ggacaagtcc 1260

aggtggcagc agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac 1320

tacacccaga agtccctgag cctgagcccc ggcaag 1356

<210> 231
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 231
Gln Gln Gly Leu Phe Tyr Pro His Thr
1 5

<210> 232
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 232
Gly Leu Phe Tyr Pro His
1 5

<210> 233
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 233
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 Asp 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

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

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

<210> 234
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 234
gacatccaga tgacacagag ccccagcaca ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gagcatctcc tcttggctgg cctggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gatctacgat gccagcagcc tggaaagcgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgag ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ttgtcagcag ggcctgttct accctcacac ctttggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 235
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 235
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 Asp 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

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

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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> 236
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 236
gacatccaga tgacacagag ccccagcaca ctgtctgcca gcgtgggaga cagagtgacc       60

atcacctgta gagccagcca gagcatctcc tcttggctgg cctggtatca gcagaagcct      120

ggcaaggccc ctaagctgct gatctacgat gccagcagcc tggaaagcgg cgtgccaagc      180

agattttctg gcagcggctc tggcaccgag ttcaccctga ccatatctag cctgcagcca      240

gaggacttcg ccacctacta ttgtcagcag ggcctgttct accctcacac ctttggccag      300
```

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 237
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 237
Asp Glu Tyr Pro Trp Gly Trp Phe Asp Val
1 5 10

<210> 238
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 238
Ala Arg Asp Glu Tyr Pro Trp Gly Trp Phe Asp Val
1 5 10

<210> 239
<211> 121
<212> PRT
<213> Artificial Sequence

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

<400> 239

```
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 Asn Ala
            20                  25                  30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

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

Tyr Cys Ala Arg Asp Glu Tyr Pro Trp Gly Trp Phe Asp Val Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 240
<211> 363
<212> DNA
<213> Artificial Sequence

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

<400> 240
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gatgagtacc cctggggatg gttcgatgtg tggggacagg gaaccctggt caccgttagt 360

<210> 241
<211> 451
<212> PRT
<213> Artificial Sequence

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

<400> 241
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 Asn Ala
20 25 30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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

Tyr Cys Ala Arg Asp Glu Tyr Pro Trp Gly Trp Phe Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val Thr Val
145 150 155 160

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala Val Glu
```

370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 242
<211> 1353
<212> DNA
<213> Artificial Sequence

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

<400> 242
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gatgagtacc cctggggatg gttcgatgtg tggggacagg gaaccctggt caccgttagt 360

tctgctagca ccaagggccc aagtgtgttt cccctggccc ccagcagcaa gtctacttcc 420

ggcggaactg ctgccctggg ttgcctggtg aaggactact tccctgtcc cgtgacagtg 480

tcctggaact ctggggctct gacttccggc gtgcacacct tccccgccgt gctgcagagc 540

agcggcctgt acagcctgag cagcgtggtg acagtgccct ccagctctct gggaacccag 600

acctatatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa gagagtggag 660

cccaagagct gcgacaagac ccacacctgc ccccccctgcc cagctccaga actgctggga 720

gggccttccg tgttcctgtt ccccccccaag cccaaggaca ccctgatgat cagcaggacc 780

cccgaggtga cctgcgtggt ggtggacgtg tcccacgagg acccagaggt gaagttcaac 840

tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agcccagaga ggagcagtac 900

aacagcacct acagggtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 960

aaagaataca agtgcaaagt ctccaacaag gccctgccag ccccaatcga aaagacaatc 1020

agcaaggcca agggccagcc acgggagccc caggtgtaca ccctgccccc cagccgggag 1080

gagatgacca agaaccaggt gtccctgacc tgtctggtga agggcttcta cccctgtgat 1140

atcgccgtgg agtgggagag caacggccag cccgagaaca actacaagac cacccccca 1200

gtgctggaca gcgacggcag cttcttcctg tacagcaagc tgaccgtgga caagtccagg 1260

tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac 1320

acccagaagt ccctgagcct gagccccggc aag 1353

<210> 243
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 243
Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 244
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 244
Gln Gln Tyr Ile Phe Tyr Pro Leu Thr

1 5

<210> 245
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 245
Ser Gln Gly Ile Ser Ser Trp
1 5

<210> 246
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 246
Tyr Ile Phe Tyr Pro Leu
1 5

<210> 247
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 247
Gln Gly Ile Ser Ser Trp
1 5

<210> 248
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

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

<400> 248
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser 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 Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

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

<210> 249
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 249
gacatccaga tgacacagag ccctagctcc gtgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatctct tcttggctgg cctggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gatctatgcc gcttccagtc tgcagagcgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag tacatcttct accctctgac cttcggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 250
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 250
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly 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 Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 251
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 251
gacatccaga tgacacagag ccctagctcc gtgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatctct tcttggctgg cctggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gatctatgcc gcttccagtc tgcagagcgg cgtgccaagc 180

agattttctg gcagcggctc tggcaccgac ttcaccctga ccatatctag cctgcagcca 240

gaggacttcg ccacctacta ctgccagcag tacatcttct accctctgac cttcggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 252
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 252
Val Ala Ser Pro Ser Ala Pro Gly Gly Phe Asp Tyr
1 5 10

<210> 253
<211> 14
<212> PRT
<213> Artificial Sequence

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

<400> 253
Ala Arg Val Ala Ser Pro Ser Ala Pro Gly Gly Phe Asp Tyr
1 5 10

<210> 254
<211> 123
<212> PRT
<213> Artificial Sequence

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

<400> 254
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 Asn Ala
20 25 30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr

65 70 75 80

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

Tyr Cys Ala Arg Val Ala Ser Pro Ser Ala Pro Gly Gly Phe Asp Tyr
100 105 110

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

<210> 255
<211> 369
<212> DNA
<213> Artificial Sequence

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

<400> 255
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtggcttctc cttctgctcc cggcggattc gattattggg gccagggaac actggtcacc 360

gtgtctagt 369

<210> 256
<211> 453
<212> PRT
<213> Artificial Sequence

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

<400> 256
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 Asn Ala
            20                  25                  30

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

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

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

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

Tyr Cys Ala Arg Val Ala Ser Pro Ser Ala Pro Gly Gly Phe Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Cys Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys
    210                 215                 220
```

```
Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Cys Asp Ile Ala
    370                 375                 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445
```

Leu Ser Pro Gly Lys
450

<210> 257
<211> 1359
<212> DNA
<213> Artificial Sequence

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

<400> 257
gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

agctgtgccg cttccggctt caccttcagc aatgcctgga tgagctgggt ccgacaggcc 120

cctggaaaag gccttgagtg ggtcggacgg atcaagagca agaccgatgc cggcaccacc 180

gattatgctg cccctgtgaa gggcagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtggcttctc cttctgctcc cggcggattc gattattggg gccagggaac actggtcacc 360

gtgtctagtg ctagcaccaa gggcccaagt gtgtttcccc tggcccccag cagcaagtct 420

acttccggcg gaactgctgc cctgggttgc ctggtgaagg actacttccc ctgtcccgtg 480

acagtgtcct ggaactctgg ggctctgact tccggcgtgc acaccttccc cgccgtgctg 540

cagagcagcg gcctgtacag cctgagcagc gtggtgacag tgccctccag ctctctggga 600

acccagacct atatctgcaa cgtgaaccac aagcccagca acaccaaggt ggacaagaga 660

gtggagccca agagctgcga caagacccac acctgccccc cctgcccagc tccagaactg 720

ctgggagggc cttccgtgtt cctgttcccc cccaagccca aggacaccct gatgatcagc 780

aggacccccg aggtgacctg cgtggtggtg gacgtgtccc acgaggaccc agaggtgaag 840

ttcaactggt acgtggacgg cgtggaggtg cacaacgcca agaccaagcc cagagaggag 900

cagtacaaca gcacctacag ggtggtgtcc gtgctgaccg tgctgcacca ggactggctg 960

aacggcaaag aatacaagtg caaagtctcc aacaaggccc tgccagcccc aatcgaaaag 1020

acaatcagca aggccaaggg ccagccacgg gagccccagg tgtacaccct gccccccagc 1080

cgggaggaga tgaccaagaa ccaggtgtcc ctgacctgtc tggtgaaggg cttctacccc 1140

tgtgatatcg ccgtggagtg ggagagcaac ggccagcccg agaacaacta caagaccacc 1200

cccccagtgc tggacagcga cggcagcttc ttcctgtaca gcaagctgac cgtggacaag 1260

tccaggtggc agcagggcaa cgtgttcagc tgcagcgtga tgcacgaggc cctgcacaac 1320

cactacaccc agaagtccct gagcctgagc cccggcaag 1359

<210> 258
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 258
Gln Gln Ser Leu Phe Ala Pro Phe Thr
1 5

<210> 259
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 259
Ser Leu Phe Ala Pro Phe
1 5

<210> 260
<211> 107
<212> PRT
<213> Artificial Sequence

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

<400> 260
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 261
<211> 321
<212> DNA
<213> Artificial Sequence

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

<400> 261
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatcagc aactacctgg cctggtatca gcagaaaccc 120

ggcaaggtgc ccaagctgct gatctacgct gccagcacac tgcagagcgg agtgcctagc 180

agattttctg gcagcggctc cggcaccgat ttcaccctga ccatatctag cctgcagcca 240

gaggacgtgg ccacctacta ctgtcagcag agcctgttcg ccccctttcac ctttggccag 300

ggcaccaagg tggaaatcaa g 321

<210> 262
<211> 214
<212> PRT
<213> Artificial Sequence

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

<400> 262
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 263
<211> 642
<212> DNA
<213> Artificial Sequence

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

<400> 263
gacatccaga tgacacagag ccctagcagc ctgtctgcca gcgtgggaga cagagtgacc 60

atcacctgta gagccagcca gggcatcagc aactacctgg cctggtatca gcagaaaccc 120

ggcaaggtgc ccaagctgct gatctacgct gccagcacac tgcagagcgg agtgcctagc 180

agattttctg gcagcggctc cggcaccgat ttcaccctga ccatatctag cctgcagcca 240

gaggacgtgg ccacctacta ctgtcagcag agcctgttcg ccccttttcac ctttggccag 300

ggcaccaagg tggaaatcaa gcgtacggtg gccgctccca gcgtgttcat cttcccccc 360

agcgacgagc agctgaagag tggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtca ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcataag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgtccagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 264
<211> 21
<212> DNA
<213> Artificial Sequence

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

<400> 264
ctctagcgcc accatgaaac a 21

<210> 265
<211> 18
<212> DNA
<213> Artificial Sequence

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

<400> 265
agcccagcaa caccaagg 18

<210> 266
<211> 20
<212> DNA
<213> Artificial Sequence

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

<400> 266
taatacgact cactataggg 20

<210> 267
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
6xHis tag"

<400> 267
His His His His His His
1 5

<210> 268
<211> 359
<212> PRT
<213> Homo sapiens

<400> 268
Met Thr Leu Glu Ser Ile Met Ala Cys Cys Leu Ser Glu Glu Ala Lys
1 5 10 15

```
Glu Ala Arg Arg Ile Asn Asp Glu Ile Glu Arg Gln Leu Arg Arg Asp
            20                  25                  30

Lys Arg Asp Ala Arg Arg Glu Leu Lys Leu Leu Leu Leu Gly Thr Gly
        35                  40                  45

Glu Ser Gly Lys Ser Thr Phe Ile Lys Gln Met Arg Ile Ile His Gly
    50                  55                  60

Ser Gly Tyr Ser Asp Glu Asp Lys Arg Gly Phe Thr Lys Leu Val Tyr
65                  70                  75                  80

Gln Asn Ile Phe Thr Ala Met Gln Ala Met Ile Arg Ala Met Asp Thr
                85                  90                  95

Leu Lys Ile Pro Tyr Lys Tyr Glu His Asn Lys Ala His Ala Gln Leu
            100                 105                 110

Val Arg Glu Val Asp Val Glu Lys Val Ser Ala Phe Glu Asn Pro Tyr
        115                 120                 125

Val Asp Ala Ile Lys Ser Leu Trp Asn Asp Pro Gly Ile Gln Glu Cys
    130                 135                 140

Tyr Asp Arg Arg Arg Glu Tyr Gln Leu Ser Asp Ser Thr Lys Tyr Tyr
145                 150                 155                 160

Leu Asn Asp Leu Asp Arg Val Ala Asp Pro Ala Tyr Leu Pro Thr Gln
                165                 170                 175

Gln Asp Val Leu Arg Val Arg Val Pro Thr Thr Gly Ile Ile Glu Tyr
            180                 185                 190

Pro Phe Asp Leu Gln Ser Val Ile Phe Arg Met Val Asp Val Gly Gly
        195                 200                 205

Gln Arg Ser Glu Arg Arg Lys Trp Ile His Cys Phe Glu Asn Val Thr
    210                 215                 220

Ser Ile Met Phe Leu Val Ala Leu Ser Glu Tyr Asp Gln Val Leu Val
```

225 230 235 240

Glu Ser Asp Asn Glu Asn Arg Met Glu Glu Ser Lys Ala Leu Phe Arg
245 250 255

Thr Ile Ile Thr Tyr Pro Trp Phe Gln Asn Ser Ser Val Ile Leu Phe
260 265 270

Leu Asn Lys Lys Asp Leu Leu Glu Glu Lys Ile Met Tyr Ser His Leu
275 280 285

Val Asp Tyr Phe Pro Glu Tyr Asp Gly Pro Gln Arg Asp Ala Gln Ala
290 295 300

Ala Arg Glu Phe Ile Leu Lys Met Phe Val Asp Leu Asn Pro Asp Ser
305 310 315 320

Asp Lys Ile Ile Tyr Ser His Phe Thr Cys Ala Thr Asp Thr Glu Asn
325 330 335

Ile Arg Phe Val Phe Ala Ala Val Lys Asp Thr Ile Leu Gln Leu Asn
340 345 350

Leu Lys Glu Tyr Asn Leu Val
355

<210> 269
<211> 6343
<212> DNA
<213> Homo sapiens

<400> 269
agactatccg ctcccaccgc gcccccggcc cacctggtgg ccccggccct ggccgccgcc 60

cccgcggcgg ttcccggagc tcgtcccgga cgcgcgcccg ggcggcgggg gctcggcggc 120

caccgctgcc tcgggggagc gagggcggga gggtgtgtgt gcgcgctgtg agcagggggt 180

gccggcgggg ctgcagcgga ggcactttgg aagaatgact ctggagtcca tcatggcgtg 240

ctgcctgagc gaggaggcca aggaagcccg gcggatcaac gacgagatcg agcggcagct 300

ccgcagggac aagcgggacg cccgccggga gctcaagctg ctgctgctcg ggacaggaga 360

gagtggcaag agtacgttta tcaagcagat gagaatcatc catgggtcag gatactctga 420

tgaagataaa aggggcttca ccaagctggt gtatcagaac atcttcacgg ccatgcaggc 480

catgatcaga gccatggaca cactcaagat cccatacaag tatgagcaca ataaggctca 540

tgcacaatta gttcgagaag ttgatgtgga gaaggtgtct gcttttgaga atccatatgt 600

agatgcaata aagagtttat ggaatgatcc tggaatccag gaatgctatg atagacgacg 660

agaatatcaa ttatctgact ctaccaaata ctatcttaat gacttggacc gcgtagctga 720

ccctgcctac ctgcctacgc aacaagatgt gcttagagtt cgagtcccca ccacagggat 780

catcgaatac ccctttgact tacaaagtgt cattttcaga atggtcgatg taggggggca 840

aaggtcagag agaagaaaat ggatacactg ctttgaaaat gtcacctcta tcatgtttct 900

agtagcgctt agtgaatatg atcaagttct cgtggagtca gacaatgaga accgaatgga 960

ggaaagcaag gctctcttta gaacaattat cacatacccc tggttccaga actcctcggt 1020

tattctgttc ttaaacaaga aagatcttct agaggagaaa atcatgtatt cccatctagt 1080

cgactacttc ccagaatatg atggacccca gagagatgcc caggcagccc gagaattcat 1140

tctgaagatg ttcgtggacc tgaacccaga cagtgacaaa attatctact cccacttcac 1200

gtgcgccaca gacaccgaga atatccgctt tgtctttgct gccgtcaagg acaccatcct 1260

ccagttgaac ctgaaggagt acaatctggt ctaattgtgc ctcctagaca cccgccctgc 1320

ccttccctgg tgggctattg aagatacaca agagggactg tatttctgtg gaaaacaatt 1380

tgcataatac taatttattg ccgtcctgga ctctgtgtga gcgtgtccac agagtttgta 1440

gtaaatatta tgattttatt taaactattc agaggaaaaa cagaggatgc tgaagtacag 1500

tcccagcaca tttcctctct atctttttt taggcaaaac cttgtgactc agtgtatttt 1560

aaattctcag tcatgcactc acaaagataa gacttgtttc tttctgtctc tctctctttt 1620

tcttttctat ggagcaaaac aaagctgatt tccctttttt cttcccccgc taattcatac 1680

ctccctcctg atgtttttcc caggttacaa tggcctttat cctagttcca ttcttggtca 1740

agtttttctc tcaaatgata cagtcaggac acatcgttcg atttaagcca tcatcagctt 1800

aatttaagtt tgtagttttt gctgaaggat tatatgtatt aatacttacg gttttaaatg 1860

tgttgctttg gatacacaca tagtttcttt tttaatagaa tatactgtct tgtctcactt 1920

tggactggga cagtggatgc ccatctaaaa gttaagtgtc atttctttta gatgtttacc 1980

ttcagccata gcttgattgc tcagagaaat atgcagaagg caggatcaaa gacacacagg 2040

agtcctttct tttgaaatgc cacgtgccat tgtctttcct cccttctttg cttctttttc 2100

ttaccctctc tttcaattgc agatgccaaa aaagatgcca acagacacta cattacccta 2160

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tgggtatgtg ttgccaaagc tggctttttg tcaaataaaa tgaatacgaa cttaaaaaat 2340

aaaagctggt atcttaaaat gtaagagagt aagactgtga agcctaaaat gactggctga 2400

gaatgaacca gaaatgccat ttgccaaaca gttgtaacta gaaatttgat tctcacggtc 2460

cattcttttc tttgtcctta agatgacatt gttagtgttc acgtcccatg ttcagtgtcc 2520

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tggttggtag tattattccg acacctttaa tttccaaaat ctgaagttcc tgctagttta 2700

ccaccttcat gatcttcttg aactggtaac tgattaggtt gaacttatgg aagatttgtg 2760

gacttaactc aaaagtaacc tctcagtgtt ctatagaaca tgtatttgtg taactgaacc 2820

taccaggaga aatgtttgga attctatatg tgcaattttt caacaaatgc aaaaaaaata 2880

cagcacatgt attgacaagc ttctgtcaag cagcttgagt tgaaatttga tttaagaaaa 2940

taaatcatga ttgttcaaag ctgctgggac gttagaatta ggccatgata ctggtctcat 3000

tttaactaca gtggtatttg gcactagtgt aaacttccat ataaatcact cttttggaac 3060

aacaaagggg gagggagaaa aatcacggcc tgttaaatga gtaccaaagc cgcccaacag 3120

taatgagatg ttctcatcct tgattctccc agcctcaaac aacacagctt actttttttt 3180

tcccttgctc agaaagtacc tgtaatttaa caaacagact gcctgtaggt atagtgcaat 3240

tacaaatgct ctaatcattg tacatacatc tctcttgata ttgcagcatc catactggct 3300

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gtattgtatg tctatagcta attcacgttt tgaataatgt tattttattt actttttaa 3420

gagaggagaa tgtaaatttg tcagtttatt tctgactagg gatattttct ttccatttag 3480

aaaagaagaa aaaaaaaaaa ccttactgtc atacagagcg gtactagcgt cgtgctgtat 3540

aaaatcattt gcacattcct gagtagaggt atactgatta taagacccaa aggtaatttc 3600

atagcaaaat acataaaatc agtcggagct tttatacaaa catggaaacc aactttgtag 3660

aactttgcc atttgatcta ggattggaat atgagctttt atacaattca tattcttatt 3720

tggcaaatgc acagtttagt attacctctc tgatggcctt tactagaaag gcagttttag 3780

aagctattgt gatccactaa ggaaatgttt taacagctag agaccactgc ttgcctgaaa 3840

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acatttgaag gcctacagtg tgtatagaga aaacctcatc acaagatcat aagtgttaca 3960

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aaaaacaaag tttactcatg ctttatatta tattgtgatt gcaagcgtta taagcgtgtg 4380

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cttgggcatg tcttattcaa aaacaaaaac ataaaacaca gaaacctttc ttcagcatac 4500

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aacaaaggga aataacacac ccattcaaaa gtaaataaat ctcctagaag tttttgtttt 4740

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aagaacctgc atatgttgtt tactagcaga tgacaactac aaaaggaatc tgaagaacac 4860

gtaaaacttg tatttttttt tttttggtag attaactagc aggcctattt taaaaaggta 4920

attcagctaa agggcaattt actttttgt acttcagact atcttgattg tcaaagtgta 4980

cgaactgtaa ttttaaaatt tatactgcca catgattgta aattttagtt gtcttaagtt 5040

aggaattggt gaaaagctat ttatgctgga tttgggtcaa aatgacttat ttgcaaaaaa 5100

ataaataatg ggaagaaagg gctgtataat gaaatactgc aagactcaca tattggttgg 5160

aaatttccct caaatcacct accgattacc cttgatttcc ctttgttttc agtttctcaa 5220

aacgaatgaa atgaaatata gcagaatgtt aacccatata aaaataaagt gtacccaaat 5280

attgtaatgt atattgctgc tcttcttcaa attaaataag ggtttaaaac cacttaattg 5340

gtaatcaaca tctcaattga tacaaataag gtgtgcttgg tatacattaa tattttcttc 5400

caaagatata tctttggtta gaaacacaaa aaaataaaac tagtaatatt gtatgtttat 5460

ctatctctac atatttccag catatgtagc gttaatagat ctgtcctggt aactgtgtct 5520

ttgggatttc attttggttc catcaaatta ggaaaagaaa tggcttagtt gtatatgatt 5580

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gcccttcaa taacactctt gcctctagaa tcatatgttc aaagtatgaa tacacaccta 5760

gcacatagta ggtgctcaaa tattaatttc ctccttgcct tccttatcta ccctgtgtcc 5820

tccatttccc cgtatgattc caacccaata tagcaaatga catttacatg ttatgaaaac 5880

atctattggg taaaatcaga tcttggataa agaaattctg acttttatat aagcttttgg 5940

tagacagaaa aaacagaaag gtattcgttg gtagaacatt tttaagttca ggaaagaaag 6000

ctggaataat actacgtaac tttgtccagg ttactttgac tgaaacacgt ttttggtgga 6060

tttcttttcc tcaaagaact ctctaaatgc aactccttgc tggattcctc acccatcatc 6120

ctgttggaaa cccttactag acctatgtat ttagggagtt ttgtcagaaa acatttttaa 6180

cttgcagtat ttaaaagaat atttactgtt cctaaaatgt cattcaaatg catgtactgt 6240

ctattgtttg gggatgggaa ctagttttgc aaaaaacacc taatgttgta taataatgcc 6300

ccaatgatct tgctggttaa aaatacagta tttttggcca taa 6343

<210> 270
<211> 359
<212> PRT
<213> Homo sapiens

<400> 270
Met Thr Leu Glu Ser Met Met Ala Cys Cys Leu Ser Asp Glu Val Lys
1 5 10 15

Glu Ser Lys Arg Ile Asn Ala Glu Ile Glu Lys Gln Leu Arg Arg Asp
20 25 30

Lys Arg Asp Ala Arg Arg Glu Leu Lys Leu Leu Leu Leu Gly Thr Gly
35 40 45

```
Glu Ser Gly Lys Ser Thr Phe Ile Lys Gln Met Arg Ile Ile His Gly
    50                  55                  60

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

Gln Asn Ile Phe Thr Ala Met Gln Ala Met Ile Arg Ala Met Glu Thr
                85                  90                  95

Leu Lys Ile Leu Tyr Lys Tyr Glu Gln Asn Lys Ala Asn Ala Leu Leu
            100                 105                 110

Ile Arg Glu Val Asp Val Glu Lys Val Thr Thr Phe Glu His Gln Tyr
        115                 120                 125

Val Ser Ala Ile Lys Thr Leu Trp Glu Asp Pro Gly Ile Gln Glu Cys
    130                 135                 140

Tyr Asp Arg Arg Arg Glu Tyr Gln Leu Ser Asp Ser Ala Lys Tyr Tyr
145                 150                 155                 160

Leu Thr Asp Val Asp Arg Ile Ala Thr Leu Gly Tyr Leu Pro Thr Gln
                165                 170                 175

Gln Asp Val Leu Arg Val Arg Val Pro Thr Thr Gly Ile Ile Glu Tyr
            180                 185                 190

Pro Phe Asp Leu Glu Asn Ile Ile Phe Arg Met Val Asp Val Gly Gly
        195                 200                 205

Gln Arg Ser Glu Arg Arg Lys Trp Ile His Cys Phe Glu Asn Val Thr
    210                 215                 220

Ser Ile Met Phe Leu Val Ala Leu Ser Glu Tyr Asp Gln Val Leu Val
225                 230                 235                 240

Glu Ser Asp Asn Glu Asn Arg Met Glu Glu Ser Lys Ala Leu Phe Arg
                245                 250                 255
```

```
Thr Ile Ile Thr Tyr Pro Trp Phe Gln Asn Ser Ser Val Ile Leu Phe
            260                 265                 270

Leu Asn Lys Lys Asp Leu Leu Glu Asp Lys Ile Leu Tyr Ser His Leu
        275                 280                 285

Val Asp Tyr Phe Pro Glu Phe Asp Gly Pro Gln Arg Asp Ala Gln Ala
    290                 295                 300

Ala Arg Glu Phe Ile Leu Lys Met Phe Val Asp Leu Asn Pro Asp Ser
305                 310                 315                 320

Asp Lys Ile Ile Tyr Ser His Phe Thr Cys Ala Thr Asp Thr Glu Asn
                325                 330                 335

Ile Arg Phe Val Phe Ala Ala Val Lys Asp Thr Ile Leu Gln Leu Asn
            340                 345                 350

Leu Lys Glu Tyr Asn Leu Val
        355
```

<210> 271
<211> 4190
<212> DNA
<213> Homo sapiens

<400> 271

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gcgcgggctg agtgcggccg cgcgggagtc cgcggctggc gcggcccgag cggggacccg      120

gcggctcgcc aggcggcggc cgaggcgggg cgggccggcc cggggccgag ggccggtggc      180

cgaggccgga gggccgcggc gggcggcggc cgaggcggct ccggccaggg ccgggccggg      240

ggccgggggg cggcggcggg caggcggccg cgtcggccgg ggccgggacg atgactctgg      300

agtccatgat ggcgtgttgc ctgagcgatg aggtgaagga gtccaagcgg atcaacgccg      360

agatcgagaa gcagctgcgg cgggacaagc gcgacgcccg gcgcgagctc aagctgctgc      420

tgctcggcac gggcgagagc gggaagagca cgttcatcaa gcagatgcgc atcatccacg      480

gcgccggcta ctcggaggag gacaagcgcg gcttcaccaa gctcgtctac cagaacatct      540

tcaccgccat gcaggccatg atccgggcca tggagacgct caagatcctc tacaagtacg      600
```

agcagaacaa ggccaatgcg ctcctgatcc gggaggtgga cgtggagaag gtgaccacct 660

tcgagcatca gtacgtcagt gccatcaaga ccctgtggga ggacccgggc atccaggaat 720

gctacgaccg caggcgcgag taccagctct ccgactctgc caagtactac ctgaccgacg 780

ttgaccgcat cgccaccttg ggctacctgc ccacccagca ggacgtgctg cgggtccgcg 840

tgcccaccac cggcatcatc gagtaccctt tcgacctgga gaacatcatc ttccggatgg 900

tggatgtggg gggccagcgg tcggagcgga ggaagtggat ccactgcttt gagaacgtga 960

catccatcat gtttctcgtc gccctcagcg aatacgacca agtcctggtg gagtcggaca 1020

acgagaaccg gatggaggag agcaaagccc tgttccggac catcatcacc tacccctggt 1080

tccagaactc ctccgtcatc ctcttcctca acaagaagga cctgctggag gacaagatcc 1140

tgtactcgca cctggtggac tacttccccg agttcgatgg tccccagcgg gacgcccagg 1200

cggcgcggga gttcatcctg aagatgttcg tggacctgaa ccccgacagc gacaagatca 1260

tctactcaca cttcacgtgt gccaccgaca cggagaacat ccgcttcgtg ttcgcggccg 1320

tgaaggacac catcctgcag ctcaacctca aggagtacaa cctggtctga gcgcccaggc 1380

ccagggagac gggatggaga cacggggcag gaccttcctt ccacggagcc tgcggctgcc 1440

gggcgggtgg cgctgccgag tccgggccgg ggcctctgcc cgcgggagga gatttttttt 1500

tttcatattt ttaacaaatg gtttttattt cacagttatc aggggatgta catctctccc 1560

tccgtacact tcgcgcacct tctcaccttt tgtcaacggc aaaggcagcc tttttctggc 1620

cttgacttat ggctcgcttt tttctaaaaa aaaaaaaaaa agaaagaaag aaaaaaagca 1680

acgaaacata aaacacacaa gcgccccgtg cccccagtga ctctgggcct cacagagccc 1740

ccgccagcca gcatggggcc ccgccctgca gccagtcacg cgcccccaca ccgcagcccc 1800

ccgtggctgt ccttccaacc ccacgtgctt tttctttctc ctgcccgctt cttttcttca 1860

tcacaaaagg cgtggagact cggagacgga cgtttttccc ctttttttaag ttattgacgc 1920

ccagcgcgcc tcgcctcttc acccatcaac gctgtgcttt gcccactgga ctcctgaaga 1980

gggggtgggg ggctccctcg gtcgcccacc ctgggaagtg cctaaccttt tattttattt 2040

tatttttttg aggaaaaaga acgcctgact cacaggttga agaaacaccc tgggccctct 2100

ctcatggccg ggttccccgt ccctctgcag aggctgggaa gggtccccgg gctggagcca 2160

cgggggcttc tctgggctgt gcctccgggg ccaacactgg ctgcttgggg ctgcccgggg 2220

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ggggagcggg aagccagcac tcgcactttg gccaggggcg cgtggaaggt ggtggcaggc 2580

accggcctgg gcagcttcca ggcctggctg gccacgacca cggcccgagg gggagcccgc 2640

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ggggctggcg ggataccccc cccccggctt ccccacacca cttctgtctc acccggaagc 3180

gtccttttt tgtgccaggt gtctacctaa gagggttggt gccagaagcc ccccatggcg 3240

agtgctgggg cccggcggtg ccctggggga gcagatgggg ccacccctgg cagggccgct 3300

acaacctttt ccagcagcgg agccctctgg ggggcctgtg cttgtggcat ctctgagggc 3360

ctagattgca caaggtgacc tggccgtggc ctgagggtgg agtcgcccag cacgcaggcc 3420

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aggagagtcc caggcagtgg ttctcgtgcc agtggcaccc aggggcaagg acagccaacc 3660

cccacccttg ccacgtgtgg ggccacgtgg gcatgtgggg tgtgtgtttt taccttggtg 3720

aatctcacct gccaacgatt tctcgtgagt gccgaccacc ttctccgacc atgttacgcc 3780

cgggcggcag cagcccccgg ccactgcaaa cccatgccct gggtcccccg gctcccccag 3840

ggaggcatcc ccgtgccaat gtcccccagt ggtggcagca gatcctgtgg ccggcctggc 3900

ggacgggacc cagtgatact tgtatattac acagtcctga tttcagacaa tttcaacctt 3960

aatctattta aaaaagaata ttctatacaa gctgttttta agccttttac catttgaaat 4020

gcatgtgttg tgcgcgttgg ggatgggagg aggggctgag gagcggctca gtgtcacctc 4080

ccacagccac cggccctgac ccttaatcca gacaccgatg gaagtcgact tttcatatct 4140

ttctcctgaa atgaactctg ttttaaattg gaataaattt tgttcctaaa 4190

<210> 272
<211> 661
<212> PRT
<213> Homo sapiens

<400> 272
Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1 5 10 15

Ala Leu Leu Ala Val Gly Ala Thr Lys Val Pro Arg Asn Gln Asp Trp
20 25 30

Leu Gly Val Ser Arg Gln Leu Arg Thr Lys Ala Trp Asn Arg Gln Leu
35 40 45

Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
50 55 60

Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65 70 75 80

Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
85 90 95

Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
100 105 110

Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
115 120 125

Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
130 135 140

```
Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp
145                 150                 155                 160

Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
                165                 170                 175

Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
            180                 185                 190

Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
        195                 200                 205

Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
    210                 215                 220

Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225                 230                 235                 240

Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
                245                 250                 255

Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
            260                 265                 270

Ala Leu Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
        275                 280                 285

Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
    290                 295                 300

Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
305                 310                 315                 320

Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
                325                 330                 335

Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
            340                 345                 350

Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
```

```
        355                 360                 365

Ala Glu Ser Thr Gly Met Thr Pro Glu Lys Val Pro Val Ser Glu Val
    370                 375                 380

Met Gly Thr Thr Leu Ala Glu Met Ser Thr Pro Glu Ala Thr Gly Met
385                 390                 395                 400

Thr Pro Ala Glu Val Ser Ile Val Val Leu Ser Gly Thr Thr Ala Ala
                405                 410                 415

Gln Val Thr Thr Thr Glu Trp Val Glu Thr Thr Ala Arg Glu Leu Pro
            420                 425                 430

Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser Ser Ile Met Ser Thr Glu
        435                 440                 445

Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu Asp Gly Thr Ala Thr Leu
    450                 455                 460

Arg Leu Val Lys Arg Gln Val Pro Leu Asp Cys Val Leu Tyr Arg Tyr
465                 470                 475                 480

Gly Ser Phe Ser Val Thr Leu Asp Ile Val Gln Gly Ile Glu Ser Ala
                485                 490                 495

Glu Ile Leu Gln Ala Val Pro Ser Gly Glu Gly Asp Ala Phe Glu Leu
            500                 505                 510

Thr Val Ser Cys Gln Gly Gly Leu Pro Lys Glu Ala Cys Met Glu Ile
        515                 520                 525

Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln Arg Leu Cys Gln Pro Val
    530                 535                 540

Leu Pro Ser Pro Ala Cys Gln Leu Val Leu His Gln Ile Leu Lys Gly
545                 550                 555                 560

Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser Leu Ala Asp Thr Asn Ser
                565                 570                 575
```

```
Leu Ala Val Val Ser Thr Gln Leu Ile Met Pro Gly Gln Glu Ala Gly
            580                 585                 590

Leu Gly Gln Val Pro Leu Ile Val Gly Ile Leu Leu Val Leu Met Ala
        595                 600                 605

Val Val Leu Ala Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp
    610                 615                 620

Phe Ser Val Pro Gln Leu Pro His Ser Ser Ser His Trp Leu Arg Leu
625                 630                 635                 640

Pro Arg Ile Phe Cys Ser Cys Pro Ile Gly Glu Asn Ser Pro Leu Leu
                645                 650                 655

Ser Gly Gln Gln Val
            660
```

<210> 273
<211> 626
<212> PRT
<213> Homo sapiens

<400> 273

```
Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1               5                   10                  15

Ala Leu Leu Ala Val Gly Ala Thr Lys Val Pro Arg Asn Gln Asp Trp
            20                  25                  30

Leu Gly Val Ser Arg Gln Leu Arg Thr Lys Ala Trp Asn Arg Gln Leu
        35                  40                  45

Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
    50                  55                  60

Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65                  70                  75                  80

Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
                85                  90                  95
```

```
Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
            100                 105                 110

Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
        115                 120                 125

Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
    130                 135                 140

Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp
145                 150                 155                 160

Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
                165                 170                 175

Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
            180                 185                 190

Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
        195                 200                 205

Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
    210                 215                 220

Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225                 230                 235                 240

Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
                245                 250                 255

Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
            260                 265                 270

Ala Leu Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
        275                 280                 285

Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
    290                 295                 300

Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
```

```
305                 310                 315                 320

Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
                325                 330                 335

Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
            340                 345                 350

Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
        355                 360                 365

Ala Glu Ser Thr Ala Ala Gln Val Thr Thr Thr Glu Trp Val Glu Thr
    370                 375                 380

Thr Ala Arg Glu Leu Pro Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser
385                 390                 395                 400

Ser Ile Met Ser Thr Glu Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu
                405                 410                 415

Asp Gly Thr Ala Thr Leu Arg Leu Val Lys Arg Gln Val Pro Leu Asp
            420                 425                 430

Cys Val Leu Tyr Arg Tyr Gly Ser Phe Ser Val Thr Leu Asp Ile Val
        435                 440                 445

Gln Gly Ile Glu Ser Ala Glu Ile Leu Gln Ala Val Pro Ser Gly Glu
    450                 455                 460

Gly Asp Ala Phe Glu Leu Thr Val Ser Cys Gln Gly Gly Leu Pro Lys
465                 470                 475                 480

Glu Ala Cys Met Glu Ile Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln
                485                 490                 495

Arg Leu Cys Gln Pro Val Leu Pro Ser Pro Ala Cys Gln Leu Val Leu
            500                 505                 510

His Gln Ile Leu Lys Gly Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser
        515                 520                 525
```

```
Leu Ala Asp Thr Asn Ser Leu Ala Val Val Ser Thr Gln Leu Ile Met
    530                 535                 540

Pro Val Pro Gly Ile Leu Leu Thr Gly Gln Glu Ala Gly Leu Gly Gln
545                 550                 555                 560

Val Pro Leu Ile Val Gly Ile Leu Leu Val Leu Met Ala Val Val Leu
                565                 570                 575

Ala Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp Phe Ser Val
            580                 585                 590

Pro Gln Leu Pro His Ser Ser Ser His Trp Leu Arg Leu Pro Arg Ile
        595                 600                 605

Phe Cys Ser Cys Pro Ile Gly Glu Asn Ser Pro Leu Leu Ser Gly Gln
    610                 615                 620

Gln Val
625
```

<210> 274
<211> 619
<212> PRT
<213> Homo sapiens

<400> 274

```
Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1               5                   10                  15

Ala Leu Leu Ala Val Gly Ala Thr Lys Val Pro Arg Asn Gln Asp Trp
            20                  25                  30

Leu Gly Val Ser Arg Gln Leu Arg Thr Lys Ala Trp Asn Arg Gln Leu
        35                  40                  45

Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
    50                  55                  60

Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65                  70                  75                  80
```

```
Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
                85                  90                  95

Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
            100                 105                 110

Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
        115                 120                 125

Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
    130                 135                 140

Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp
145                 150                 155                 160

Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
                165                 170                 175

Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
            180                 185                 190

Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
        195                 200                 205

Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
    210                 215                 220

Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225                 230                 235                 240

Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
                245                 250                 255

Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
            260                 265                 270

Ala Leu Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
        275                 280                 285

Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
```

```
    290                 295                 300

Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
305                 310                 315                 320

Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
                325                 330                 335

Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
            340                 345                 350

Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
        355                 360                 365

Ala Glu Ser Thr Ala Ala Gln Val Thr Thr Thr Glu Trp Val Glu Thr
    370                 375                 380

Thr Ala Arg Glu Leu Pro Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser
385                 390                 395                 400

Ser Ile Met Ser Thr Glu Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu
                405                 410                 415

Asp Gly Thr Ala Thr Leu Arg Leu Val Lys Arg Gln Val Pro Leu Asp
            420                 425                 430

Cys Val Leu Tyr Arg Tyr Gly Ser Phe Ser Val Thr Leu Asp Ile Val
        435                 440                 445

Gln Gly Ile Glu Ser Ala Glu Ile Leu Gln Ala Val Pro Ser Gly Glu
    450                 455                 460

Gly Asp Ala Phe Glu Leu Thr Val Ser Cys Gln Gly Gly Leu Pro Lys
465                 470                 475                 480

Glu Ala Cys Met Glu Ile Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln
                485                 490                 495

Arg Leu Cys Gln Pro Val Leu Pro Ser Pro Ala Cys Gln Leu Val Leu
            500                 505                 510
```

```
His Gln Ile Leu Lys Gly Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser
        515                 520                 525

Leu Ala Asp Thr Asn Ser Leu Ala Val Val Ser Thr Gln Leu Ile Met
    530                 535                 540

Pro Gly Gln Glu Ala Gly Leu Gly Gln Val Pro Leu Ile Val Gly Ile
545                 550                 555                 560

Leu Leu Val Leu Met Ala Val Val Leu Ala Ser Leu Ile Tyr Arg Arg
                565                 570                 575

Arg Leu Met Lys Gln Asp Phe Ser Val Pro Gln Leu Pro His Ser Ser
            580                 585                 590

Ser His Trp Leu Arg Leu Pro Arg Ile Phe Cys Ser Cys Pro Ile Gly
        595                 600                 605

Glu Asn Ser Pro Leu Leu Ser Gly Gln Gln Val
    610                 615
```

<210> 275
<211> 575
<212> PRT
<213> Homo sapiens

<400> 275

```
Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1               5                   10                  15

Ala Leu Leu Ala Val Gly Ala Thr Lys Gly Ser Gln Val Trp Gly Gly
            20                  25                  30

Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp Ala Cys Ile Phe Pro Asp
        35                  40                  45

Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser Gln Lys Arg Ser Phe Val
    50                  55                  60

Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp Gln Val Leu Gly Gly Pro
65                  70                  75                  80
```

```
Val Ser Gly Leu Ser Ile Gly Thr Gly Arg Ala Met Leu Gly Thr His
                85                  90                  95

Thr Met Glu Val Thr Val Tyr His Arg Arg Gly Ser Arg Ser Tyr Val
            100                 105                 110

Pro Leu Ala His Ser Ser Ser Ala Phe Thr Ile Thr Asp Gln Val Pro
        115                 120                 125

Phe Ser Val Ser Val Ser Gln Leu Arg Ala Leu Asp Gly Gly Asn Lys
    130                 135                 140

His Phe Leu Arg Asn Gln Pro Leu Thr Phe Ala Leu Gln Leu His Asp
145                 150                 155                 160

Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu Ser Tyr Thr Trp Asp Phe
                165                 170                 175

Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg Ala Leu Val Val Thr His
            180                 185                 190

Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala Gln Val Val Leu Gln Ala
        195                 200                 205

Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser Pro Val Pro Gly Thr Thr
    210                 215                 220

Asp Gly His Arg Pro Thr Ala Glu Ala Pro Asn Thr Thr Ala Gly Gln
225                 230                 235                 240

Val Pro Thr Thr Glu Val Val Gly Thr Thr Pro Gly Gln Ala Pro Thr
                245                 250                 255

Ala Glu Pro Ser Gly Thr Thr Ser Val Gln Val Pro Thr Thr Glu Val
            260                 265                 270

Ile Ser Thr Ala Pro Val Gln Met Pro Thr Ala Glu Ser Thr Gly Met
        275                 280                 285

Thr Pro Glu Lys Val Pro Val Ser Glu Val Met Gly Thr Thr Leu Ala
```

```
    290                 295                 300

Glu Met Ser Thr Pro Glu Ala Thr Gly Met Thr Pro Ala Glu Val Ser
305                 310                 315                 320

Ile Val Val Leu Ser Gly Thr Thr Ala Ala Gln Val Thr Thr Thr Glu
                325                 330                 335

Trp Val Glu Thr Thr Ala Arg Glu Leu Pro Ile Pro Glu Pro Glu Gly
            340                 345                 350

Pro Asp Ala Ser Ser Ile Met Ser Thr Glu Ser Ile Thr Gly Ser Leu
        355                 360                 365

Gly Pro Leu Leu Asp Gly Thr Ala Thr Leu Arg Leu Val Lys Arg Gln
    370                 375                 380

Val Pro Leu Asp Cys Val Leu Tyr Arg Tyr Gly Ser Phe Ser Val Thr
385                 390                 395                 400

Leu Asp Ile Val Gln Gly Ile Glu Ser Ala Glu Ile Leu Gln Ala Val
                405                 410                 415

Pro Ser Gly Glu Gly Asp Ala Phe Glu Leu Thr Val Ser Cys Gln Gly
            420                 425                 430

Gly Leu Pro Lys Glu Ala Cys Met Glu Ile Ser Ser Pro Gly Cys Gln
        435                 440                 445

Pro Pro Ala Gln Arg Leu Cys Gln Pro Val Leu Pro Ser Pro Ala Cys
    450                 455                 460

Gln Leu Val Leu His Gln Ile Leu Lys Gly Gly Ser Gly Thr Tyr Cys
465                 470                 475                 480

Leu Asn Val Ser Leu Ala Asp Thr Asn Ser Leu Ala Val Val Ser Thr
                485                 490                 495

Gln Leu Ile Met Pro Gly Gln Glu Ala Gly Leu Gly Gln Val Pro Leu
            500                 505                 510
```

```
Ile Val Gly Ile Leu Leu Val Leu Met Ala Val Val Leu Ala Ser Leu
        515                 520                 525


Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp Phe Ser Val Pro Gln Leu
    530                 535                 540


Pro His Ser Ser Ser His Trp Leu Arg Leu Pro Arg Ile Phe Cys Ser
545                 550                 555                 560


Cys Pro Ile Gly Glu Asn Ser Pro Leu Leu Ser Gly Gln Gln Val
                565                 570                 575


<210> 276
<211> 668
<212> PRT
<213> Homo sapiens

<400> 276
Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1               5                   10                  15


Ala Leu Leu Ala Val Gly Ala Thr Lys Val Pro Arg Asn Gln Asp Trp
            20                  25                  30


Leu Gly Val Ser Arg Gln Leu Arg Thr Lys Ala Trp Asn Arg Gln Leu
        35                  40                  45


Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
    50                  55                  60


Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65                  70                  75                  80


Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
                85                  90                  95


Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
            100                 105                 110


Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
        115                 120                 125
```

```
Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
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Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp
145                 150                 155                 160

Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
                165                 170                 175

Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
            180                 185                 190

Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
        195                 200                 205

Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
    210                 215                 220

Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225                 230                 235                 240

Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
                245                 250                 255

Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
            260                 265                 270

Ala Leu Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
        275                 280                 285

Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
    290                 295                 300

Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
305                 310                 315                 320

Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
                325                 330                 335

Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
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            340                 345                 350

Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
        355                 360                 365

Ala Glu Ser Thr Gly Met Thr Pro Glu Lys Val Pro Val Ser Glu Val
    370                 375                 380

Met Gly Thr Thr Leu Ala Glu Met Ser Thr Pro Glu Ala Thr Gly Met
385                 390                 395                 400

Thr Pro Ala Glu Val Ser Ile Val Val Leu Ser Gly Thr Thr Ala Ala
                405                 410                 415

Gln Val Thr Thr Thr Glu Trp Val Glu Thr Thr Ala Arg Glu Leu Pro
            420                 425                 430

Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser Ser Ile Met Ser Thr Glu
        435                 440                 445

Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu Asp Gly Thr Ala Thr Leu
    450                 455                 460

Arg Leu Val Lys Arg Gln Val Pro Leu Asp Cys Val Leu Tyr Arg Tyr
465                 470                 475                 480

Gly Ser Phe Ser Val Thr Leu Asp Ile Val Gln Gly Ile Glu Ser Ala
                485                 490                 495

Glu Ile Leu Gln Ala Val Pro Ser Gly Glu Gly Asp Ala Phe Glu Leu
            500                 505                 510

Thr Val Ser Cys Gln Gly Gly Leu Pro Lys Glu Ala Cys Met Glu Ile
        515                 520                 525

Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln Arg Leu Cys Gln Pro Val
    530                 535                 540

Leu Pro Ser Pro Ala Cys Gln Leu Val Leu His Gln Ile Leu Lys Gly
545                 550                 555                 560
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Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser Leu Ala Asp Thr Asn Ser
                565                 570                 575

Leu Ala Val Val Ser Thr Gln Leu Ile Met Pro Val Pro Gly Ile Leu
            580                 585                 590

Leu Thr Gly Gln Glu Ala Gly Leu Gly Gln Val Pro Leu Ile Val Gly
        595                 600                 605

Ile Leu Leu Val Leu Met Ala Val Val Leu Ala Ser Leu Ile Tyr Arg
    610                 615                 620

Arg Arg Leu Met Lys Gln Asp Phe Ser Val Pro Gln Leu Pro His Ser
625                 630                 635                 640

Ser Ser His Trp Leu Arg Leu Pro Arg Ile Phe Cys Ser Cys Pro Ile
                645                 650                 655

Gly Glu Asn Ser Pro Leu Leu Ser Gly Gln Gln Val
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<211> 2195
<212> DNA
<213> Homo sapiens

<400> 277

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tggctgtgat aggtgctttg ctggctgtgg gggctacaaa agtacccaga aaccaggact      180

ggcttggtgt ctcaaggcaa ctcagaacca aagcctggaa caggcagctg tatccagagt      240

ggacagaagc ccagagactt gactgctgga gaggtggtca agtgtccctc aaggtcagta      300

atgatgggcc tacactgatt ggtgcaaatg cctccttctc tattgccttg aacttccctg      360

gaagccaaaa ggtattgcca gatgggcagg ttatctgggt caacaatacc atcatcaatg      420

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tccctgatgg tggaccttgc ccatctggct cttggtctca gaagagaagc tttgtttatg      540

tctggaagac ctggggccaa tactggcaag ttctaggggg cccagtgtct gggctgagca      600
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ggggatcccg gagctatgtg cctcttgctc attccagctc agccttcacc attactgacc 720

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ttgtgggtac tacacctggt caggcgccaa ctgcagagcc ctctggaacc acatctgtgc 1140

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caggtatgac acctgagaag gtgccagttt cagaggtcat gggtaccaca ctggcagaga 1260

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gccttgggca ggttccgctg atcgtgggca tcttgctggt gttgatggct gtggtccttg 1920

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<210> 278
<211> 1902
<212> DNA
<213> Homo sapiens

<400> 278
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acaaaaggga gccaggtgtg gggaggacag ccagtgtatc cccaggaaac tgacgatgcc 180

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<212> DNA
<213> Homo sapiens

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acaaaagtac ccagaaacca ggactggctt ggtgtctcaa ggcaactcag aaccaaagcc 180

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<213> Homo sapiens

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<212> PRT
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<220>
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Ala Met Pro Glu Asn Leu
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