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NCT01122199, ClinicalTrials.gov Archive, published 11 October 2011, [online]. Viewed on 6 September 2016. <URL:https://clinicaltrials.gov/archive/NCT01122199/2011_10_11>
QUEK R, et al., 'Combination mTOR and IG-1R Inhibtion: Phase 1 Trial of Everolimus and Figitumumab in Patients with Advanced Sarcomas and Other Solid Tumors,' Clinical Cancer Research, (2011), Vol 17, pp 871-879.
BELTRAN PF, et al., 'Efficacy of Ganitumab (AMG 479), Alone and in Combination with Rapamycin, in Ewing's and Osteogenic Sarcoma Models,' J Pharmacol Exp Ther, (March 2011), Vol 337, pp 644-654.

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

(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 medicament 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.

[00010] In yet another embodiment, the administering to the subject is simultaneous. In other embodiments, the administering to the subject is sequential.

[00011] 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 inhibitoris administered in an amount of about 12mg/kg or an amount of about 20 mg/kg.

[00012] 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.

[00013] 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 ±20% or ±10%, more preferably ±5%, even more preferably ±1%, and still more preferably ±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 (Insmed); 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 develop 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 inhibitorcan 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, Melvilee, 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 (Insmed, 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 (γ4), deposited at the ATCC under number PTA-5214, and a light chain encoded by a polynucleotide in plasmid 15H12/19D12 LCF (κ), 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/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, 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™, chlorambucil (CHL; e.g. LEUKERAN™), cisplatin (C is P; e.g. PLATINOL™) busulfan (e.g. MYLERAN™), melphalan, carmustine (BCNU), streptozotocin, triethylenemelamine (TEM), mitomycin C, and the like; anti-metabolites, such as methotrexate (MTX), etoposide (VP16; e.g. VEPESID™), 6-mercaptopurine (6 MP), 6-thiocguanine (6TG), cytarabine (Ara-C), 5-fluorouracil (5-FU), capecitabine (e.g. XELODA™), dacarbazine (DTIC), and the like; antibiotics, such as actinomycin D, doxorubicin (DXR; e.g. ADRIAMYCIN™), 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™) and pactitaxel derivatives, the cytostatic agents, glucocorticoids such as dexamethasone (DEX; e.g. DECADRON™) 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™), dactinomycin,

mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, lomustine (CCNU), doxorubicin lipo (e.g. DOXIL™), gemcitabine (e.g. GEMZAR™), daunorubicin lipo (e.g. DAUNOXOME™), procarbazine, mitomycin, docetaxel (e.g. TAXOTERE™, 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, triethylameine, 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 sue 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 ≥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 insterstitial lung disease, *e.g.*, pneumonitis or pulmonary fibrosis, or any evidence of interstitial ling disease on baseline chest CT scan; proteinuria at screening as demonstrated by either urine protein: creatine (UPC ratio >1.0 or 24hr collection > 1g/24hr 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 ≥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, cholanglocarcinoma

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 Grade 3 thrombocytopenia
-1	8*	None
1-b	6	Grade 2 intolerable skin rash and oral mucositis†

* 2 subjects were inevaluable for DLT

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

Table 4: Treatment-Related Grade ≥3 Adverse Events

Toxicity	**Grade 3**	**Grade 4**
Hematologic		
Neutropenia	1	0
Thrombocytopenia	3	0
Nonhematologic		
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 mucosilis. 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 a solid tumor 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, wherein the IGF1R inhibitor is ganitumab and the mTOR inhibitor is everolimus, wherein the solid tumor cancer is non-small cell lung cancer, a neuroendocrine tumor, a thymoma, a fibrous tumor, or an mCRC.

2. The method of claim 1, wherein the subject is refractory to standard therapy.

3. The method as in a claim 1 or claim 2, wherein the IGF1R inhibitor and mTOR inhibitor are co-administered to the subject in the same formulation.

4. 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.

5. 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.

6. 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.

7. The method as in any one of the preceding claims, wherein the administering to the subject is simultaneous.

8. The method as in any one of the preceding claims, wherein the administering to the subject is sequential.

9. The method as in any one of claims 1-8, in which the IGF1R inhibitor is administered in an amount of about 0.1 mg/kg to about 20 mg/kg or in an amount of about 5 mg/kg to about 15 kg.

10. The method according to claim 9, wherein the IGF1R inhibitor is administered in an amount of 12 mg/kg or in an amount of 20 mg/kg.

11. The method as in any one of claims 1-8, in which the mTOR inhibitor is administered in an amount of about 0.1 mg to about 10 mg, ~~or~~ in an amount of about 2 mg to about 8 mg, or in an amount of 5 mg.

12. The method as in any one of claims 1-11, 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.

13. The method as in any one of claims 1-11, 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.

14. 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.

15. 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.

16. The method of any one of claims 1-15 wherein the non-small cell lung cancer is an adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

17. The method of any of the preceding claims, wherein the subject is treated for at least two weeks, at least four weeks, at least eight weeks, at least three months, at least four months, at least six months, at least nine months, or at least one year.

18. A method of treating a non-small cell lung cancer (NSCLC), a neuroendocrine tumor, a thymoma, a fibrous tumor, or an mCRC in a subject, comprising administering to said subject 12 mg/kg ganitumab every two weeks and 5 mg everolimus daily, five days a week, or three days a week.

19. The method of claim 18 wherein the non-small cell lung cancer is an adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

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20. Use of an IGFIR inhibitor in combination with an mTOR inhibitor, wherein the IGFIR inhibitor is ganitumab and the mTOR inhibitor is everolimus, in the manufacture of a composition for the treatment of a non-small cell lung cancer (NSCLC), a neuroendocrine tumor, a thymoma, a fibrous tumor, or an mCRC.

Fig. 1

L1 (SEQ ID NO:1)

GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC
CTGGAGAGCC GGCCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT
AGTAGTGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG
ACAGGTTCAG 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 ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG
ACAGGTTCAG 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 ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG
ACAGGTTCAG 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 TACAACTATT 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 CAACTATTTG GATTGGTACC TGCAGAAGCC AGGGCAGTCT
CCACAGCTCC TGATCTATTT GGGTTCTAAT CGGGCCTCCG GGGTCCCTGA
CAGGTTCAGT GGCAGTGGAT CAGGCACAGA TTTTACACTG 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 ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG
ACAGGTTCAG 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 ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG
ACAGGTTCAG TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC
AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA
AACTCCTCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

L8 (SEQ ID NO:15)

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC 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
CAGGTTCAGT GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA
GAGTGGAGGC TGAGGATGTT GGGGTTTATT ACTGCATGCA AGCTCTACAA
ACTCCGTTCA CCTTCGGCCA AGGGACACGA CTGGAGATTA AA

L10 (SEQ ID NO:19)

GATGTTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA CCCCTGGAGA
GCCGGCCTCC ATCTCCTGCA GGTCTAGTCA GAGCCTCCTG CATAGTAATG
GATACAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA GTCTCCACAG
CTCCTGATCT ATTTGGGTTC TAATCGGGCC TCCGGGGTCC CTGACAGGTT
CAGTGGCAGT GGATCAGGCA CAGATTTTAC ACTGAAAATC AGCAGAGTGG
AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAGCTCT ACAAACTCCT
CTGGCGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAA

Fig. 1 (cont)

L11 (SEQ ID NO:21)

GAAATTGT GCTGACTCAG TCTCCACTCT CCCTGCCCGT 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
ACAGGTTCAG 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
TGACAGGTTC AGTGGCAGTG GATCAGGCAC AGATTTTACA CTGAAAATCA
GCAGAGTGGA GGCTGAGGAT GTTGGGGTTT ATTACTGCAT GCAAGCTCTA
CAAACTCCTC TTACTTTCGG CGGAGGGACC AAGGTGGAGA TCAAA

L15 (SEQ ID NO:29)

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAACT 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 CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA
GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGGGTG
GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGGTA CACACTGGCC
TCTGACGTTC GGCCAAGGGA CCAAGGTGGA GATCAAA

L17 (SEQ ID NO:33)

GAAATTG TGATGACGCA GTCTCCACTC TCCCTGCCCG TCACCCCTGG
AGAGCCGGCC TCCATCTCCT GCAGGTCTAG TCAGAGCCTC CTGCATAGTA
ATGGATACAA CTATTTGGAT TGGTACCTGC AGAAGCCAGG GCAGTCTCCA
CAGCTCCTGA TCTATTTGGG TTCTAATCGG GCCTCCGGGG TCCCTGACAG
GTTCAGTGGC AGTGGATCAG GCACAGATTT TACACTGAAA ATCAGCAGAG
TGGAGGCTGA GGATGTTGGG GTTTATTACT GCATGCAAGC TCTACAAACT
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 GACAGATTTC ACTCTCACCA TCAGCAACCT GCAGCCTGAA
GATTTTGCAA CTTACTATTG TCAACAGGCT AGCAGTTTTC 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
ACAGGTTCAG TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC
AGAGTGGAGG CTGAGGATGT TGGAGTTTAT TACTGCATGC AAGCTCTACA
AACTCCGTAC ACTTTTGGCC AGGGGACCAA GCTGGAGATC AAA

L20 (SEQ ID NO:39)

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC AGTCTCCACA
GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTAACAGGT
TCAGTGGCAG TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG
GAGGCTGAGG ATGTTGGGGT TTATTACTGC ATGCAAGCTC TACAAACTCC
ATTCACTTTC GGCCCTGGGA CCAAAGTGGA TATCAAA

Fig. 1 (cont)

L21 (SEQ ID NO:41)

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTCAT
GGATACAACT 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
ACAGGTTCAG 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
ACAGGTTCAG TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC
AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA
AACTCCTAAC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

L25 (SEQ ID NO:49)

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

Fig. 1 (cont)

L26 (SEQ ID NO:51)

GATGTTGT GATGACTCAG TCTCCACTCT CCCTGCCCGT 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
TGTTGGCTGG TATCAGCAAA AGGCAGGCCA AGCCCCTGTT TTGGTCATCT
ATCAAGACAA CAAGCGACCC TCAGGGATCC CTGAGCGATT CTCTGGCTCC
AACTCTGGGA ACACAGCCAG TCTGACCATC AGCGGGACCC AGGCTATGGA
TGAGGCTGAC TATTACTGTC AGGCGTGGGA CAGCGGCACG GTGTTCGGCG
GAGGGACCAA GCTGACCGTC CTA

L29 (SEQ ID NO:57)

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

L30 (SEQ ID NO:59)

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

Fig. 1 (cont)

L31 (SEQ ID NO:61)

GACATC CAGTTGACCC AGTCTCCATC CTCCCTGTCT GCGTCTGTGG
GAGACAGAGT CACCATCACT TGCCGGTCAA GTCAAGGCAT TGGTTACTTC
TTAAATTGGT ATCAGCAGGA ACCAGGGAAA 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 GGCCTCCATC TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT
AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG
ACAGGTTCAG TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC
AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA
AACTCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

L33 (SEQ ID NO:65)

GAAATTGTG CTGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAACT 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 CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAACT 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 CAACAACTAT
GTGCAGTGGT ACCAGCAGCG CCCGGGCAAT TCCCCCACCA ATGTGATTTA
TGAGGATAAC CGAAGACCCT CTGGGGTCCC GGATCGCTTC TCTGGCTCCA
TCGACAGCTC CTCCAACTCT GCCTCCCTCA CCATCTCTGG ACTGCAGCCT
GAGGACGAGG CTGACTACTA TTGTCAGTCT 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 TCCCCCACCA CTGTGATCTA
TGAGGATAAC CAAAGACCCT CTGGGGTCCC TGATCGATTC TCTGGCTCCA
TCGACAGCTC CTCCAACTCT GCCTCCCTCA CCATCTCTGG ACTGAAGACT
GAGGACGAGG CTGACTACTA CTGTCAGTCT TATGATAGCA GCAATGTGGT
GTTCGGCGGA GGGACCAAGC TGACCGTCCT A

L37 (SEQ ID NO:73)

GATGTTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA CCCCTGGGGA
GCCGGCCTCC ATCTCCTGCA GGTCTAGTCA GAGCCTCCTG CATAGTAATG
GATACAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA GTCTCCACAG
CTCCTGATCT ATTTGGGTTC TAACCGGGAC TCTGGGGTCC CAGACAGATT
CAGCGGCAGT GGGTCAGGCA CTGATTTCAC ACTGAAAATC AGCAGGGTGG
AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAGGTAC ACACTGGCCG
TACACTTTTG GCCAGGGGAC CAGGCTGGAG ATCAAA

L38 (SEQ ID NO:75)

GATGTTGT GATGACTCAG TCTCCACTCT CCCTGCCCGT CACCCCTGGA
GAGTCGGCCT CCATCTCCTG CAGGTCTAGT CAGAGCCTCC TGCATAGTAA
TGGATACAAC TTTTTGGATT GGTACCTGCA GAAGCCAGGG CAGTCTCCAC
AGCTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG
TTCAGTGGCA GTGGATCAGG CACAGATTTT ACACTGAAAA TCAGCAGAGT
GGAGGCTGAG GATGTTGGGG TTTATTACTG CATGCAAGCT CTACAAACTC
CTCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

L39 (SEQ ID NO:77)

GA TGTTGTGATG ACTCAGTCTC CACTCTCCCT GCCCGTCACC
CCTGGAGAGC CGGCCTCCAT CTCCTGCAGG TCTAGTCAGA GCCTCCTGCA
TAGTAATGGA TACAACTATT TGGATTGGTA CCTGCAGAAG CCAGGGCAGT
CTCCACAGCT CCTGATCTAT TTGGGTTCTA ATCGGGCCTC CGGGGTCCCT
GACAGGTTCA GTGGCAGTGG ATCAGGCACA GATTTTACAC TGAAAATCAG
CAGAGTGGAG GCTGAGGATG TTGGGGTTTA TTACTGCATG 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 CCAGGTTCAG 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 AGCCCCTAAA CTCCTGATCT
ACGCTACATC CACTCTGGAA AGTGGGGTCC CCCCCAGGTT CACCGGCAGT
GGATCTGGGA CAGATTTCAC TCTCACCATC AGCAGTCTGC AACCTGAGGA
CTTTGCAACT TACTACTGTC AACAGAGTAA CAGTGTTCCG CTCACTTTCG
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
AGGTTCAGTG 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 AGCCAGGTTC AGTGGCAGTG
GGTCTGGGAC AGACTTCACT CTCACCATCA GCAGACTGGA GCCTGAAGAT
TTTGCAGTGT ATTACTGTCA GCAGCGTAGC AACTGGCCCC TCACTTTCGG
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
AGGTTCAGTG 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 ACAACTATTT GGATTGGTAC CTGCAGAAGC CAGGGCAGTC
TCCACAGCTC CTGATCTACT TGGGTTCTAC TCGGGCCTCC GGCGTCCCTG
ACAGGTTCAG TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC
AGAGTGGAGG CTGAGGATGT TGGGGTTTAT TACTGCATGC AAGCTCTACA
AACTCCTTAC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

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 GGTTCTAATC GGGCCTCCGG GGTCCCTGAC
AGGTTCAGTG 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 GGTTTTAATC GGGCCTCCGG GGTCCCTGAC
AGGTTCAGTG GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG
AGTGGAGGCT GAGGATGTTG GGGTTTATTA CTGTATGCAA GGTCTACAAA
CTCCCCTCAC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A

L48 (SEQ ID NO:95)

GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG
AGCCGGCCTC CATCTCCTGC AGGTCTAGTC AGAGCCTCCT GCATAGTAAT
GGATACAACT 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 GTGCCCCCAC CATTGTAATC
TATGAGGATA ACCAAAGACC CTCTGCGGTC CCTACTCGGT TCTCTGGCTC
CATCGACAGG TCCTCCAACT CTGCCTCCCT CACCATCTCT GGACTGACGA
CTGAGGACGA GGCTGACTAC TACTGTCAGT CTTATGATAG CGCCAATGTC
ATTTTCGGCG GGGGGACCAA GCTGACCGTC CTA

L50 (SEQ ID NO:99)

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

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 CTCCTCCAAC TCTGCCTCCC TCACCATCTC TGGACTGAAG
ACTGAAGACG AGGCTGACTA CTACTGTCAG TCTTATGATC CCTACAATCG
AGTGTTCGGC 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
CAGGTTCAGT GGCAGTGGAT CGGGCACAGA TTTTACACTG AAAATCAGCA
GAGTGGAGGC TGAGGATGTT GGGGTTTATT ACTGCATGCA AGCTTTTCAA
ACTCCGCTCA CTTTCGGCGG AGGGACCAAG ATGGAGATCA AA

H1 (SEQ ID NO:105)

GAGGTGCAGC TGGTGGAGAC 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 GAGATTTAAT
TACTATGATA GTAGTGTCTG GGGCCAGGGA ACCCTGGTCA CCGTCTCAAG
C

H2 (SEQ ID NO:107)

GAGGTGCAGC TGGTGGAGAC 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 GAGAGGGGTT
GAGCAGATTG ACTACTGGGG CCAGGGAACC CTGGTCACCG TCTCAAGC

H3 (SEQ ID NO:109)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC
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

Fig. 1 (cont)

H4 (SEQ ID NO:111)

CAGGTGCAG CTACAGCAGT GGGGCGCAGG ACTGTTGAAG CCTTCGGAGA
CCCTGTCCCT CACCTGCGCT GTCTCTGGTG GGTCCTTCAG 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 GGCCCAGGAC 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 TTACTGTGCG
AGGTATAGCA GCAGCCGCAA TGATGCTTTT GATATCTGGG GCCAAGGGAC
AATGGTCACC GTCTCAAGC

H6 (SEQ ID NO:115)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA 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 GAGAGATGGG
CAGCTGGATG CTTTTGATAT CTGGGGCCAA GGGACAATGG TCACCGTCTC
AAGC

H7 (SEQ ID NO:117)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA 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 GAGATTTTGG
GACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG TCACCGTCTC
AAGC

Fig. 1 (cont)

H8 (SEQ ID NO:119)

CAGGTG CAGCTACAGC AGTGGGGCCC AGGACTGGTG AAGCCTTCGG
GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC 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 TTACTGTGCG
AGATGGAGCT ACTTGGATGC TTTTGATATC TGGGGCCAAG GGACAATGGT
CACCGTCTCA AGC

H10 (SEQ ID NO:123)

GAGGTGC AGCTGGTGGA GTCTGGCCCA GGACTGGTGA 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 CTGGAGTGGA
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 TGACTAGTGC 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
GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC 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
GTAACTGGTG 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
GGACCCTGTC 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
GGACCCTGTC CCTCACCTGC TCTGTCTCTG GTGTCTCCAT CACCAGTAAT
ATCTGGTGGA GTTGGGTCCG CCAGTCCCCA GGGAAGGGGC TGGAGTGGAT
TGGGGAAGTC 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 AGAGGTCCTC
GGCCCGGGAG AGATGGCTAC AATTACTTTG ACAACTGGGG CCAGGGCACC
CTGGTCACCG TCTCAAGC

H23 (SEQ ID NO:149)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA 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 GAGAGGTATA
GCAGCAGCTG GTCAAGGTGA CTACTGGGGC CAGGGAACCC TGGTCACCGT
CTCAAGC

Fig. 1 (cont)

H24 (SEQ ID NO:151)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC
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
GGACCCTGTC CCTCACCTGC GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT
AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC TGGAGTGGAT
TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA
GTCGAGTCAC CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG
CTGAGCTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGTAG
TGGTTATGAT 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 AGGGCACCCT GGTCACCGTC
TCAAGC

Fig. 1 (cont)

H28 (SEQ ID NO:159)

CAG GTGCAGCTGC AGGAGTCCGG CCCAGGACTG GTGAAGCCTT
CGGAGACCCT GTCCCTCACC TGCACTGTCT CTGGTGGCTC CATTAGAAAT
TACTACTGGA GTTGGATCCG GCAGCCCCCA GGGAAGGGAC 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 GGCCCAGGAC 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 TTACTGTGCG
AGAGTGGGCA GTGGCTGGTA CGTTGACTAC TGGGGCCAGG GAACCCTGGT
CACCGTCTCA AGC

H30 (SEQ ID NO:163)

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 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
CGATTCACCA 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 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 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 AACCCTGGTC 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 GGGAACCCTG
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 GGACTGGTGA 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 CATAGTGGGA 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 AGCAAACTAC GCACAGAAGT TCCAGGGCAG
AGTCACGATT ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA
GCAGCCTGAG ATCTGAGGAC ACGGCCGTGT ATTACTGTGC ATATGGTTCG
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 ATAGCAAACT ACGCACAGAA GTTCCAGGGC
AGAGTCACGA TTACCGCGGA CAAATCCACG AGCACAGCCT ACATGGAGCT
GAGCAGCCTG AGATCTGAGG ACACGGCCGT GTATTACTGT GCGAGAGATC
ATAGGTTCGA CTACGCCTGG TACTTCGATC TCTGGGGCCG TGGCACCCTG
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 TTTGATATCT GGGGCCAAGG 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 GGGCACCCTG
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 ATATTCACAG 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 CTTCAGTGGT
TACTACTGGA GCTGGATCCG CCAGCCCCCA GGGAAGGGGC 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
TGACTGGAGT 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 TCACCATTAC 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
TTCGGGGACC CTGTCCCTCA CCTGCGCTGT CTCTGGTGGC TCCATCAGCA
GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA GGGGCTGGAG
TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT
CAAGAGTCGA GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC
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)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSSGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPIT***FGQGTRLEIK

L2 (SEQ ID NO:4)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPIT***FGQGTRLEIK

L3 (SEQ ID NO:6)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK

L4 (SEQ ID NO:8)
EIVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPHT***FGGGTKVEIK

L5 (SEQ ID NO:10)
EIVLTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGPGTKVDIK

L6 (SEQ ID NO:12)
DVVMTQSPLSLAVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK

L7 (SEQ ID NO:14)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK

L8 (SEQ ID NO:16)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK

L9 (SEQ ID NO:18)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPFT***FGQGTRLEIK

L10 (SEQ ID NO:20)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLA***FGQGTKVEIK

L11 (SEQ ID NO:22)
EIVLTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLN***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSASGSGTDFTLKISRVEAEDVGVYYC***MQALQTPIT***FGQGTRLEIK

L12 (SEQ ID NO:24)
NFMLTQPHSVSESPGKTVTISC***TRSSGSIASNYVQ***WYQQRPGSSPTTVIY***EDNQRPS***GVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC***QSYDSSNQRV***FGGGTKLTVL

L13 (SEQ ID NO:26)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK

L14 (SEQ ID NO:28)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK

L15 (SEQ ID NO:30)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSYRAS***GVPDRFSASGSGTDFTLKISRVEAEDVGVYYC***MQALQTPIT***FGQGTRLEIK

Fig. 2 (cont)

L16 (SEQ ID NO:32)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQGTHWPLT***FGQGTKVEIK
L17 (SEQ ID NO:34)
EIVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L18 (SEQ ID NO:36)
DIQLTQSPSSVSASVGDRVTITC***RASQGISRWLA***WYQQKPGKAPRLLIY***AASGLQS***GVPSRFSGSGSGTDFTLTISNLQPEDFATYYCQQASS***FPITFGQGT***RLETK
L19 (SEQ ID NO:38)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPYT***FGQGTKLEIK
L20 (SEQ ID NO:40)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPNRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPFT***FGPGTKVDIK
L21 (SEQ ID NO:42)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSHGYNYLD***WYLQKPGQSPQLLIY***LGSYRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQSLEVPFT***FGQGTKLEIK
L22 (SEQ ID NO:44)
SSELTQDPAVSVALGQTVRITC***QGDSLRIYYTG***WYQQKPGQAPVLVLF***GKNNRPS***GIPDRFSGSHSGNTASLTITGAQAEDEADYYC***NSRDITGVHR***FGGGTKLTVL
L23 (SEQ ID NO:46)
EIVLTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L24 (SEQ ID NO:48)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPNT***FGGGTKVEIK
L25 (SEQ ID NO:50)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPIT***FGPGTKVDIK
L26 (SEQ ID NO:52)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYTYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEPEDVGVYYC***MQALEMPLT***FGGGTKVEIK
L27 (SEQ ID NO:54)
DIQLTQSPSFLSASVGDRVTITC***RASQGISSYLA***WYQQKPGKAPKLLIY***AASTLQS***GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC***QQLNSYPLT***FGGGTKVEIK
L28 (SEQ ID NO:56)
SYVLTQPPSVSVSPGQTASITC***SGDKLGDKYVG***WYQQKAGQAPVLVIY***QDNKRPS***GIPERFSGSNSGNTASLTISGTQAMDEADYYC***QAWDSGTV***FGGGTKLTVL
L29 (SEQ ID NO:58)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ***ALQTPLT***FGGGTKVEIK
L30 (SEQ ID NO:60)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MEALQTPFT***FGPGTKVEIK
L31 (SEQ ID NO:62)
DIQLTQSPSSLSASVGDRVTITC***RSSQGIGYFLN***WYQQEPGKAPKILIS***AASTLQS***GVPSRFSGSGSGTDFTLSINNLQPADFATYYC***QQSHSPPYT***FGQGTKVEIK
L32 (SEQ ID NO:64)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L33 (SEQ ID NO:68)
EIVLTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLMY***LVSNRAS***GVPERFSGSGSGTDFTLKISRVEAEDVGVYYC***MQTLQTPLS***FGQGTKLEIK

Fig. 2 (cont)

L34 (SEQ ID NO:70)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L35 (SEQ ID NO:72)
NFMLTQPHSVSASPGKTVTISC***TRSSGDIDNNYVQ***WYQQRPGNSPTNVIY***EDNRRPS***GVPDRFSGSIDSSSNSASLTISGLQPEDEADYYC***QSYQSDNWV***FGGGTKVTVL
L36 (SEQ ID NO:74)
NFMLTQPHSVSESPGKTVTISC***TRSSGSIASNYVQ***WYQQRPGSSPTTVIY***EDNQRPS***GVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC***QSYDSSNVV***FGGGTKLTVL
L37 (SEQ ID NO:76)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRDS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQGTHWPYT***FGQGTRLEIK
L38 (SEQ ID NO:78)
DVVMTQSPLSLPVTPGESASISC***RSSQSLLHSNGYNFLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L39 (SEQ ID NO:80)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L40 (SEQ ID NO:82)
ETTLTQSPATLSLSPGQRATLSC***RASQSVYNYLA***WYQQKPGQAPRLLIY***DASRRAT***GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC***QQRNNWPLT***FGGGTKVEIK
L41 (SEQ ID NO:84)
DIQLTQSPSSLSASVGDSVTISC***RASQSPGIFLN***WYQQIPGKAPKLLIY***ATSTLES***GVPPRFTGSGSGTDFTLTISSLQPEDFATYYC***QQSNSVPLT***FGGGTKVEIK
L42 (SEQ ID NO:86)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGQGTRLEIK
L43 (SEQ ID NO:88)
EIVMTQSPATLSVSPGERATFSC***RASQSVGSNLA***WYQQKPGQAPRLLIY***DASNRAT***GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC***QQRSNWPLT***FGGGTKVEIK
L44 (SEQ ID NO:90)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L45 (SEQ ID NO:92)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSTRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPYT***FGGGTKVEIK
L46 (SEQ ID NO:94)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQALQTPLT***FGGGTKVEIK
L47 (SEQ ID NO:96)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHTNGYNYLD***WYLQKPGQSPRLLIY***LGFNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQGLQTPLT***FGGGTKVEIK
L48 (SEQ ID NO:98)
DVVMTQSPLSLPVTPGEPASISC***RSSQSLLHSNGYNYLD***WYLQKPGQSPQLLIY***LGSNRAS***GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC***MQATHWPYT***FGQGTKLEIK
L49 (SEQ ID NO:100)
NFMLTQPHSVSESPGKTVSISC***TRNSGSIASNFVQWYQ***QRPGSAPTIVIY***EDNQRPS***AVPTRFSGSIDRSSNSASLTISGLTTEDEADYYC***QSYDSANVI***FGGGTKLTVL
L50 (SEQ ID NO:102)
ETTLTQSPGTLSLSPGERATLSC***RASQTISSSHLA***WYQQKPGQSPRLLIY***GAGYRAT***GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC***QHYGSSLRT***FGQGTKVEIK
L52 (SEQ ID NO:104)
EIVMTQSPLSLPVTPGEPASISC***RSSQSLLHTNGYDYLD***WYLQKP

Fig. 3

HEAVY CHAIN VARIABLE REGION SEQUENCES

FR1 *CDR1* FR2 *CDR2* FR3 *CDR3* FR4

H1 (SEQ ID NO:106)
EVQLVETGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***FNYYDSSV***WGQGTLVTVS
S
H2 (SEQ ID NO:108)
EVQLVETGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***GVEQIDY***WGQGTLVTVSS
H3 (SEQ ID NO:110)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAK***NLAAGAVAY***WGQGTLVTV
SS
H4 (SEQ ID NO:112)
QVQLQQWGAGLLKPSETLSLTCAVSGGSFS***GYYWS***WIRQPPGKGLEWIG***EINHSGSTNYNRSLKS***RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***LSYGSGVDY***WGQGTLVTVS
S
H5 (SEQ ID NO:114)
QLQLQESGPGLVKPSQTLSLTCTVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***YSSSRNDAFDI***WGQGTMV
TVSS
H6 (SEQ ID NO:116)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DGQLDAFDI***WGQGTMVTV
SS
H7 (SEQ ID NO:118)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***FWDYYGMDV***WGQGTTVTV
SS
H8 (SEQ ID NO:120)
QVQLQQWGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLES***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DRYYGMDV***WGQGTTVTVS
S
H9 (SEQ ID NO:122)
EVQLVESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***YIYYSGSTYYNPSLKS***RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR***WSYLDAFDI***WGQGTMVTV
SS
H10 (SEQ ID NO:124)
EVQLVESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DYDIFGMDV***WGQGTTVTV
SS
H11 (SEQ ID NO:126)
QLQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQSSLKLSSVTAADTAVYYCAR***ANRDDAFDI***WGQGTMVTV
SS

Fig. 3 (cont)

H12 (SEQ ID NO:128)
EVQLVESGGGLVQPGGSLRLSCAASGFTFS***SYAMS***WVRQAPGKGLEWVS***AISGSGGSTYYADSVKG***RFTISRDNSKNTLYLQMNSLSADDTAVYFCAS***GGWYGDYFDY***WGQGTLVT
VSS
H13 (SEQ ID NO:130)
QVQLQESGPGLVKPSETLSLTCTVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***EGNRTVTSAFDI***WGQGTM
VTVSS
H14 (SEQ ID NO:132)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***GLGDSSGYIL***WGQGTMVT
VSS
H15 (SEQ ID NO:134)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***GLGDSSGYIL***WGQGTMVT
VSS
H16 (SEQ ID NO:136)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***WTGRTDAFDI***WGQGTMVT
VSS
H17 (SEQ ID NO:138)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***QGALDAFDI***WGQGTTVTV
SS
H18 (SEQ ID NO:140)
EVQLVESGGGVVRPGGSLRLSCAASGFTFS***SYAM***SWVRQAPGKGLEWVS***TISGSGGSTYYADSVKG***RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK***ERGSGWSLDNMDV***WGQGT
TVTVSS
H19 (SEQ ID NO:142)
QVQLVESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DSSGFYGMDV***WGQGTTVT
VSS
H20 (SEQ ID NO:144)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***SSSWYWNAFDI***WGQGTMV
TVSS
H21 (SEQ ID NO:146)
QVQLQQWGPALVKPSGTLSLTCSVSGVSIT***SNIWWS***WVRQSPGKGLEWIG***EVYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAG***YRSFGESY***WGQGTLVTVS
S
H22 (SEQ ID NO:148)
QVQLQQWGAGLLKPSETLSLTCVVYGGSFS***DFYWS***WIRQPPGKGPEWIG***EVNPRGSTNYNPSLKS***RATISLDTSKNQFSLKLSSVTAADTAVYFCAR***GPRPGRDGYNYFDN***WGQGT
LVTVSS
H23 (SEQ ID NO:150)
QVQLQESGPGLVKPSETLSLTCTVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***GIAAAGQGDY***WGQGTLVT
VSS

Fig. 3 (cont)

H24 (SEQ ID NO:152)
QVQLQESGPGLVKPSETLSLTCTVSGGSIS***SSSYYWG***WIRQPPGKGLEWIG***SIYYSGSTYYNPSLKS***RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***DGGYYYYGMDV***WGQGTT
VTVSS

H25 (SEQ ID NO:154)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAS***SGYDAFDI***WGQGTTVTVS
S

H26 (SEQ ID NO:156)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***YSYGTVGIDY***WGQGTLVT
VSS

H27 (SEQ ID NO:158)
EVQLVQSGGGVVQPGTSLRLSCAASGFSFR***SHGMH***WVRQAPGKGLEWVA***VISYDGSNKYYADSVKG***RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAT***IGPGGFDY***WGQGTLVTVS
S

H28 (SEQ ID NO:160)
QVQLQESGPGLVKPSETLSLTCTVSGGSIR***NYYWS***WIRQPPGKGLEWIG***YISDSGNTNYNPSLKS***RVTISVDTSKNQFSLKLTSVTATDTAAYFCAR***HRSSWAWYFDL***WGRGTLVT
VSS

H29 (SEQ ID NO:162)
QVQLQESGPGLVKPSETLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***VGSGWYVDY***WGQGTLVTV
SS

H30 (SEQ ID NO:164)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***VSGYYYYGMDV***WGQGTTV
TVSS

H31 (SEQ ID NO:166)
EVQLVQSGGGVVQPGRSLRLSCAASGFTFS***SYGMH***WVRQAPGKGLEWVA***VISYDGSNKYYADSVKG***RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK***AYSSGWYDYYGMDV***WGQG
TTVTVSS

H32 (SEQ ID NO:168)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***ASVDAFDI***WGQGTMVTVS
S

H33 (SEQ ID NO:170)
QVQLQESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***GLGDSSGYIL***WGQGTMVT
VSS

H34 (SEQ ID NO:172)
QVQLQQSGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTPEDTAVYYCAR***DHGPFDY***WGRGTLVTVSS

H35 (SEQ ID NO:174)
QVQLVQSGGGVVQPGRSLRLSCAASGFAFS***SYGMH***WVRQAPGKGLEWVS***YISSSSSTIYYADSVKG***RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR***DRFGSGHLPDY***WGQGTLV
TVSS

H36 (SEQ ID NO:176)
QVQLQQWGAGLLKPSETLSLTCAVYGGSFS***GYYWS***WIRQPPGKGLEWIG***EINHSGSTNYNPSLKS***RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***VGYSSGRDVDY***WGQGTLVT
VSS

Fig. 3 (cont)

H37 (SEQ ID NO:178)
EVQLVESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WIRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DSSSWYYGMDV***WGQGTTV
TVSS
H38 (SEQ ID NO:180)
EVQLVESGPGLVKPSETLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***STWSLDY***WGQGTLVTVSS
H39 (SEQ ID NO:182)
EVQLVESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***LSFADPFDI***WGQGTMVTV
SS
H40 (SEQ ID NO:184)
QVQLVQSGAEVKKPGSSVKVSCKASGGTFS***SYAIS***WVRQAPGQGLEWMG***RIIPILGIANYAQKFQG***RVTITADKSTSTAYMELSSLRSEDTAVYYCAY***GSGSYYDYYYMDV***WGKGT
TVTVSS
H41 (SEQ ID NO:186)
EVQLVQSGGGLVQPGGSLRLSCSASGFTFS***SYAMH***WVRQAPGKGLEYVS***TISSNGDSTYYADSVKG***RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK***EEVWLQAFDI***WGQGTMVT
VSS
H42 (SEQ ID NO:188)
QLQLQESGPGLVKPSETLSLTCTVSGGSIS***SNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***DKGYMDV***WGKGTTVTVSS
H43 (SEQ ID NO:190)
QVQLQQSGAEVKKPGSSVKVSCKASGGTFS***SYAIS***WVRQAPGQGLEWMG***RIIPILGIANYAQKFQG***RVTITADKSTSTAYMELSSLRSEDTAVYYCAR***DHRFDYAWYFDL***WGRGTL
VTVSS
H44 (SEQ ID NO:192)
QVQLQESGPGLLKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGEGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DLTGSLDY***WGQGTLVTVS
S
H45 (SEQ ID NO:194)
QVQLQESGPGLVKPSGTSLTCAVSGGSISS***SNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***IRYDAFDI***WGQGTMVTVSS
H46 (SEQ ID NO:196)
QVQLQESGPGLVKPSETLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAV***TAAHDAFDI***WGQGTMVTV
SS
H47 (SEQ ID NO:198)
QVQLQQWGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***DSSGQGYFDY***WGQGTLVT
VSS
H48 (SEQ ID NO:200)
EVQLVQSGAEVKKPGASVKVSCKASGYTFT***SYAMH***WVRQAPGQRLEWMG***WINAGNGNTKYSQKFQG***RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR***HSYYYGMDV***WGQGTLVTV
SS
H49 (SEQ ID NO:202)
QVQLQQWGAGLLKPSETLSLTCAVYGGSFS***GYYWS***WIRQPPGKGLEWIG***EINHSGSTNYNPSLKS***RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***VGYSHGEEVLDV***WGKGTTV
TVSS

Fig. 3 (cont)

H50 (SEQ ID NO:204)
QVQLQESGPGLVKPSETLSLTCTVSGGSIG***NYDWS***WIRQPPGKGLEWIG***TIYSSGSTYYSPSLKS***RLTISVDKSKNRFSLKLSSVTAADTAVYYCAR***ARGYSSPFDP***WGQGTLVTV
SS
H51 (SEQ ID NO:206)
QVQLVQSGAEVKKPGSSVKVSCKASGGTFS***SYAIS***WVRQAPGQGLEWMG***IINPSGGSTSYAQKFQG***RVTITRDTSASTAYMELSSLRSEDTAVYYCAR***DRWRYDAFDI***WGQGTMVT
VSS
H52 (SEQ ID NO:208)
VQLVESGPGLVKPSGTLSLTCAVSGGSIS***SSNWWS***WVRQPPGKGLEWIG***EIYHSGSTNYNPSLKS***RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR***EKSGMDV***WGQGTTVTVSS

Fig.4

Light Chain	CDR1 Sequence															
L2, L3, L4, L5, L6, L7, L8, L9, L10, L13, L14, L15, L16, L17, L19, L20, L23, L24, L25, L29, L30, L32, L33, L34, L37, L39, L42, L44, L45, L46, L48	R	S	S	Q	S	L	L	H	S	N	G	Y	N	Y	L	D
L1	R	S	S	Q	S	L	L	H	S	S	G	Y	N	Y	L	D
L11	R	S	S	Q	S	L	L	H	S	N	G	Y	N	Y	L	N
L21	R	S	S	Q	S	L	L	H	S	H	G	Y	N	Y	L	D
L26	R	S	S	Q	S	L	L	H	S	N	G	Y	T	Y	L	D
L38	R	S	S	Q	S	L	L	H	S	N	G	Y	N	F	L	D
L47	R	S	S	Q	S	L	L	H	T	N	G	Y	N	Y	L	D
L52	R	S	S	Q	S	L	L	H	T	N	G	Y	D	Y	L	D
CONSENSUS	R	S	S	Q	S	L	L	H	S	N	G	Y	N	Y	L	D
L51	T G	S	G	G	N	I	A	S	N	Y	V	Q				
L12, L36	T R	S	S	G	S	I	A	S	N	Y	V	Q				
L35	T R	S	S	G	D	I	D	N	N	Y	V	Q				
L49	T R	N	S	G	S	I	A	S	N	F	V	Q	W	Y	Q	
L50	R	A	S	Q	T	I	S	S	S^ H	L	A					
L18	R	A	S	Q	G	I	S	R	W	L	A					
L27	R	A	S	Q	G	I	S	S	Y	L	A					
L40	R	A	S	Q	S	V	Y	N	Y	L	A					
L43	R	A	S	Q	S	V	G	S	N	L	A					
L31	R	S	S	Q	G	I	G	Y	F	L	N					
L41	R	A	S	Q	S	P	G	I	F	L	N					
CONSENSUS	R	A	S	Q	G S	I V	G S	X	Y F	L	A N					
L28	S	G	D	K	L	G	D	K	Y	V	G					
L22	Q	G	D	S	L	R	I	Y	Y	T	G					
OVERALL CONSENSUS	R	S	S	Q	S	L I	X	X	X	X	X	X	X	X	X	X

Fig.5

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

Fig.6

Light Chain	CDR3 Sequence									
L3, L5, L6, L7, L8 L13, L14, L17, L23, L29, L32, L34, L38, L39, L42, L44, L46	M	Q	A	L	Q	T	P	L	T	
L52	M	Q	A	F	Q	T	P	L	T	
L1, L2, L11, L15, L25	M	Q	A	L	Q	T	P	I	T	
L19, L45	M	Q	A	L	Q	T	P	Y	T	
L9, L20	M	Q	A	L	Q	T	P	F	T	
L4	M	Q	A	L	Q	T	P	H	T	
L24	M	Q	A	L	Q	T	P	N	T	
L10	M	Q	A	L	Q	T	P	L	A	
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 S	N S	S N	*	P	L	T	

"" = 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

Fig.7

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

Fig.8

Heavy Chain	CDR2 Sequence															
H1, H2, H3, H5, H6, H7, H10, H11, H13, H14, H15, H16, H17, H19, H20, H23, H25, H26, H29, H30, H32, H33, H34, H37, H38, H39, H42, H44, H45, 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/Y	I/V	Y/N	H/Y	S	G	S	T	N/Y	Y	N	P	S	L	K	S
H18	T	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
H12	A	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
H41	T	I	S	S	N	G	D	S	T	Y	Y	A	D	S	V	K	G
H27, H31	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S	V	K	G
H35	Y	I	S	S	S	S	S	T	I	Y	Y	A	D	S	V	K	G
CONSENSUS	X	I	S	G/S	S	G	G/S	S	T	Y	Y	A	D	S	V	K	G
H40, H43	R	I	I	P	I	L	G	I	A	N	Y	A	Q	K	F	Q	G
H48	W	I	N	A	G	N	G	N	T	K	Y	S	Q	K	F	Q	G
H51	I	I	N	P	S	G	G	S	T	S	Y	A	Q	K	F	Q	G

Fig.9

Heavy Chain	CDR3 Sequence															
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					

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 V
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
cctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataa
cgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagc
ctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtca
cccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt

Amino acid sequence

rtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstys
lsstltlskadyekhkvyacevthqglsspvtksfnrgec

IgG1 heavy chain constant region

Nucleotide Sequence

gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacag
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Amino acid sequence

astkgpsvfplapsskstsggtaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslss
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