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## (54) Title: COMBINATION DRUG THERAPY FOR THE TREATMENT OF SOLID TUMORS

Fig. 1

## L1 (SEQ ID NO:1)

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCGGTACGCC  
CTGGAGAGCC GGCCTCCATC TCCCTCCAGT CTAGTCAGAG CCGCTCCGAT  
AGTATGGAT ACAACTATT TGGATTGGTAC CTGCAGAGC CAGGGCAGTC  
TCCACAGCTC CTGATCTATT TGGGTCTTAA TCGGGCTCC GGGGTCCCTG  
ACAGGTTGAG TGGCAGTGA TCGAGCAGAG ATTTTACACT GAAATCAGC  
AGAGTGGAGG CTGAGGATCT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AAGTCCGATC ACGTTCGGCC AAGGGACAGC ACTGGAGATT AAA

## L2 (SEQ ID NO:3)

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCGGTACGCC  
CTGGAGAGCC GGCCTCCATC TCCCTCCAGT CTAGTCAGAG CCGCTCCGAT  
AGTATGGAT ACAACTATT TGGATTGGTAC CTGCAGAGC CAGGGCAGTC  
TCCACAGCTC CTGATCTATT TGGGTCTTAA TCGGGCTCC GGGGTCCCTG  
ACAGGTTGAG TGGCAGTGA TCGAGCAGAG ATTTTACACT GAAATCAGC  
AGAGTGGAGG CTGAGGATCT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AAGTCCGATC ACGTTCGGCC AAGGGACAGC ACTGGAGATT AAA

## L3 (SEQ ID NO:5)

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCGGTACGCC  
CTGGAGAGCC GGCCTCCATC TCCCTCCAGT CTAGTCAGAG CCGCTCCGAT  
AGTATGGAT ACAACTATT TGGATTGGTAC CTGCAGAGC CAGGGCAGTC  
TCCACAGCTC CTGATCTATT TGGGTCTTAA TCGGGCTCC GGGGTCCCTG  
ACAGGTTGAG TGGCAGTGA TCGAGCAGAG ATTTTACACT GAAATCAGC  
AGAGTGGAGG CTGAGGATCT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AAGTCCGATC ACGTTCGGCC AAGGGACAGC ACTGGAGATT AAA

## L4 (SEQ ID NO:7)

GA AATTGTGATG ACGCAGTCTC CACTCTCCCT GCGGTACGCC  
CCTGAGAGCC GGCCTCCATC CTCTGTCAGG TCTAGTCAGA GCTCTCCGAT  
TACTAATGGA TACAACTATT TGGATTGGTAC CTGCAGAGC CAGGGCAGTC  
CTCCACAGCTC CTGATCTATT TGGGTCTTAA TCGGGCTCC GGGGTCCCTG  
ACAGGTTGAG TGGCAGTGA TCGAGCAGAG ATTTTACACT GAAATCAGC  
AGAGTGGAGG CTGAGGATCT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AAGTCCGATC ACGTTCGGCC AAGGGACAGC ACTGGAGATT AAA

## L5 (SEQ ID NO:9)

GAAA TGTGTGATG TCACTCTCCA CTCTCCCTG CCGGTACGCC  
TGGAGAGCC GGCCTCCATC CTCTGTCAGG TCTAGTCAGA GCTCTCCGAT  
GTAATGGATA CAACTATTG GATTGGTACC TGCAGAGCC AAGGGCAGTC  
CCACAGCTCC TGAATCTATT TGGGTCTTAA TCGGGCTCC GGGGTCCCTG  
CAGCTTCAGT GGCAGTGGAT CAGGCACAGA TTTTACACTG AAGCTCTACA  
AGAGTGGAGG CTGAGGATCT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AAGTCCGATC ACGTTCGGCC AAGGGACAGC ACTGGAGATT AAA

(57) Abstract: The present invention relates to a pharmaceutical combination that comprises an IGF1R inhibitor and an mTOR inhibitor for the treatment of cancer in a subject; a pharmaceutical composition comprising such a combination; the use of such a combination for the preparation of medication for the treatment of cancer; a kit comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and a method of treating cancer in a subject, especially a human.

# COMBINATION DRUG THERAPY FOR THE TREATMENT OF SOLID TUMORS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/558,732, filed November 11, 2011, which is hereby incorporated by reference herein in its entirety.

## BACKGROUND OF THE INVENTION

[0001] IGF1R is a transmembrane RTK that binds primarily to IGF-1 but also to IGF-II and insulin with lower affinity. Binding of IGF-1 to its receptor results in receptor oligomerization, activation of tyrosine kinase, intermolecular receptor autophosphorylation and phosphorylation of cellular substrates (major substrates are IRS1 and Shc). The ligand-activated IGF1R induces mitogenic activity in normal cells and plays an important role in abnormal growth. A major physiological role of the IGF-1 system is the promotion of normal growth and regeneration. Overexpressed IGF1R (type 1 insulin-like growth factor receptor) can initiate mitogenesis and promote ligand-dependent neoplastic transformation. Furthermore, IGF1R plays an important role in the establishment and maintenance of the malignant phenotype. Unlike the epidermal growth factor (EGF) receptor, no mutant oncogenic forms of the IGF1R have been identified. However, several oncogenes have been demonstrated to affect IGF-1 and IGF1R expression. The correlation between a reduction of IGF1R expression and resistance to transformation has been seen. Exposure of cells to the mRNA antisense to IGF1R RNA prevents soft agar growth of several human tumor cell lines. IGF1R abrogates progression into apoptosis, both in vivo and in vitro. It has also been shown that a decrease in the level of IGF1R below wild-type levels causes apoptosis of tumor cells in vivo. The ability of IGF1R disruption to cause apoptosis appears to be diminished in normal, non-tumorigenic cells.

[0002] The IGF-1 pathway in human tumor development has an important role. IGF1R overexpression is frequently found in various tumors (breast, colon, lung, sarcoma) and is often associated with an aggressive phenotype. High circulating IGF1 concentrations are strongly correlated with prostate, lung and breast cancer risk. Furthermore, IGF1R is required for establishment and maintenance of the transformed phenotype in vitro and in vivo (Baserga R. Exp. Cell. Res., 1999, 253, 1-6). The kinase activity of IGF1R is essential for the transforming

activity of several oncogenes: EGFR, PDGFR, SV40 T antigen, activated Ras, Raf, and v-Src. The expression of IGF1R in normal fibroblasts induces neoplastic phenotypes, which can then form tumors in vivo. IGF1R expression plays an important role in anchorage-independent growth. IGF1R has also been shown to protect cells from chemotherapy-, radiation-, and cytokine-induced apoptosis. Conversely, inhibition of endogenous IGF1R by dominant negative IGF1R, triple helix formation or antisense expression vector has been shown to repress transforming activity in vitro and tumor growth in animal models.

[0003] It has been shown that mammalian target of rapamycin (mTOR) inhibition can induce upstream insulin-like growth factor 1 receptor (IGF1R) signaling resulting in AKT activation in cancer cells. This phenomenon has been suggested to play a role in the attenuation of cellular responses to mTOR inhibition and may attenuate the clinical activity of mTOR inhibitors. Increase in pAKT has for instance been found in approximately 50% in the tumours of all patients in a Phase I study in patients with advanced solid tumours (Taberno et al., Journal of Clinical Oncology, 26 (2008), pp 1603-1610).

#### SUMMARY OF THE DISCLOSURE

[0004] The present invention provides a method for treating cancer in a subject, comprising, consisting of, or consisting essentially of administering to the subject in combination (e.g., simultaneously, sequentially, or alternately) therapeutically effective amounts of an IGF1R inhibitor and an mTOR inhibitor.

[0005] Another aspect of the present invention provides a method of treating cancer in a subject refractory to standard therapy, comprising, consisting of, or consisting essentially of administering to the subject a therapeutically effective amount of an IGF1R inhibitor in combination with a therapeutically effective amount of an mTOR inhibitor.

[0006] In certain embodiments, the IGF1R inhibitor comprises, consists of, or consists essentially of an antibody. In other embodiments, the antibody is a monoclonal antibody. In certain embodiments, the antibody comprises ganitumab (also known as AMG 479).

[0007] In another embodiment, the mTOR inhibitor is selected from the group consisting of rapamycin (sirolimus) and derivatives and/or analogs thereof, such as everolimus

or RAD001; CCI-779, ABT578, SAR543, ascomycin (an ethyl analog of FK506), AP23573, AP23841, KU-0063794, INK-128, EX2044, EX3855, EX7518, or compounds that bind to the ATP-binding cleft of mTOR, such as AZD08055 and OSI027, and combinations thereof. In preferred embodiments, the mTOR inhibitor comprises everolimus.

[0008] In yet another embodiment, the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject in the same formulation. In other embodiments, the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject in different formulations (e.g., an intravenous formulation and an oral formulation).

[0009] In other embodiments, the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject by the same route. Alternatively, in other embodiments the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject by different routes.

[0010] In yet another embodiment, the administering to the subject is simultaneous. In other embodiments, the administering to the subject is sequential.

[0011] In other embodiments, the IGF1R inhibitor is administered in an amount of about 0.1 mg/kg to about 50 mg/kg. In certain embodiments, the IGF1R inhibitor is administered in an amount of about 5 mg/kg to about 25 mg/kg, about 10 mg/kg to about 22 mg/kg, or about 12 mg/kg to 20 mg/kg. In specific embodiments, the IGF1R inhibitor is administered in an amount of about 12mg/kg or an amount of about 20 mg/kg.

[0012] In yet other embodiments, the mTOR inhibitor is administered in an amount of about 0.1 mg to about 10 mg. In certain embodiments, the mTOR inhibitor is administered in an amount of about 2 mg to about 8 mg.

[0013] In other embodiments, the IGF1R inhibitor is administered in a manner selected from the group consisting of once every day, three times every week, two times every week, once every week, once every two weeks, once every three weeks, once every four weeks, or combinations thereof, with or without breaks, changes, or alterations, according to medical need.

[00014] In yet other embodiments, the mTOR inhibitor is administered in a manner selected from the group consisting of daily, six days a week, five days a week, four days a week, three days a week, two days a week, one day a week, or combinations thereof.

[00015] In certain embodiments, the methods comprise administering to the subject ganitumab at 12 mg/kg every two weeks and everolimus at 5 mg five times weekly.

[00016] Another aspect of the present invention provides a method of treating a solid tumor disease in a subject, comprising, consisting of, or consisting essentially of administering to the subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus daily.

[00017] Another aspect of the present invention provides a method of treating a solid tumor disease in a subject comprising, consisting of, or consisting essentially of administering to the subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus five days per week.

[00018] Another aspect of the present invention provides a method of treating a solid tumor disease in a subject comprising, consisting of, or consisting essentially of administering to the subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus three days per week.

[00019] In some embodiments, the cancer is a non-small cell lung cancer, such as an adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and the like.

[00020] In yet other embodiments, the subject is treated for at least two weeks, four weeks, eight weeks, at least three months, at least four months, at least six months, at least nine months, or at least for one year.

[00021] In certain embodiments, the solid tumor disease is a neuroendocrine tumor, a thyoma, a fibrous tumor or a metastatic colorectal cancer (mCRC).

[00022] In certain embodiments, the methods further comprise, consist of, or consist essentially of administering to the subject a therapeutically effective amount of at least one of the following additional treatments selected from the group consisting of radiation, cytotoxic agents, chemotherapeutic agents, anti-cancer agents, and combinations thereof.

[00023] Another aspect of the present invention provides a pharmaceutical composition comprising, consisting of, or consisting essentially of an IGF1R inhibitor and an mTOR inhibitor in a pharmaceutically acceptable carrier.

[00024] In yet another aspect, the present invention provides a kit comprising, consisting of, or consisting essentially of a container, the container comprising an IGF1R inhibitor and an mTOR inhibitor, and printed instructions directing the use of a combined treatment of an IGF1R inhibitor and an mTOR inhibitor to a subject as a method for treating cancer in a subject. In certain embodiments, the kit further comprises a sterile diluent. In some embodiments, the IGF-1R inhibitor and the mTOR inhibitor are in separate sub-containers.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[00025] **Figure 1** provides nucleotide sequences encoding light chain variable domains L1 through L52 and heavy chain variable domains H1 through H52.

[00026] **Figure 2** provides amino acid sequences of light chain variable domains L1 through L52. CDR and FR regions are indicated.

[00027] **Figure 3** provides amino acid sequences of heavy chain variable domains H1 through H52. CDR and FR regions are indicated.

[00028] **Figure 4** provides amino acid sequences of the light chain CDR1 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

[00029] **Figure 5** provides amino acid sequences of the light chain CDR2 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

[00030] **Figure 6** provides amino acid sequences of the light chain CDR3 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

[00031] **Figure 7** provides amino acid sequences of the heavy chain CDR1 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

[00032] **Figure 8** provides amino acid sequences of the heavy chain CDR2 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

[00033] **Figure 9** provides amino acid sequences of the heavy chain CDR3 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

[00034] **Figure 10** provides the polypeptide sequence of a human kappa light chain antibody constant region and a human IgG1 heavy chain antibody constant region.

#### DESCRIPTION OF EMBODIMENTS

[00035] For the purposes of promoting an understanding of the principles of the present disclosure, reference will now be made to preferred embodiments and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the disclosure is thereby intended, such alteration and further modifications of the disclosure as illustrated herein, being contemplated as would normally occur to one skilled in the art to which the disclosure relates.

[00036] Definitions

[00037] The following terms are believed to have well-recognized meanings in the art. However, the following definitions are set forth to facilitate explanation of the invention.

[00038] Articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, at least one) of the grammatical object of the article. By way of example, "an element" means at least one element, and thus can include more than one element.

[00039] The term "about" as used herein when referring to a measurable value such as an amount of weight, time, dose, etc. is meant to encompass variations of  $\pm 20\%$  or  $\pm 10\%$ , more preferably  $\pm 5\%$ , even more preferably  $\pm 1\%$ , and still more preferably  $\pm 0.1\%$  from the specified amount, as such variations are appropriate to perform the disclosed method.

[00040] As used herein, the term "subject" and "patient" are used interchangeably herein and refer to both human and nonhuman animals. The term "nonhuman animals" of the disclosure includes all vertebrates, *e.g.*, mammals and non-mammals, such as nonhuman primates, sheep, dog, cat, horse, cow, chickens, amphibians, reptiles, and the like, for medical and/or laboratory research purposes. Preferably, the subject is a human patient. More preferably, the subject is a human patient that has cancer.

[00041] As used herein, the term "cancer" in a subject refers to the presence of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, and certain morphological features. Often, cancer cells will be in the form of a tumor or mass, but such cells may exist alone within a subject, or may circulate in the blood stream as independent cells, such as leukemic or lymphoma cells. Suitable examples for cancer as used herein include, but are not limited to, non-small cell lung (NSCL), pancreatic, head and neck, colon, ovarian or breast cancers, or Ewing's sarcoma. However, cancers that may be treated by the methods described herein include lung cancer, bronchioloalveolar cell lung cancer, bone cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, Ewing's sarcoma, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the ureter, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, cancer of the kidney, renal cell carcinoma, chronic or acute leukemia, lymphocytic lymphomas, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwannomas, ependymomas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenomas, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. The precancerous condition or lesion includes, for example,

the group consisting of oral leukoplakia, actinic keratosis (solar keratosis), precancerous polyps of the colon or rectum, gastric epithelial dysplasia, adenomatous dysplasia, hereditary nonpolyposis colon cancer syndrome (HNPCC), Barrett's esophagus, bladder dysplasia, and precancerous cervical conditions. Also included within this definition is the term "solid tumor disease." As used herein, the term "solid tumor disease" refers to those conditions, such as cancer, that form an abnormal tumor mass, such as sarcomas, carcinomas, and lymphomas. Suitable examples of solid tumor diseases include, but are not limited to, non-small cell lung cancer (NSCLC), neuroendocrine tumors, thyomas, fibrous tumors, metastatic colorectal cancer (mCRC), and the like. In certain embodiments, the solid tumor disease is an adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and the like.

[00042] As used herein, the term "IGF1R inhibitor" refers to any IGF1R inhibitor that is currently known in the art or that will be identified in the future, and includes any chemical entity that, upon administration to a subject, results in inhibition of a biological activity associated with activation of the IGF-1 receptor in the subject, including any of the downstream biological effects otherwise resulting from the binding to IGF1R of any of its natural ligands. Such IGF1R inhibitors include any agent that can block IGF1R activation or any of the downstream biological effects of IGF1R activation that are relevant to treating cancer in a subject.

[00043] An IGF1R inhibitor can act by any mechanism. Non-limiting examples of such mechanisms include binding directly to the intracellular domain of the receptor and inhibiting its kinase activity. Alternatively, such an inhibitor can act by occupying the ligand binding site or a portion thereof of the IGF-1 receptor, thereby making the receptor inaccessible to its natural ligand so that its normal biological activity is prevented or reduced. Alternatively, such an inhibitor can act by modulating the dimerization of IGF1R polypeptides, or interaction of IGF1R polypeptide with other proteins, reduce the amount of active IGF1R present on the cell surface (*e.g.*, by reducing the amount of IGF1R that is transcribed, translated, post-translationally modified, or transported to the surface of the cell, or by increasing the rate at which IGF1R is removed from the cell surface) or enhance ubiquitination and endocytotic degradation of IGF1R. An IGF1R inhibitor can also act by reducing the amount of IGF-1 available to activate IGF1R, by for example antagonizing the binding of IGF-1 to its receptor, by reducing the level of IGF-1, or by promoting the association of IGF-1 with proteins other than IGF1R such as IGF binding proteins (*e.g.*, IGFBP2 or IGFBP3). IGF1R inhibitors include, but are not limited to, low

molecular weight inhibitors, antibodies or antibody fragments, antisense constructs, small inhibitory RNAs (*i.e.*, RNA interference by dsRNA; RNAi), soluble receptor fragments, peptibodies, avimers, and ribozymes.

[00044] In some embodiments, IGF1R inhibitors may include, for example, imidazopyrazine IGF1R inhibitors, quinazoline IGF1R inhibitors, pyrido-pyrimidine IGF1R inhibitors, pyrimido-pyrimidine IGF1R inhibitors, pyrrolo-pyrimidine IGF1R inhibitors, pyrazolo-pyrimidine IGF1R inhibitors, phenylamino-pyrimidine IGF1R inhibitors, oxindole IGF1R inhibitors, indolocarbazole IGF1R inhibitors, phthalazine IGF1R inhibitors, isoflavone IGF1R inhibitors, quinalone IGF1R inhibitors, and tyrphostin IGF1R inhibitors, and all pharmaceutically acceptable salts and solvates of such IGF1R inhibitors, imidazopyrazine IGF1R inhibitors, pyrimidine-based IGF-1R inhibitors, cyclolignans, cyclolignans, pyrrolopyrimidines, pyrrolotriazine, pyrrolo[2,3-d], heteroaryl-aryl ureas, and the like.

[00045] Additional, specific examples of suitable IGF1R inhibitors include h7C10 (Centre de Recherche Pierre Fabre), an IGF-1 antagonist; EM-164 (ImmunoGen Inc.), an IGF1R modulator; CP-751871 (Pfizer Inc.), an IGF-1 antagonist; lanreotide (Ipsen), an IGF-1 antagonist; IGF1R oligonucleotides (Lynx Therapeutics Inc.); IGF-1 oligonucleotides (National Cancer Institute); IGF1R protein-tyrosine kinase inhibitors in development by Novartis (*e.g.*, NVP-AEW541, Garcia-Echeverria, C. et al. (2004) *Cancer Cell* 5:231-239; or NVP-ADW742, Mitsiades, C. S. et al. (2004) *Cancer Cell* 5:221-230); IGF1R protein-tyrosine kinase inhibitors (Ontogen Corp); AG-1024 (Camirand, A. et al. (2005) *Breast Cancer Research* 7:R570-R579 (DOI 10.1186/bcr1028); Camirand, A. and Pollak, M. (2004) *Brit. J. Cancer* 90:1825-1829; Pfizer Inc.), an IGF-1 antagonist; the tyrphostins-AG-538 and I-OMe-AG 538; BMS-536924, a small molecule inhibitor of IGF1R; PNU-145156E (Pharmacia & Upjohn SpA), an IGF-1 antagonist; BMS 536924, a dual IGF1R and IR kinase inhibitor (Bristol-Myers Squibb); AEW541 (Novartis); GSK621659A and GSK1838705 (Glaxo Smith-Kline); INSM-18 (Insmad); linsitinib (OSI); BMS 754807 (Bristol-Myers Squibb); AXL-1717 (Axelar); NVP-ADW742 (Novartis); ANT-429 (Antyra); A-928605 (Abbott); AZD4253 (AstraZeneca); TAE226 (Novartis); AG1024 (Merck); KW-2450 (Kyowa); and XL-228 (Exelixis).

[00046] In yet other embodiments, the IGF1R inhibitor may include an antibody or antibody fragment that can partially or completely block IGF1R activation by its natural ligand. Antibody-based IGF1R inhibitors also include any anti-IGF-1 antibody or antibody fragment

that can partially or completely block IGF1R activation. Non-limiting examples of antibody-based IGF1R inhibitors include those described in Larsson, O. et al (2005) Brit. J. Cancer 92:2097-2101 and Ibrahim, Y. H. and Yee, D. (2005) Clin. Cancer Res. 11:944s-950s; or being developed by Imclone (*e.g.*, IMC-A12), or ganitumab, an anti-IGF1R antibody (Amgen), as described in "RECOMMENDED International Nonproprietary Names: List 65," published by the World Health Organization, Avenue Appia 2, 1211 Geneva 27, Switzerland; R1507, an anti-IGF1R antibody (Genmab/Roche); AVE-1642, an anti-IGF1R antibody (Immunogen/Sanofi-Aventis); MK 0646 or h7C10, an anti-IGF1R antibody (Merck); or antibodies being developed by Schering-Plough Research Institute (*e.g.*, SCH 717454 or 19D12; or as described in US Patent Application Publication Nos. US 2005/0136063 A1 and US 2004/0018191 A1). The IGF1R inhibitor can be a monoclonal antibody, or an antibody or antibody fragment having the binding specificity thereof. In a preferred embodiment, the IGF1R inhibitor is an antibody that binds specifically to the human IGF1R. More preferably, the antibody is ganitumab.

[00047] Any treatment that results in a reduction of an activity or signal mediated by IGF1R can be used in the methods of the present invention. Examples of such treatments are provided in Sachdev et al., 2007, Mol Cancer Ther. 6:1-12. In one embodiment, the treatment comprises administering to the subject a substance that reduces an activity mediated by IGF1R. Examples of such substances include, but are not limited to, antibodies (including fragments and derivatives thereof), peptibodies, and AVIMERS™ (Amgen, Inc., Thousand Oaks, CA) that bind to IGF1R, IGF-1, or IGF-2, soluble, IGF-1- and/or IGF-2-binding derivatives of IGF1R, small molecules that bind to IGF1R, IGF-1, IGF-2, IRS1, SHC, GRB2, SOS1, PI3K, SHP2, or any other molecule that acts in the IGF1R signaling cascade, IGF-1 or IGF-2 binding proteins (and derivatives thereof), inhibitory nucleic acids (such as siRNA) and derivatives thereof (including peptide nucleic acids). Non-limiting examples of such molecules can be found in, for example, US Pat. No. 7,329,734 (issued February 12, 2008) 7,173,005 (issued February 6, 2007), 7,071,300 (issued July 4, 2006), 7,020,563 (issued March 28, 2006), 6,875,741 (issued April 5, 2005); US Pat. App. Pub. No. 07/0299010 (published December 27, 2007), 07/0265189 (published November 15, 2007), 07/0135340 (published June 14, 2007), 07/0129399 (published June 7, 2007), 07/0004634 A1 (published January 4, 2007), 05/0282761 A1 (published December 22, 2005), 05/0054638 A1 (published March 10, 2005), 04/0023887 A1 (published February 5, 2004), 03/0236190 A1 (published December 25, 2003), 03/0195147 A1 (published October 16, 2003); PCT Pub. No. WO 07/099171 (published September 7, 2007), WO 07/099166 (published September 7, 2007), 07/031745 (published March 22, 2007), WO

07/029106 (published March 15, 2007), WO 07/029107 (published March 15, 2007), WO 07/004060 (published January 11, 2007), WO 06/074057 A2 (published July 13, 2006), WO 06/069202 A2 (published June 29, 2006), WO 06/017443 A2 (published February 16, 2006), WO 06/012422 A1 (published February 2, 2006), WO 06/009962 A2 (published January 26, 2006), WO 06/009950 A2 (published January 26, 2006), WO 06/009947 A2 (published January 26, 2006), WO 06/009933 A2 (published January 26, 2006), WO 05/097800 A1 (October 20, 2005), WO 05/082415 A2 (published September 9, 2005), WO 05/037836 A2 (published April 28, 2005), WO 03/070911 A2 (published August 28, 2003), WO 99/28347 A2 (published June 10, 1999); European Pat. No. EP 1 732 898 B1 (published January 23, 2008), EP 0 737 248 B1 (published November 14, 2007), European Pat. App. No. EP 1 496 935 A2 (published January 19, 2005) and EP 1 432 433 A2 (published June 30, 2004), and D'ambrosio et al., 1996, Cancer Res. 56:4013-20, each of which is incorporated herein by reference in its entirety. Specific examples of such molecules include OSI-906 (OSI Pharmaceuticals, Melville, NY), BMS 536924 (Wittman et al., 2005, J Med Chem. 48:5639-43; Bristol Myers Squibb, New York, NY), XL228 (Exelexis, South San Francisco, CA), INSM-18, NDGA, and rhIGFBP-3 (Insmad, Inc., Richmond, VA; Breuhahn et al, 2002006, Curr Cancer Ther Rev. 2:157-67; Youngren et al., 2005, Breast Cancer Res Treatment 94:37-46; US Pat. No. 6,608,108), each of which reference is incorporated herein by reference in its entirety.

[00048] In one aspect, any suitable anti-IGF1R antibody, antibody fragment, or antibody derivative can be used in the methods of the present invention. In one embodiment, the antibody, antibody fragment, or antibody derivative binds to the extracellular domain of IGF1R. In another embodiment, the antibody, antibody fragment, or antibody derivative competes for binding to IGFR with IGF-1 and/or IGF-2. In another embodiment, the antibody, antibody fragment, or antibody derivative, when bound to IGF1R, reduces the amount of IGF-1 and/or IGF-2 that binds to the IGF1R. In another embodiment, the antibody, antibody fragment, or antibody derivative binds to the L1 subdomain of the IGF1R extracellular domain. In another embodiment, the antibody, antibody fragment, or antibody derivative binds to the CR subdomain of the IGF1R extracellular domain. In another embodiment, the antibody, antibody fragment, or antibody derivative binds to the L2 subdomain of the IGF1R extracellular domain. In another embodiment, the antibody, antibody fragment, or antibody derivative binds to the FnIII1 subdomain of the IGF1R extracellular domain. In another embodiment, the antibody, antibody fragment, or antibody derivative binds to the FnIII2-ID subdomain of the IGF1R extracellular domain. In another embodiment, the antibody, antibody fragment, or antibody derivative binds

to the FnIII subdomain of the IGF-1R extracellular domain. In another embodiment, the antibody, antibody fragment, or antibody derivative binds to more than one IGF1R extracellular domain. Non-limiting examples of anti-IGF1R antibodies that can be used in the methods of the present invention include each of the antibodies identified herein as L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52, and IGF1R-binding fragments and derivatives thereof. Such antibodies, and methods of making and using them, are described in US Pat. No. 7,871,611 and PCT Pub. No WO 2008/108986, incorporated herein by reference in their entirety. In one particular embodiment, the antibody comprises the light chain variable domain sequence of L16, the heavy chain variable domain sequence of H16, the human kappa light chain antibody constant region as herein described, and the human IgG1 heavy chain antibody constant region as herein described. Other non-limiting examples of anti-IGF1R antibodies for use in the methods of the present invention include dalotuzumab (MK 0646; Merck/Pierre Fabre); cixutumumab (IMC-A12; Eli Lilly/ImClone); figitumumab (CP-751,871; Pfizer); robatumumab (SCH 717454; Schering-Plough); AVE-1642a (Sanofi-Aventis/Immunogen); RG1507 (Roche); BIIB022 (Biogen-Idec); rhuMab IGFR (Genentech/Roche); MED1573 (MedImmune); IGF1R MoAb (GSK); as well as those described in US Pat. App. Pub. No. 06/0040358 (published February 23, 2006), 05/0008642 (published January 13, 2005), 04/0228859 (published November 18, 2004), e.g., antibody 1A (DSMZ Deposit No. DSM ACC 2586), antibody 8 (DSMZ Deposit No. DSM ACC 2589), antibody 23 (DSMZ Deposit No. DSM ACC 2588) and antibody 18 as described therein; PCT Pub. No. WO 06/138729 (published December 28, 2006), WO 05/016970 (published February 24, 2005), and Lu et al., 2004, J Biol Chem. 279:2856-65, e.g., antibodies 2F8, A12, and IMC-A12 as described therein; PCT Pub. No. WO 07/012614 (published February 1, 2007), WO 07/000328 (published January 4, 2007), WO 06/013472 (published February 9, 2006), 05/058967 (published June 30, 2005), 03/059951 (published July 24, 2003), US Pat. App. Pub. No. 05/0084906 (published April 21, 2005), e.g., antibody 7C10, chimaeric antibody C7C10, antibody h7C10, antibody 7H2M, chimaeric antibody \*7C10, antibody GM 607, humanized antibody 7C10 version 1, humanized antibody 7C10 version 2, humanized antibody 7C10 version 3, and antibody 7H2HM, as described therein; US Pat. App. Pub. No. 05/0249728 (published November 10, 2005), 05/0186203 (published August 25, 2005), 04/0265307 (published December 30, 2004),

03/0235582 (published December 25, 2003), Maloney et al., 2003, Cancer Res. 63:5073-83, e.g., antibody EM164, resurfaced EM164, humanized EM164, huEM164 v1.0, huEM164 v1.1, huEM164 v1.2, and huEM164 v1.3, as described therein; US Pat. No. 7,037,498 (issued May 2, 2006), US Pat. App. No. 05/0244408 (published November 30, 2005), 04/0086503 (published May 6, 2004), Cohen, et al., 2005, Clinical Cancer Res. 11:2063-73, e.g., antibody CP-751,871, each of the antibodies produced by the hybridomas having the ATCC accession numbers PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789, PTA-2793, and antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, and 4.17.3, as described therein; US Pat. App. No. 05/0136063 (published June 23, 2005), 04/0018191 (published January 29, 2004), e.g. antibody 19D12 and an antibody comprising a heavy chain encoded by a polynucleotide in plasmid 15H12/19D12 HCA ( $\gamma$ 4), deposited at the ATCC under number PTA-5214, and a light chain encoded by a polynucleotide in plasmid 15H12/19D12 LCF ( $\kappa$ ), deposited at the ATCC under number PTA-5220, as described therein; US Pat. App. No. 04/0202655 (published October 14, 2004), e.g., antibodies PINT-6A1, PINT-7A2, PINT-7A4, PINT-7A5, PINT-7A6, PINT-8A1, PINT-9A2, PINT-11A1, PINT-11A2, PINT-11A3, PINT-11A4, PINT-11A5, PINT-11A7, PINT-11A12, PINT-12A1, PINT-12A2, PINT-12A3, PINT-12A4, and PINT-12A5, as described therein; US Pat. App. No. 07/0243194 (published October 18, 2007), e.g., antibodies M13-C06, M14-G11, M14-C03, M14-B01, M12-E01, and M12-G04, and antibodies produced by hybridomas P2A7.3E11, 20C8.3B8, P1A2.2B11, 20D8.24B11, P1E2.3B12, and P1G10.2B8. Each of the foregoing references is incorporated herein by reference in its entirety. Also suitable for use are antibodies, antibody fragments, or antibody derivatives that compete for binding to IGF1 receptor with one of the aforementioned antibodies. In one embodiment, the antibody, antibody fragment, or antibody derivative binds to the same epitope as one of the aforementioned antibodies, or to an epitope that overlaps with the epitope of one of the aforementioned antibodies.

**[00049]** As used herein, the term "mTOR inhibitor that binds to and directly inhibits both mTORC1 and mTORC2 kinases" refers to any mTOR inhibitor that binds to and directly inhibits both mTORC1 and mTORC2 kinases that is currently known in the art, or will be identified in the future, and includes any chemical entity that, upon administration to a patient, binds to and results in direct inhibition of both mTORC1 and mTORC2 kinases in the patient. Examples of mTOR inhibitors useful in the invention described herein include, but are not limited to, RAD rapamycin (sirolimus) and derivatives/analogues thereof such as everolimus or RAD001; CCI-779, ABT578, SAR543, ascomycin (an ethyl analog of FK506), AP23573, AP23841, KU-0063794,

INK-128, EX2044, EX3855, EX7518, AZD08055 and OSI027. Particularly preferred mTOR inhibitors in accordance with the present invention are sirolimus and/or everolimus.

[00050] "Cell growth", as used herein, for example in the context of "tumor cell growth", unless otherwise indicated, is used as commonly used in oncology, where the term is principally associated with growth in cell numbers, which occurs by means of cell reproduction (*i.e.*, proliferation) when the rate of the latter is greater than the rate of cell death (*e.g.*, by apoptosis or necrosis), to produce an increase in the size of a population of cells, although a small component of that growth may in certain circumstances be due also to an increase in cell size or cytoplasmic volume of individual cells. An agent that inhibits cell growth can thus do so by either inhibiting proliferation or stimulating cell death, or both, such that the equilibrium between these two opposing processes is altered.

[00051] "Tumor growth" or "tumor metastases growth", as used herein, unless otherwise indicated, is used as commonly used in oncology, where the term is principally associated with an increased mass or volume of the tumor or tumor metastases, primarily as a result of tumor cell growth.

[00052] "Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (*e.g.*, loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or over-expression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate by receptor tyrosine kinases; (4) any tumors that proliferate by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs.

[00053] The term "treating" as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing, either partially or completely, the growth of tumors, tumor metastases, or other cancer-causing or neoplastic cells in a patient. The term "treatment" as used herein, unless otherwise indicated, refers to the act of treating.

[00054] The phrase "a method of treating" or its equivalent, when applied to, for example, cancer, refers to a procedure or course of action that is designed to reduce or eliminate the

number of cancer cells in an animal, or to alleviate the symptoms of a cancer. "A method of treating" cancer or another proliferative disorder does not necessarily mean that the cancer cells or other disorder will, in fact, be eliminated, that the number of cells or disorder will, in fact, be reduced, or that the symptoms of a cancer or other disorder will, in fact, be alleviated. Often, a method of treating cancer will be performed even with a low likelihood of success, but which, given the medical history and estimated survival expectancy of an animal, is nevertheless deemed an overall beneficial course of action.

[00055] The term "therapeutically effective agent" means an agent or composition comprising the same that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[00056] The term "therapeutically effective amount" or "effective amount" means the amount of the subject compound or agent or combination that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[00057] The term "method for manufacturing a medicament" or "use of for manufacturing a medicament" relates to the manufacturing of a medicament for use in the indication as specified herein, and in particular for use in tumors, tumor metastases, or cancer in general. The term relates to the so-called "Swiss-type" claim format in the indication specified.

[00058] Unless otherwise defined, all technical terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[00059] The present invention provides methods for treating cancer in a subject comprising, consisting of, or consisting essentially of administering to the subject a therapeutically effective amount of an IGF1R inhibitor, or pharmaceutical compositions thereof, in combination with an mTOR inhibitor, or pharmaceutical compositions thereof.

[00060] The present invention further provides methods for the treatment of cancer in a subject comprising administering to the subject in need of such treatment an amount of an IGF1R inhibitor and an amount of an mTOR inhibitor; wherein at least one of the amounts is administered as a sub-therapeutic amount.

[00061] The present invention also provides methods of treating cancer in a subject refractory to standard therapy, comprising administering to the subject a therapeutically effective amount of an IGF1R inhibitor in combination with an mTOR inhibitor.

[00062] In the preceding methods the order of administration of the first and second amounts can be simultaneous or sequential, *i.e.*, the IGF1R inhibitor can be administered before the mTOR inhibitor, after the mTOR inhibitor, or at the same time as the mTOR inhibitor.

[00063] In the context of this invention, an "effective amount" of an IGF1R or mTOR inhibitor is as defined above. A "sub-therapeutic amount" of such inhibitors is an amount less than the effective amount for that inhibitor when used alone, but when combined with an effective or sub-therapeutic amount of another inhibitor can produce a result desired by the physician, due to, for example, synergy in the resulting efficacious effects, and may also result in reduced side effects.

[00064] The term "refractory" as used herein is used to define a cancer for which treatment (*e.g.*, chemotherapy drugs, biological agents, and/or radiation therapy) has proven to be ineffective or insufficient. A refractory cancer tumor may shrink, but not to the point where the treatment is determined to be effective or sufficient. Typically however, the tumor stays the same size as it was before treatment (stable disease), or it grows (progressive disease).

[00065] For purposes of the present invention, administration "in combination", "co-administration of" and "co-administering" an IGF1R inhibitor and an mTOR inhibitor refer to any administration of the two inhibitors, either separately or together, where the two inhibitors are administered as part of an appropriate dose regimen designed to obtain the benefit of the combination therapy. Thus, the two inhibitors can be administered either as part of the same pharmaceutical composition or in separate pharmaceutical compositions. The IGF1R inhibitor can be administered prior to, at the same time as, or subsequent to administration of the mTOR inhibitor, or in some combination thereof. Where the mTOR inhibitor is administered to the patient at repeated intervals, *e.g.*, during a standard course of treatment, the IGF1R inhibitor can be administered prior to, at the same time as, or subsequent to, each administration of the mTOR inhibitor, or some combination thereof, or at different intervals in relation to therapy with the

mTOR inhibitor, or in a single dose prior to, at any time during, or subsequent to the course of treatment with the mTOR inhibitor.

[00066] The IGFR1 and mTOR inhibitors will typically be administered to the patient in a dose regimen that provides for the most effective treatment of the cancer (from both efficacy and safety perspectives) for which the subject is being treated, as known in the art. In conducting the treatment methods of the present invention, the inhibitors can be administered in any effective manner known in the art, such as by oral, topical, intravenous, intra-peritoneal, intramuscular, intra-articular, subcutaneous, intranasal, intra-ocular, vaginal, rectal, or intradermal routes, depending upon the type of cancer being treated, and the medical judgment of the prescribing physician as based, *e.g.*, on the results of published clinical studies. For those embodiments further requiring the administration of radiation or a radiochemical, the agent or treatment can be administered in any effective manner known in the art, as described briefly herein, above.

[00067] The amount of the IGF1R and mTOR inhibitors administered and the timing of administration will depend on the type (species, gender, age, weight, etc.) and condition of the subject being treated, the severity of the disease or condition being treated, and on the route of administration. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day. For example, the dose of IGF1R inhibitor may be in, but not limited to, the range of about 0.1 mg/kg to about 20 mg/kg, 1 mg/kg to about 19 mg/kg, 2 mg/kg to about 18 mg/kg, 3 mg/kg to about 17 mg/kg, 4 mg/kg to about 16 mg/kg, 5 mg/kg to about 15 mg/kg, 6 mg/kg to about 14 mg/kg, 7 mg/kg to about 13 mg/kg, 8 mg/kg to about 12 mg/kg. In certain embodiments, the dose is 12 mg/kg. Similarly, the dose of mTOR inhibitor may be in, but not limited to, the range of about 0.1 mg to about 10 mg, 1 mg to about 9 mg, 2 mg to about 8 mg, 3 mg to about 7 mg, 4 mg to about 6 mg. In certain embodiments, the dose is 5 mg.

[00068] The mTOR inhibitor and the IGF1R inhibitor can be administered with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Administration of such dosage forms can be carried out in single or multiple doses. Carriers include solid diluents or fillers, sterile aqueous media and

various non-toxic organic solvents, etc. Oral pharmaceutical compositions can be suitably sweetened and/or flavored.

[00069] The mTOR inhibitor and the IGF1R inhibitor can be combined together with various pharmaceutically acceptable inert carriers in the form of sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, and the like. Administration of such dosage forms can be carried out in single or multiple doses. Carriers include solid diluents or fillers, sterile aqueous media, and various non-toxic organic solvents, etc.

[00070] Methods of preparing pharmaceutical compositions comprising mTOR inhibitors are known in the art. Methods of preparing pharmaceutical compositions comprising IGF1R inhibitors are also known in the art. In view of the teaching of the present invention, methods of preparing pharmaceutical compositions comprising both an mTOR inhibitor and an IGF1R inhibitor will be apparent from the art, from other known standard references, such as Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 18th edition (1990).

[00071] For oral administration of the mTOR inhibitor or the IGF1R inhibitor, tablets containing one or both of the active agents are combined with any of various excipients such as, for example, micro-crystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine, along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinyl pyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, active agents may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[00072] For parenteral administration of either or both of the inhibitors, solutions in either sesame or peanut oil or in aqueous propylene glycol may be employed, as well as sterile aqueous

solutions comprising the active agent or a corresponding water-soluble salt thereof. Such sterile aqueous solutions are preferably suitably buffered, and are also preferably rendered isotonic, *e.g.*, with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. The oily solutions are suitable for intra-articular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

[00073] Additionally, it is possible to topically administer either or both of the inhibitors, by way of, for example, creams, lotions, jellies, gels, pastes, ointments, salves and the like, in accordance with standard pharmaceutical practice. For example, a topical formulation comprising either the mTOR inhibitor and/or an IGF1R inhibitor in about 0.1% (w/v) to about 5% (w/v) concentration can be prepared.

[00074] In certain embodiments, the inhibitors are used for veterinary purposes. In such cases, the inhibitors can be administered separately or together to animals using any of the forms and by any of the routes described above. In a preferred embodiment, the mTOR inhibitor and/or an IGF1R inhibitor are administered in the form of a capsule, bolus, tablet, liquid drench, by injection or as an implant. As an alternative, the inhibitors can be administered with the animal feedstuff, and for this purpose a concentrated feed additive or premix may be prepared for a normal animal feed. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice.

[00075] The present invention also encompasses the use of a therapeutically effective amount of a combination of an mTOR inhibitor and an IGF1R inhibitor for use in treating cancer or for the manufacture of a medicament for the treatment of cancer (*e.g.*, tumors or tumor metastases) in a subject in need thereof, wherein each inhibitor in the combination can be administered to the patient either simultaneously or sequentially. The present invention also encompasses the use of a synergistically effective combination of mTOR inhibitor and an IGF1R inhibitor for use in treating cancer or for use in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein each inhibitor in the combination can be administered to the subject either simultaneously or sequentially. The present invention also encompasses the use of a combination of an mTOR inhibitor and an IGF1R inhibitor for use in treating abnormal cell growth or for the manufacture of a medicament for the treatment of

abnormal cell growth in a subject in need thereof, wherein each inhibitor in the combination can be administered to the patient either simultaneously or sequentially. In some embodiments, the IGF1R inhibitor is administered in a manner selected from the group consisting of once a week, once every two weeks, once every three weeks, once every four weeks, or combinations thereof. In other embodiments, the mTOR inhibitor is administered in a manner selected from the group consisting of daily, six days a week, five days a week, three days a week, two days a week, one day a week, or combinations thereof.

[00076] In an alternative embodiment of any of the above uses the present invention also encompasses the use of a combination of an mTOR inhibitor and an IGF1R inhibitor in combination with another cytotoxic, chemotherapeutic or anti-cancer agents, or compounds that enhance the effects of such agents, for use in treating cancer or for the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein each inhibitor or agent in the combination can be administered to the subject either simultaneously or sequentially. In this context, the "other anti-cancer agent or agent that enhances the effect of such an agent" can be any of the agents listed herein above that can be added to the anti-cancer agent/treatment and IGF1R inhibitor combination when treating subjects.

[00077] In the context of this invention, other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds that enhance the effects of such agents, include, for example: alkylating agents or agents with an alkylating action, such as cyclophosphamide (CTX; e.g. CYTOXAN<sup>TM</sup>, chlorambucil (CHL; e.g. LEUKERAN<sup>TM</sup>), cisplatin (C is P; e.g. PLATINOL<sup>TM</sup>) busulfan (e.g. MYLERAN<sup>TM</sup>), melphalan, carmustine (BCNU), streptozotocin, triethylenemelamine (TEM), mitomycin C, and the like; anti-metabolites, such as methotrexate (MTX), etoposide (VP16; e.g. VEPESID<sup>TM</sup>), 6-mercaptopurine (6 MP), 6-thioguanine (6TG), cytarabine (Ara-C), 5-fluorouracil (5-FU), capecitabine (e.g. XELODA<sup>TM</sup>), dacarbazine (DTIC), and the like; antibiotics, such as actinomycin D, doxorubicin (DXR; e.g. ADRIAMYCIN<sup>TM</sup>), daunorubicin (daunomycin), bleomycin, mithramycin and the like; alkaloids, such as vinca alkaloids such as vincristine (VCR), vinblastine, and the like; and other antitumor agents, such as paclitaxel (e.g. TAXOL<sup>TM</sup>) and paclitaxel derivatives, the cytostatic agents, glucocorticoids such as dexamethasone (DEX; e.g. DECADRON<sup>TM</sup>) and corticosteroids such as prednisone, nucleoside enzyme inhibitors such as hydroxyurea, amino acid depleting enzymes such as asparaginase, leucovorin and other folic acid derivatives, and similar, diverse antitumor agents. The following agents may also be used as additional agents: arnifostine (e.g. ETHYOL<sup>TM</sup>), dactinomycin,

mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, lomustine (CCNU), doxorubicin lipo (e.g. DOXIL<sup>TM</sup>), gemcitabine (e.g. GEMZAR<sup>TM</sup>), daunorubicin lipo (e.g. DAUNOXOME<sup>TM</sup>), procarbazine, mitomycin, docetaxel (e.g. TAXOTERE<sup>TM</sup>, aldesleukin, carboplatin, oxaliplatin, cladribine, camptothecin, CPT 11 (irinotecan), 10-hydroxy 7-ethyl-camptothecin (SN38), floxuridine, fludarabine, ifosfamide, idarubicin, mesna, interferon beta, interferon alpha, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil.

[00078] With regards to radiation or a radiopharmaceutical, the source of radiation can be either external or internal to the patient being treated. When the source is external to the patient, the therapy is known as external beam radiation therapy (EBRT). When the source of radiation is internal to the patient, the treatment is called brachytherapy (BT). Radioactive atoms for use in the context of this invention can be selected from the group including, but not limited to, radium, cesium-137, iridium-192, americium-241, gold-198, cobalt-57, copper-67, technetium-99, iodine-123, iodine-131, and indium-111.

[00079] Radiation therapy is a standard treatment for controlling unresectable or inoperable tumors and/or tumor metastases. Improved results have been seen when radiation therapy has been combined with chemotherapy. Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (Gy), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various considerations, but the two most important are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. A typical course of treatment for a patient undergoing radiation therapy will be a treatment schedule over a 1 to 6 week period, with a total dose of between 10 and 80 Gy administered to the patient in a single daily fraction of about 1.8 to 2.0 Gy, 5 days a week. Parameters of adjuvant radiation therapies are, for example, contained in International Patent Publication WO 99/60023.

[00080] The present invention further provides for any of the "methods of treatment" (or methods for reducing the side effects caused by treatment) described herein, a corresponding "use for treating" and/or "method for manufacturing a medicament" for administration with an

mTOR inhibitor and use with the same indications and under identical conditions or modalities described for the method of treatment, characterized in that an IGF1R inhibitor is used, and such that where any additional agents, inhibitors or conditions are specified in alternative embodiments of the method of treatment they are also included in the corresponding alternative embodiment for the use for treating and/or method for manufacturing a medicament. In an alternative embodiment, the present invention further provides for any of the "methods of treatment" (or methods for reducing the side effects caused by treatment) described herein, a corresponding "method for medical treatment" or "method for manufacturing a medicament" for use with the same indications and under identical conditions or modalities described for the method of treatment, characterized in that a combination of an mTOR inhibitor and an IGF1R inhibitor is used, such that where any additional agents, inhibitors or conditions are specified in alternative embodiments of the method of treatment they are also included in the corresponding alternative embodiment for the method for medical use or for manufacturing a medicament.

[00081] The present invention further provides, for any of the methods, compositions or kits of the invention described herein in which a step or ingredient includes the phrase "comprising . . . a combination of an mTOR inhibitor and an IGF1R inhibitor", a corresponding method, composition or kit in which that phrase is substituted with the phrase "consisting essentially of . . . a combination of an mTOR inhibitor and an IGF1R inhibitor".

[00082] The present invention further provides, for any of the methods, compositions or kits of the invention described herein in which a step or ingredient includes the phrase "comprising . . . a combination of an mTOR inhibitor and an IGF1R inhibitor", a corresponding method, composition or kit in which that phrase is substituted with the phrase "consisting of a combination of an mTOR inhibitor and an IGF1R inhibitor".

[00083] The invention also encompasses a pharmaceutical composition that is comprised of a combination of an mTOR inhibitor and an IGF1R inhibitor in combination with a pharmaceutically acceptable carrier.

[00084] Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof).

[00085] Moreover, within this preferred embodiment, the invention encompasses a pharmaceutical composition for the treatment of cancer, the use of which results in the inhibition of growth of neoplastic cells, benign or malignant tumors, or metastases, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof).

[00086] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When a compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (cupric and cuprous), ferric, ferrous, lithium, magnesium, manganese (manganic and manganous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N',N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[00087] When a compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

[00088] The pharmaceutical compositions of the present invention comprise a combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof) as active ingredients, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Other therapeutic agents may include those cytotoxic, chemotherapeutic or anti-cancer agents, or agents which enhance the effects of such agents, as listed above. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00089] In practice, the compounds represented by the combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof) of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, a combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof) may also be administered by controlled release means and/or delivery devices. The combination compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredients with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[00090] Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a combination of an mTOR inhibitor and an IGF1R

inhibitor (including pharmaceutically acceptable salts of each component thereof). A combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof), can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds. Other therapeutically active compounds may include those cytotoxic, chemotherapeutic or anti-cancer agents, or agents which enhance the effects of such agents, as listed above.

[00091] Thus in one embodiment of this invention, a pharmaceutical composition can comprise a combination of an mTOR inhibitor and an IGF1R inhibitor in combination with another anticancer agent, wherein said anti-cancer agent is a member selected from the group consisting of alkylating drugs, antimetabolites, microtubule inhibitors, podophyllotoxins, antibiotics, nitrosoureas, hormone therapies, kinase inhibitors, activators of tumor cell apoptosis, and antiangiogenic agents.

[00092] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00093] In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

[00094] A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by

molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05 mg to about 5 g of the active ingredient and each cachet or capsule preferably contains from about 0.05 mg to about 5 g of the active ingredient.

[00095] For example, a formulation intended for the oral administration to humans may contain from about 0.5 mg to about 5 g of active agent, compounded with an appropriate and convenient amount of carrier material that may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1 mg to about 2 g of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

[00096] Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00097] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00098] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a combination of a combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof) of this invention, via conventional processing methods. As an example, a cream or ointment is

prepared by admixing hydrophilic material and water, together with about 5 wt % to about 10 wt % of the compound, to produce a cream or ointment having a desired consistency.

[00099] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[000100] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a combination of an mTOR inhibitor and an IGF1R inhibitor (including pharmaceutically acceptable salts of each component thereof) may also be prepared in powder or liquid concentrate form.

[000101] Dosage levels for the compounds of the combination of this invention will be approximately as described herein, or as described in the art for these compounds. It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[000102] The disclosure may be better understood by reference to the following non-limiting Examples, which are provided as exemplary of the disclosure. The following examples are presented in order to more fully illustrate the preferred embodiments of the disclosure and should in no way be construed, however, as limiting the broad scope of the disclosure.

## [000103] EXAMPLES

[000104] Example 1: Phase I Study of the IGF1R Antibody Ganitumab in Combination with Everolimus in Patients with Advanced Solid Tumors

[000105] The maximum tolerated doses/recommended phase II dose for the doublet combination, ganitumab (G) plus everolimus (E) followed by an expanded cohort was evaluated to better understand the safety and tolerability profile of this drug combination.

[000106] The primary objective of this study was to determine the maximum tolerated dose (MTD) and Recommended Phase II Dose (RPTD) of G + E in patients with advanced solid tumors. Secondary objectives were to describe any toxicities associated with this regimen and to preliminarily describe clinical activity (progression-free survival (PFS)), overall survival (OS), partial response (PR), complete response (CR) or stable disease (SD)>6 months.

[000107] *Materials and Methods:* For dose escalation, eligible patients had advanced solid tumors with adequate organ function and no increased risk for class-related toxicities. G was given intravenously, and E was orally administered; cycle length was 28 days. Stage I was a dose escalation; cohort size: 3-6 patients; Stage II was an expansion at MTD with a cohort size of 20 patients.

[000108] As shown in Table I below, G was dosed at 12 mg/kg every 14 days; E was dosed at 5 mg daily in cohort 1 and 5 mg three times weekly in cohort -1. An intermediate dose of E at 5 mg five times weekly was added to better maximize dose intensity. Dose limiting toxicity (DLT) was assessed in cycle 1.

**Table I: Dosing Scheme**

| Dose Level | Ganitumab (mg/kg) every two weeks | Everolimus (mg)  |
|------------|-----------------------------------|------------------|
| 1          | 12                                | 5, daily         |
| -1         | 12                                | 5, 3 days weekly |
| 1-b        | 12                                | 5, 5 days weekly |

[000109] *Assessments:* AEs were graded according to the NCI Common Toxicity Criteria version 4.0. Efficacy was assessed every 2 cycles with computed tomography (CT) using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines.

[000110] *Eligibility:* (1) Key inclusion criteria included: histologically confirmed solid tumor malignancy for which standard therapy or palliative measures do not exist or are no longer effective; disease measurable by RECIST; age  $\geq 18$  years; Kamofsky performance status  $> 70\%$ ; life expectancy of at least 3 months; and adequate organ and marrow function. (2) Key exclusion criteria included: inadequately controlled hypertension ( $>150/100$  mmHg); significant or poorly controlled cardiovascular or vascular disease events within previous 6 months; history of significant bleeding episode within the 6 months prior to day 1 of the study; history of interstitial lung disease, *e.g.*, pneumonitis or pulmonary fibrosis, or any evidence of interstitial lung disease on baseline chest CT scan; proteinuria at screening as demonstrated by either urine protein: creatine (UPC ratio  $>1.0$  or 24hr collection  $> 1\text{g}/24\text{hr}$  at screening; and required therapy with inhibitors or inducers of CYP3A4.

[000111] *Results:* Dose escalation was complete with 17 subjects evaluable for DLT toxicity and 16 evaluable for efficacy (see Table 2). Two out of 5 subjects experienced DLTs in cohort 1 due to dose holdings related to grade 3 hematologic toxicities: thrombocytopenia and neutropenia plus thrombocytopenia. No DLTs were observed out of 6 subjects in cohort -1; one DLT was observed out of 6 subjects in the intermediate cohort due to dose holding related to grade 2 intolerable skin rash and oral mucositis. Possible grade 3 treatment-related adverse events included neutropenia, thrombocytopenia, elevated AST/ALT, hypertriglyceridemia, vomiting and erythema multiforme minor. There were no grade  $\geq 4$  treatment-related toxicities. One non-treatment-related death was due to disease progression. Two subjects had clinically significant skin rashes which resulted in protocol discontinuation. Twelve subjects have available efficacy data; 4 subjects have not yet been restaged. Two subjects with refractory NSCLC achieved a complete response. Six additional subjects had stable disease as best response. In 2 out of 3 cutaneous biopsies, dermapathology evaluation revealed hypersensitivity reaction in the form of superficial perivascular dermatitis to G (mild perivascular lymphocytic infiltrate with eosinophils). The third biopsy revealed spongiotic dermatitis with mixed inflammatory infiltrate with abundant eosinophils and is interpreted as part of the skin toxicity to G.

**Table 2: Patient Information**

Twenty-six subjects treated: 19 in dose escalation; 7 in expanded cohort

| Characteristic                 | Patients (n=26)  |
|--------------------------------|------------------|
| Median age, years (range)      | 56, (33-72)      |
| Female:male, no. (%)           | 11 (42): 15 (58) |
| Type of primary tumor; no. (%) |                  |
| NSCLC                          | 10 (38)          |
| Colorectal                     | 8 (31)           |
| Neuroendocrine                 | 2 (8)            |
| Other*                         | 6 (23)           |

\*Other includes: gastroesophageal, GIST, appendiceal, thymoma, solitary fibrous tumor, cholangiocarcinoma

**Table 3: Determination of MTD/RPTD**

Nineteen subjects treated; 17 subjects evaluable for DLT

| Cohort | Subjects | DLT Toxicity                                                         |
|--------|----------|----------------------------------------------------------------------|
| 1      | 5        | Grade 3 thrombocytopenia and neutropenia<br>Grade 3 thrombocytopenia |
| -1     | 8*       | None                                                                 |
| 1-b    | 6        | Grade 2 intolerable skin rash and oral mucositis <sup>†</sup>        |

\* 2 subjects were inevaluable for DLT

<sup>†</sup> Unable to receive 85% or scheduled doses G and/or E

**Table 4: Treatment-Related Grade  $\geq 3$  Adverse Events**

| Toxicity              | Grade 3 | Grade 4 |
|-----------------------|---------|---------|
| <b>Hematologic</b>    |         |         |
| Neutropenia           | 1       | 0       |
| Thrombocytopenia      | 3       | 0       |
| <b>Nonhematologic</b> |         |         |
| Vomiting              | 1       | 0       |
| Hypertriglyceridemia  | 1       | 0       |

[000112] *Efficacy:* 25 out of 26 subjects are evaluable for efficacy. To date, and as shown in Table 3, 23 subjects have been restaged, two subjects have not yet been restaged. Two subjects with refractory NSCLC achieved CR after 4 months on the protocol. One of these subjects had sustained CR for over one year, the other subject has sustained CR for 5 months. Eight subjects achieved SD as best response. Of the subjects who achieved SD as a best

response, one had a neuroendocrine tumor (unknown primary), one had a thymoma, one had a solitary fibrous tumor, one had mCRC, and four had NSCLC. In each of these cases, SD status was maintained for four months. Median PFS is 4 months, with a range of 4-13 months.

[000113] *Conclusion:* The results of the trial demonstrate that G + E at MTD is well-tolerated. The recommended phase II dose for this doublet combination is G at 12 mg/kg every two weeks and E at 5 mg five times weekly. At this dose, this novel regimen is well-tolerated with potential activity in NSCLC. DLTs were grade 3 thrombocytopenia and neutropenia, grade 3 thrombocytopenia, grade 2 intolerable skin rash and oral mucositis. Potential clinical activity was observed in subjects with refractory NSCLC. Skin toxicities consistent with hypersensitivity to Ganitumab have been observed.

[000114] *References:*

- [000115] 1. King, E.R. et al. (2011) Recent Pat Anticancer Drug Discov.
- [000116] 2. Tolcher, A.W. et al. (2009) *J. Clin. Oncol.* 27:5800-5807.
- [000117] 3. Schmelzle, T. et al. (2000) *Cell* 103:253-262.
- [000118] 4. O'Reilly, K.E. et al. (2006) *Cancer Res.* 66:1500-1508.
- [000119] 5. Wan, X. et al. (2007) *Oncogene* 26:1932-1940.

[000120] Variations and modifications of the herein described systems, apparatuses, methods and other applications will undoubtedly suggest themselves to those skilled in the art. Accordingly, the foregoing description should be taken as illustrative and not in a limiting sense.

[000121] Any patents or publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. These patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

We claim:

1. A method for treating cancer in a subject comprising administering to the subject a therapeutically effective amount of an IGF1R inhibitor, or a pharmaceutical composition thereof, in combination with an mTOR inhibitor, or a pharmaceutical composition thereof.
2. A method of treating cancer in a subject refractory to standard therapy, comprising administering to the subject a therapeutically effective amount of an IGF1R inhibitor in combination with an mTOR inhibitor.
3. The method as in any one of the preceding claims wherein the IGF1R inhibitor comprises an antibody.
4. The method according to claim 3, wherein the antibody is a monoclonal antibody.
5. The method according to claim 4, wherein the antibody is ganitumab.
6. The method as in any one of the preceding claims wherein the mTOR inhibitor is selected from the group consisting of rapamycin (sirolimus) and derivatives and/or analogs thereof, such as everolimus or RAD001; CCI-779, ABT578, SAR543, ascomycin (an ethyl analog of FK506), AP23573, AP23841, KU-0063794, INK-128, EX2044, EX3855, EX7518, or compounds that bind to the ATP-binding cleft of mTOR, such as AZD08055 and OSI027, and combinations thereof.
7. The method according to claim 6, wherein the mTOR inhibitor comprises everolimus.
8. The method as in any one of the preceding claims, wherein the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject in the same formulation.
9. The method as in any one of the preceding claims, wherein the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject in different formulations.
10. The method as in any one of the preceding claims, wherein the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject by the same route.
11. The method as in any one of the preceding claims, wherein the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject by different routes.

12. The method as in any one of the preceding claims, wherein the administering to the subject is simultaneous.
13. The method as in any one of the preceding claims, wherein the administering to the subject is sequential.
14. The method as in any one of claims 1-13, in which the IGF1R inhibitor is administered in an amount of about 0.1 mg/kg to about 20 mg/kg.
15. The method according to claim 14, wherein the IGF1R inhibitor is administered in an amount of about 5 mg/kg to about 15 mg/kg.
16. The method according to claim 14, wherein the IGF1R inhibitor is administered in an amount of 12 mg/kg.
17. The method according to claim 14, wherein the IGF1R inhibitor is administered in an amount of 20 mg/kg.
18. The method as in any one of claims 1-13, in which the mTOR inhibitor is administered in an amount of about 0.1 mg to about 10 mg.
19. The method according to claim 16, wherein the mTOR inhibitor is administered in an amount of about 2 mg to about 8 mg.
20. The method as in any one of the preceding claims, wherein the mTOR inhibitor is administered in an amount of 5 mg.
21. The method as in any one of claims 1-20, wherein the IGF1R inhibitor is administered in a manner selected from the group consisting of once a week, once every two weeks, once every three weeks, once every four weeks, and combinations thereof.
22. The method as in any one of claim 1-20, wherein the mTOR inhibitor is administered in a manner selected from the group consisting of daily, six days a week, five days a week, four days a week, three days a week, two days a week, one day a week, or combinations thereof.
23. The method as in any one of the preceding claims further comprising administering to the subject a therapeutically effective amount of at least one of the following additional treatments selected from the group consisting of radiation, cytotoxic agents, chemotherapeutic agents, anti-cancer agents, and combinations thereof.

24. The method of claim 1 comprising administering to the subject ganitumab at 12 mg/kg every two weeks and everolimus at 5 mg five times weekly.
25. The method of claim 1 or 24 wherein the subject has non-small cell lung cancer.
26. The method of claim 25 wherein the non-small cell lung cancer is an adenocarcinoma.
27. The method of claim 25 wherein the non-small cell lung cancer is a squamous cell carcinoma.
28. The method of claim 25 wherein the non-small cell lung cancer is a large cell carcinoma.
29. The method of claim 1 or 25 wherein the subject is treated for at least two weeks.
30. The method of claim 1 or 25 wherein the subject is treated for at least four weeks.
31. The method of claim 1 or 25 wherein the subject is treated for at least eight weeks.
32. The method of claim 1 or 25 wherein the subject is treated for at least three months.
33. The method of claim 1 or 25 wherein the subject is treated for at least four months.
34. The method of claim 1 or 25 wherein the subject is treated for at least six months.
35. The method of claim 1 or 25 wherein the subject is treated for at least nine months.
36. The method of claim 1 or 25 wherein the subject is treated for at least one year.
37. A method of treating a solid tumor disease in a subject, comprising administering to said subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus daily.
38. A method of treating a solid tumor disease in a subject, comprising administering to said subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus five days per week.
39. A method of treating a solid tumor disease in a subject, comprising administering to said subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus three days per week.
40. The method of any one of claims 37-39, wherein said solid tumor disease is a non-small cell lung cancer (NSCLC).
41. The method of claim 40, wherein said NSCLC is an adenocarcinoma.
42. The method of claim 40, wherein said NSCLC is a squamous cell carcinoma.

43. The method of claim 40, wherein said NSCLC is a large cell carcinoma.
44. The method of any one of claims 37-39, wherein said solid tumor disease is a neuroendocrine tumor, a thymoma, a fibrous tumor, or an mCRC.
45. A pharmaceutical composition comprising an IGF1R inhibitor and an mTOR inhibitor in a pharmaceutically acceptable carrier.
46. A kit comprising a container, the container comprising an IGF1R inhibitor and an mTOR inhibitor, and printed instructions directing the use of a combined treatment of an IGF1R inhibitor and an mTOR inhibitor to a subject as a method for treating cancer in a subject.
47. The kit of claim 46, further comprising a sterile diluent.

1/40

Fig. 1

**L1 (SEQ ID NO:1)**

|             |             |            |            |            |
|-------------|-------------|------------|------------|------------|
| GAT         | GTTGTGATGA  | CTCAGTCTCC | ACTCTCCCTG | CCCGTCACCC |
| CTGGAGAGCC  | GGCCTCCATC  | TCCTGCAGGT | CTAGTCAGAG | CCTCCTGCAT |
| AGTAGTGGAT  | ACAAC TATTT | GGATTGGTAC | CTGCAGAAGC | CAGGGCAGTC |
| TCCACAGCTC  | CTGATCTATT  | TGGGTTCTAA | TCGGGCCTCC | GGGGTCCCTG |
| ACAGGTTTCAG | TGGCAGTGGA  | TCAGGCACAG | ATTTTACACT | GAAAATCAGC |
| AGAGTGGAGG  | CTGAGGATGT  | TGGGGTTTAT | TACTGCATGC | AAGCTCTACA |
| AACTCCGATC  | ACCTTCGGCC  | AAGGGACACG | ACTGGAGATT | AAA        |

**L2 (SEQ ID NO:3)**

|             |             |            |            |            |
|-------------|-------------|------------|------------|------------|
| GAT         | GTTGTGATGA  | CTCAGTCTCC | ACTCTCCCTG | CCCGTCACCC |
| CTGGAGAGCC  | GGCCTCCATC  | TCCTGCAGGT | CTAGTCAGAG | CCTCCTGCAT |
| AGTAATGGAT  | ACAAC TATTT | GGATTGGTAC | CTGCAGAAGC | CAGGGCAGTC |
| TCCACAGCTC  | CTGATCTATT  | TGGGTTCTAA | TCGGGCCTCC | GGGGTCCCTG |
| ACAGGTTTCAG | TGGCAGTGGA  | TCAGGCACAG | ATTTTACACT | GAAAATCAGC |
| AGAGTGGAGG  | CTGAGGATGT  | TGGGGTTTAT | TACTGCATGC | AAGCTCTACA |
| AACTCCGATC  | ACCTTCGGCC  | AAGGGACACG | ACTGGAGATT | AAA        |

**L3 (SEQ ID NO:5)**

|             |             |            |            |            |
|-------------|-------------|------------|------------|------------|
| GAT         | GTTGTGATGA  | CTCAGTCTCC | ACTCTCCCTG | CCCGTCACCC |
| CTGGAGAGCC  | GGCCTCCATC  | TCCTGCAGGT | CTAGTCAGAG | CCTCCTGCAT |
| AGTAATGGAT  | ACAAC TATTT | GGATTGGTAC | CTGCAGAAGC | CAGGGCAGTC |
| TCCACAGCTC  | CTGATCTATT  | TGGGTTCTAA | TCGGGCCTCC | GGGGTCCCTG |
| ACAGGTTTCAG | TGGCAGTGGA  | TCAGGCACAG | ATTTTACACT | GAAAATCAGC |
| AGAGTGGAGG  | CTGAGGATGT  | TGGGGTTTAT | TACTGCATGC | AAGCTCTACA |
| AACTCCACTC  | ACTTTCGGCG  | GCGGGACCAA | GGTGGAGATC | AAA        |

**L4 (SEQ ID NO:7)**

|            |             |            |            |            |
|------------|-------------|------------|------------|------------|
| GA         | AATTGTGATG  | ACGCAGTCTC | CACTCTCCCT | GCCCGTCACC |
| CCTGGAGAGC | CGGCCTCCAT  | CTCCTGCAGG | TCTAGTCAGA | GCCTCCTGCA |
| TAGTAATGGA | TACAAC TATT | TGGATTGGTA | CCTGCAGAAG | CCAGGGCAGT |
| CTCCACAGCT | CCTGATCTAT  | TTGGGTTCTA | ATCGGGCCTC | CGGGGTCCCT |
| GACAGGTTCA | GTGGCAGTGG  | ATCAGGCACA | GATTTTACAC | TGAAAATCAG |
| CAGAGTGGAG | GCTGAGGATG  | TTGGGGTTTA | TTACTGCATG | CAAGCTCTAC |
| AAACTCCTCA | CACTTTCGGC  | GGAGGGACCA | AGGTGGAGAT | CAAA       |

**L5 (SEQ ID NO:9)**

|             |             |            |             |            |
|-------------|-------------|------------|-------------|------------|
| GAAA        | TTGTGCTGAC  | TCAGTCTCCA | CTCTCCCTGC  | CCGTCACCCC |
| TGGAGAGCCG  | GCCTCCATCT  | CCTGCAGGTC | TAGTCAGAGC  | CTCCTGCATA |
| GTAATGGATA  | CAAC TATTTG | GATTGGTACC | TGCAGAAGCC  | AGGGCAGTCT |
| CCACAGCTCC  | TGATCTATTT  | GGGTTCTAAT | CGGGCCTCCG  | GGGTCCCTGA |
| CAGGTTTCAGT | GGCAGTGGAT  | CAGGCACAGA | TTTTTACACTG | AAAATCAGCA |
| GAGTGGAGGC  | TGAGGATGTT  | GGGGTTTATT | ACTGCATGCA  | AGCTCTACAA |
| ACCCCTCTCA  | CTTTCGGCCC  | TGGGACCAAA | GTGGATATCA  | AA         |

**Fig. 1 (cont)****L6 (SEQ ID NO:11)**

|             |             |            |            |            |
|-------------|-------------|------------|------------|------------|
| GAT         | GTTGTGATGA  | CTCAGTCTCC | ACTCTCCCTG | GCCGTCACCC |
| CTGGAGAGCC  | GGCCTCCATC  | TCCTGCAGGT | CTAGTCAGAG | CCTCCTGCAT |
| AGTAATGGAT  | ACAAC TATTT | GGATTGGTAC | CTGCAGAAGC | CAGGGCAGTC |
| TCCACAGCTC  | CTGATCTATT  | TGGGTTCTAA | TCGGGCCTCC | GGGGTCCCTG |
| ACAGGTTTCAG | TGGCAGTGGA  | TCAGGCACAG | ATTTTACACT | GAAAATCAGC |
| AGAGTGGAGG  | CTGAGGATGT  | TGGGGTTTAT | TACTGCATGC | AAGCTCTACA |
| AACTCCGCTC  | ACTTTCGGCG  | GAGGGACCAA | GGTGGAGATC | AAA        |

**L7 (SEQ ID NO:13)**

|             |             |            |            |            |
|-------------|-------------|------------|------------|------------|
| GAT         | GTTGTGATGA  | CTCAGTCTCC | ACTCTCCCTG | CCCGTCACCC |
| CTGGAGAGCC  | GGCCTCCATC  | TCCTGCAGGT | CTAGTCAGAG | CCTCCTGCAT |
| AGTAATGGAT  | ACAAC TATTT | GGATTGGTAC | CTGCAGAAGC | CAGGGCAGTC |
| TCCACAGCTC  | CTGATCTATT  | TGGGTTCTAA | TCGGGCCTCC | GGGGTCCCTG |
| ACAGGTTTCAG | TGGCAGTGGA  | TCAGGCACAG | ATTTTACACT | GAAAATCAGC |
| AGAGTGGAGG  | CTGAGGATGT  | TGGGGTTTAT | TACTGCATGC | AAGCTCTACA |
| AACTCCTCTC  | ACTTTCGGCG  | GAGGGACCAA | GGTGGAGATC | AAA        |

**L8 (SEQ ID NO:15)**

|            |            |            |             |            |
|------------|------------|------------|-------------|------------|
| GATGTTGTG  | ATGACTCAGT | CTCCACTCTC | CCTGCCCCGTC | ACCCCTGGAG |
| AGCCGGCCTC | CATCTCCTGC | AGGTCTAGTC | AGAGCCTCCT  | GCATAGTAAT |
| GGATACAACT | ATTTGGATTG | GTACCTGCAG | AAGCCAGGGC  | AGTCTCCACA |
| GCTCCTGATC | TATTTGGGTT | CTAATCGGGC | CTCCGGGGTC  | CCTGACAGGT |
| TCAGTGGCAG | TGGATCAGGC | ACAGATTTTA | CACTGAAAAT  | CAGCAGAGTG |
| GAGGCTGAAG | ATGTTGGGGT | TTATTACTGT | ATGCAAGCTC  | TACAAACCCC |
| CCTCACTTTC | GGCGGAGGGA | CCAAGGTGGA | GATCAAA     |            |

**L9 (SEQ ID NO:17)**

|             |            |            |             |            |
|-------------|------------|------------|-------------|------------|
| GATG        | TTGTGATGAC | TCAGTCTCCA | CTCTCCCTGC  | CCGTCACCCC |
| TGGAGAGCCG  | GCCTCCATCT | CCTGCAGGTC | TAGTCAGAGC  | CTCCTGCATA |
| GTAATGGATA  | CAACTATTTG | GATTGGTACC | TGCAGAAGCC  | AGGGCAGTCT |
| CCACAGCTCC  | TGATCTATTT | GGGTTCTAAT | CGGGCCTCCG  | GGGTCCCTGA |
| CAGGTTTCAGT | GGCAGTGAT  | CAGGCACAGA | TTTTTACACTG | AAAATCAGCA |
| GAGTGGAGGC  | TGAGGATGTT | GGGGTTTATT | ACTGCATGCA  | AGCTCTACAA |
| ACTCCGTTCA  | CCTTCGGCCA | AGGGACACGA | CTGGAGATTA  | AA         |

**L10 (SEQ ID NO:19)**

|             |            |            |             |            |
|-------------|------------|------------|-------------|------------|
| GATGTTGTGA  | TGACTCAGTC | TCCACTCTCC | CTGCCCCGTCA | CCCCTGGAGA |
| GCCGGCCTCC  | ATCTCCTGCA | GGTCTAGTCA | GAGCCTCCTG  | CATAGTAATG |
| GATACAACTA  | TTTGGATTGG | TACCTGCAGA | AGCCAGGGCA  | GTCTCCACAG |
| CTCCTGATCT  | ATTTGGGTTT | TAATCGGGCC | TCCGGGGTCC  | CTGACAGGTT |
| CAGTGGCAGT  | GGATCAGGCA | CAGATTTTAC | ACTGAAAATC  | AGCAGAGTGG |
| AGGCTGAGGA  | TGTTGGGGTT | TATTACTGCA | TGCAAGCTCT  | ACAAACTCCT |
| CTGGCGTTTCG | GCCAAGGGAC | CAAGGTGGAA | ATCAAA      |            |

**Fig. 1 (cont)****L11 (SEQ ID NO:21)**

GAAATTGT GCTGACTCAG TCTCCACTCT CCCTGCCCCGT CACCCCTGGA  
 GAGCCGGCCT CCATCTCCTG CAGGTCTAGT CAGAGCCTCC TGCATAGTAA  
 TGGATACAAC TATTTGAATT GGTACCTGCA GAAGCCAGGG CAGTCTCCAC  
 AGCTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG  
 TTCAGTGCCA GTGGATCAGG CACAGATTTT ACACTGAAAA TCAGCAGAGT  
 GGAGGCTGAG GATGTTGGGG TTTATTACTG CATGCAAGCT CTACAAACTC  
 CTATCACCTT CGGCCAAGGG ACACGACTGG AGATTAAA

**L12 (SEQ ID NO:23)**

AATT TTATGCTGAC TCAGCCCCAC TCTGTGTCGG AGTCTCCGGG  
 GAAGACGGTA ACCATCTCCT GCACCCGCAG CAGTGGCAGC ATTGCCAGCA  
 ACTATGTGCA GTGGTACCAG CAGCGCCCGG GCAGTTCCCC CACCACTGTG  
 ATCTATGAGG ATAACCAAAG ACCCTCTGGG GTCCCTGATC GGTTCTCTGG  
 CTCCATCGAC AGCTCCTCCA ACTCTGCCTC CCTCACCATC TCTGGACTGA  
 AGACTGAGGA CGAGGCTGAC TACTACTGTC AGTCTTATGA TAGCAGCAAT  
 CAGAGAGTGT TCGGCGGAGG GACCAAGCTG ACCGTCCTA

**L13 (SEQ ID NO:25)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC  
 CTGGAGAGCC GGCCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT  
 AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC  
 TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG  
 ACAGGTTTCA TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC  
 AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
 AACCCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L14 (SEQ ID NO:27)**

G ATGTTGTGAT GACTCAGTCT CCACTCTCCC TGCCCGTCAC  
 CCCTGGAGAG CCGGCCTCCA TCTCCTGCAG GTCTAGTCAG AGCCTCCTGC  
 ATAGTAATGG ATACAACTAT TTGGATTGGT ACCTGCAGAA GCCAGGGCAG  
 TCTCCACAGC TCCTGATCTA TTTGGGTTCT AATCGGGCCT CCGGGGTCCC  
 TGACAGGTTT AGTGGCAGTG GATCAGGCAC AGATTTTACA CTGAAAATCA  
 GCAGAGTGGA GGCTGAGGAT GTTGGGGTTT ATTACTGCAT GCAAGCTCTA  
 CAAACTCCTC TTACTTTCGG CGGAGGGACC AAGGTGGAGA TCAAA

**L15 (SEQ ID NO:29)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
 AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
 GGATACAAC ATTTGGATTG GTACCTGCAA AAGCCAGGGC AGTCTCCACA  
 GCTCCTGATC TATTTGGGTT CTTATCGGGC CTCCGGGGTC CCTGACAGGT  
 TCAGTGCCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
 GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGCTC TACAAACTCC  
 GATCACCTTC GGCCAAGGGA CACGACTGGA GATTAAA

**Fig. 1 (cont)****L16 (SEQ ID NO:31)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
GGATACAAC TTTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT  
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGGGTG  
GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGGTA CACACTGGCC  
TCTGACGTTT GGCCAAGGGA CCAAGGTGGA GATCAAA

**L17 (SEQ ID NO:33)**

GAAATTG TGATGACGCA GTCTCCACTC TCCCTGCCCCG TCACCCCTGG  
AGAGCCGGCC TCCATCTCCT GCAGGTCTAG TCAGAGCCTC CTGCATAGTA  
ATGGATACAA CTATTTGGAT TGGTACCTGC AGAAGCCAGG GCAGTCTCCA  
CAGCTCCTGA TCTATTTGGG TTCTAATCGG GCCTCCGGGG TCCCTGACAG  
GTTCACTGGC AGTGGATCAG GCACAGATTT TACACTGAAA ATCAGCAGAG  
TGGAGGCTGA GGATGTTGGG GTTTATTACT GCATGCAAGC TCTACAACT  
CCTCTCACTT TCGGCGGAGG GACCAAGGTG GAGATCAAA

**L18 (SEQ ID NO:35)**

GAC ATCCAGTTGA CCCAGTCTCC ATCTTCCGTG TCTGCGTCTG  
TCGGAGACAG AGTCACCATC ACTTGTCGGG CGAGTCAGGG TATTAGCAGG  
TGGTTAGCCT GGTATCAACA GAAACCAGGG AAAGCCCCTA GACTCCTGAT  
CTATGCTGCG TCCGGTTTAC AAAGTGGGGT CCCATCAAGG TTCAGCGGCA  
GTGGATCTGG GACAGATTTT ACTCTCACCA TCAGCAACCT GCAGCCTGAA  
GATTTTGCAA CTTACTATTG TCAACAGGCT AGCAGTTTTT CAATCACCTT  
CGGCCAAGGG ACACGACTGG AGACTAAA

**L19 (SEQ ID NO:37)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC  
CTGGAGAGCC GGCCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT  
AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC  
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG  
ACAGGTTTCA TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC  
AGAGTGGAGG CTGAGGATGT TGGAGTTTAT TACTGCATGC AAGCTCTACA  
AACTCCGTAC ACTTTTGGCC AGGGGACCAA GCTGGAGATC AAA

**L20 (SEQ ID NO:39)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
GGATACAAC TTTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTAACAGGT  
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGCTC TACAACTCC  
ATTCACCTTC GGCCCTGGGA CCAAGTGGGA TATCAAA

Fig. 1 (cont)

**L21 (SEQ ID NO:41)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTCAT  
GGATACAAC ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
ACTTCTGATC TATTTGGGTT CTTATCGGGC CTCCGGGGTC CCTGACAGGT  
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAATCTC TAGAAGTTCC  
GTTCACTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA

**L22 (SEQ ID NO:43)**

TCT TCTGAGCTGA CTCAGGACCC TGCTGTGTCT GTGGCCTTGG  
GACAGACAGT CAGGATCACA TGCCAAGGAG ACAGCCTCAG AATTTATTAT  
ACAGGCTGGT ACCAACAGAA GCCAGGACAG GCCCCTGTGC TTGTCCTCTT  
TGGTAAGAAC AATCGGCCCT CAGGGATCCC AGACCGATTC TCTGGCTCCC  
ACTCAGGGAA CACAGCTTCC TTGACCATCA CTGGGGCTCA AGCGGAAGAT  
GAGGCTGACT ATTACTGTAA CTCCCGGGAC ATCACTGGTG TCCATCGATT  
CGGCGGAGGG ACCAAGCTGA CCGTCCTA

**L23 (SEQ ID NO:45)**

GAA ATTGTGCTGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC  
CTGGAGAGCC GGCCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT  
AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC  
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG  
ACAGGTTTCA TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC  
AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AACTCCTCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L24 (SEQ ID NO:47)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC  
CTGGAGAGCC GGCCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT  
AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC  
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG  
ACAGGTTTCA TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC  
AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
AACTCCTAAC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L25 (SEQ ID NO:49)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
GGATACAAC ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT  
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGCTC TACAACTCC  
AATCACTTTC GGCCCTGGGA CCAAAGTGGA TATCAAA

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**Fig. 1 (cont)****L26 (SEQ ID NO:51)**

GATGTTGT GATGACTCAG TCTCCACTCT CCCTGCCCCGT CACCCCTGGA  
 GAGCCGGCCT CCATCTCCTG CAGGTCTAGT CAGAGCCTCC TGCATAGTAA  
 TGGATACACC TATTTGGATT GGTACCTGCA GAAGCCAGGG CAGTCTCCAC  
 AACTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG  
 TTCAGCGGCA GTGGATCAGG CACAGATTTT ACACTGAAAA TCAGCAGAGT  
 GGAGCCTGAG GATGTTGGGG TCTATTACTG CATGCAAGCT CTAGAAATGC  
 CCCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

**L27 (SEQ ID NO:53)**

GAC ATCCAGTTGA CCCAGTCTCC ATCCTTCCTG TCTGCATCTG  
 TAGGAGACAG AGTCACCATC ACTTGCCGGG CCAGTCAGGG CATTAGCAGT  
 TATTTAGCCT GGTATCAGCA AAAACCAGGG AAAGCCCCTA AGCTCCTGAT  
 CTATGCTGCA TCCACTTTGC AAAGTGGGGT CCCATCAAGG TTCAGCGGCA  
 GTGGATCTGG GACAGAATTC ACTCTCACAA TCAGCAGCCT GCAGCCTGAA  
 GATTTTGCAA CTTATTACTG TCAACAGCTT AATAGTTACC CCCTCACTTT  
 CGGCGGAGGG ACCAAGGTGG AGATCAAA

**L28 (SEQ ID NO:55)**

TC CTATGTGCTG ACTCAGCCAC CCTCAGTGTC CGTGTCCCCA  
 GGACAGACAG CCAGCATCAC CTGCTCTGGA GATAAATTGG GGGATAAATA  
 TGTGCTGCTG TATCAGCAAA AGGCAGGCCA AGCCCCTGTT TTGGTCATCT  
 ATCAAGACAA CAAGCGACCC TCAGGGATCC CTGAGCGATT CTCTGGCTCC  
 AACTCTGGGA ACACAGCCAG TCTGACCATC AGCGGGACCC AGGCTATGGA  
 TGAGGCTGAC TATTACTGTC AGGCGTGGGA CAGCGGCACG GTGTTGCGCG  
 GAGGGACCAA GCTGACCGTC CTA

**L29 (SEQ ID NO:57)**

GATG TTGTGATGAC TCAGTCTCCA CTCTCCCTGC CCGTCACCCC  
 TGGAGAGCCG GCCTCCATCT CCTGCAGGTC TAGTCAGAGC CTCCTGCATA  
 GTAATGGATA CAACTATTG GATTGGTACC TGCAGAAGCC AGGGCAGTCT  
 CCACAGCTCC TGATCTATTT GGGTTCTAAT CGGGCCTCCG GGGTCCCTGA  
 CAGGTTTCACT GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA  
 GAGTGGAGGC TGAGGATGTT GGGGTTTATT ACTGCATGCA AGCTCTACAA  
 ACCCCCCTCA CTTTCGGCGG AGGGACCAAG GTGGAGATCA AA

**L30 (SEQ ID NO:59)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGT ACCCCTGGAG  
 AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
 GGATACAACCT ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
 GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT  
 TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
 GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGGAAGCTC TACAACTCC  
 ATTCACTTTC GGCCCTGGGA CCAAGGTGGA AATCAAA

**Fig. 1 (cont)****L31 (SEQ ID NO:61)**

GACATC CAGTTGACCC AGTCTCCATC CTCCCTGTCT GCGTCTGTGG  
 GAGACAGAGT CACCATCACT TGCCGGTCAA GTCAAGGCAT TGGTTACTTC  
 TTAAATTGGT ATCAGCAGGA ACCAGGGGAAA GCCCCAAAGA TCCTGATCTC  
 TGCTGCATCC ACTTTGCAAA GTGGGGTCCC ATCAAGGTTC AGTGGCAGTG  
 GATCTGGGAC AGATTTCACA CTCTCCATCA ACAATCTGCA ACCCGCAGAT  
 TTTGCGACAT ACTACTGTCA ACAGAGTCAC AGTCCCCCGT ACACTTTCGG  
 CCAGGGGACC AAGGTGGAGA TCAAA

**L32 (SEQ ID NO:63)**

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC  
 CTGGAGAGCC GGCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT  
 AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC  
 TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG  
 ACAGGTTTCA TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAATCAGC  
 AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA  
 AACTCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

**L33 (SEQ ID NO:65)**

GAAATTGTG CTGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
 AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
 GGATACAAC ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
 GCTCCTGATG TATTTGGTTT CTAATCGGGC CTCCGGGGTC CCTGAGAGGT  
 TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
 GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAACTC TACAAACTCC  
 TCTCAGTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA

**L34 (SEQ ID NO:67)**

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG  
 AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT  
 GGATACAAC ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA  
 GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT  
 TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG  
 GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGCTC TACAAACTCC  
 GCTCACTTTC GGCGGAGGGA CCAAGGTGGA GATCAAA

**L35 (SEQ ID NO:69)**

AATTTTATG CTGACTCAGC CCCACTCTGT GTCGGCGTCT CCGGGGAAGA  
 CGGTTACCAT CTCCTGCACC CGCAGCAGTG GCGACATTGA CAACAACAT  
 GTGCAGTGGT ACCAGCAGCG CCCGGGCAAT TCCCCACCA ATGTGATTTA  
 TGAGGATAAC CGAAGACCCT CTGGGGTCCC GGATCGCTTC TCTGGCTCCA  
 TCGACAGCTC CTCCAACCTC GCCTCCCTCA CCATCTCTGG ACTGCAGCCT  
 GAGGACGAGG CTGACTACTA TTGTCACTCT TATCAAAGCG ACAATTGGGT  
 GTTCGGCGGA GGGACCAAGG TGACCGTCCT A

**Fig. 1 (cont)****L36 (SEQ ID NO:71)**

AATTTTATG CTGACTCAGC CCCACTCTGT GTCGGAGTCT CCGGGGAAGA  
 CGGTAACCAT CTCCTGCACC CGCAGCAGTG GCAGCATTGC CAGCAACTAT  
 GTGCAGTGGT ACCAGCAGCG CCCGGGCAGT TCCCCACCA CTGTGATCTA  
 TGAGGATAAC CAAAGACCCT CTGGGGTCCC TGATCGATTG TCTGGCTCCA  
 TCGACAGCTC CTCCAACCTCT GCCTCCCTCA CCATCTCTGG ACTGAAGACT  
 GAGGACGAGG CTGACTACTA CTGTCAGTCT TATGATAGCA GCAATGTGGT  
 GTTCGGCGGA GGGACCAAGC TGACCGTCCT A

**L37 (SEQ ID NO:73)**

GATGTTGTGA TGACTCAGTC TCCACTCTCC CTGCCCCGTCA CCCCTGGGGA  
 GCCGGCCTCC ATCTCCTGCA GGTCTAGTCA GAGCCTCCTG CATAGTAATG  
 GATACAATA TTTGGATTGG TACCTGCAGA AGCCAGGGCA GTCTCCACAG  
 CTCCTGATCT ATTTGGGTTC TAACCGGGAC TCTGGGGTCC CAGACAGATT  
 CAGCGGCAGT GGGTCAGGCA CTGATTTTAC ACTGAAAATC AGCAGGGTGG  
 AGGCTGAGGA TGTGGGGTT TATTACTGCA TGCAAGGTAC AACTGGCCG  
 TACACTTTTG GCCAGGGGAC CAGGCTGGAG ATCAAA

**L38 (SEQ ID NO:75)**

GATGTTGT GATGACTCAG TCTCCACTCT CCCTGCCCCGT CACCCCTGGA  
 GAGTCGGCCT CCATCTCCTG CAGGTCTAGT CAGAGCCTCC TGCATAGTAA  
 TGGATACAAC TTTTGGATT GGTACCTGCA GAAGCCAGGG CAGTCTCCAC  
 AGCTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG  
 TTCAGTGGCA GTGGATCAGG CACAGATTTT AACTGAAAA TCAGCAGAGT  
 GGAGGCTGAG GATGTTGGGG TTTATTACTG CATGCAAGCT CTACAACTC  
 CTCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

**L39 (SEQ ID NO:77)**

GA TGTGTGATG ACTCAGTCTC CACTCTCCCT GCCCGTCACC  
 CCTGGAGAGC CGGCCTCCAT CTCCTGCAGG TCTAGTCAGA GCCTCCTGCA  
 TAGTAATGGA TACAACCTATT TGGATTGGTA CCTGCAGAAG CCAGGGCAGT  
 CTCCACAGCT CCTGATCTAT TTGGGTCTA ATCGGGCCTC CGGGGTCCCT  
 GACAGGTTCA GTGGCAGTGG ATCAGGCACA GATTTTACAC TGAAAATCAG  
 CAGAGTGGAG GCTGAGGATG TTGGGGTTTA TTAGTGCATG CAAGCTCTAC  
 AAACCCCCCT CACTTTCGGC GGAGGGACCA AGGTGGAGAT CAAA

**L40 (SEQ ID NO:79)**

GAAACGAC ACTCACGCAG TCTCCAGCCA CCCTGTCTTT GTCTCCAGGG  
 CAAAGAGCCA CCCTCTCCTG CAGGGCCAGT CAGAGTGTCT ACAACTACTT  
 AGCCTGGTAC CAACAGAAGC CTGGCCAGGC TCCCAGGCTC CTCATCTATG  
 ATGCATCCAG AAGGGCAACT GGCATCCCAG CCAGGTTTCTG TGGCAGTGGG  
 TCTGGGACAG ACTTCACTCT CACCATCAGC AGCCTAGAGC CTGAAGATTT  
 TGCAGTTTAT TACTGTCAGC AGCGTAACAA CTGGCCGCTC ACTTTCGGTG  
 GAGGGACCAA GGTGGAGATC AAA

**Fig. 1 (cont)****L41 (SEQ ID NO:81)**

|            |            |            |            |             |
|------------|------------|------------|------------|-------------|
| GACAT      | CCAGTTGACC | CAGTCTCCAT | CCTCCCTGTC | TGCTTCTGTT  |
| GGAGACAGCG | TCACCATCTC | TTGCCGGGCA | AGTCAGAGTC | CTGGCATCTT  |
| TTTAAATTGG | TATCAGCAGA | TACCAGGGAA | AGCCCCATAA | CTCCTGATCT  |
| ACGCTACATC | CACTCTGGAA | AGTGGGGTCC | CCCCCAGGTT | CACCGGCAGT  |
| GGATCTGGGA | CAGATTTTAC | TCTCACCATC | AGCAGTCTGC | AACCTGAGGA  |
| CTTTGCAACT | TACTACTGTC | AACAGAGTAA | CAGTGTTCCG | CTCACTTTTCG |
| GCGGCGGGAC | CAAGGTGGAG | ATCAAA     |            |             |

**L42 (SEQ ID NO:83)**

|            |            |            |            |            |
|------------|------------|------------|------------|------------|
| GATGT      | TGTGATGACT | CAGTCTCCAC | TCTCCCTGCC | CGTCACCCCT |
| GGAGAGCCGG | CCTCCATCTC | CTGCAGGTCT | AGTCAGAGCC | TCCTGCATAG |
| TAATGGATAC | AACTATTTGG | ATTGGTACCT | GCAGAAGCCA | GGGCAGTCTC |
| CACAGCTCCT | GATCTATTTG | GGTTCTAATC | GGGCCTCCGG | GGTCCCTGAC |
| AGGTTCACTG | GCAGTGGATC | AGGCACAGAT | TTTACACTAA | AAATCAGCAG |
| AGTGGAGGCT | GAGGATGTTG | GGGTTTATTA | CTGCATGCAA | GCTCTACAAA |
| CTCCTCTAAC | CTTCGGCCAA | GGGACACGAC | TGGAGATTAA | A          |

**L43 (SEQ ID NO:85)**

|            |            |            |            |             |
|------------|------------|------------|------------|-------------|
| GAAATT     | GTGATGACGC | AGTCTCCAGC | CACCCTGTCT | GTGTCTCCAG  |
| GGGAAAGAGC | CACCTTCTCC | TGTAGGGCCA | GTCAGAGTGT | TGGCAGCAAC  |
| TTAGCCTGGT | ACCAGCAGAA | ACCTGGCCAG | GCTCCCAGGC | TCCTCATCTA  |
| TGATGCATCC | AACAGGGCCA | CTGGCATCCC | AGCCAGGTTT | AGTGGCAGTG  |
| GGTCTGGGAC | AGACTTCACT | CTCACCATCA | GCAGACTGGA | GCCTGAAGAT  |
| TTTGCAGTGT | ATTACTGTCA | GCAGCGTAGC | AACTGGCCCC | TCACTTTTCGG |
| CGGAGGGACC | AAGGTGGAGA | TCAAA      |            |             |

**L44 (SEQ ID NO:87)**

|            |            |            |            |            |
|------------|------------|------------|------------|------------|
| GATGT      | TGTGATGACT | CAGTCTCCAC | TCTCCCTGCC | CGTCACCCCT |
| GGAGAGCCGG | CCTCCATCTC | CTGCAGGTCT | AGTCAGAGCC | TCCTGCATAG |
| TAATGGATAC | AACTATTTGG | ATTGGTACCT | GCAGAAGCCA | GGGCAGTCTC |
| CACAGCTCCT | GATCTATTTG | GGTTCTAATC | GGGCCTCCGG | GGTCCCTGAC |
| AGGTTCACTG | GCAGTGGATC | AGGCACAGAT | TTTACACTGA | AAATCAGCAG |
| AGTGGAGGCT | GAGGATGTTG | GGGTTTATTA | CTGCATGCAA | GCTCTACAAA |
| CTCCGCTCAC | TTTCGGCGGA | GGGACCAAGG | TGGAGATCAA | A          |

**L45 (SEQ ID NO:89)**

|            |            |            |            |            |
|------------|------------|------------|------------|------------|
| GAT        | GTTGTGATGA | CTCAGTCTCC | ACTCTCCCTG | CCCGTCACCC |
| CTGGAGAGCC | GGCCTCCATC | TCCTGCAGGT | CTAGTCAGAG | CCTCCTGCAT |
| AGTAATGGAT | ACAACATTTT | GGATTGGTAC | CTGCAGAAGC | CAGGGCAGTC |
| TCCACAGCTC | CTGATCTACT | TGGGTTCTAC | TCGGGCCTCC | GGCGTCCCTG |
| ACAGGTTTCA | TGGCAGTGGA | TCAGGCACAG | ATTTTACACT | GAAAATCAGC |
| AGAGTGGAGG | CTGAGGATGT | TGGGGTTTAT | TACTGCATGC | AAGCTCTACA |
| AACTCCTTAC | ACTTTCGGCG | GAGGGACCAA | GGTGGAGATC | AAA        |

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**Fig. 1 (cont)****L46 (SEQ ID NO:91)**

```
GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT
GGAGAGCCGG CCTCCATCTC CTGCAGGTCT AGTCAGAGCC TCCTGCATAG
TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA GGGCAGTCTC
CACAGCTCCT GATCTATTTG GGTTCCTAATC GGGCCTCCGG GGTCCCTGAC
AGGTTTCAGTG GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG
AGTGGAGGCT GAGGATGTTG GGGTTTATTA CTGCATGCAA GCTCTACAAA
CTCCCCTCAC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A
```

**L47 (SEQ ID NO:93)**

```
GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT
GGAGAGCCGG CCTCCATCTC CTGCAGGTCT AGTCAGAGCC TCCTGCATAC
TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA GGGCAGTCTC
CACGGCTCCT GATCTATTTG GGTTTTAAATC GGGCCTCCGG GGTCCCTGAC
AGGTTTCAGTG GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG
AGTGGAGGCT GAGGATGTTG GGGTTTATTA CTGTATGCAA GGTCTACAAA
CTCCCCTCAC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A
```

**L48 (SEQ ID NO:95)**

```
GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAAC ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA
GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGGGTG
GAGGCTGAGG ATGTTGGGGT TTATTATTGC ATGCAAGCTA CACACTGGCC
GTACACTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA
```

**L49 (SEQ ID NO:97)**

```
AATTTTA TGCTGACTCA GCCCCACTCT GTGTCGGAGT CTCCGGGGAA
GACGGTAAGC ATCTCCTGCA CCCGCAACAG TGGCAGCATT GCCAGCAACT
TTGTGCAGTG GTACCAGCAG CGCCCGGGCA GTGCCCCCAG CATTGTAATC
TATGAGGATA ACCAAAGACC CTCTGCGGTC CCTACTCGGT TCTCTGGCTC
CATCGACAGG TCCTCCAACCT CTGCCTCCCT CACCATCTCT GGA CTGACGA
CTGAGGACGA GGCTGACTAC TACTGTCAGT CTTATGATAG CGCCAATGTC
ATTTTCGGCG GGGGGACCAA GCTGACCGTC CTA
```

**L50 (SEQ ID NO:99)**

```
GAAACG AACTCACGC AGTCTCCAGG CACCCTGTCT TTGTCTCCAG
GGGAGAGAGC CACCCTCTCC TGCAGGGCCA GTCAGACTAT CAGCAGCAGC
CACTTAGCCT GGTACCAGCA GAAACCTGGC CAGTCTCCCA GGCTCCTCAT
CTATGGTGCG GGCTACAGGG CCACCGGCAT TCCAGACAGG TTCAGTGGCA
GTGGGTCTGG CACAGACTTC ACTCTACCA TCAGCAGACT GGAGCCTGAA
GATTTTGCAG TGTATTACTG TCAGCACTAT GGTAGTTCAC TCCGGACGTT
CGGCCAAGGG ACCAAGGTGG AAATCAAA
```

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**Fig. 1 (cont)****L51 (SEQ ID NO:101)**

AATTTT ATGCTGACTC AGCCCCACTC TGTGTCGGAG TCTCCGGGGA  
 AGACGGTAAC CATCTCCTGC ACCGGCAGCG GTGGCAACAT TGCCAGCAAT  
 TATGTGCAGT GGTACCAGCA GCGCCCGGGC AGGGCCCCCA CCACTGTGAT  
 CTATGAGGAT AATCGAAGAC CCTCTGGGGT CCCTGATCGG TTCTCTGGCT  
 CCATCGACAG CTCTTCCAAC TCTGCCTCCC TCACCATCTC TGGACTGAAG  
 ACTGAAGACG AGGCTGACTA CTACTGTCAG TCTTATGATC CCTACAATCG  
 AGTGTTCCGC GGAGGGACCA AGCTGACCGT CCTA

**L51 (SEQ ID NO:103)**

GAAA TTGTGATGAC GCAGTCTCCA CTCTCCCTGC CCGTCACCCC  
 TGGAGAGCCG GCCTCCATCT CCTGCAGGTC TAGTCAGAGC CTCCTGCATA  
 CTAATGGATA CGACTATTTG GATTGGTACC TGCAGAAGCC AGGGCAGTCT  
 CCACAGCTTC TGATCTATTT GGGTTCTACT CGGGCCTCCG GGGTCCCTGA  
 CAGGTTGAGT GGCAGTGGAT CGGGCACAGA TTTTACACTG AAAATCAGCA  
 GAGTGGAGGC TGAGGATGTT GGGGTTTATT ACTGCATGCA AGCTTTTCAA  
 ACTCCGCTCA CTTTCGGCGG AGGGACCAAG ATGGAGATCA AA

**H1 (SEQ ID NO:105)**

GAGGTGCAGC TGGTGGAGAC CGGCCCAGGA CTGGTGAAGC CTTCCGGGGAC  
 CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
 GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
 GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
 AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
 GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGATTTAAT  
 TACTATGATA GTAGTGTCTG GGGCCAGGGA ACCCTGGTCA CCGTCTCAAG  
 C

**H2 (SEQ ID NO:107)**

GAGGTGCAGC TGGTGGAGAC CGGCCCAGGA CTGGTGAAGC CTTCCGGGGAC  
 CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
 GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
 GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
 AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
 GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGAGGGGTT  
 GAGCAGATTG ACTACTGGGG CCAGGGAACC CTGGTCACCG TCTCAAGC

**H3 (SEQ ID NO:109)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCCGGGGAC  
 CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
 GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
 GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
 AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
 GCTCTGTGAC TGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAAAAATTTA  
 GCAGCAGGGG CGGTTGCCTA CTGGGGCCAG GGCACCCTGG TCACCGTCTC  
 AAGC

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**Fig. 1 (cont)****H4 (SEQ ID NO:111)**

CAGGTGCAG CTACAGCAGT GGGGCGCAGG ACTGTTGAAG CCTTCGGAGA  
CCCTGTCCCT CACCTGCGCT GTCTCTGGTG GGTCTTCAG TGGTTACTAC  
TGGAGCTGGA TCCGTCAGCC CCCAGGGAAG GGGCTGGAGT GGATTGGGGA  
AATCAATCAT AGTGGAAGTA CCAACTACAA CCGGTCCCTC AAGAGTCGAG  
TCACCATATC AGTAGACACG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC  
TCTGTGACCG CCGCGGACAC GGCTGTGTAT TACTGTGCGA GACTTTCATA  
TGGTTCGGGC GTTGACTACT GGGGCCAGGG CACCCTGGTC ACCGTCTCAA  
GC

**H5 (SEQ ID NO:113)**

C AGCTGCAGCT GCAGGAGTCG GGGCCAGGAC TGGTGAAGCC  
TTCACAGACC CTGTCCCTCA CCTGCACTGT CTCTGGTGGC TCCATCAGCA  
GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA GGGGCTGGAG  
TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT  
CAAGAGTCGA GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC  
TGAAGCTGAG CTCTGTGACC GCCGCGGACA CGGCCGTGTA TTAAGTGCGG  
AGGTATAGCA GCAGCCGCAA TGATGCTTTT GATATCTGGG GCCAAGGGAC  
AATGGTCACC GTCTCAAGC

**H6 (SEQ ID NO:115)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTGCGGGAC  
CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCAGGGA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGAGATGGG  
CAGCTGGATG CTTTTGATAT CTGGGGCCAA GGGACAATGG TCACCGTCTC  
AAGC

**H7 (SEQ ID NO:117)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTGCGGGAC  
CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCAGGGA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGATTTTGG  
GACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG TCACCGTCTC  
AAGC

**Fig. 1 (cont)****H8 (SEQ ID NO:119)**

CAGGTG CAGCTACAGC AGTGGGGCCC AGGACTGGTG AAGCCTTCGG  
 GGACCCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
 AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGAAGGGGC TGGAGTGGAT  
 TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCGAGA  
 GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
 CTGAGCTCTG TGACCGCCGC AGACACGGCC GTGTATTACT GTGCGAGAGA  
 TCGGTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT  
 CAAGC

**H9 (SEQ ID NO:121)**

G AGGTGCAGCT GGTCGAGTCT GGCCCAGGAC TGGTGAAGCC  
 TTCGGGGACC CTGTCCCTCA CCTGCGCTGT CTCTGGTGGC TCCATCAGCA  
 GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA GGGGCTGGAG  
 TGGATTGGGT ACATCTATTA TAGTGGGAGC ACCTACTACA ACCCGTCCCT  
 CAAGAGTCGA GTCACCATGT CAGTAGACAC GTCCAAGAAC CAGTTCTCCC  
 TGAAGCTGAG CTCTGTGACC GCCGCAGACA CGGCCGTGTA TTA CTGTGCG  
 AGATGGAGCT ACTTGGATGC TTTTGATATC TGGGGCCAAG GGACAATGGT  
 CACCGTCTCA AGC

**H10 (SEQ ID NO:123)**

GAGGTGC AGCTGGTGGA GTCTGGCCCA GGA CTGGTGA AGCCTTCGGG  
 GACCCTGTCC CTCACCTGCG CTGTCTCTGG TGGCTCCATC AGCAGTAGTA  
 ACTGGTGGAG TTGGGTCCGC CAGCCCCCAG GGAAGGGGCT GGAGTGGATT  
 GGGGAAATCT ATCATAGTGG GAGCACCAAC TACAACCCGT CCCTCAAGAG  
 TCGAGTCACC ATATCAGTAG ACAAGTCCAA GAACCAGTTC TCCCTGAAGC  
 TGAGCTCTGT GACCGCCGCG GACACGGCCG TGTATTACTG TGCGAGAGAT  
 TACGATATTT TCGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT  
 CTCAAGC

**H11 (SEQ ID NO:125)**

CAGCT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG  
 GGGACCCTGT CCCTCACCTG CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG  
 TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG CTGGAGTGGG  
 TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG  
 AGTCGAGTCA CCATATCAGT AGACAAGTCC AAGAACCAGT CCTCCCTGAA  
 GCTGAGCTCT GTGACCGCCG CGGACACGGC CGTGTATTAC TGTGCGAGAG  
 CCAACAGAGA TGATGCTTTT GATATCTGGG GCCAAGGGAC AATGGTCACC  
 GTCTCAAGC

**Fig. 1 (cont)****H12 (SEQ ID NO:127)**

GAGGTGC AGCTGGTGGA GTCTGGGGGA GGCTTGGTAC AGCCGGGGGG  
GTCCCTGAGA CTCTCCTGTG CAGCCTCTGG ATTCACCTTT AGCAGCTATG  
CCATGAGCTG GGTCCGCCAG GCTCCAGGGA AGGGGCTGGA GTGGGTCTCA  
GCTATTAGTG GTAGTGGTGG TAGCACATAC TACGCAGACT CCGTGAAGGG  
CCGGTTCACC ATCTCCAGAG ACAATTCCAA GAACACGCTG TATCTGCAAA  
TGAACAGTCT GAGCGCCGAC GACACGGCCG TATATTTCTG TGCGTCGGGT  
GGCTGGTACG GGGACTACTT TGACTACTGG GGCCAGGGAA CCCTGGTCAC  
CGTCTCAAGC

**H13 (SEQ ID NO:129)**

CAGGTGCAGC TGCAGGAGTC CGGCCCAGGA CTGGTGAAGC CTTCGGAGAC  
CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGAGAAGGG  
AACCGAACGG TGACTIONAGTGC TTTTGATATC TGGGGCCAAG GGACAATGGT  
CACCGTCTCA AGC

**H14 (SEQ ID NO:131)**

CAGGTGCA GCTGCAGGAG TCCGGCCCAG GACTGGTGAA GCCTTCGGGG  
ACCCTGTCCC TCACCTGCGC TGTCTCTGGT GGCTCCATCA GCAGTAGTAA  
CTGGTGGAGT TGGGTCCGCC AGCCCCCAGG GAAGGGGCTG GAGTGGATTG  
GGGAAATCTA TCATAGTGGG AGCACCAACT ACAACCCGTC CCTCAAGAGT  
CGAGTCACCA TATCAGTAGA CAAGTCCAAG AACCAGTTCT CCCTGAAGCT  
GAGCTCTGTG ACCGCTGCGG ACACGGCCGT GTACTACTGT GCGAGAGGGC  
TGGGGGATAG TAGTGGTTAT ATCCTTTGGG GCCAAGGGAC AATGGTCACC  
GTCTCAAGC

**H15 (SEQ ID NO:133)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG  
GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC TGGAGTGGAT  
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACCGCTGC GGACACGGCC GTGTACTACT GTGCGAGAGG  
GCTGGGGGAT AGTAGTGGTT ATATCCTTTG GGGCCAAGGG ACAATGGTCA  
CCGTCTCAAG C

**Fig. 1 (cont)****H16 (SEQ ID NO:135)**

CAGGTG CAGCTGCAGG AGTCGGGCCC AGGACTGGTG AAGCCTTCGG  
GGACCCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGAAGGGGC TGGAGTGGAT  
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGATG  
GACCGGGCGT ACTGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA  
CCGTCTCAAG C

**H17 (SEQ ID NO:137)**

CAGG TGCAGCTGCA GGAGTCCGGC CCAGGACTGG TGAAGCCTTC  
GGGGACCCTG TCCCTCACCT GCGCTGTCTC TGGTGGCTCC ATCAGCAGTA  
GTAAGTGGTG GAGTTGGGTC CGCCAGCCCC CAGGGAAGGG GCTGGAGTGG  
ATTGGGGAAA TCTATCATAG TGGGAGCACC AACTACAACC CGTCCCTCAA  
GAGTCGAGTC ACCATATCAG TAGACAAGTC CAAGAACCAG TTCTCCCTGA  
AGCTGAGCTC TGTGACCGCC GCGGACACGG CCGTGTATTA CTGTGCGAGA  
CAAGGGGCGT TAGATGCTTT TGATATCTGG GGCCAAGGGA CCACGGTCAC  
CGTCTCAAGC

**H18 (SEQ ID NO:139)**

GCAGCTGGTG GAGTCCGGGG GAGGCGTGGT CCGACCTGGG GGGTCCCTGA  
GACTCTCCTG TGCAGCGTCT GGATTCACCT TTAGCAGCTA TGCCATGAGC  
TGGGTCCGCC AGGCTCCAGG GAAGGGGCTG GAGTGGGTCT CAACTATTAG  
TGGTAGTGGT GGTAGCACAT ACTACGCAGA CTCCGTGAAG GGCCGGTTCA  
CCATCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA GATGAACAGC  
CTGAGAGCCG AGGACACGGC CGTATATTAC TGTGCGAAAG AGCGTGGCAG  
TGGCTGGTCC TTAGACAATA TGGACGTCTG GGGCCAAGGG ACCACGGTCA  
CCGTCTCAAG C

**H19 (SEQ ID NO:141)**

CAGGTGCAGC TGGTGGAGTC TGGCCCAGGA CTGGTGAAGC CTTCGGGGAC  
CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCTGCGGAC ACGGCCGTGT ATTACTGTGC GAGAGATAGC  
AGTGGGTTCT ACGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT  
CTCAAGC

**Fig. 1 (cont)****H20 (SEQ ID NO:143)**

CAGGTG CAGCTGCAGG AGTCGGGCCC AGGACTGGTG AAGCCTTCGG  
GGACCCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC TGGAGTGGAT  
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACTGCCGC GGACACGGCC GTGTATTACT GTGCGAGAAG  
CAGCAGCTGG TACTGGAATG CTTTTGATAT CTGGGGCCAA GGGACAATGG  
TCACCGTCTC AAGC

**H21 (SEQ ID NO:145)**

CAGGTG CAGCTACAGC AGTGGGGCCC AGCACTGGTG AAGCCTTCGG  
GGACCCCTGTC CCTCACCTGC TCTGTCTCTG GTGTCTCCAT CACCAGTAAT  
ATCTGGTGGA GTTGGGTCCG CCAGTCCCCA GGGAAGGGGC TGGAGTGGAT  
TGGGGAAAGTC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACCGCCGC GGACACGGCT GTGTATTACT GTGCGGGGTA  
CCGTAGCTTC GGGGAGTCCT ACTGGGGCCA GGGAACCCTG GTCACCGTCT  
CAAGC

**H22 (SEQ ID NO:147)**

CAGGTGCA GCTACAGCAG TGGGGCGCAG GGCTGTTGAA GCCTTCGGAG  
ACCCTGTCTC TCACCTGCGT TGTCTATGGT GGGTCCTTCA GCGATTTCTA  
CTGGAGCTGG ATCCGCCAGC CCCCAGGGAA GGGGCCAGAG TGGATTGGGG  
AAGTCAATCC TAGAGGAAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA  
GCCACCATAT CACTAGACAC GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG  
TTCTGTGACC GCCGCGGACA CGGCTGTGTA TTTCTGTGCG AGAGGTCCCTC  
GGCCCGGGAG AGATGGCTAC AATTACTTTG ACAACTGGGG CCAGGGCACC  
CTGGTCACCG TCTCAAGC

**H23 (SEQ ID NO:149)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCCGAGAC  
CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCAGGGAA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGAGGTATA  
GCAGCAGCTG GTCAAGGTGA CTACTGGGGC CAGGGAACCC TGGTCACCGT  
CTCAAGC

**Fig. 1 (cont)****H24 (SEQ ID NO:151)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCCGGAGAC  
CCTGTCCCTC ACCTGCACTG TCTCTGGTGG CTCCATCAGC AGTAGTAGTT  
ACTACTGGGG CTGGATCCGC CAGCCCCCAG GGAAGGGGCT GGAGTGGATT  
GGGAGTATCT ATTATAGTGG GAGCACCTAC TACAACCCGT CCCTCAAGAG  
TCGAGTCACC ATATCCGTAG ACACGTCCAA GAACCAGTTC TCCCTGAAGC  
TGAGCTCTGT GACCGCCGCG GACACGGCCG TGTATTACTG TGCGAGAGAT  
GGGGGATACT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  
CACCGTCTCA AGC

**H25 (SEQ ID NO:153)**

CAGGTG CAGCTGCAGG AGTCGGGCCC AGGACTGGTG AAGCCTTCGG  
GGACCTGTG CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGAAGGGGGC TGGAGTGGAT  
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGTAG  
TGTTTATGAT GCTTTTGATA TCTGGGGCCA AGGGACCACG GTCACCGTCT  
CAAGC

**H26 (SEQ ID NO:155)**

CAGGT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG  
GGGACCCTGT CCCTCACCTG CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG  
TAATTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG CTGGAGTGGA  
TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG  
AGTCGAGTCA CCATATCAGT AGACAAGTCC AAGAACCAGT TCTCCCTGAA  
GCTGAGCTCT GTGACCGCCG CGGACACGGC CGTGTATTAC TGTGCACGAT  
ACAGCTATGG AACGGTAGGA ATTGACTACT GGGGCCAGGG AACCCTGGTC  
ACCGTCTCAA GC

**H27 (SEQ ID NO:157)**

GAGGT GCAGCTGGTG CAGTCTGGGG GAGGCGTGGT CCAGCCTGGG  
ACGTCCCTGA GACTCTCCTG TGCAGCCTCT GGATTCAGCT TCAGAAGTCA  
TGGCATGCAC TGGGTCCGCC AGGCTCCAGG CAAGGGGCTG GAGTGGGTGG  
CAGTTATATC ATATGATGGA AGTAATAAAT ACTATGCAGA CTCCGTGAAG  
GGCCGATTCA CCATCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA  
AATGAACAGC CTGAGAGCTG AGGACACGGC TGTGTATTAC TGTGCGACTA  
TAGGGCCGGG GGGATTTGAC TACTGGGGCC AGGGCACCCCT GGTACCGTCT  
TCAAGC

**Fig. 1 (cont)****H28 (SEQ ID NO:159)**

CAG GTGCAGCTGC AGGAGTCCGG CCCAGGACTG GTGAAGCCTT  
 CGGAGACCCT GTCCCTCACC TGCAGTGTCT CTGGTGGCTC CATTAGAAAT  
 TACTACTGGA GTTGGATCCG GCAGCCCCCA GGAAGGGAC TGGAGTGGAT  
 TGGGTATATT TCTGACAGTG GGAATACCAA CTACAATCCC TCCCTCAAGA  
 GTCGAGTCAC CATATCAGTA GACACGTCCA AGAACCAGTT CTCCCTAAAG  
 CTGACCTCTG TGACCGCCAC AGACACGGCT GCGTATTTCT GTGCGAGACA  
 TCGAAGCAGC TGGGCATGGT ACTTCGATCT CTGGGGCCGT GGCACCCTGG  
 TCACCGTCTC AAGC

**H29 (SEQ ID NO:161)**

C AGGTGCAGCT GCAGGAGTCG GGCCAGGAC TGGTGAAGCC  
 TTCGGAGACC CTGTCCCTCA CCTGCGCTGT CTCTGGTGGC TCCATCAGCA  
 GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA GGGGCTGGAG  
 TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT  
 CAAGAGTCGA GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC  
 TGAAGCTGAG CTCTGTGACC GCCGCGGACA CGGCCGTGTA TTAGTGTGCG  
 AGAGTGGGCA GTGGCTGGTA CGTTGACTAC TGGGGCCAGG GAACCCTGGT  
 CACCGTCTCA AGC

**H30 (SEQ ID NO:163)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG  
 GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
 AACTGGTGGG GTTGGGTCCG CCAGCCCCCA GGAAGGGGC TGGAGTGGAT  
 TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
 GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
 CTGAGCTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGAGT  
 TTCTGGCTAC TACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG  
 TCACCGTCTC AAGC

**H31 (SEQ ID NO:165)**

GAGGTCCA GCTGGTACAG TCTGGGGGAG GCGTGGTCCA GCCTGGGAGG  
 TCCCTGAGAC TCTCCTGTGC AGCCTCTGGA TTCACCTTCA GTAGCTATGG  
 CATGCACTGG GTCCGCCAGG CTCCAGGCAA GGGGCTGGAG TGGGTGGCAG  
 TTATATCATA TGATGGAAGT AATAAATACT ATGCAGACTC CGTGAAGGGC  
 CGATTCAACCA TCTCCAGAGA CAATTCCAAG AACACGCTGT ATCTGCAAAT  
 GAACAGCCTG AGAGCTGAGG ACACGGCTGT GTATTACTGT GCGAAAGCGT  
 ATAGCAGTGG CTGGTACGAC TACTACGGTA TGGACGTCTG GGGCCAAGGG  
 ACCACGGTCA CCGTCTCAAG C

**Fig. 1 (cont)****H32 (SEQ ID NO:167)**

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCTGGGGAC  
CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGAGCCAGC  
GTTGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCAAG  
C

**H33 (SEQ ID NO:169)**

CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG  
GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC TGGAGTGGAT  
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACCGCTGC GGACACGGCC GTGTACTACT GTGCGAGAGG  
GCTGGGGGAT AGTAGTGGTT ATATCCTTTG GGGCCAAGGG ACAATGGTCA  
CCGTCTCAAG C

**H34 (SEQ ID NO:171)**

CAGGTA CAGCTGCAGC AGTCAGGCCC AGGACTGGTG AAGCCTTCGG  
GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT  
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC TGGAGTGGAT  
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA  
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG  
CTGAGCTCTG TGACTCCCGA GGACACGGCT GTGTATTACT GTGCAAGAGA  
TCACGGCCCC TTTGACTACT GGGGCCGGGG AACCTGGTC ACCGTCTCAA  
GC

**H35 (SEQ ID NO:173)**

CAGGT GCAGCTGGTG CAATCTGGGG GAGGCGTGGT CCAGCCTGGG  
AGGTCCCTGA GACTCTCCTG TGCAGCCTCT GGATTCGCCT TCAGTAGCTA  
TGGCATGCAC TGGGTCCGCC AGGCTCCAGG GAAGGGGCTG GAGTGGGTTT  
CATACATTAG TAGTAGTAGT AGTACCATAT ACTACGCAGA CTCTGTGAAG  
GGCCGATTCA CCATCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA  
AATGAACAGC CTGAGAGCCG AGGACACGGC TGTGTATTAC TGTGCGAGAG  
ATCGATTTGG GTCGGGGCAC TTGCCCGACT ACTGGGGCCA GGAACCCCTG  
GTCACCGTCT CAAGC

**Fig. 1 (cont)****H36 (SEQ ID NO:175)**

CAGGT GCAGCTACAG CAGTGGGGCG CAGGACTGTT GAAGCCTTCG  
GAGACCCTGT CCCTCACCTG CGCTGTCTAT GGTGGGTCCT TCAGTGGTTA  
CTACTGGAGC TGGATCCGCC AGCCCCCAGG GAAGGGGCTG GAGTGGATTG  
GGGAAATCAA TCATAGTGGA AGCACCAACT ACAACCCGTC CCTCAAGAGT  
CGAGTCACCA TATCAGTAGA CACGTCCAAG AACCAGTTCT CCCTGAAGCT  
GAGCTCTGTG ACCGCCGCGG ACACGGCTGT GTATTACTGT GCGAGAGTTG  
GGTATAGCAG TGGCCGTGAC GTTGACTACT GGGGCCAGGG CACCCTGGTC  
ACCGTCTCAA GC

**H37 (SEQ ID NO:177)**

GAGGTCC AGCTGGTGGA GTCTGGCCCA GGAAGTGGTGA AGCCTTCGGG  
GACCCTGTCC CTCACCTGCG CTGTCTCTGG TGGCTCCATC AGCAGTAGTA  
ACTGGTGGAG TTGGATCCGG CAGCCCCCAG GGAAGGGGCT GGAGTGGATT  
GGGGAAATCT ATCATAGTGG GAGCACCAAC TACAACCCGT CCCTCAAGAG  
TCGAGTCACC ATATCAGTAG ACAAGTCCAA GAACCAGTTC TCCCTGAAGC  
TGAGCTCTGT GACCGCCGCG GACACGGCCG TGTATTACTG TGCGAGAGAT  
AGCAGCAGCT GGTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT  
CACCGTCTCA AGC

**H38 (SEQ ID NO:179)**

GAGGT CCAGCTGGTG GAGTCCGGCC CAGGACTGGT GAAGCCTTCG  
GAGACCCTGT CCCTCACCTG CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG  
TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG CTGGAGTGGA  
TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG  
AGTCGAGTCA CCATATCAGT AGACAAGTCC AAGAACCAGT TCTCCCTGAA  
GCTGAGCTCT GTGACCGCTG CGGACACGGC CGTATATTAT TGTGCGAGAT  
CGACGTGGTC CCTTGACTAC TGGGGCCAGG GCACCCTGGT CACCGTCTCA  
AGC

**H39 (SEQ ID NO:181)**

GAGGTCCAG CTGGTGGAGT CTGGCCCAGG ACTGGTGAAG CCTTCGGGGA  
CCCTGTCCCT CACCTGCGCT GTCTCTGGTG GCTCCATCAG CAGTAGTAAC  
TGGTGGAGTT GGGTCCGCCA GCCCCCAGGG AAGGGGCTGG AGTGGATTGG  
GGAAATCTAT CATAGTGGA GCACCAACTA CAACCCGTCC CTCAAGAGTC  
GAGTCACCAT ATCAGTAGAC AAGTCCAAGA ACCAGTTCTC CCTGAAGCTG  
AGCTCTGTGA CCGCTGCGGA CACGGCCGTA TATTACTGTG CGAGACTCTC  
GTTTGCCGAT CCTTTTGATA TCTGGGGCCA AGGGACAATG GTCACCGTCT  
CAAGC

**Fig. 1 (cont)****H40 (SEQ ID NO:183)**

CAGGTCCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGTCCTC  
GGTGAAGGTC TCCTGCAAGG CTTCTGGAGG CACCTTCAGC AGCTATGCTA  
TCAGCTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG GATGGGAAGG  
ATCATCCCCA TCCTTGGTAT AGCAAACCTAC GCACAGAAGT TCCAGGGCAG  
AGTCACGATT ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA  
GCAGCCTGAG ATCTGAGGAC ACGGCCGTGT ATTACTGTGC ATATGGTTTCG  
GGGAGTTATT ACGACTACTA CTACATGGAC GTCTGGGGCA AAGGGACCAC  
GGTCACCGTC TCAAGC

**H41 (SEQ ID NO:185)**

GAGGTCC AGCTGGTGCA GTCTGGGGGA GGCTTGGTCC AGCCTGGGGG  
GTCCCTGAGA CTCTCCTGTT CAGCCTCCGG ATTCACCTTC AGTAGCTATG  
CTATGCACTG GGTCCGCCAG GCTCCAGGGA AGGGACTGGA ATATGTTTCA  
ACTATTAGTA GTAATGGGGA TAGCACATAC TACGCAGACT CCGTGAAGGG  
CAGATTCACC ATCTCCAGAG ACAATTCCAA GAACACGCTG TATCTGCAAA  
TGAACAGCCT GAGAGCTGAG GACACGGCTG TGTATTACTG TGCGAAAGAA  
GAAGTATGGC TACAGGCTTT TGATATCTGG GGCCAAGGGA CAATGGTCAC  
CGTCTCAAGC

**H42 (SEQ ID NO:187)**

CA GCTGCAGCTG CAGGAGTCGG GCCCAGGACT GGTGAAGCCT  
TCGGAGACCC TGTCCCTCAC CTGCACTGTC TCTGGTGGCT CCATCAGTAG  
TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG CTGGAGTGGA  
TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC CTCCCTCAAG  
AGTCGAGTCA CCATCTCAGT AGACACGTCC AAGAACCAGT TCTCCCTGAA  
GCTGAGCTCT GTGACCGCTG CGGACACGGC CGTGTATTAC TGTGCGAGAG  
ATAAGGGATA CATGGACGTC TGGGGCAAAG GGACCACGGT CACCGTCTCA  
AGC

**H43 (SEQ ID NO:189)**

CAGGTACA GCTGCAGCAG TCAGGGGCTG AGGTGAAGAA GCCTGGGTCC  
TCGGTGAAGG TCTCCTGCAA GGCTTCTGGA GGCACCTTCA GCAGCTATGC  
TATCAGCTGG GTGCGACAGG CCCCTGGACA AGGGCTTGAG TGGATGGGAA  
GGATCATCCC TATCCTTGGT ATAGCAAACCT ACGCACAGAA GTTCCAGGGC  
AGAGTCACGA TTACCGCGGA CAAATCCACG AGCACAGCCT ACATGGAGCT  
GAGCAGCCTG AGATCTGAGG ACACGGCCGT GTATTACTGT GCGAGAGATC  
ATAGGTTCTGA CTACGCCTGG TACTTCGATC TCTGGGGCCG TGGCACCCCTG  
GTCACCGTCT CAAGC

**Fig. 1 (cont)****H44 (SEQ ID NO:191)**

CA GGTGCAGCTG CAGGAGTCGG GCCCAGGACT GCTGAAGCCT  
TCGGGGACCC TGTCCCTCAC CTGCGCTGTC TCTGGTGGCT CCATCAGCAG  
TAGCAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGGAG GGGCTGGAGT  
GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC  
AAGAGTCGAG TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT  
GAAGCTGAGC TCTGTGACCG CCGCGGACAC GGCCGTCTAT TACTGTGCGA  
GAGATCTAAC GGGGAGTCTT GACTACTGGG GCCAGGGAAC CCTGGTCACC  
GTCTCAAGC

**H45 (SEQ ID NO:193)**

CAGGTGCAGC TGCAGGAGTC CGGCCCAGGA CTGGTGAAGC CTTCGGGGAC  
CCTGTCCCTC ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGTAACT  
GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA GTGGATTGGG  
GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG  
AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA  
GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGAATACGC  
TATGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCAAG  
C

**H46 (SEQ ID NO:195)**

CA GGTGCAGCTG CAGGAGTCGG GCCCAGGACT GGTGAAGCCT  
TCGGAGACCC TGTCCCTCAC CTGCGCTGTC TCTGGTGGCT CCATCAGCAG  
TAGTAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGAAG GGGCTGGAGT  
GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC  
AAGAGTCGAG TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT  
GAAGCTGAGC TCTGTGACCG CTGCGGACAC GGCCGTGTAT TACTGTGCCG  
TGACGGCAGC CCATGATGCT TTGATATCTT GGGGCAAGG GACAATGGTC  
ACCGTCTCAA GC

**H47 (SEQ ID NO:197)**

CA GGTGCAGCTA CAGCAGTGGG GCCCAGGACT GGTGAAGCCT  
TCGGGGACCC TGTCCCTCAC CTGCGCTGTC TCTGGTGGCT CCATCAGCAG  
TAGTAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGAAG GGGCTGGAGT  
GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC  
AAGAGTCGAG TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT  
GAAGCTGAGC TCTGTGACCG CCGCGGACAC GGCCGTGTAT TACTGTGCGA  
GAGACAGCAG TGGCCAAGGG TACTTTGACT ACTGGGGCCA GGGCACCTG  
GTCACCGTCT CAAGC

**Fig. 1 (cont)****H48 (SEQ ID NO:199)**

GAGGTG CAGCTGGTGC AGTCTGGGGC TGAGGTGAAG AAGCCTGGGG  
 CCTCAGTGAA GGTCTCCTGC AAGGCTTCTG GATACACCTT CACTAGCTAT  
 GCTATGCATT GGGTGCGCCA GGCCCCCGGA CAAAGGCTTG AGTGGATGGG  
 ATGGATCAAC GCTGGCAATG GTAACACAAA ATATTACAG AAGTTCCAGG  
 GCAGAGTCAC CATGACCAGG GACACGTCCA CGAGCACAGT CTACATGGAG  
 CTGAGCAGCC TGAGATCTGA GGACACGGCC GTGTATTACT GTGCTAGACA  
 CTCGTACTAC TACGGTATGG ACGTCTGGGG CCAAGGCACC CTGGTCACCG  
 TCTCAAGC

**H49 (SEQ ID NO:201)**

CAG GTGCAGCTAC AGCAGTGGGG CGCAGGACTG TTGAAGCCTT  
 CGGAGACCCT GTCCCTCACC TGCGCTGTCT ATGGTGGGTC CTTCACTGGT  
 TACTACTGGA GCTGGATCCG CCAGCCCCCA GGAAGGGGC TGGAGTGGAT  
 TGGGGAAATC AATCATAGTG GAAGCACCAA CTACAACCCG TCCCTCAAGA  
 GTCGAGTCAC CATATCGGTA GACACGTCCA AGAACCAGTT CTCCCTGAAG  
 CTGAGCTCTG TGACCGCCGC GGACACGGCT GTGTATTACT GTGCGAGAGT  
 CGGGTATAGC CACGGCGAAG AAGTCCTGGA CGTCTGGGGC AAAGGGACCA  
 CGGTCACCGT CTCAAGC

**H50 (SEQ ID NO:203)**

CAGGT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG  
 GAGACCCTGT CCCTCACCTG CACTGTCTCT GGTGGCTCCA TCGGCAATTA  
 TGA CTGGAGT TGGATCCGGC AGCCCCCAGG GAAGGGACTG GAGTGGATTG  
 GGACTATCTA CTCTAGTGGG AGTACGTACT ACAGTCCGTC CCTCAAGAGT  
 CGACTCACCA TATCAGTAGA CAAGTCCAAG AACCGGTTCT CCCTGAAGCT  
 GAGCTCTGTG ACCGCCGCGG ACACGGCCGT GTATTACTGT GCGAGAGCAC  
 GAGGGTATAG CAGCCCCTTC GACCCCTGGG GCCAGGGCAC CCTGGTCACC  
 GTCTCAAGC

**H51 (SEQ ID NO:205)**

CA GGTCCAGCTG GTACAGTCTG GGGCTGAGGT GAAGAAGCCT  
 GGGTCCTCGG TGAAGGTCTC CTGCAAGGCT TCTGGAGGCA CCTTCAGCAG  
 CTATGCTATC AGCTGGGTGC GACAGGCCCC TGGACAAGGG CTTGAGTGGA  
 TGGGAATAAT CAACCCTAGT GGTGGTAGCA CAAGCTACGC ACAGAAGTTC  
 CAGGGCAGAG TCACCATAC CAGGGACACA TCCGCGAGCA CAGCCTACAT  
 GGAGCTGAGC AGCCTGAGAT CTGAAGACAC GGCTGTGTAT TACTGTGCGA  
 GAGATCGGTG GAGGTACGAT GCTTTTGATA TCTGGGGCCA AGGGACAATG  
 GTCACCGTCT CAAGC

**Fig. 1 (cont)****H52 (SEQ ID NO:207)**

```
      G AGGTGCAGCT GGTGGAGTCT GGCCCAGGAC TGGTGAAGCC
TTCGGGGGACC CTGTCCCTCA CCTGCGCTGT CTCTGGTGGC TCCATCAGCA
GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA GGGGCTGGAG
TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT
CAAGAGTCGA GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCCTCC
TGAAGCTGAG CTCTGTGACC GCCGCGGACA CGGCCGTGTA TTACTGTGCG
AGAGAAAAAT CGGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT
CTCAAGC
```

Fig. 2

## LIGHT CHAIN VARIABLE REGION SEQUENCES

| FR1                | CDR1                                                                                                                                                                                                                                                                                                           | FR2 | CDR2 | FR3 | CDR3 | FR4 |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|------|-----|------|-----|
| L1 (SEQ ID NO:2)   | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L2 (SEQ ID NO:4)   | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L3 (SEQ ID NO:6)   | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L4 (SEQ ID NO:8)   | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L5 (SEQ ID NO:10)  | EIVLTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK |     |      |     |      |     |
| L6 (SEQ ID NO:12)  | EIVLTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK |     |      |     |      |     |
| L7 (SEQ ID NO:14)  | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L8 (SEQ ID NO:16)  | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L9 (SEQ ID NO:18)  | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L10 (SEQ ID NO:20) | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L11 (SEQ ID NO:22) | EIVLTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK |     |      |     |      |     |
| L12 (SEQ ID NO:24) | NFMTQSP <sup>1</sup> SHSVESPGK <sup>2</sup> TVTIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK |     |      |     |      |     |
| L13 (SEQ ID NO:26) | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L14 (SEQ ID NO:28) | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |
| L15 (SEQ ID NO:30) | DVMTQSP <sup>1</sup> SLPVT <sup>2</sup> PGEPASIS <sup>3</sup> CRSSQ <sup>4</sup> SL <sup>5</sup> HS <sup>6</sup> GYNYL <sup>7</sup> DWYLQ <sup>8</sup> KPGQSP <sup>9</sup> QLLIY <sup>10</sup> <u>LGSN</u> RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ <sup>11</sup> TPIT <sup>12</sup> FGG <sup>13</sup> TRLEIK  |     |      |     |      |     |

Fig. 2 (cont)

L16 (SEQ ID NO:32) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQGTHWFLTFGGGTKVEIK  
 L17 (SEQ ID NO:34) EIVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>LT</sup>LTFGGTKVEIK  
 L18 (SEQ ID NO:36) DIQLTQSP<sup>SV</sup>SVASV<sup>GD</sup>RV<sup>TI</sup>TCRASQGISRW<sup>LA</sup>WYQQKPGKAPR<sup>LL</sup>IYAASGLQSGVPSRFSGSGSGTDFTLTISNLPEDFATY<sup>YC</sup>QQAASSFPI<sup>LT</sup>FGQGTLETK  
 L19 (SEQ ID NO:38) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>YT</sup>YTFGGTKLEIK  
 L20 (SEQ ID NO:40) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>FT</sup>FTFGPGTKVDIK  
 L21 (SEQ ID NO:42) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSYRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQSLEVP<sup>FT</sup>FTFGGTKLEIK  
 L22 (SEQ ID NO:44) SSELTDPAVSVALGQTV<sup>RI</sup>TCQGDSLRIY<sup>TY</sup>TGWYQQKPGQAPV<sup>LV</sup>LFGKNRPSGIPDRFSGSHSGNTASLTITGAQAEDEADY<sup>YC</sup>NSRDI<sup>TV</sup>TVHRFGGTKLTVL  
 L23 (SEQ ID NO:46) EIVLTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>LT</sup>LTFGGTKVEIK  
 L24 (SEQ ID NO:48) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>NT</sup>NTFGGTKVEIK  
 L25 (SEQ ID NO:50) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>IT</sup>ITFGPGTKVDIK  
 L26 (SEQ ID NO:52) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALEMP<sup>LT</sup>LTFGGTKVEIK  
 L27 (SEQ ID NO:54) DIQLTQSP<sup>SF</sup>LSASV<sup>GD</sup>RV<sup>TI</sup>TCRASQGISSY<sup>LA</sup>WYQQKPGKAPK<sup>LL</sup>IYAAS<sup>TL</sup>QSGVPSRFSGSGSGTEFTLTISSLQPEDFATY<sup>YC</sup>QQLNSY<sup>PL</sup>LTFGGTKVEIK  
 L28 (SEQ ID NO:56) SYVLTQPPSVSVSPGQTASITCSGDKLGDKYVGVWYQQKAGQAPV<sup>LV</sup>IYQDNKRPSSGIPERFSGSNSGNTASLTISGTQAMDEADY<sup>YC</sup>QAWDSGT<sup>TV</sup>TVFGGTKLTVL  
 L29 (SEQ ID NO:58) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>LT</sup>LTFGGTKVEIK  
 L30 (SEQ ID NO:60) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MEALQTP<sup>FT</sup>FTFGPGTKVEIK  
 L31 (SEQ ID NO:62) DIQLTQSP<sup>SV</sup>SVLSASV<sup>GD</sup>RV<sup>TI</sup>TCRSSQGI<sup>GY</sup>FLWYQQEPGKAPK<sup>IL</sup>ISAAS<sup>TL</sup>QSGVPSRFSGSGSGTDFTLSINNLPADFATY<sup>YC</sup>QQSHSP<sup>PY</sup>YTFGGTKVEIK  
 L32 (SEQ ID NO:64) DVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLGSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQALQTP<sup>LT</sup>LTFGGTKVEIK  
 L33 (SEQ ID NO:68) EIVLTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASISCRSSQ<sup>SL</sup>LLHSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLVSNRASGV<sup>PD</sup>DRFSGSGSGTDFTLKISRVEAEDVGVY<sup>YC</sup>MQTLQTP<sup>LT</sup>LTLSFGGTKLEIK

Fig. 2 (cont)

L34 (SEQ ID NO:70)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>LT<sup>LT</sup>FTGGGTKVEIK  
 L35 (SEQ ID NO:72)  
 NFMLTQPHSVSASP<sup>GK</sup>TVT<sup>IS</sup>CRSSGDI<sup>DN</sup>NYVQYQORPGNSPTNVIYED<sup>NR</sup>RRPSGVPDRFSGSIDSSNSASLTISGLQPEDEADYYCQSYQSDNWVFTGGGTKVTVL  
 L36 (SEQ ID NO:74)  
 NFMLTQPHSVSESP<sup>GK</sup>TVT<sup>IS</sup>CRSSGSIASNYVQYQORPGSSPTTVIYED<sup>NR</sup>QRP<sup>SG</sup>VDPDRFSGSIDSSNSASLTISGLKTEDEADYYCQSYDSSNVVFTGGGTKLTVL  
 L37 (SEQ ID NO:76)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPY<sup>TF</sup>FGQTRLEIK  
 L38 (SEQ ID NO:78)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNFLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>LT<sup>LT</sup>FTGGGTKVEIK  
 L39 (SEQ ID NO:80)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>LT<sup>LT</sup>FTGGGTKVEIK  
 L40 (SEQ ID NO:82)  
 ETTLTQSPATLSLSPGQRATLS<sup>CR</sup>ASQSVNYLAWYQQKPGQAPRLLIYDASRRATGIPARFSGSGSGTDFTLTIS<sup>SL</sup>EPEDFAVYYCQQRNNWPL<sup>LT</sup>FTGGGTKVEIK  
 L41 (SEQ ID NO:84)  
 DIQLTQSPSSLSASVGDST<sup>IS</sup>CRASQSPGIFLNWYQQIPGKAPKLLIYATSTLESGVP<sup>PR</sup>FTGSGSGTDFTLTIS<sup>SL</sup>QPEDFATYYCQQSN<sup>SV</sup>PL<sup>LT</sup>FTGGGTKVEIK  
 L42 (SEQ ID NO:86)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>LT<sup>LT</sup>FTGGQTRLEIK  
 L43 (SEQ ID NO:88)  
 EIVMTQSPATLSVSPGERATF<sup>CR</sup>ASQSVGSNLAWYQQKPGQAPRLLIYDASNRA<sup>TG</sup>IPARFSGSGSGTDFTLTISRL<sup>EP</sup>EDFAVYYCQQRNNWPL<sup>LT</sup>FTGGGTKVEIK  
 L44 (SEQ ID NO:90)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>LT<sup>LT</sup>FTGGGTKVEIK  
 L45 (SEQ ID NO:92)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>ST</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>Y<sup>TF</sup>FTGGGTKVEIK  
 L46 (SEQ ID NO:94)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ<sup>TP</sup>LT<sup>LT</sup>FTGGGTKVEIK  
 L47 (SEQ ID NO:96)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>LHTNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>FN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQ<sup>TP</sup>LT<sup>LT</sup>FTGGGTKVEIK  
 L48 (SEQ ID NO:98)  
 DVVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>HSNGYNYLDWYLQKPGQSPQ<sup>LL</sup>IYLG<sup>SN</sup>RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQATHWPY<sup>TF</sup>FGQGKLEIK  
 L49 (SEQ ID NO:100)  
 NFMLTQPHSVSESP<sup>GK</sup>TVS<sup>IS</sup>CTRNSGSIASNFVQYQORPGSAPTIVIYED<sup>NR</sup>QRP<sup>SA</sup>VPT<sup>RF</sup>SGSIDRSSNSASLTISGLTTEDEADYYCQSYDSANVIFGGGTKLTVL  
 L50 (SEQ ID NO:102)  
 ETTLTQSPG<sup>TL</sup>SLSPGERATLS<sup>CR</sup>ASQATISSSHLAWYQQKPGQSPQ<sup>LL</sup>IYGAGYRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSLR<sup>LT</sup>FTGGGTKVEIK  
 L52 (SEQ ID NO:104)  
 EIVMTQSP<sup>SL</sup>SLPVT<sup>PG</sup>EPASIS<sup>CR</sup>SSQSL<sup>L</sup>LHTNGYDYLDWYLQK

Fig. 3

## HEAVY CHAIN VARIABLE REGION SEQUENCES

|                     | FR1                | CDR1                         | FR2 | CDR2 | FR3 | CDR3 | FR4 |
|---------------------|--------------------|------------------------------|-----|------|-----|------|-----|
| H1 (SEQ ID NO:106)  | EVQLVETGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | ILTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H2 (SEQ ID NO:108)  | EVQLVETGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | ILTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H3 (SEQ ID NO:110)  | QVQLQESGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | SLTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H4 (SEQ ID NO:112)  | QVQLQWAGLLKPSGTL   | <u>GYIYWSWVRQPPGKGLEWIG</u>  |     |      |     |      |     |
| S                   | ILTCAVSGGSI        | <u>GYIYWSWVRQPPGKGLEWIG</u>  |     |      |     |      |     |
| H5 (SEQ ID NO:114)  | QVQLQESGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | ILTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H6 (SEQ ID NO:116)  | QVQLQESGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | SLTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H7 (SEQ ID NO:118)  | QVQLQESGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | SLTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H8 (SEQ ID NO:120)  | QVQLQWAGLLKPSGTL   | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | SLTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H9 (SEQ ID NO:122)  | EVQLVETGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | ILTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H10 (SEQ ID NO:124) | EVQLVETGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | SLTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| H11 (SEQ ID NO:126) | QVQLQESGPGLVKPSGTL | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |
| S                   | SLTCAVSGGSI        | <u>SSNNWWSWVRQPPGKGLEWIG</u> |     |      |     |      |     |

Fig. 3 (cont)

H12 (SEQ ID NO:128)  
 EVQLVESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGLEWVSAISGSGGSIYYADSVKGRFTISRDNSKNTLYLQMNLSADDTAVYFCASGGWYGDYFDYWGQGTLLVT  
 VSS  
 H13 (SEQ ID NO:130)  
 QVQLQESGPGLVKPSGTLSTCTVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAREGNRFVTISAFDIWGQGT  
 MVT  
 H14 (SEQ ID NO:132)  
 QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARGLGDSSGYILLWGQGT  
 MVT  
 VSS  
 H15 (SEQ ID NO:134)  
 QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARGLGDSSGYILLWGQGT  
 MVT  
 VSS  
 H16 (SEQ ID NO:136)  
 QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARWTGRTDADFIDWGQGT  
 MVT  
 VSS  
 H17 (SEQ ID NO:138)  
 QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARQALDAFDIDWGQGT  
 MVT  
 SS  
 H18 (SEQ ID NO:140)  
 EVQLVESGGGVVRPGGSLRLSCAASGFTFSYAMSWVRQAPGKGLEWVSTISGSGGSIYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAVYYCAKERGSGWSLDNMDVWGQGT  
 TVTVSS  
 H19 (SEQ ID NO:142)  
 QVQLVESGPGLVKPSGTLSTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARDSSGFYGMVWGQGT  
 MVT  
 VSS  
 H20 (SEQ ID NO:144)  
 QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARSSWYNAFDIWGQGT  
 MVT  
 TVSS  
 H21 (SEQ ID NO:146)  
 QVQLQWGPALVKPSGTLSTCSVSGVSITSNIIWWSWVRQSPGKGLEWIGEIVYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAGYRSFGESYWGQGT  
 LTVSS  
 H22 (SEQ ID NO:148)  
 QVQLQWGPALVKPSGTLSTCVVYGGSFDFYWSWVRQPPGKGPEWIGEIVNPRGSTINYNPSLKSRATISLDTSKNQFSLKLSVTAADTAVYYCARGPRPGRDGYNFYDNWGQGT  
 LTVSS  
 H23 (SEQ ID NO:150)  
 QVQLQESGPGLVKPSGTLSTCTVSGGSISSSNNWWSWVRQPPGKGLEWIGEIIYHSGSTINYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARGIAAGQGDYWGQGT  
 LTVSS

Fig. 3 (cont)

H24 (SEQ ID NO:152)  
 QVQLQESGPGLVKPSSETLSLTCTVSGGSISSSSSYYHWNIQPPGKGLEWIGISYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARTDGGYYIYGMDVWGQGT  
 TVVSS

H25 (SEQ ID NO:154)  
 QVQLQESGPGLVKPSGTLTLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCASSSGYDAFDIWGQGTITVVS  
 S

H26 (SEQ ID NO:156)  
 QVQLQESGPGLVKPSGTLTLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARYSYGTVGIDYWGQGLTIVT  
 VSS

H27 (SEQ ID NO:158)  
 EVQLVQSGGTVQPGTSLRSLCAASGFSFRSHGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCATIGPGGFFDYWGQGTITVVS  
 S

H28 (SEQ ID NO:160)  
 QVQLQESGPGLVKPSSETLSLTCTVSGGSIRNYYSWIRQPPGKGLEWIGYISDSGNTNNYNPSLKSRVTISVDTSKNQFSLKLSVTATDTAAVFCARHRSSWAWYFDLWGRGLTIVT  
 VSS

H29 (SEQ ID NO:162)  
 QVQLQESGPGLVKPSSETLSLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARVSGGWYVDYWGQGLTIVT  
 SS

H30 (SEQ ID NO:164)  
 QVQLQESGPGLVKPSGTLTLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARVSGGWYVDYWGQGLTIVT  
 TVVSS

H31 (SEQ ID NO:166)  
 EVQLVQSGGTVQPGTSLRSLCAASGFTFSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAYSSGWYDYIYGMVDYWGQ  
 GTIVT

H32 (SEQ ID NO:168)  
 QVQLQESGPGLVKPSGTLTLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARASVDAFDIWGQGTITVVS  
 S

H33 (SEQ ID NO:170)  
 QVQLQESGPGLVKPSGTLTLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARGLDSSGYILWQGLTIVT  
 VSS

H34 (SEQ ID NO:172)  
 QVQLQSGPGLVKPSGTLTLTCAVSGGSISSSNNWWSWVRQPPGKGLEWIGEIYHSGSTNNYNPSLKSRVTISVDKSKNQFSLKLSSVTPEDTAVYYCARDHGPFFDYWGRTLVTVSS

H35 (SEQ ID NO:174)  
 QVQLVQSGGTVQPGTSLRSLCAASGFAFSYGMHWVRQAPGKGLEWVSYISSSSSSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDRFGSGHLPDYWGQGLTIV  
 TVSS

H36 (SEQ ID NO:176)  
 QVQLQWAGALLKPSSETLSLTCAVYGGSFSGYYYSWIRQPPGKGLEWIGEINHSGSTNNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVGYSSGRDVDYWGQGLTIVT  
 VSS

Fig. 3 (cont)

H37 (SEQ ID NO:178)  
 EVQLVESGPGLVKPSGTLSTLTCAVSGGSISSSNWWSWIRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARDSSSWYYGMDVWGQGTTV  
 TVSS

H38 (SEQ ID NO:180)  
 EVQLVESGPGLVKPSGTLSTLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARSTWSLDVWGQGLTLTVSS

H39 (SEQ ID NO:182)  
 EVQLVESGPGLVKPSGTLSTLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARLSFADEFDVWGQGTMTTV  
 SS

H40 (SEQ ID NO:184)  
 QVQLVQSGAEVKKPGSSVKVCSKASGFTFSSYAISWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDATVYYCAYGSGSYDYDYMDVWGKGT  
 TTVTVSS

H41 (SEQ ID NO:186)  
 EVQLVQSGGLVQPGGSLRLSCSASGFTFSSYAMHWVRQAPGKGLYYVSTISSNGDSITYYADSVKGRFTISRDNKNTLYIQMNSLRAEDTAVYYCAKEEVWLQAFDINWGQGTMTV  
 VSS

H42 (SEQ ID NO:188)  
 QLQLQESGPGLVKPSGTLSTLCTVSGGSISSNWWSWVRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARDKGYMDVWGKGTTVTVSS

H43 (SEQ ID NO:190)  
 QVQLVQSGAEVKKPGSSVKVCSKASGFTFSSYAISWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDATVYYCARDHREFDYAWYFDLWGRGTL  
 VTVSS

H44 (SEQ ID NO:192)  
 QVQLQESGPGLLKPSGTLSTLTCAVSGGSISSSNWWSWVRQPPGEGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARDLTGSLDVWGQGLTLTVS  
 S

H45 (SEQ ID NO:194)  
 QVQLQESGPGLVKPSGTLSTLTCAVSGGSISSNWWSWVRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARIRYDAFDINWGQGTMTVSS

H46 (SEQ ID NO:196)  
 QVQLQESGPGLVKPSGTLSTLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCAVTAAHDAFDINWGQGTMTV  
 SS

H47 (SEQ ID NO:198)  
 QVQLQWGPGLVKPSGTLSTLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSVTAADTAVYYCARDSSGGQYFDYWGQGLTLV  
 TVSS

H48 (SEQ ID NO:200)  
 EVQLVQSGAEVKKPGASVKASGYTFTSYAMHWVRQAPGQRLWWMGWINAGNGNTKYSQKFQGRVTMTTRDTSTSTVYMELSSLRSEDATVYYCARHSYYYGMDVWGQGLTLTV  
 SS

H49 (SEQ ID NO:202)  
 QVQLQWGAAGLLKPSGTLSTLTCAVYGGSFGYIYWSWIRQPPGKGLEWIGGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSVTAADTAVYYCARVGYSHGEVLDVWGKGTTV  
 TVSS

**Fig. 3 (cont)**

H50 (SEQ ID NO:204)  
QVQLQESGPGGLVKPSETLSLTCTVSGGSIGNVDWSWIRQPPGKGLEWIGTIYSSGSTYYSPSLKSRLLTISVDKSKNRFSILKLSVTAADTAVYYCARARGYSSPEDPWGQGITLVTV  
SS

H51 (SEQ ID NO:206)  
QVQLVQSGAEVKKPGSSVKVCKASGGTFSSYALISWVRQAPGQGLEWMGLINPSSGGSTSYAQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDRWRYDAFDINWGQGTMTVT  
VSS

H52 (SEQ ID NO:208)  
VQLVESGPGGLVKPSGTLTLTCAVSGGSISSSNHWSWVRQPPGKGLEWIGETIYHSGSTINYPSLKSRVTISVDKSKNQFSILKLSVTAADTAVYYCAREKSGCMDVWGQGTITVTIVSS

[illegible]

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Fig.5

| <u>Light Chain</u>                                                                                                                                                                                        | <u>CDR2 Sequence</u>                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| L1, L2, L3, L4, L5, L6, L7, L8,<br>L9, L10, L11, L13, L14, L16,<br>L17, L19, L20, L23, L24, L25,<br>L26, L29, L30, L32, L34, L38,<br>L39, L42, L44, L46, L48<br>L15, L21<br>L33<br>L37<br>L45, L52<br>L47 | L G S N R A S<br>L G S Y R A S<br>L V S N R A S<br>L G S N R D S<br>L G S T R A S<br>L G F N R A S |
| CONSENSUS                                                                                                                                                                                                 | L G S N R A S                                                                                      |
| L27, L31<br>L18<br>L41                                                                                                                                                                                    | A A S T L Q S<br>A A S G L Q S<br>A T S T L E S                                                    |
| CONSENSUS                                                                                                                                                                                                 | A A S T L Q S                                                                                      |
| L12, L36, L49<br>L35, L51<br>L28<br>L22                                                                                                                                                                   | E D N Q R P S<br>E D N R R P S<br>Q D N K R P S<br>G K N N R P S                                   |
| CONSENSUS                                                                                                                                                                                                 | E D N X R P S                                                                                      |
| L40<br>L43<br>L50                                                                                                                                                                                         | D A S R R A T<br>D A S N R A T<br>G A G Y R A T                                                    |

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Fig.6

| <u>Light Chain</u>                   | <u>CDR3 Sequence</u> |   |   |   |   |   |   |   |     |
|--------------------------------------|----------------------|---|---|---|---|---|---|---|-----|
| L3, L5, L6, L7, L8                   | M                    | Q | A | L | Q | T | P | L | T   |
| L13, L14, L17, L23,                  | M                    | Q | A | F | Q | T | P | L | T   |
| L29, L32, L34, L38,                  | M                    | Q | A | L | Q | T | P | I | T   |
| L39, L42, L44, L46                   | M                    | Q | A | L | Q | T | P | Y | T   |
| L52                                  | M                    | Q | A | L | Q | T | P | F | T   |
| L1, L2, L11, L15, L25                | M                    | Q | A | L | Q | T | P | H | T   |
| L19, L45                             | M                    | Q | A | L | Q | T | P | N | T   |
| L9, L20                              | M                    | Q | A | L | Q | T | P | L | A   |
| L4                                   | M                    | Q | A | L | Q | T | P | L | T   |
| L24                                  | M                    | Q | A | L | Q | T | P | L | T   |
| L10                                  | M                    | Q | A | L | Q | T | P | L | T   |
| L47                                  | M                    | Q | G | L | Q | T | P | L | T   |
| L26                                  | M                    | Q | A | L | E | M | P | L | T   |
| L30                                  | M                    | E | A | L | Q | T | P | F | T   |
| L33                                  | M                    | Q | T | L | Q | T | P | L | S   |
| L16                                  | M                    | Q | G | T | H | W | P | L | T   |
| L21                                  | M                    | Q | S | L | E | V | P | F | T   |
| L48                                  | M                    | Q | A | T | H | W | P | Y | T   |
| L37                                  | M                    | Q | G | T | H | W | P | Y | T   |
| CONSENSUS                            | M                    | Q | A | L | Q | T | P | * | T   |
| "*" = nonpolar side chain amino acid |                      |   |   |   |   |   |   |   |     |
| L40                                  | Q                    | Q | R | N | N | W | P | L | T   |
| L43                                  | Q                    | Q | R | S | N | W | P | L | T   |
| L41                                  | Q                    | Q | S | N | S | V | P | L | T   |
| L27                                  | Q                    | Q | L | N | S | Y | P | L | T   |
| L31                                  | Q                    | Q | S | H | S | P | P | Y | T   |
| L18                                  | Q                    | Q | A | S | S | F | P | I | T   |
| CONSENSUS                            | Q                    | Q | R | N | S | * | P | L | T   |
| S S N                                |                      |   |   |   |   |   |   |   |     |
| "*" = nonpolar side chain amino acid |                      |   |   |   |   |   |   |   |     |
| L12                                  | Q                    | S | Y | D | S | S | N | Q | R V |
| L51                                  | Q                    | S | Y | D | P | Y | N | R | V   |
| L36                                  | Q                    | S | Y | D | S | S | N | V | - V |
| L35                                  | Q                    | S | Y | Q | S | D | N | W | - V |
| L49                                  | Q                    | S | Y | D | S | A | N | V | I   |
|                                      | Q                    | S | Y | D | S | S | N | X | V   |
| L28                                  | Q                    | A | W | D | S | G | T | V |     |
| L50                                  | Q                    | H | Y | G | S | S | L | R | T   |
| L22                                  | N                    | S | R | D | I | T | G | V | H R |

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**Fig.7**

| <u>Heavy Chain</u>                                                                                                                                                                          | <u>CDR1 Sequence</u> |   |   |   |   |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---|---|---|---|-----|
| H1, H2, H3, H5, H6,<br>H7, H8, H9, H10, H11,<br>H13, H14, H15, H16,<br>H17, H19, H20, H23,<br>H25, H26, H29, H30,<br>H32, H33, H34, H37,<br>H38, H39, H44, H46, H47, H52<br>H42, H45<br>H21 | S                    | S | N | W | W | S   |
|                                                                                                                                                                                             | -                    | S | N | W | W | S   |
|                                                                                                                                                                                             | S                    | N | I | W | W | S   |
| CONSENSUS                                                                                                                                                                                   | S                    | S | N | W | W | S   |
| H4, H36, H49<br>H50<br>H28<br>H22                                                                                                                                                           | G                    | Y | Y | W | S |     |
|                                                                                                                                                                                             | N                    | Y | D | W | S |     |
|                                                                                                                                                                                             | N                    | Y | Y | W | S |     |
|                                                                                                                                                                                             | D                    | F | Y | W | S |     |
| CONSENSUS                                                                                                                                                                                   | X                    | Y | Y | W | S |     |
| H12, H18<br>H40, H43, H51<br>H31, H35<br>H41, H48                                                                                                                                           | S                    | Y | A | M | S |     |
|                                                                                                                                                                                             | S                    | Y | A | I | S |     |
|                                                                                                                                                                                             | S                    | Y | G | M | H |     |
|                                                                                                                                                                                             | S                    | Y | A | M | H |     |
| CONSENSUS                                                                                                                                                                                   | S                    | Y | A | M | S | H   |
| H27                                                                                                                                                                                         | S                    | H | G | M | H |     |
| H24                                                                                                                                                                                         | S                    | S | S | Y | Y | W G |

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Fig.8

| <u>Heavy Chain</u>                                                                                                                                                            |  | <u>CDR2 Sequence</u> |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H1, H2, H3, H5, H6,<br>H7, H10, H11, H13,<br>H14, H15, H16, H17,<br>H19, H20, H23, H25,<br>H26, H29, H30, H32,<br>H33, H34, H37, H38,<br>H39, H42, H44, H45,<br>H46, H47, H52 |  | E                    | I | Y | H | S | G | S | T | N | Y | N | P | S | L | K | S |
| H8                                                                                                                                                                            |  | E                    | I | Y | H | S | G | S | T | N | Y | N | P | S | L | E | S |
| H36, H49                                                                                                                                                                      |  | E                    | I | N | H | S | G | S | T | N | Y | N | P | S | L | K | S |
| H21                                                                                                                                                                           |  | E                    | V | Y | H | S | G | S | T | N | Y | N | P | S | L | K | S |
| H4                                                                                                                                                                            |  | E                    | I | N | H | S | G | S | T | N | Y | N | R | S | L | K | S |
| H9                                                                                                                                                                            |  | Y                    | I | Y | Y | S | G | S | T | Y | Y | N | P | S | L | K | S |
| H50                                                                                                                                                                           |  | T                    | I | Y | S | S | G | S | T | Y | Y | S | P | S | L | K | S |
| H24                                                                                                                                                                           |  | S                    | I | Y | Y | S | G | S | T | Y | Y | N | P | S | L | K | S |
| H28                                                                                                                                                                           |  | Y                    | I | S | D | S | G | N | T | N | Y | N | P | S | L | K | S |
| H22                                                                                                                                                                           |  | E                    | V | N | P | R | G | S | T | N | Y | N | P | S | L | K | S |
| CONSENSUS                                                                                                                                                                     |  | E                    | I | Y | H | S | G | S | T | N | Y | N | P | S | L | K | S |
|                                                                                                                                                                               |  | Y                    | V | N | Y |   |   |   |   | Y |   |   |   |   |   |   |   |
| H18                                                                                                                                                                           |  | T                    | I | S | G | S | G | G | S | T | Y | Y | A | D | S | V | K |
| H12                                                                                                                                                                           |  | A                    | I | S | G | S | G | G | S | T | Y | Y | A | D | S | V | K |
| H41                                                                                                                                                                           |  | T                    | I | S | S | N | G | D | S | T | Y | Y | A | D | S | V | K |
| H27, H31                                                                                                                                                                      |  | V                    | I | S | Y | D | G | S | N | K | Y | Y | A | D | S | V | K |
| H35                                                                                                                                                                           |  | Y                    | I | S | S | S | S | S | T | I | Y | Y | A | D | S | V | K |
| CONSENSUS                                                                                                                                                                     |  | X                    | I | S | G | S | G | G | S | T | Y | Y | A | D | S | V | K |
|                                                                                                                                                                               |  |                      |   |   | S |   |   | S |   |   |   |   |   |   |   |   |   |
| H40, H43                                                                                                                                                                      |  | R                    | I | I | P | I | L | G | I | A | N | Y | A | Q | K | F | Q |
| H48                                                                                                                                                                           |  | W                    | I | N | A | G | N | G | N | T | K | Y | S | Q | K | F | Q |
| H51                                                                                                                                                                           |  | I                    | I | N | P | S | G | G | S | T | S | Y | A | Q | K | F | Q |

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Fig.9

| <u>Heavy Chain</u> | <u>CDR3 Sequence</u> |   |   |   |   |   |   |   |   |   |   |   |         |
|--------------------|----------------------|---|---|---|---|---|---|---|---|---|---|---|---------|
| H5                 | -                    | Y | S | S | S | R | N | D | A | F | D | I |         |
| H6                 | -                    | - | - | D | G | Q | L | D | A | F | D | I |         |
| H9                 | -                    | - | - | W | S | Y | L | D | A | F | D | I |         |
| H11                | -                    | - | - | A | N | R | D | D | A | F | D | I |         |
| H13                | E                    | G | N | R | T | V | T | S | A | F | D | I |         |
| H16                | -                    | - | W | T | G | R | T | D | A | F | D | I |         |
| H17                | -                    | - | - | Q | G | A | L | D | A | F | D | I |         |
| H20                | -                    | S | S | S | W | Y | W | N | A | F | D | I |         |
| H25                | -                    | - | - | - | S | G | Y | D | A | F | D | I |         |
| H32                | -                    | - | - | - | A | S | V | D | A | F | D | I |         |
| H39                | -                    | - | - | L | S | F | A | D | P | F | D | I |         |
| H41                | -                    | - | E | E | V | W | L | Q | A | F | D | I |         |
| H45                | -                    | - | - | - | I | R | Y | D | A | F | D | I |         |
| H46                | -                    | - | - | T | A | A | H | D | A | F | D | I |         |
| H51                |                      |   | D | R | W | R | Y | D | A | F | D | I |         |
| CONSENSUS          | -                    | - | - | X | S | R | L | D | A | F | D | I |         |
|                    |                      |   |   |   |   |   |   |   |   |   |   |   |         |
| H7                 |                      |   | - | - | - | - | - | F | W | D | Y | Y | G M D V |
| H52                |                      |   |   |   |   |   |   |   |   | E | K | S | G M D V |
| H8                 |                      |   | - | - | - | - | - | - | D | R | Y | Y | G M D V |
| H10                |                      |   | - | - | - | - | - | D | Y | D | I | F | G M D V |
| H18                |                      |   | - | E | R | G | S | G | W | S | L | D | N M D V |
| H19                |                      |   | - | - | - | - | D | S | S | G | F | Y | G M D V |
| H24                |                      |   | - | - | - | D | G | G | Y | Y | Y | Y | G M D V |
| H48                |                      |   |   |   |   |   |   | H | S | Y | Y | Y | G M D V |
| H30                |                      |   | - | - | - | V | S | G | Y | Y | Y | Y | G M D V |
| H31                |                      |   | A | Y | S | S | G | W | Y | D | Y | Y | G M D V |
| H37                |                      |   | - | - | - | D | S | S | S | W | Y | Y | G M D V |
| H40                |                      |   | - | G | S | G | S | Y | Y | D | Y | Y | Y M D V |
| H42                |                      |   | - | - | - | - | - | - | - | D | K | G | Y M D V |
| CONSENSUS          |                      |   | - | - | - | - | S | X | Y | D | Y | Y | G M D V |
|                    |                      |   |   |   |   |   |   |   |   |   |   |   |         |
| H2                 | -                    | - | - | - | G | V | E | Q | I | D | Y |   |         |
| H3                 | -                    | - | N | L | A | A | G | A | V | A | Y |   |         |
| H4                 | -                    | - | L | S | Y | G | S | G | V | D | Y |   |         |
| H12                | -                    | G | G | W | Y | G | D | Y | F | D | Y |   |         |
| H23                | -                    | G | I | A | A | A | G | Q | G | D | Y |   |         |
| H26                | -                    | Y | S | Y | G | T | V | G | I | D | Y |   |         |
| H27                | -                    | - | - | I | G | P | G | G | F | D | Y |   |         |
| H29                | -                    | - | V | G | S | G | W | Y | V | D | Y |   |         |
| H34                | -                    | - | - | - | D | H | G | P | F | D | Y |   |         |
| H35                | D                    | R | F | G | S | G | H | L | P | D | Y |   |         |
| H36                | V                    | G | Y | S | S | G | R | D | V | D | Y |   |         |
| H38                | -                    | - | - | - | S | T | W | S | L | D | Y |   |         |
| H44                | -                    | - | - | D | L | T | G | S | L | D | Y |   |         |
| H47                | -                    | D | S | S | G | Q | G | Y | F | D | Y |   |         |
| CONSENSUS          | -                    | - | X | X | G | G | G | X | * | D | Y |   |         |

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**Fig.9 (cont)***"\*" = nonpolar side chain amino acids*

|               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H22           | G | P | R | P | G | R | D | G | Y | N | Y | F | D | N |
| H28           | - | - | - | H | R | S | S | W | A | W | Y | F | D | L |
| H43           | - | - | D | H | R | F | D | Y | A | W | Y | F | D | L |
| CONSENSUS     | - | - | X | H | R | X | D | X | A | W | Y | F | D | L |
| H1            | F | N | Y | Y | D | S | S | V |   |   |   |   |   |   |
| H14, H15, H33 | - | G | L | G | D | S | S | G | Y | I | L |   |   |   |
| H19           | - | - | - | - | D | S | S | G | F | Y | G | M | D | V |
| H37           | - | - | - | - | D | S | S | S | W | Y | Y | G | M | D |
| H47           | - | - | - | - | D | S | S | G | Q | G | Y | F | D | Y |
| CONSENSUS     | - | - | - | - | D | S | S | G | X | X | X | - | - | - |
| H21           | Y | R | S | F | G | E | S | Y |   |   |   |   |   |   |
| H49           | V | G | Y | S | H | G | E | E | V | L | D | V |   |   |
| H50           | A | R | G | Y | S | S | P | F | D | P |   |   |   |   |

Fig.10

**Kappa light chain constant region*****Nucleotide Sequence***

cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactg  
cctctgttgtgtgacctgctgaataacttctatcccagagaggccaaagtacagtggaagggtggataa  
cgccctccaatcgggtaactcccaggagagtggtcacagagcaggacagcaaggacagcacctacagc  
ctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtca  
cccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtggt

***Amino acid sequence***

rtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstys  
lsstltlskadyekhkvyacevthqglsspvtksfnrgec

**IgG1 heavy chain constant region*****Nucleotide Sequence***

gcctccaccaaggggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggacacag  
cgccctgggctgacctggtcaaggactacttccccgaaccgggtgacgggtgtcgtggaactcaggcgc  
cctgaccagcggcggtgcacaccttccgggtgtcctacagtcctcaggactctactccctcagcagc  
gtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagccca  
gcaacaccaaggtggacaagaaagttgagcccaaactcttgtagacaaaactcacacatgccaccgtg  
cccagcacctgaactcctgggggggaccgtcagtccttcttccccccaaaacccaaggacaccctc  
atgatctcccgaccctgaggtcacatgcgtgggtggacgtgagccacgaagaccctgaggtca  
agttcaactggtacgtggacggcggtggaggtgcataatgccaagacaaagccgcgggaggagcagta  
caacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactgggtgaatggcaaggag  
tacaagtgaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaag  
ggcagccccgagaaccacaggtgtacaccctgcccccatcccggtatgagctgaccaagaaccaggt  
cagcctgacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtgggagagcaatggg  
cagccggagaacaactacaagaccacgcctcccggtgctggactccgacggctccttcttctctata  
gcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatga  
ggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa

***Amino acid sequence***

astkgpsvfplapsskstsggtaalgclvkdyfpepvtvswnsgaltsgvhtfpavllqssglyslss  
vvtvpssslgtqtyicnvnhkpsntkvdkkvepkscdkthtcppcpapellggpsvflfppkpkdtl  
misrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngke  
ykckvsnkalpapiektiskakgqprepvytlppsrdeitknqvsitclvkgfypsdiavewesng  
qpennykttppvldsdgsfflyskltvdksrwqqgnvfscsvmhealhnhytqkslslspgk