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Description**FIELD OF THE INVENTION**

5 **[0001]** IL-6 antagonists, including anti-IL-6 antibodies and antibody fragments thereof, may be used to reduce C-reactive protein ("CRP levels") and inflammation and in methods and compositions for the treatment and prevention of mucositis, including oral, alimentary, and gastrointestinal tract mucositis.

BACKGROUND OF THE INVENTION

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Interleukin-6 (IL-6)

[0002] Interleukin-6 ("IL-6") is a multifunctional cytokine involved in numerous biological processes such as the regulation of the acute inflammatory response, the modulation of specific immune responses including B- and T-cell differentiation, bone metabolism, thrombopoiesis, epidermal proliferation, menses, neuronal cell differentiation, neuroprotection, aging, cancer, and the inflammatory reaction occurring in Alzheimer's disease. See Papassotiropoulos, et al. (2001) *Neurobiology of Aging* 22: 863-871.

15 **[0003]** IL-6 is a member of a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 and the IL-6 receptor ("IL-6R") (also known as gp80). The IL-6R may also be present in a soluble form ("sIL-6R"). IL-6 binds to IL-6R, which then dimerizes the signal-transducing receptor gp130. See Jones (2005) *Immunology* 175: 3463-3468.

20 **[0004]** IL-6 is a pleiotropic pro-inflammatory cytokine, which regulates the acute phase response and the transition from the innate to the adaptive immune response. IL-6 increases hepatic synthesis of proteins that are involved in the 'acute phase response' leading to symptoms such as fever, chills, and fatigue. It stimulates B cell differentiation and secretion of antibodies and prevents apoptosis of activated B cells. IL-6 activates and induces proliferation of T cells and in the presence of IL-2, induces differentiation of mature and immature CD8 T cells into cytotoxic T cells. IL-6 is also involved in the differentiation of Th17 cells and IL-17 production and inhibits regulatory T cells (Treg) differentiation. IL-6 also activates osteoclasts, synoviocytes, neutrophils, and other hematopoietic cells. Park, et al. (2007) *Bulletin of the NYU Hospital for Joint Diseases* 65 (suppl 1): S4-10; Guerne, et al. (1989) *J Clin Invest.* 83(2): 585-92; Houssiau, et al. (1988) *Arthritis Rheum.* 31(6): 784-8; Nishimoto, et al. (2006) *Nat Clin Pract Rheumatol.* 2(11): 619-26; Kishimoto (1989) *Blood* 74(1): 1-10; and Van Snick (1990) *Annu Rev Immunol.* 8: 253-78.

25 **[0005]** In humans, the gene encoding IL-6 is organized in five exons and four introns, and maps to the short arm of chromosome 7 at 7p21. Translation of IL-6 RNA and post-translational processing result in the formation of a 21 to 28 kDa protein with 184 amino acids in its mature form. See Papassotiropoulos, et al. (2001) *Neurobiology of Aging* 22:863-871.

30 **[0006]** The function of IL-6 is not restricted to the immune response as it acts in hematopoiesis, thrombopoiesis, osteoclast formation, elicitation of hepatic acute phase response resulting in the elevation of C-reactive protein (CRP) and serum amyloid A (SAA) protein. It is known to be a growth factor for epidermal keratinocytes, renal mesangial cells, myeloma and plasmacytoma cells. Grossman, et al. (1989) *Prot Natl Acad Sci.* 86(16): 6367-6371; Horii, et al. (1989) *J Immunol.* 143(12): 3949-3955; and Kawano, et al. (1988) *Nature* 332: 83-85. IL-6 is produced by a wide range of cell types including monocytes/macrophages, fibroblasts, epidermal keratinocytes, vascular endothelial cells, renal mesangial cells, glial cells, chondrocytes, T and B-cells and some tumor cells. Akira, et al. (1990) *FASEB J.* 4(11): 2860-2867. Except for tumor cells that constitutively produce IL-6, normal cells do not express IL-6 unless appropriately stimulated.

35 **[0007]** Elevated IL-6 levels have been observed in many types of cancer, including breast cancer, leukemia, ovarian cancer, prostate cancer, pancreatic cancer, lymphoma, lung cancer, renal cell carcinoma, colorectal cancer, and multiple myeloma. See, e.g., Chopra, et al. (2004) *MJAFI* 60:45-49; Songur, et al. (2004) *Tumori* 90:196-200; Blay, et al. (1992) *Cancer Research* 52: 3317-3322; Nikiteas, et al. (2005) *World J. Gastroenterol.* 11:1639-1643; reviewed in Heikkila, et al. (2008) *Eur J Cancer* 44:937-945. Clinical studies (reviewed in Trikha, et al. (2003) *Clinical Cancer Research* 9: 4653-4665) have shown some improvement in patient outcomes due to administration of various anti-IL-6 antibodies, particularly in those cancers in which IL-6 plays a direct role promoting cancer cell proliferation or survival.

40 **[0008]** As noted above, IL-6 stimulates the hepatic acute phase response, resulting in increased production of CRP and elevated serum CRP levels. For this reason, C-reactive protein (CRP) has been reported to comprise a surrogate marker of IL-6 activity. Thus, elevated IL-6 activity can be detected through measurement of serum CRP. Conversely, effective suppression of IL-6 activity, e.g., through administration of a neutralizing anti-IL-6 antibody, can be detected by the resulting decrease in serum CRP levels.

45 **[0009]** IL-6 is believed to play a role in the development of a multitude of diseases and disorders, including but not limited to fatigue, cachexia, autoimmune diseases, diseases of the skeletal system, cancer, heart disease, obesity, diabetes, asthma, Alzheimer's disease and multiple sclerosis. See, e.g., WO 2011/066374, WO 2011/066371, WO

2011/066378, and WO 2011/066369.

[0010] A recent clinical trial demonstrated that administration of rosuvastatin to apparently healthy individuals having elevated CRP (greater than 2.0 mg/l) reduced their CRP levels by 37% and greatly decreased the incidence of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Ridker et al., N Engl J Med. 2008 Nov 9 [Epub ahead of print].

[0011] In addition to its direct role in pathogenesis of some cancers and other diseases, chronically elevated IL-6 levels appear to adversely affect patient well-being and quality of life. For example, elevated IL-6 levels have been reported to be associated with cachexia and fever, and reduced serum albumin. Gauldie, et al. (1987) PNAS 84: 7251-7253; Heinric, et al. (1990) Biochem J. 265(3): 621-636; Zamir, et al. (1993) Metabolism 42: 204-208; Zamir, et al. (1992) Arch Surg 127: 170-174. Inhibition of IL-6 by a neutralizing antibody has been reported to ameliorate fever and cachexia in cancer patients, though improvement in these patients' serum albumin level has not been reported. Emille, et al. (1994) Blood 84: 2472-2479; Blay, et al. (1992) Cancer Research 52: 3317-3322; Bataille, et al. (1995) Blood 86: 685-691.

Mucositis

[0012] Mucositis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer. Ridge, et al. "Head and Neck Tumors" in Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ (Eds) Cancer Management: A Multidisciplinary Approach. [11 Ed.] (2008). Mucositis can occur anywhere along the gastrointestinal (GI) tract. Oral mucositis is marked by inflammation and ulceration in the mouth and is a common and often debilitating complication of cancer treatment. Sonis (2004) J Supportive Oncology 2(Suppl 3): 3-8.

[0013] Oral and gastrointestinal mucositis is a toxicity of many forms of radiotherapy and chemotherapy. It has a significant impact on health, quality of life and economic outcomes that are associated with treatment. It also indirectly affects the success of antineoplastic therapy by limiting the ability of patients to tolerate optimal tumoricidal treatment. The complex pathogenesis of mucositis has only recently been appreciated and reflects the dynamic interactions of all of the cells and tissue types that comprise the epithelium and submucosa. The identification of the molecular events that lead to treatment-induced mucosal injury has provided targets for mechanistically based interventions to prevent and treat mucositis.

[0014] Historically, mucositis was thought to arise solely as a consequence of epithelial injury. It was hypothesized that radiation or chemotherapy nonspecifically targeted the rapidly proliferating cells of the basal epithelium, causing the loss of the ability of the tissue to renew itself. The atrophy, thinning and ulceration of the mucosal epithelium that is associated with mucositis was thought to be a consequence of these events. Furthermore, it was believed that the process was facilitated by trauma and oral microorganisms.

[0015] Radiation-induced mucositis was typically recognized as an 'outside-in' process, in which DNA strand breaks occurred in oral basal-epithelial cells. Chemotherapy-induced mucositis has mainly been attributed to basal-cell damage that results when drugs permeate to these cells from the submucosal blood supply. A role for saliva-borne chemotherapeutic agents in the induction of mucositis has been also been proposed, but not proven. Chemotherapy-induced mucositis can be further compounded by concomitant myelosuppression.

[0016] Radiation- or chemotherapy-induced mucositis is initiated by direct injury to basal epithelial cells and cells in the underlying tissue. DNA-strand breaks can result in cell death or injury. Non-DNA injury is initiated through a variety of mechanisms, some of which are mediated by the generation of reactive oxygen species. Radiation and chemotherapy are effective activators of several injury-producing pathways in endothelia, fibroblasts and epithelia. In these cells, the activation of transcription factors such as nuclear factor- κ B (NF- κ B) and NRF2 leads to the upregulation of genes that modulate the damage response. Immune cells (macrophages) produce pro-inflammatory cytokines, such as tumour-necrosis factor- α (TNF- α) and interleukin 6, which causes further tissue injury. These signaling molecules also participate in a positive-feedback loop that amplifies the original effects of radiation and chemotherapy. For example, TNF- α activates NF- κ B and sphingomyelinase activity in the mucosa, leading to more cell death. In addition, direct and indirect damage to epithelial stem cells results in a loss of renewal capacity. As a result, the epithelium begins to thin and patients start to experience the early symptoms of mucositis.

[0017] Mucositis is observed during chemotherapeutic or radiation treatment of many different cancers including head and neck cancer, multiple myeloma, colorectal cancers, Because of the problems caused by mucositis which may preclude further radiation or chemotherapy and also impede nutrition because of the discomfort caused by mucositis during swallowing and digestion

[0018] The most common symptoms of mucositis include redness, dryness, or swelling of the mouth, burning or discomfort when eating or drinking, open sores in the mouth and throat, abdominal cramps, and tenderness or rectal redness or ulcers. Essentially mucositis involves the inflammation of the lining of the mouth and digestive tract, and frequently occurs in cancer patients after chemotherapy and radiation therapy. The cheek, gums, soft plate, oropharynx,

top and sides of tongue, and floor of the mouth may be affected, as well as the esophagus and rectal areas. Along with redness and swelling, patients typically experience a strong, burning pain.

[0019] Oral and gastrointestinal (GI) mucositis can affect up to 100% of patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT), 80% of patients with malignancies of the head and neck receiving radiotherapy, and a wide range of patients receiving chemotherapy. Alimentary tract mucositis increases mortality and morbidity and contributes to rising health care costs. Rubenstein, et al. (2004) Cancer 100(9 Suppl): 2026-46.

[0020] For most cancer treatment, about 5-15% of patients get mucositis. However, with 5-fluorouracil (5-FU), up to 40% get mucositis, and 10-15% get grade 3-4 oral mucositis. Irinotecan is associated with severe GI mucositis in over 20% of patients. 75-85% of bone marrow transplantation recipients experience mucositis, of which oral mucositis is the most common and most debilitating, especially when melphalan is used. In grade 3 oral mucositis, the patient is unable to eat solid food, and in grade 4, the patient is unable to consume liquids as well. Rubenstein, et al. (2004) Cancer 100(9 Suppl): 2026-46.

[0021] Radiotherapy to the head and neck or to the pelvis or abdomen is associated with Grade 3 and Grade 4 oral or GI mucositis, respectively, often exceeding 50% of patients. Among patients undergoing head and neck radiotherapy, pain and decreased oral function may persist long after the conclusion of therapy. Fractionated radiation dosage increases the risk of mucositis to > 70% of patients in most trials. Oral mucositis is particularly profound and prolonged among HSCT recipients who receive total-body irradiation. Rubenstein, et al. (2004) Cancer 100(9 Suppl): 2026-46.

[0022] Although there are factors that increase the likelihood and severity of mucositis, there is no reliable manner to predict who will be affected. Not only is mucositis more common in elderly patients, the degree of breakdown is often more debilitating. The severity of mucositis tends to be increased if a patient exercises poor oral hygiene or has a compromised nutritional status. A preexisting infection or irritation to the mucous membrane may also result in a more severe case of mucositis.

[0023] The types of drug used to treat cancer and the schedule by which they are given may influence the risk of developing mucositis. Doxorubicin and methotrexate, for example, frequently cause mucositis. The chemotherapy agent fluorouracil does not usually severely affect the mucous membranes when administered in small doses over continuous intravenous (IV) infusion. When the schedule is adjusted so that a higher dose is given over a shorter period of time (typically over five days), fluorouracil can cause very severe, painful, dose-limiting cases of mucositis. Patients undergoing treatment with high-dose chemotherapy and bone marrow rescue often develop mucositis.

[0024] In addition, mucositis also tends to develop in radiation therapy administered to the oral cavity, or in dosages that exceed 180 cGy per day over a five-day period. Combination therapy, either multiple chemotherapy agents or chemotherapy and radiation therapy to the oral cavity, can increase the incidence of mucositis.

[0025] Currently there is no real cure for mucositis, treatment is aimed at prevention and management of symptoms. Mucositis typically resolves a few weeks after treatment as the cells regenerate, and treatment cessation is only occasionally required. In some cases, drug therapy will be altered so that a less toxic agent is given.

[0026] Patients at risk for mucositis should be meticulous about their oral hygiene, brushing frequently with a soft toothbrush and flossing carefully with unwaxed dental floss. If bleeding of the gums develops, patients should replace their toothbrushes with soft toothettes or gauze. Dentures should also be cleaned regularly. Patients should be well-hydrated, drinking fluids frequently and rinsing the mouth several times a day. Mouthwashes that contain alcohol or hydrogen peroxide should be avoided as they may dry out the mouth and increase pain. Lips should also be kept moist. Physical irritation to the mouth should be avoided. If time permits, dental problems, such as cavities or ill-fitting dentures, should be resolved with a dentist prior to beginning cancer treatment. Patients are generally more comfortable eating mild, medium-temperature foods. Spicy, acidic, very hot or very cold foods can irritate the mucosa. Tobacco and alcohol should also be avoided.

[0027] Hospital personnel and the patients themselves should inspect the mouth frequently to look for signs and symptoms of mucositis. Evidence of mucositis (inflammation, white or yellow shiny mucous membranes developing into red, raw, painful membranes) may be present as early as four days after chemotherapy administration. Sodium bicarbonate mouth rinses are sometimes used to decrease the amount of oral flora and promote comfort, though there is no scientific evidence that this is beneficial. Typically, patients will rinse every few hours with a solution containing 1/2 teaspoon (tsp) salt and 1/2 tsp baking soda in one cup of water.

[0028] Pain relief is often required in patients with mucositis. In some cases, rinsing with a mixture of maalox, xylocaine, and diphenhydramine hydrochloride relieves pain. However, because of xylocaine's numbing effects, taste sensation may be altered. Worse, it may reduce the body's natural gag reflex, possibly causing problems with swallowing. Coating agents such as kapectate and aluminum hydroxide gel may also help relieve symptoms. Rinsing with benzydamine has also shown promise, not only in managing pain, but also in preventing the development of mucositis. More severe pain may require liquid Tylenol with codeine, or even intravenous opioid drugs. Patients with severe pain may not be able to eat, and may also require nutritional supplements through an I.V. (intravenous line).

[0029] A treatment called cryotherapy has shown promise in patients being treated with fluorouracil administered in the aforementioned five-day, high-dose schedule. Patients continuously swish ice chips in their mouth during the thirty-

minute infusion of the drug, causing the blood vessels to constrict, thereby reducing the drug's ability to affect the oral mucosa.

[0030] Chamomile and allopurinol mouthwashes have been tried in the past to manage mucositis, but studies have found them to be ineffective. Biologic response modifiers are being evaluated to determine their possible role in managing mucositis. Recent studies using topical antimicrobial lozenges have shown promise as well, but more research is needed.

[0031] Patients with multiple myeloma receiving chemotherapy (dexamethasone and melphelan) and autologous stem cell transplantation (ASCT) who were in addition administered an anti-IL-6 antibody (BE8) had reduced CRP levels and a significant reduction in fever as well as reduced onset and severity of mucositis. Rossi, et al. (2005) Bone Marrow Transplantation 36: 771-779. Particularly, the mucositis in the treated patients was a lower grade of toxicity requiring no morphine infusion as compared to patients not receiving the anti-IL-6 antibody. Also, gastrointestinal mucositis symptoms such as diarrhea were reduced and quality of life was improved as evidenced by better oral intake of nutrition and daily activity.

[0032] Therefore, there is a strong need in the art for improved methods of treating and preventing mucositis, both oral and gastrointestinal mucositis, as this condition compromises the efficacy of chemotherapy or radiation cancer treatments as well as adversely affecting the quality of life of cancer patients because of the extreme pain and discomfort caused by this condition. The invention described herein provides compositions comprising anti-IL-6 antibodies and antibody fragments thereof, and methods of use which may be used to treat IL-6 related conditions.

Rajesh V Lalla et al. (2006) Supportive Care in Cancer 14(6): 558-565 is a review article which discusses the use of anti-inflammatory agents in the management of mucositis. It describes that pro-inflammatory cytokines, including IL-6, are elevated in patients suffering from mucositis following radiation and/or chemotherapy.

SUMMARY OF THE INVENTION

[0033] The invention is as defined in the claims.

[0034] The present invention provides a composition for use in the treatment or prevention of mucositis associated with radiotherapy, comprising an effective amount of an IL-6 antagonist antibody, wherein said anti-IL-6 antibody comprises the humanized variable light sequence of amino acid sequence of SEQ ID NO: 709 and the humanized variable heavy sequence of amino acid sequence of SEQ ID NO: 657.

[0035] In one embodiment, the mucositis may be oral, gastrointestinal, or alimentary mucositis associated with radiotherapy.

[0036] The present invention provides compositions for use in accordance with the claims that comprise humanized monoclonal antibodies that selectively bind IL-6 and which are as defined in the claims.

[0037] Anti-IL-6 antibodies (*e.g.*, ALD518 antibodies, *also known as* Ab1) in accordance with the claims are used in methods for the treatment or prevention of mucositis associated with radiotherapy. The anti-IL-6 antibody or antibody fragment may be administered prophylactically to patients at significant risk of developing mucositis.

[0038] Compositions for use in treating or preventing mucositis associated with radiotherapy comprise an effective amount of an IL-6 antagonist antibody in accordance with the claims. In another embodiment, compositions for use in treating or preventing oral mucositis associated with radiotherapy may comprise an effective amount of an IL-6 antagonist antibody in accordance with the claims. In another embodiment, compositions for use in treating or preventing alimentary tract mucositis associated with radiotherapy may comprise an effective amount of an IL-6 antagonist antibody in accordance with the claims. In another embodiment, compositions for use in treating or preventing gastrointestinal tract mucositis associated with radiotherapy may comprise an effective amount of an IL-6 antagonist antibody in accordance with the claims.

[0039] The invention provides a composition for use in the treatment or prevention of mucositis associated with radiotherapy, comprising an effective amount of an Ab1 antibody, or an antibody fragment thereof, in accordance with the claims wherein the antibody, or antibody fragment thereof, specifically binds to IL-6.

[0040] The invention provides a composition for use in the treatment or prevention of oral mucositis associated with radiotherapy, comprising an effective amount of an Ab1 antibody, or an antibody fragment thereof, in accordance with the claims, wherein the antibody, or antibody fragment thereof, specifically binds to IL-6.

[0041] The invention provides a composition for use in the treatment or prevention of gastrointestinal tract mucositis associated with radiotherapy, comprising an effective amount of an Ab1 antibody, or an antibody fragment thereof, in accordance with the claims, wherein the antibody, or antibody fragment thereof, specifically binds to IL-6.

[0042] The invention provides a composition for use in the treatment or prevention of alimentary tract mucositis associated with radiotherapy, comprising an effective amount of an Ab1 antibody, or an antibody fragment thereof, in accordance with the claims, wherein the antibody, or antibody fragment thereof, specifically binds to IL-6.

[0043] The anti-IL6 antibody for use according to the invention comprises a light chain comprising the amino acid sequence of SEQ ID NO: 709 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 657.

[0044] In one embodiment, the antibody or antibody fragment thereof may be asialated. In one embodiment, the

antibody or antibody fragment thereof may be humanized. In one embodiment, the antibody or antibody fragment thereof may have a half-life of at least about 30 days. In accordance with the claims, the antibody or antibody fragment thereof comprises the humanized variable light sequence of amino acid sequence of SEQ ID NO: 709. In accordance with the claims, the antibody or antibody fragment thereof comprises the humanized variable heavy sequence of amino acid sequence of SEQ ID NO: 657. The antibody or antibody fragment thereof comprises the light chain CDRs as set forth in the amino acid sequence of SEQ ID NOs: 4, 5, and 6. The antibody or antibody fragment thereof comprises the heavy chain CDRs as set forth in the amino acid sequence of SEQ ID NOs: 7, 120, and 9. In further embodiment, the antibody or antibody fragment thereof may be an asialated, humanized anti-IL-6 monoclonal antibody with a half-life of -30 days comprising the humanized variable light and heavy sequences as set forth in SEQ ID NO: 709 and 657.

[0045] Preferably these antibodies will be aglycosylated. In more specific embodiments of the invention these antibodies will block gp130 activation and/or possess binding affinities (K_{ds}) less than 50 picomolar and/or K_{off} values less than or equal to 10^{-4} s^{-1} .

[0046] In one embodiment, binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv and scFv fragments.

[0047] In one embodiment, the anti-IL-6 antibodies block the effects of IL-6. In another embodiment, the anti-IL-6 antibody is a humanized monoclonal antibody that binds to free human IL-6 and soluble IL-6R/IL-6 complex with an affinity of at least about 4 pM. In another embodiment, the anti-IL-6 antibody, has a serum half-life about at least 30 days. In another embodiment, the anti-IL-6 antibody is based on a consensus human IgG1 kappa framework that had asparagines modified to alanine to eliminate N-glycosylation sites.

[0048] In another embodiment, the antibodies and humanized versions may be derived from rabbit immune cells (B lymphocytes) and may be selected based on their homology (sequence identity) to human germ line sequences. These antibodies may require minimal or no sequence modifications, thereby facilitating retention of functional properties after humanization. In exemplary embodiments, the humanized antibodies may comprise human frameworks which are highly homologous (possess high level of sequence identity) to that of a parent (e.g. rabbit) antibody.

[0049] An anti-IL6 antibody or antibody fragment or variant thereof may specifically bind to the same linear or conformational epitopes on an intact IL-6 polypeptide or fragment thereof which may include at least fragments selected from those encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72.

[0050] According to the present invention the anti-IL-6 antibody for use according to the invention comprises the variable heavy and light chain sequences in SEQ ID NO: 657 and SEQ ID NO: 709.

[0051] In a preferred embodiment the humanized anti-IL-6 antibody will comprise the variable heavy and variable light chain sequences respectively set forth in SEQ ID NO: 657 and SEQ ID NO: 709, and preferably further comprising the heavy chain and light chain constant regions respectively set forth in SEQ ID NO: 588 and SEQ ID NO: 586, and variants thereof comprising at least one amino acid substitutions or deletions that do not substantially affect IL-6 binding and/or desired effector function. This embodiment also contemplates polynucleotides comprising, or alternatively consisting of, at least one of the nucleic acids encoding the variable heavy chain (SEQ ID NO: 700) and variable light chain (SEQ ID NO: 723) sequences and the constant region heavy chain (SEQ ID NO: 589) and constant region light chain (SEQ ID NO: 587) sequences.

[0052] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be aglycosylated or substantially aglycosylated, e.g., as a result of one or more modifications in the Fc region of the antibody.

[0053] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation. Preferably the Fc region is modified to eliminate glycosylation.

[0054] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be a human, humanized, single chain or chimeric antibody.

[0055] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody.

[0056] In an embodiment of the invention, the framework regions (FRs) in the variable light region and the variable heavy regions of said anti-IL-6 antibody or antibody fragment or variant thereof respectively may be human FRs which are unmodified or which have been modified by the substitution of at most 2 or 3 human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and the human FRs may have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library. As disclosed in detail infra in a preferred embodiment the antibody will comprise human FRs which are selected based on their high level of homology (degree of sequence identity) to that of the parent antibody that is humanized.

[0057] The variable heavy and light sequences comprise those in SEQ ID NO: 657 and 709.

[0058] In an embodiment of the invention, at least one of said FR residues may be substituted with an amino acid present at the corresponding site in a parent rabbit anti-IL-6 antibody from which the complementarity determining regions

(CDRs) contained in said VH or VL polypeptides have been derived or by a conservative amino acid substitution.

[0059] In an embodiment of the invention, said anti-IL-6 antibody, or antibody fragment or variant thereof, may be humanized. In an embodiment of the invention, said anti-IL-6 antibody, or antibody fragment or variant thereof, may be chimeric.

5 **[0060]** In an embodiment of the invention, said anti-IL-6 antibody, or antibody fragment or variant thereof, further may comprise a human Fc, e.g., an Fc region comprised of the variable heavy and light chain constant regions set forth in SEQ ID NO: 704 and 702.

[0061] In an embodiment of the invention, said human Fc may be derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19.

10 **[0062]** In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may have an elimination half-life of at least about 30 days.

[0063] In one embodiment, the antibody, or antibody fragment thereof, may inhibit at least one activity associated with IL-6. In another embodiment, the at least one activity associated with IL-6 may be an *in vitro* activity comprising stimulation of proliferation of T1165 cells; binding of IL-6 to IL-6R; activation (dimerization) of the gp130 signal-transducing glyco-protein; formation of IL-6/IL-6R/gp130 multimers; stimulation of haptoglobin production by HepG2 cells modified to express human IL-6 receptor; or any combination thereof. In one embodiment, prior to administration of the antibody, or antibody fragment thereof, the subject may have exhibited or may be at risk for developing at least one of the following symptoms: elevated serum C-reactive protein ("CRP"); elevated erythrocyte sedimentation rate; or a combination thereof.

15 **[0064]** In one embodiment, the antibody or antibody fragment thereof may comprise a Fab, Fab', F(ab')₂, Fv, scFv, IgNAR, or SMIP. In one embodiment, the antibody or antibody fragment thereof may have an *in vivo* half-life of at least about 30 days in a healthy human subject. In one embodiment, the antibody or antibody fragment thereof may have a binding affinity (K_d) for IL-6 of less than about 50 picomolar, or a rate of dissociation (K_{off}) from IL-6 of less than or equal to 10⁻⁴ S⁻¹. In one aspect of the disclosure, the antibody or antibody fragment thereof may specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising the polypeptides of SEQ ID NO: 702 and SEQ ID NO: 704 or the polypeptides of SEQ ID NO: 2 and SEQ ID NO: 3. In an aspect of the disclosure, the binding to the same linear or conformational epitope(s) and/or competition for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof is ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide and includes at least one residues comprised in IL-6 fragments selected from those respectively encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72 of SEQ ID NO: 1.

25 **[0065]** In one embodiment, the antibody or antibody fragment thereof, may be aglycosylated. In one embodiment, the antibody, or antibody fragment thereof, may contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation. In one embodiment, the antibody, or antibody fragment thereof, may be a human, humanized, single chain, or chimeric antibody. In one embodiment, the antibody, or antibody fragment thereof, may comprise a Fab, Fab', F(ab')₂, Fv, or scFv. In one embodiment, the antibody, or antibody fragment thereof, may further comprise a human F_c. In another embodiment, the F_c may be derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18, or IgG19.

30 **[0066]** In one embodiment, the composition for use in accordance with the claims may comprise at least about 25, 80, 100, 160, 200, or 320 mg. In one embodiment, the effective amount may be between about 0.1 and 100 mg/kg of body weight of the subject. In one embodiment, the subject may be administered at least 1, 2, 3, 4, or 5 doses. In one embodiment, the composition may be administered every 4 weeks. In one embodiment, the subject may be administered 25 mg every 4 weeks. In one embodiment, the subject may be administered 80 mg every 4 weeks. In one embodiment, the subject may be administered 100 mg every 4 weeks. In one embodiment, the subject may be administered 160 mg every 4 weeks. In one embodiment, the subject may be administered 200 mg every 4 weeks. In one embodiment, the subject may be administered 320 mg every 4 weeks. In another embodiment, the composition may be administered every 4 weeks for at least 16 weeks. In another embodiment, the composition may be administered every 4 weeks for at least 24 weeks.

35 **[0067]** In this embodiment, anti-IL-6 antibodies, or antibody fragments thereof may be administered at effective doses to lessen inflammation, pain, and loss of mobility experienced from mucositis, e.g., dosages ranging from about 25-500 mg, more preferably at least about 25, 80, 100, 120, 160, 200, 240, or 320 mg dosages.

[0068] The antibody or antibody fragment comprises a humanized variable light sequence of amino acid sequence of SEQ ID NO: 709.

40 **[0069]** The antibody or antibody fragment comprises a humanized variable heavy sequence of amino acid sequence of SEQ ID NO: 657.

[0070] The antibody or antibody fragment comprises the light chain CDRs as set forth in the amino acid sequence of SEQ ID NOs: 4, 5, and 6.

[0071] The antibody or antibody fragment comprises the heavy chain CDRs as set forth in the amino acid sequence of SEQ ID NOs: 7, 120, and 9.

[0072] In one embodiment, the antibody or antibody fragment may be an asialated, humanized anti-IL-6 monoclonal antibody with a half-life of -30 days comprising the humanized variable light and heavy sequences as set forth in SEQ ID NO: 709 and 657.

[0073] In one embodiment, the antibody or antibody fragment may be expressed from a recombinant cell. In another embodiment, the cell may be a mammalian, yeast, bacterial, and insect cell. In another embodiment, the cell may be a yeast cell. In another embodiment, the cell may be a diploidal yeast cell. In another embodiment, the yeast cell may be a *Pichia* yeast. In one embodiment, the antibody may be asialated. In one embodiment, the antibody may be humanized.

[0074] In one embodiment, the antibody or antibody fragment thereof may comprise a Fab, Fab', F(ab')₂, Fv, scFv, IgNAR, or SMIP.

[0075] In one embodiment, the antibody or antibody fragment thereof may have an *in vivo* half-life of at least about 30 days.

[0076] In one embodiment, the antibody or antibody fragment thereof may have a binding affinity (K_d) for IL-6 of less than about 50 picomolar, or a rate of dissociation (K_{off}) from IL-6 of less than or equal to 10⁻⁴ S⁻¹.

[0077] In one aspect of the disclosure, the antibody or antibody fragment thereof may specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising the polypeptides of SEQ ID NO: 702 and SEQ ID NO: 704 or the polypeptides of SEQ ID NO: 2 and SEQ ID NO: 3.

[0078] In one aspect, the antibody or antibody fragment thereof binding to the same linear or conformational epitope(s) and/or competing for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof is ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide and includes at least one residues comprised in IL-6 fragments selected from those respectively encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72 of SEQ ID NO: 1.

[0079] In one embodiment, the antibody or antibody fragment thereof may be aglycosylated. In one embodiment, the antibody or antibody fragment thereof may comprise an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation. In one embodiment, the antibody or antibody fragment thereof may be a human, humanized, single chain, or chimeric antibody. In one embodiment, the antibody or antibody fragment thereof may further comprise a human Fc, preferably wherein said human Fc is derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18, or IgG19.

[0080] In one embodiment, the patient may have elevated C-reactive protein ("CRP"). In one embodiment, the patient may have elevated IL-6 serum level. In one embodiment, the patient may have elevated IL-6 level in the joints.

[0081] In one embodiment, the IL-6-antagonist antibody may inhibit at least one activity associated with IL-6. In another embodiment, the at least one activity associated with IL-6 is an *in vitro* activity comprising stimulation of proliferation of T1165 cells; binding of IL-6 to IL-6R; activation (dimerization) of the gp130 signal-transducing glycoprotein; formation of IL-6/IL-6R/gp130 multimers; stimulation of haptoglobin production by HepG2 cells modified to express human IL-6 receptor; or any combination thereof.

[0082] In another embodiment, prior to administration of the IL-6 antagonist antibody, the subject to be treated has exhibited or is at risk for developing at least one of the following symptoms: decreased serum albumin; elevated serum C-reactive protein ("CRP"); elevated erythrocyte sedimentation rate; fatigue; fever; anorexia (loss of appetite); weight loss; cachexia; weakness; decreased Glasgow Prognostic Score ("GPS"); elevated serum D-dimer; abnormal coagulation profile; and any combination thereof.

[0083] According to the invention, the mucositis is a side-effect of radiotherapy administered to the subject prior to, concurrent with, or subsequent to administration of the antibody or antibody fragment. In another embodiment, the method may further comprise monitoring the subject to assess said symptom subsequent to administration of the antibody. In another embodiment, the symptom may be exhibited prior to administration of said IL-6 antagonist antibody. In another embodiment, the symptom may be improved or restored to a normal condition within about 1-5 weeks of administration of said IL-6 antagonist antibody. In another embodiment, the symptom may thereafter remains improved for an entire period intervening two consecutive administrations of said IL-6 antagonist antibody. In another embodiment, the patient treated may have at least one symptom of oral, alimentary, or gastrointestinal tract mucositis.

[0084] In another embodiment, the patient treated may have cancer or is being treated for cancer. In one embodiment, the cancer is selected from the group consisting of Acanthoma, Acinic cell carcinoma, Acoustic neuroma, Acral lentiginous melanoma, Acrospiroma, Acute eosinophilic leukemia, Acute lymphoblastic leukemia, Acute megakaryoblastic leukemia, Acute monocytic leukemia, Acute myeloblastic leukemia with maturation, Acute myeloid dendritic cell leukemia, Acute myeloid leukemia, Acute promyelocytic leukemia, Adamantinoma, Adenocarcinoma, Adenoid cystic carcinoma, Adenoma, Adenomatoid odontogenic tumor, Adrenocortical carcinoma, Adult T-cell leukemia, Aggressive NK-cell leukemia, AIDS-Related Cancers, AIDS-related lymphoma, Alveolar soft part sarcoma, Ameloblastic fibroma, Anal cancer, Ana-

plastic large cell lymphoma, Anaplastic thyroid cancer, Angioimmunoblastic T-cell lymphoma, Angiomyolipoma, Angiosarcoma, Appendix cancer, Astrocytoma, Atypical teratoid rhabdoid tumor, Basal cell carcinoma, Basal-like carcinoma, B-cell leukemia, B-cell lymphoma, Bellini duct carcinoma, Biliary tract cancer, Bladder cancer, Blastoma, Bone Cancer, Bone tumor, Brain Stem Glioma, Brain Tumor, Breast Cancer, Brenner tumor, Bronchial Tumor, Bronchioloalveolar carcinoma, Brown tumor, Burkitt's lymphoma, Cancer of Unknown Primary Site, Carcinoid Tumor, Carcinoma, Carcinoma *in situ*, Carcinoma of the penis, Carcinoma of Unknown Primary Site, Carcinosarcoma, Castleman's Disease, Central Nervous System Embryonal Tumor, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Cholangiocarcinoma, Chondroma, Chondrosarcoma, Chordoma, Choriocarcinoma, Choroid plexus papilloma, Chronic Lymphocytic Leukemia, Chronic monocytic leukemia, Chronic myelogenous leukemia, Chronic Myeloproliferative Disorder, Chronic neutrophilic leukemia, Clear-cell tumor, Colon Cancer, Colorectal cancer, Craniopharyngioma, Cutaneous T-cell lymphoma, Degos disease, Dermatofibrosarcoma protuberans, Dermoid cyst, Desmoplastic small round cell tumor, Diffuse large B cell lymphoma, Dysembryoplastic neuroepithelial tumor, Embryonal carcinoma, Endodermal sinus tumor, Endometrial cancer, Endometrial Uterine Cancer, Endometrioid tumor, Enteropathy-associated T-cell lymphoma, Ependymoblastoma, Ependymoma, Epithelioid sarcoma, Erythroleukemia, Esophageal cancer, Esthesioneuroblastoma, Ewing Family of Tumor, Ewing Family Sarcoma, Ewing's sarcoma, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Extramammary Paget's disease, Fallopian tube cancer, Fetus in fetu, Fibroma, Fibrosarcoma, Follicular lymphoma, Follicular thyroid cancer, Gallbladder Cancer, Gallbladder cancer, Ganglioglioma, Ganglioneuroma, Gastric Cancer, Gastric lymphoma, Gastrointestinal cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumor, Gastrointestinal stromal tumor, Germ cell tumor, Germinoma, Gestational choriocarcinoma, Gestational Trophoblastic Tumor, Giant cell tumor of bone, Glioblastoma multiforme, Glioma, Gliomatosis cerebri, Glomus tumor, Glucagonoma, Gonadoblastoma, Granulosa cell tumor, Hairy Cell Leukemia, Hairy cell leukemia, Head and Neck Cancer, Head and neck cancer, Heart cancer, Hemangioblastoma, Hemangiopericytoma, Hemangiosarcoma, Hematological malignancy, Hepatocellular carcinoma, Hepatosplenic T-cell lymphoma, Hereditary breast-ovarian cancer syndrome, Hodgkin Lymphoma, Hodgkin's lymphoma, Hypopharyngeal Cancer, Hypothalamic Glioma, Inflammatory breast cancer, Intraocular Melanoma, Islet cell carcinoma, Islet Cell Tumor, Juvenile myelomonocytic leukemia, Kaposi Sarcoma, Kaposi's sarcoma, Kidney Cancer, Klatzkin tumor, Krukenberg tumor, Laryngeal Cancer, Laryngeal cancer, Lentigo maligna melanoma, Leukemia, Leukemia, Lip and Oral Cavity Cancer, Liposarcoma, Lung cancer, Luteoma, Lymphangioma, Lymphangiosarcoma, Lymphoepithelioma, Lymphoid leukemia, Lymphoma, Macroglobulinemia, Malignant Fibrous Histiocytoma, Malignant fibrous histiocytoma, Malignant Fibrous Histiocytoma of Bone, Malignant Glioma, Malignant Mesothelioma, Malignant peripheral nerve sheath tumor, Malignant rhabdoid tumor, Malignant triton tumor, MALT lymphoma, Mantle cell lymphoma, Mast cell leukemia, Mediastinal germ cell tumor, Mediastinal tumor, Medullary thyroid cancer, Medulloblastoma, Medulloblastoma, Medulloepithelioma, Melanoma, Melanoma, Meningioma, Merkel Cell Carcinoma, Mesothelioma, Mesothelioma, Metastatic Squamous Neck Cancer with Occult Primary, Metastatic urothelial carcinoma, Mixed Mullerian tumor, Monocytic leukemia, Mouth Cancer, Mucinous tumor, Multiple Endocrine Neoplasia Syndrome, Multiple Myeloma, Multiple myeloma, Mycosis Fungoides, Mycosis fungoides, Myelodysplastic Disease, Myelodysplastic Syndromes, Myeloid leukemia, Myeloid sarcoma, Myeloproliferative Disease, Myxoma, Nasal Cavity Cancer, Nasopharyngeal Cancer, Nasopharyngeal carcinoma, Neoplasm, Neurinoma, Neuroblastoma, Neuroblastoma, Neurofibroma, Neuroma, Nodular melanoma, Non-Hodgkin Lymphoma, Non-Hodgkin lymphoma, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Ocular oncology, Oligoastrocytoma, Oligodendroglioma, Oncocytoma, Optic nerve sheath meningioma, Oral Cancer, Oral cancer, Oropharyngeal Cancer, Osteosarcoma, Osteosarcoma, Ovarian Cancer, Ovarian cancer, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Paget's disease of the breast, Pancoast tumor, Pancreatic Cancer, Pancreatic cancer, Papillary thyroid cancer, Papillomatosis, Paraganglioma, Paranasal Sinus Cancer, Parathyroid Cancer, Penile Cancer, Perivascular epithelioid cell tumor, Pharyngeal Cancer, Pheochromocytoma, Pineal Parenchymal Tumor of Intermediate Differentiation, Pineoblastoma, Pituicytoma, Pituitary adenoma, Pituitary tumor, Plasma Cell Neoplasm, Pleuropulmonary blastoma, Polyembryoma, Precursor T-lymphoblastic lymphoma, Primary central nervous system lymphoma, Primary effusion lymphoma, Primary Hepatocellular Cancer, Primary Liver Cancer, Primary peritoneal cancer, Primitive neuroectodermal tumor, Prostate cancer, Pseudomyxoma peritonei, Rectal Cancer, Renal cell carcinoma, Respiratory Tract Carcinoma Involving the NUT Gene on Chromosome 15, Retinoblastoma, Rhabdomyoma, Rhabdomyosarcoma, Richter's transformation, Sacrococcygeal teratoma, Salivary Gland Cancer, Sarcoma, Schwannomatosis, Sebaceous gland carcinoma, Secondary neoplasm, Seminoma, Serous tumor, Sertoli-Leydig cell tumor, Sex cord-stromal tumor, Sézary Syndrome, Signet ring cell carcinoma, Skin Cancer, Small blue round cell tumor, Small cell carcinoma, Small Cell Lung Cancer, Small cell lymphoma, Small intestine cancer, Soft tissue sarcoma, Somatostatinoma, Soot wart, Spinal Cord Tumor, Spinal tumor, Splenic marginal zone lymphoma, Squamous cell carcinoma, Stomach cancer, Superficial spreading melanoma, Supratentorial Primitive Neuroectodermal Tumor, Surface epithelial-stromal tumor, Synovial sarcoma, T-cell acute lymphoblastic leukemia, T-cell large granular lymphocyte leukemia, T-cell leukemia, T-cell lymphoma, T-cell prolymphocytic leukemia, Teratoma, Terminal lymphatic cancer, Testicular cancer, Thecoma, Throat Cancer, Thymic Carcinoma, Thymoma, Thyroid cancer, Transitional Cell Cancer of Renal Pelvis and Ureter, Transitional cell carcinoma, Urachal cancer,

Urethral cancer, Urogenital neoplasm, Uterine sarcoma, Uveal melanoma, Vaginal Cancer, Verner Morrison syndrome, Verrucous carcinoma, Visual Pathway Glioma, Vulvar Cancer, Waldenström's macroglobulinemia, Warthin's tumor, Wilms' tumor, and combination thereof. In one embodiment, the cancer is Colorectal Cancer, Non-Small Cell Lung Cancer, Cholangiocarcinoma, Mesothelioma, Castleman's disease, Renal Cell Carcinoma, or any combination thereof.

5 In one embodiment, the patient may have a cancer selected from head and neck cancer, esophageal cancer, throat cancer, lung cancer, gastrointestinal cancers such as stomach cancer, colorectal cancer, pancreatic cancer, as well as hematological cancers such as multiple myeloma, leukemia, and lymphoma.

[0085] In one aspect of the disclosure, the patient suffers from a disease or disorder selected from the group consisting of general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS).

[0086] In one embodiment, the patient has or is to receive autologous stem cell or bone marrow transplant.

25 **[0087]** In one embodiment, the IL-6 antagonist antibody, may be administered prior, concurrent or after chemotherapy or radiotherapy. In one embodiment, the chemotherapeutic is an EGFR inhibitor. In one embodiment, the EGFR inhibitor is selected from the group consisting of Cetuximab (Erbix), Erlotinib (Tarceva), Gefitinib (Iressa), Lapatinib (Tykerb), Panitumumab (Vectibx), Sunitinib or Sutent (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide), Gefitinib or N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine, and Zalutumumab. In one embodiment, the patient may have a cancer that has exhibited resistance to said chemotherapeutic or radiation after at least one round of chemotherapy or radiation. In one embodiment, the chemotherapeutic or radiation reduces or prevents the treated cancer from invading or metastasizing to other sites in the body. In one embodiment, the chemotherapeutic or radiation results in increased apoptosis of the treated cancer cells.

35 **[0088]** In one embodiment, the treated cancer is selected from advanced and non-advanced cancers including metastasized cancers such as metastatic and non-metastatic lung cancer, breast cancer, head and neck cancer, (HNSCC), pharyngeal cancer, pancreatic cancer, colorectal cancer, anal cancer, glioblastoma multiforme, epithelial cancers, renal cell carcinomas, acute or chronic myelogenous leukemia and other leukemias.

[0089] In one embodiment, the results are used to facilitate design of an appropriate therapeutic regimen for mucositis or a disease associated with mucositis.

40 **[0090]** In one embodiment, the IL-6 antagonist antibody, is co-administered with another therapeutic agent selected from the group consisting of analgesics, antibiotics, anti-cachexia agents, anti-coagulants, anti-cytokine agents, antiemetic agents, anti-fatigue agent, anti-fever agent, anti-inflammatory agents, anti-nausea agents, antipyretics, antiviral agents, anti-weakness agent, chemotherapy agents, cytokine antagonist, cytokines, cytotoxic agents, gene therapy agents, growth factors, IL-6 antagonists, immunosuppressive agents, local anesthetic, statins, other therapeutic agents, or any combination thereof.

45 **[0091]** In another embodiment, the analgesic is acetaminophen, amitriptyline, benzocaine, carbamazepine, codeine, dyclonine hydrochloride (HCl), dihydromorphone, fentanyl patch, Flupirtine, fluriprofen, gabapentin, hydrocodone APAP, hydromorphone, ibuprofen, ketoprofen, lidocaine, morphine, an opiate and derivatives thereof, oxycodone, pentazocine, pethidine, phenacetin, pregabalin, propoxyphene, propyl APA, salicylamide, tramadol, tramadol APAP, Ulcerase® (0.6% Phenol), or voltaren.

50 **[0092]** In another embodiment, the local anesthetic is amethocaine, articaine, benzocaine, bupivacaine, mepivacaine, cocaine, cinchocaine, chloroprocaine, cyclomethycaine, dibucaine, dimethocaine, EMLA® (eutectic mixture of lidocaine and prilocaine), etidocaine, larocaine, levobupivacaine, lidocaine, lignocaine, procaine, piperocaine, prilocaine, proparacaine, propoxycaine, ropivacaine, saxitoxin, tetracaine, tetrodotoxin, or trimecaine.

55 **[0093]** In another embodiment, the anti-cachexia agent is cannabis, dronabinol (Marinol®), nabilone (Cesamet), cannabidiol, cannabichromene, tetrahydrocannabinol, Sativex, megestrol acetate, or any combination thereof.

[0094] In another embodiment, the anti-coagulant is abciximab (ReoPro®), acenocoumarol, antithrombin III, arga-

troban, aspirin, bivalirudin (Angiomax®), clopidogrel, dabigatran, dabigatran etexilate (Pradaxa®/Pradax®), desirudin (Revasc®/Iprivask®), dipyridamole, eptifibatide (Integrilin®), fondaparinux, heparin, hirudin, idraparinux, lepirudin (Refludan®), low molecular weight heparin, melagatran, phenindione, phenprocoumon, ticlopidine, tirofiban (Aggrastat®), warfarin, ximelagatran, ximelagatran (Exanta®/Exarta®), or any combination thereof.

[0095] In another embodiment, the anti-inflammatory agent is acetaminophen, azapropazone, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic, meloxicam, nabumetone, naproxen, phenylbutazone, piroxicam, a salicylate, sulindac, tenoxicam, tiaprofenic acid, or tolfenamic acid. In still further embodiment, the salicylate is acetylsalicylic acid, amoxiprin, benorylate, choline magnesium salicylate, ethenzamide, faislamine, methyl salicylate, magnesium salicylate, salicyl salicylate, or salicylamide.

[0096] In another embodiment, the anti-nausea agent or antiemetic agent is comprising 5-HT₃ receptor antagonists, ajwain, alizapride, anticholinergics, antihistamines, aprepitant, benzodiazepines, cannabichromene, cannabidiol, cannabinoids, cannabis, casopitant, chlorpromazine, cyclizine, dexamethasone, dexamethasone, dimenhydrinate (Gravol®), diphenhydramine, dolasetron, domperidone, dopamine antagonists, doxylamine, dronabinol (Marinol®), droperidol, emetrol, ginger, granisetron, haloperidol, hydroxyzine, hyoscine, lorazepam, meclizine, metoclopramide, midazolam, muscimol, nabilone (Cesamet), nk1 receptor antagonists, ondansetron, palonosetron, peppermint, Phenergan, prochlorperazine, Promacot, promethazine, Pentazine, propofol, sativex, tetrahydrocannabinol, trimethobenzamide, tropisetron, nandrolone, stilbestrol, thalidomide, lenalidomide, ghrelin agonists, myostatin antagonists, anti-myostatin antibodies, selective androgen receptor modulators, selective estrogen receptor modulators, angiotensin II antagonists, beta two adrenergic receptor agonists, beta three adrenergic receptor agonists, or any combination thereof.

[0097] In another embodiment, the antiviral agent is selected from the group consisting of abacavir, aciclovir, acyclovir, adefovir, amantadine, amprenavir, an antiretroviral fixed dose combination, an antiretroviral synergistic enhancer, arbidol, atazanavir, atripla, brivudine, cidofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, entry inhibitors, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, fusion inhibitor, ganciclovir, gardasil, ibacitabine, idoxuridine, imiquimod, imunovir, indinavir, inosine, integrase inhibitor, interferon, interferon type I, interferon type II, interferon type III, lamivudine, lopinavir, loviride, maraviroc, MK-0518, moroxydine, nelfinavir, nevirapine, nexavir, nucleoside analogues, oseltamivir, penciclovir, peramivir, pleconaril, podophyllo-toxin, protease inhibitor, reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, saquinavir, stavudine, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, zidovudine, or any combination thereof.

[0098] In another embodiment, the cytotoxic agent, chemotherapeutic agent, or immunosuppressive agent is comprising 1-dehydrotestosterone, 1-methylnitrosourea, 5-fluorouracil, 6-mercaptopurine, 6-mercaptopurine, 6-thioguanine, Abatacept, abraxane, acitretin, aclarubicin, Actinium-225 (²²⁵Ac), actinomycin, Adalimumab, adenosine deaminase inhibitors, Afelimomab, Aflibercept, Afutuzumab, Alefacept, alitretinoin, alkyl sulfonates, alkylating agents, altretamine, alvocidib, aminolevulinic acid/methyl aminolevulinate, aminopterin, aminopterin, amrubicin, amsacrine, amsacrine, anagrelide, Anakinra, anthracenediones, anthracyclines, anthracyclines, anthracyclines, anthramycin (AMC); antimetabolic agents, antibiotics, anti-CD20 antibodies, antifolates, Anti-lymphocyte globulin, Antimetabolites, Anti-thymocyte globulin, arsenic trioxide, Aselizumab, asparaginase, asparagine depleters, Astatine-211 (²¹¹At), Atlizumab, Atorolimumab, at-rasentan, Avastin®, azacitidine, Azathioprine, azelastine, aziridines, Basiliximab, BAYX antibodies, Belatacept, Belimumab, belotecan, bendamustine, Bertilimumab, bexarotene, bisantrene, Bismuth-213 (²¹³Bi), Bismuth-212 (²¹²Bi), bleomycin, bleomycin, bleomycin, BLYS antibodies, bortezomib, busulfan, busulfan, Calcineurin inhibitors, calicheamicin, camptothecin, camptothecins, capecitabine, carboplatin (paraplatin), carboquone, carminomycin, carmustine, carmustine (BSNU), CAT antibodies, CD11a antibodies, CD147/Basigin antibodies, CD154 antibodies, CD18 antibodies, CD20 antibodies, CD23 antibodies, CD3 antibodies, CD4 antibodies, CD40 antibodies, CD62L/L-selectin antibodies, CD80 antibodies, CDK inhibitors, Cedelizumab, celecoxib, Certolizumab pegol, chlorambucil, chlorambucils, Ciclosporin, cis-dichlorodiamine platinum (II) (DDP) cisplatin, cladribine, Clenoliximab, clofarabine, colchicin, Complement component 5 antibodies, Copper-67 (⁶⁷Cu), corticosteroids, CTLA-4 antibodies, CTLA-4 fusion proteins, Cyclophilin inhibitors, cyclophosphamides, cyclophosphamide, cytarabine, cytarabine, cytochalasin B, cytotoxic ribonucleases, dacarbazine, Daclizumab, dactinomycin, dactinomycin (actinomycin D), daunorubicin, daunorubicin, daunorubicin (formerly daunomycin), decitabine, Deforolimus, demecolcine, detorubicin, dibromomannitol, diethylcarbamazine, dihydrofolate reductase inhibitors, dihydroxy anthracin dione, diphtheria toxin, DNA polymerase inhibitors, docetaxel, Dorlimomab aritox, Dorlizumab, doxorubicin (adriamycin), DXL625, Eculizumab, Efalizumab, efaproxiral, EGFR antagonists, elesclomol, elsamitrucin, Elsilimumab, emetine, endothelin receptor antagonists, epipodophyllotoxins, epirubicin, epothilones, Erbitux®, Erlizumab, estramustine, Etanercept, ethidium bromide, etoglucid, etoposide, etoposide phosphate, Everolimus, Faralimumab, farnesyltransferase inhibitors, FKBP inhibitors, floxuridine, fludarabine, fluorouracil, Fontolizumab, fotemustine, Galiximab, Gallium-67 (⁶⁷Ga), Gantenerumab, Gavilimumab, gemcitabine, glucocorticoids, Golimumab, Gomaliximab, gramicidin D, Gusperimus, Herceptin®, hydrazines, hydroxyurea, hypomethylating agents, idarubicin, Idarubicine, ifosfamide, IL-1 antagonists, IL-1 receptor antagonists, IL-12, IL-12 antibodies, IL-12R antagonists, IL-13 antibodies, IL-2, IL-2 inhibitors, IL-2 receptor/CD25 antibodies, IL-6 antibodies, imatinib mesylate, Immunoglobulin E anti-

bodies, IMP dehydrogenase inhibitors, Infliximab, Inolimomab, Integrin antibodies, Interferon antibodies, interferons, Interleukin 5 antibodies, Interleukin-6 receptor antibodies, interleukins, Iodine-125 (^{125}I), Iodine-131 (^{131}I), Ipilimumab, irinotecan, ixabepilone, Keliximab, larotaxel, Lead-212 (^{212}Pb), Lebrilizumab, Leflunomide, Lenalidomide, Lerdelimumab, leucovorine, LFA-1 antibodies, lidocaine, lipoxxygenase inhibitors, lomustine (CCNU), lonidamine, lucanthone, Lumiliximab, Lutetium-177 (^{177}Lu), Macrolides, mannosulfan, Maslimomab, masoprocil, mechlorethamine, melphalan, Mepolizumab, mercaptopurine, Metelimomab, Methotrexate, microtubule assembly inhibitors, microtubule stability enhancers, mithramycin, mitobronitol, mitoguazone, mitomycin, mitomycin C, mitotane, mitoxantrone, Morolimumab, mTOR inhibitors, Muromonab-CD3, mustines, Mycophenolic acid, mytotane (O,P'-(DDD)), Natalizumab, nedaplatin, Nerelimomab, nimustine, nitrogen mustards, nitrosoureas, nordihydroguaiaretic acid, oblimersen, ocrelizumab, Ocrelizumab, Odulimomab, ofatumumab, olaparib, Omalizumab, ortataxel, Otelixizumab, oxaliplatin, oxaliplatin, paclitaxel (taxol), Pascolizumab, PDGF antagonists, pegaspargase, pemetrexed, Pentostatin, Pertuzumab, Pexelizumab, phosphodiesterase inhibitors, Phosphorus-32 (^{32}P), Pimecrolimus Abetimus, pirarubicin, pixantrone, platins, plicamycin, poly ADP ribose polymerase inhibitors, porfimer sodium, porphyrin derivatives, prednimustine, procaine, procarbazine, procarbazine, propranolol, proteasome inhibitors, pseudomonas exotoxin, *Pseudomonas* toxin, purine synthesis inhibitors, puromycin, pyrimidine synthesis inhibitors, radionuclides, radiotherapy, raltitrexed, ranimustine, Reslizumab, retinoid X receptor agonists, retinoids, Rhenium-186 (^{186}Re), Rhenium-188 (^{188}Re), ribonucleotide reductase inhibitors, ricin, Rilonacept, Rituxan®, Rovelizumab, rubitecan, Ruplizumab, Samarium-153 (^{153}Sm), satraplatin, Scandium-47 (^{47}Sc), selective androgen receptor modulators, selective estrogen receptor modulators, seliciclib, semustine, sex hormone antagonists, sipilizumab, sirolimus, steroid aromatase inhibitors, steroids, streptozocin, streptozotocin, Tacrolimus, talaporfin, Talizumab, taxanes, taxols, tegafur, Telimomab aritox, temoporfin, temozolomide, temsirolimus, Temsirolimus, Teneliximab, teniposide, Teplizumab, Teriflunomide, tesetaxel, testolactone, tetracaine, Thalidomide, thioepa chlorambucil, thiopurines thioguanine, ThioTEPA, thymidylate synthase inhibitors, tiazofurin, tipifarnib, T-lymphocyte antibodies, TNF antagonists, TNF antibodies, TNF fusion proteins, TNF receptor fusion proteins, TNF- α inhibitors, Tocilizumab, topoisomerase inhibitors, topotecan, Toralizumab, trabectedin, Tremelimomab, treosulfan, tretinoin, triazenes, triaziquone, triethylenemelamine, triplatin tetranitrate, trofosfamide, tumor antigen specific monoclonal antibodies, tyrosine kinase inhibitors, uramustine, Ustekinumab, valrubicin, Valrubicine, Vapaliximab, VEGF antagonists, Vepalimomab, verteporfin, vinblastine, vinca alkaloids, vincristine, vindesine, vinflunine, vinorelbine, Visilizumab, vorinostat, Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Zanolimumab, zileuton, Ziralimumab, Zolimomab aritox, zorubicin, Zotarolimus, or any combination thereof.

[0099] In another embodiment, the chemotherapy agent is selected from the group consisting of VEGF antagonists, EGFR antagonists, platins including cisplatin and carboplatin, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids, vinblastine, vincristine, vindesine, vinorelbine, mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1 antagonists, interleukins, IL-12, IL-2, IL-12R antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux®, Avastin®, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

[0100] In another embodiment, the cytokine antagonist is an antagonist of tumor necrosis factor- α , interferon gamma, interleukin 1 alpha, interleukin 1 beta, interleukin 6, TNF- α , IL-1 α , IL-1 β , IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN- α , IFN- γ , BAFF, CXCL13, IP-10, leukemia-inhibitory factor, or a combination thereof.

[0101] In another embodiment, the growth factor is VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, or any combination thereof.

[0102] In another embodiment, the statin is comprising atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

[0103] In another embodiment, the other therapeutic agent is an antagonist of a factor comprising tumor necrosis factor- α , Interferon gamma, Interleukin 1 alpha, Interleukin 1 beta, Interleukin 6, proteolysis inducing factor, leukemia-inhibitory factor, tamoxifen, BCL-2 antagonists, estrogen, bisphosphonates, teriparatide, strontium ranelate, sodium alendronate (Fosamax), risedronate (Actonel), raloxifene, ibandronate (Boniva), Obatoclax, ABT-263, gossypol, gefitinib, epidermal growth factor receptor tyrosine kinase inhibitors, erlotinib, epidermal growth factor receptor inhibitors, psoralens, trioxysalen, methoxsalen, bergapten, retinoids, etretinate, acitretin, infliximab (Remicade®), adalimumab, infliximab, etanercept, Zenapax®, Cyclosporine, Methotrexate, granulocyte-colony stimulating factor, filgrastim, lenograstim, Neupogen, Neulasta, 2-Arylpropionic acids, Aceclofenac, Acemetacin, Acetylsalicylic acid (Aspirin), Alclofenac, Alminoprofen, Amoxiprin, Ampyrone, Arylalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxaprofen, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofezone, COX-2 inhibitors, Dexibuprofen, Dexketoprofen, Diclofenac, Diflunisal, Droxicam, Ethenzamide, Etodolac, Etoricoxib, Faislamine, fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuprofen, Indometacin, Indoprofen, Kebuzone, Ketoprofen, Ketorolac, Lornoxicam, Loxoprofen, Lumiracoxib, Magnesium salicylate, Meclofenamic acid, Mefenamic acid, Meloxicam, Metamizole, Methyl salicylate, Mofebutazone, Nabumetone, Naproxen, N-Arylanthranilic acids, Oxametacin, Ox-

aprozin, Oxicams, Oxyphenbutazone, Parecoxib, Phenazone, Phenylbutazone, Phenylbutazone, Piroxicam, Pirprofen, profens, Proglumetacin, Pyrazolidine derivatives, Rofecoxib, Salicyl salicylate, Salicylamide, Salicylates, Sulfipyrazone, Sulindac, Suprofen, Tenoxicam, Tiaprofenic acid, Tolfenamic acid, Tolmetin, and Valdecoxib. Antibiotics include Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ansamycins, Arsphenamine, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenems, Carbenicillin, Cefaclor, Cefadroxil, Cefalexin, Cefalothin, Cefalotin, Cefamandole, Cefazolin, Cefdinir, Cefditoren, Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefoxitin, Cefpodoxime, Cefprozil, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftobiprole, Ceftriaxone, Cefuroxime, Cephalosporins, Chloramphenicol, Cilastatin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacillin, Colistin, Co-trimoxazole, Dalfopristin, Demeclocycline, Diclloxacin, Dirithromycin, Doripenem, Doxycycline, Enoxacin, Ertapenem, Erythromycin, Ethambutol, Flucloxacillin, Fosfomycin, Furazolidone, Fusidic acid, Gatifloxacin, Geldanamycin, Gentamicin, Glycopeptides, Herbimycin, Imipenem, Isoniazid, Kanamycin, Levofloxacin, Lincomycin, Linezolid, Lomefloxacin, Loracarbef, Macrolides, Mafenide, Meropenem, Meticillin, Metronidazole, Mezlocillin, Minocycline, Monobactams, Moxifloxacin, Mupirocin, Nafcillin, Neomycin, Netilmicin, Nitrofurantoin, Norfloxacin, Ofloxacin, Oxacillin, Oxytetracycline, Paromomycin, Penicillin, Penicillins, Piperacillin, Platensimycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulfacetamide, Sulfamethizole, Sulfanilimide, Sulfasalazine, Sulfisoxazole, Sulfonamides, Teicoplanin, Telithromycin, Tetracycline, Tetracyclines, Ticarcillin, Tinidazole, Tobramycin, Trimethoprim, Trimethoprim-Sulfamethoxazole, Troleandomycin, Trovafloxacin, and Vancomycin. Active agents also include Aldosterone, Beclometasone, Betamethasone, Corticosteroids, Cortisol, Cortisone acetate, Deoxycorticosterone acetate, Dexamethasone, Fludrocortisone acetate, Glucocorticoids, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Steroids, and Triamcinolone, an agonist, antagonist, or modulator of a factor comprising TNF- α , IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN- α , IFN- γ , BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hecidin, or any combination thereof.

[0104] In one embodiment, the antibody or antibody fragment may be directly or indirectly coupled to a detectable label, half-life increasing moiety, cytotoxic agent, therapeutic agent, or an immunosuppressive agent. In another embodiment, the detectable label is comprising fluorescent dyes, bioluminescent materials, radioactive materials, chemiluminescent moieties, streptavidin, avidin, biotin, radioactive materials, enzymes, substrates, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, β -galactosidase, luciferase, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin, dansyl chloride, luminol, luciferin, aequorin, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^3H), Phosphorus 32 (^{32}P), or any combination thereof.

[0105] In one embodiment, the subject may receive concomitant chemotherapy. In another embodiment, the subject may receive concomitant radiotherapy.

[0106] In another embodiment, the antibody may be the Ab1 antibody.

[0107] In another embodiment, the composition may be administered intravenously for at least about 1 hour. In another embodiment, the effective amount is or medicament comprises between about 0.1 and 20 mg/kg of body weight of recipient subject of said IL-6 antagonist. In another embodiment, the the effective amount is or medicament comprises at least about 25, 80, 100, 160, 200, or 320 mg. In another embodiment, the the effective amount is or medicament comprises between about 0.1 and 100 mg/kg of body weight of the subject.

[0108] In another embodiment, the subject may be administered at least 1, 2, 3, 4, or 5 doses. In another embodiment, the composition may be administered every 4 weeks. In another embodiment, the composition may be administered administered 160 mg every 4 weeks for a total of 2 doses. In another embodiment, the composition may be administered administered 160 mg every 4 weeks for a total of 2 doses. In another embodiment, the composition may be administered administered 320 mg every 4 weeks for a total of 2 doses.

[0109] In another embodiment, the oral and oropharyngeal mucositis may be induced by chemoradiation (CRT) regimens used for the treatment of cancers of the head and neck.

[0110] In another embodiment, the method may further comprise assessment of the status of the oral mucositis or head and neck cancer.

[0111] In another embodiment, the assessment may comprise imaging modality selected from the group consisting of CAT, PET, and MRI exams.

[0112] In another embodiment, the subject may be administered 5-fluoracil (5-FU) or Irinotecan.

[0113] In one embodiment, the composition may be administered subcutaneously. In another embodiment, the composition may be a pharmaceutical composition. In a further embodiment, the composition may be formulated for subcutaneous administration.

[0114] In one embodiment, the patient may have an elevated C-reactive protein ("CRP"). In one embodiment, the patient may have an elevated IL-6 serum level. In one embodiment, the patient may have an elevated IL-6 level in the joints. In one embodiment, the patient may have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs). In one embodiment, the patient may have had an inadequate response to non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs).

[0115] In one embodiment, the antibody or antibody fragment may be directly or indirectly coupled to a detectable

label, cytotoxic agent, therapeutic agent, or an immunosuppressive agent. In one embodiment, the detectable label may comprise a fluorescent dye, bioluminescent material, radioactive material, chemiluminescent moiety, streptavidin, avidin, biotin, radioactive material, enzyme, substrate, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, β -galactosidase, luciferase, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin, dansyl chloride, luminol, luciferin, aequorin, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^3H), Phosphorus 32 (^{32}P), or any combination thereof. In another embodiment, the IL-6 antagonist may be coupled to a half-life increasing moiety.

[0116] In one embodiment, the antibody or antibody fragment may be co-administered with another therapeutic agent selected from the group consisting of analgesics, antibiotics, anti-cachexia agents, anti-coagulants, anti-cytokine agents, antiemetic agents, anti-fatigue agent, anti-fever agent, anti-inflammatory agents, anti-nausea agents, antipyretics, antiviral agents, anti-weakness agent, chemotherapy agents, cytokine antagonist, cytokines, cytotoxic agents, gene therapy agents, growth factor, IL-6 antagonists, immunosuppressive agents, statins, or any combination thereof. In one embodiment, the cytokine antagonist may be an antagonist of a factor comprising tumor necrosis factor-alpha, interferon gamma, interleukin 1 alpha, interleukin 1 beta, interleukin 6, or any combination thereof. In one embodiment, the cytokine antagonist may be an antagonist of TNF- α , IL-1 α , IL-1 β , IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN- α , IFN- γ , BAFF, CXCL13, IP-10, leukemia-inhibitory factor, or a combination thereof. In one embodiment, the growth factor may be VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hecidin, or any combination thereof. One embodiment encompasses specific humanized antibodies and fragments and variants thereof for treatment or prevention of mucositis capable of binding to IL-6 and/or the IL-6/IL-6R complex. These antibodies may bind soluble IL-6 or cell surface expressed IL-6. Also, these antibodies may inhibit the formation or the biological effects of at least one of IL-6, IL-6/IL-6R complexes, IL-6/IL-6R/gp130 complexes and/or multimers of IL-6/IL-6R/gp130. The present invention relates to novel therapies and therapeutic protocols using anti-IL-6 antibodies, preferably those described herein.

[0117] The invention also contemplates the administration of conjugates of anti-IL-6 antibodies and humanized, chimeric or single chain versions thereof and other binding fragments and variants thereof conjugated to at least one functional or detectable moieties.

[0118] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be directly or indirectly attached to a detectable label or therapeutic agent.

[0119] In one embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be administered to the patient with a frequency at most once per period of approximately 4, 8, 12, 16, 20, or 24 weeks.

[0120] In an embodiment of the invention, the patient's quality of life may be improved.

[0121] This invention relates to novel anti-IL-6 antibodies, novel therapies and therapeutic protocols utilizing anti-IL-6 antibodies, and pharmaceutical formulations containing anti-IL-6 antibodies, wherein said antibodies are as defined in the claims and said antibodies or said formulations are for use in the treatment or prevention of mucositis associated with radiotherapy. In preferred embodiments, the anti-IL-6 antibody has an *in vivo* half-life of at least about 30 days, has an *in vivo* effect of lowering C-reactive protein, possesses a binding affinity (K_d) for IL-6 of less than about 50 picomolar, and/or has a rate of dissociation (K_{off}) from IL-6 of less than or equal to 10^{-4} s^{-1} .

[0122] In an embodiment of the invention, the patient's serum CRP level may remain decreased for an entire period intervening two consecutive anti-IL-6 antibody administrations.

[0123] In one embodiment, the patient may have been diagnosed mucositis.

[0124] In one embodiment, the antibody, or antibody fragment thereof, may be expressed from a recombinant cell. In another embodiment, the cell may be selected from a mammalian, yeast, bacterial, and insect cell. In another embodiment, the cell may be a yeast cell. In another embodiment, the cell may be a diploidal yeast cell. In another embodiment, the yeast cell may be a *Pichia* yeast. In another embodiment, the anti-IL-6 antibody may be produced in a yeast based (*Pichia pastoris*) expression system using conventional fermentation processes and downstream purification. In one embodiment, the antibodies and antibody fragments described herein may be expressed in yeast cells. In one embodiment, the mating competent yeast may a member of the Saccharomycetaceae family, which includes the genera *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*. Other types of yeast potentially useful in the invention include *Yarrowia*, *Rhodsporidium*, *Candida*, *Hansenula*, *Filobasium*, *Filobasidella*, *Sporidiobolus*, *Bullera*, *Leucosporidium*, and *Filobasidella*. In a preferred embodiment, the mating competent yeast may a member of the genus *Pichia*. In a further preferred embodiment, the mating competent yeast of the genus *Pichia* is one of the following species: *Pichia pastoris*, *Pichia methanolica*, and *Hansenula polymorpha* (*Pichia angusta*). In a particularly preferred embodiment, the mating competent yeast of the genus *Pichia* may the species *Pichia pastoris*.

[0125] In one embodiment, a composition for use in treating oral mucositis associated with radiotherapy in a subject with head and neck cancer receiving concomitant chemotherapy may comprise an effective amount of a humanized monoclonal antibody in accordance with the claims that selectively binds IL-6.

[0126] In one embodiment, a composition for use in the treatment or prevention of oral mucositis associated with

radiotherapy may comprise a humanized monoclonal antibody in accordance with the claims that selectively binds IL-6, and saline solution.

[0127] In one embodiment, the composition for use in accordance with the claims may comprise an anti-IL-6 antibody or antibody fragment in accordance with the claims contained in a composition that comprises, or alternatively consists of, said anti-IL-6 antibody or antibody fragment, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80.

[0128] In one embodiment, the composition for use in accordance with the claims may comprise an anti-IL-6 antibody or antibody fragment in accordance with the claims contained in a composition that comprises, or alternatively consists of, said anti-IL-6 antibody or antibody fragment, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 to 280 mM sorbitol or sorbitol in combination with sucrose, and 0.015% (w/w) Polysorbate 80, said formulation having a nitrogen headspace in the shipping vials.

[0129] In one embodiment, the composition for use in accordance with the claims may comprise an anti-IL-6 antibody or antibody fragment in accordance with the claims contained in a composition comprising, or alternatively consisting of, anti-IL-6 antibody or antibody fragment, 25 mM Histidine base, Phosphoric acid q.s. to pH 6, and 250 mM sorbitol.

[0130] In one embodiment, the composition for use in accordance with the claims may comprise an anti-IL-6 antibody or antibody fragment in accordance with the claims contained in a composition comprising, or alternatively consisting of, said anti-IL-6 antibody or antibody fragment, 12.5 mM Histidine base, 12.5 mM Histidine HCl (or 25 mM Histidine base and Hydrochloric acid q.s. to pH 6), 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80.

[0131] In one embodiment, the composition for use in accordance with the claims may comprise an anti-IL-6 antibody or antibody fragment in accordance with the claims contained in a composition comprising, or alternatively consisting of, said anti-IL-6 antibody or antibody fragment, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80.

[0132] In one embodiment, the composition may comprise a concentration of an anti-IL-6 antibody or antibody fragment is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 mg/mL or at least about 10-100 mg/mL.

[0133] In one embodiment, the composition may comprise at least about 50 or 100 mg of an anti-IL-6 antibody or antibody fragment.

[0134] In one embodiment, the composition may comprise at least about 80 mg, about 160 mg, or about 320 mg of an anti-IL-6 antibody or antibody fragment.

[0135] In one embodiment, the effective amount is between about 0.1 and 20 mg/kg of body weight of recipient subject.

[0136] In one embodiment, the effective amount is between about 0.1 and 100 mg/kg of body weight of the subject.

[0137] In one embodiment, the composition may comprise at least about 25, 80, 100, 160, 200, or 320 mg.

[0138] In one embodiment, the composition may be formulated for intravenous administration.

[0139] In one embodiment, the composition may comprise an excipient selected from the group consisting of histidine, sorbitol, and polysorbate 80.

[0140] In one embodiment, the composition may be administered every 4 weeks. In one embodiment, the composition may be administered 80 mg every 4 weeks for a total of 2 doses. In one embodiment, the composition may be administered 160 mg every 4 weeks for a total of 2 doses. In one embodiment, the composition may be administered 320 mg every 4 weeks for a total of 2 doses.

[0141] The anti-IL-6 antibody comprises a light chain polypeptide comprising a polypeptide having 100% identity to SEQ ID NO: 709.

[0142] In one embodiment, the anti-IL-6 antibody may comprise a light chain polypeptide comprising a polypeptide encoded by a polynucleotide that has at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 96%, at least 97% identity, at least 98%, at least 99% identity, or 100% identity to SEQ ID NO: 723.

[0143] The anti-IL-6 antibody comprises a heavy chain polypeptide comprising a polypeptide having 100% identity to SEQ ID NO: 657.

[0144] In one embodiment, the anti-IL-6 antibody may comprise a heavy chain polypeptide comprising a polypeptide encoded by a polynucleotide having at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 96%, at least 97% identity, at least 98%, at least 99% identity, or 100% identity to SEQ ID NO: 700.

[0145] In one embodiment, the anti-IL-6 antibody may comprise a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 723, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723; and a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 700, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a

polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700; wherein the Ab1 antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6.

[0146] In one embodiment, the anti-IL-6 antibody may comprise anti-IL-6 antibody further comprises the constant light chain sequence contained in SEQ ID NO: 586.

5 **[0147]** In one embodiment, the anti-IL-6 antibody may comprise the constant heavy chain sequence contained in SEQ ID NO: 588.

[0148] In one embodiment, the composition may further comprise methotrexate.

[0149] In one embodiment, the composition may further comprise at least one anti-inflammatory agent, analgesic agent, or disease-modifying antirheumatic drug (DMARD).

10 **[0150]** In one embodiment, the anti-inflammatory agent is selected from the group consisting of steroids, Cortisone, Glucocorticoids, prednisone, prednisolone, Hydrocortisone (Cortisol), Cortisone acetate, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone, Beclometasone, and Fludrocortisone acetate, non-steroidal anti-inflammatory drug (NSAIDs), ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac, tolementin, choline magnesium salicylate, diclofenac, diflusal, indomethacin, Ketoprofen, Oxaprozin, piroxicam, and nimesulide, Salicylates, Aspirin (acetylsalicylic acid), Diflunisal, Salsalate, p-amino phenol derivatives, Paracetamol, phenacetin, Propionic acid derivatives, Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen, Acetic acid derivatives, Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone, Enolic acid (Oxicam) derivatives, Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, Fenamic acid derivatives (¹²⁵I), Fenamates), Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid, Selective COX-2 inhibitors (Coxibs), Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, Firocoxib, Sulphonanilides, Nimesulide, and Licofelone.

15 **[0151]** In one embodiment, the analgesic agent is selected from the group consisting of NSAIDs, COX-2 inhibitors, Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, Firocoxib, acetaminophen, opiates, Dextropropoxyphene, Codeine, Tramadol, Anileridine, Pethidine, Hydrocodone, Morphine, Oxycodone, Methadone, Diacetylmorphine, Hydromorphone, Oxymorphone, Levorphanol, Buprenorphine, Fentanyl, Sufentanyl, Etorphine, Carfentanil, dihydromorphone, dihydrocodeine, Thebaine, Papaverine, diproqualone, Flupirtine, Tricyclic antidepressants, and lidocaine.

20 **[0152]** In one embodiment, the DMARD may be selected from the group consisting of mycophenolate mofetil (CellCept), calcineurin inhibitors, cyclosporine, sirolimus, everolimus, oral retinoids, azathioprine, fumeric acid esters, D-penicillamine, cyclophosphamide, immunoadsorption column, Prosorba(r) column, a gold salt, auranofin, sodium aurothiomalate (Myocrisin), hydroxychloroquine, chloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine (SSZ), tumor necrosis factor alpha (TNFα) blockers, etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers, e.g., anakinra (Kineret), monoclonal antibodies against B cells, rituximab (Rituxan), T cell costimulation blockers, abatacept (Orencia), Interleukin 6 (IL-6) blockers, tocilizumab, RoActemra, and Actemra.

35 **[0153]** In one embodiment, the DMARD is not an antibody.

[0154] In one embodiment, the administration of a composition described herein to a patient in need thereof results in an improvement in at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP, (vii) improvement in one or more SF-36 domain scores, (viii) an improvement in SF-6D score, wherein said efficacy is measured relative to said patient's baseline prior to administration of said antibody or antibody fragment, relative untreated patients, relative to patients receiving a placebo or control formulation, or relative to age/gender norms.

40 **[0155]** In one embodiment, the administration of a composition described herein to a patient in need thereof results in a prolonged improvement in disease (observed at least 4, 6, 8, 10, 12, 14 or 16 weeks after antibody administration) as manifested by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP, (vii) improvement in one or more SF-36 domain scores, (viii) an improvement in SF-6D score, wherein said efficacy is measured relative to said patient's baseline prior to administration of said antibody or antibody fragment, relative untreated patients, relative to patients receiving a placebo or control formulation, or relative to age/gender norms.

45 **[0156]** In a further embodiment, the improvement in SF-6D score is at least equal to the Minimum Important Difference (MID) relative to the patient's SF-6D prior to said administration.

[0157] In a further embodiment, the improvement in SF-6D score is at least twice the MID relative to the patient's SF-6D prior to said administration.

[0158] In a further embodiment, the improvement in SF-6D score is at least three times the MID relative to the patient's SF-6D prior to said administration.

55 **[0159]** In another embodiment, the improvement in SF-36 may comprise an improvement in the physical functioning domain score, said improvement being at least equal to the minimum clinically important difference (MCID), at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0160] In another embodiment, the improvement in SF-36 may comprise an improvement in the role physical domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0161] In another embodiment, the improvement in SF-36 may comprise an improvement in the bodily pain domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0162] In another embodiment, the improvement in SF-36 may comprise an improvement in the general health domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0163] In another embodiment, the improvement in SF-36 may comprise an improvement in the role emotional domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0164] In another embodiment, the improvement in SF-36 may comprise an improvement in the vitality domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0165] In another embodiment, the improvement in SF-36 may comprise an improvement in the social functioning domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0166] In another embodiment, the improvement in SF-36 may comprise an improvement in the mental health domain score, said improvement being at least equal to the MCID, at least 2 times the MCID, at least 3 times the MCID, at least 4 times the MCID, at least 5 times the MCID, or at least 6 times the MCID for that domain score.

[0167] In one embodiment, there is a composition for use in a method of treating or preventing oral mucositis associated with radiotherapy, the method comprising administering a composition comprising 160 mg of an Ab1 antibody or antibody fragment thereof in accordance with the claims, wherein said patient does not develop oral mucositis more severe than a Grade 3 according to the WHO Oral Mucositis Scale. In another embodiment, the patient may be undergoing chemotherapy. In another embodiment, the patient may be undergoing radiotherapy. In another embodiment, the patient has head and neck cancer. In another embodiment, the patient may not develop oral mucositis more severe than Grade 2, 1, or 0.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0168]

FIGURE 1 depicts alignments of variable light and variable heavy sequences between a rabbit antibody variable light and variable heavy sequences and homologous human sequences and the humanized sequences. Framework regions are identified FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Amino acid residues are numbered as shown. The initial rabbit sequences are called RbtVL and RbtVH for the variable light and variable heavy sequences respectively. Three of the most similar human germline antibody sequences, spanning from Framework 1 through to the end of Framework 3, are aligned below the rabbit sequences. The human sequence that is considered the most similar to the rabbit sequence is shown first. In this example those most similar sequences are L12A for the light chain and 3-64-04 for the heavy chain. Human CDR3 sequences are not shown. The closest human Framework 4 sequence is aligned below the rabbit Framework 4 sequence. The vertical dashes indicate a residue where the rabbit residue is identical with at least one of the human residues at the same position. The bold residues indicate that the human residue at that position is identical to the rabbit residue at the same position. The final humanized sequences are called VLh and VHh for the variable light and variable heavy sequences respectively. The underlined residues indicate that the residue is the same as the rabbit residue at that position but different than the human residues at that position in the three aligned human sequences.

FIGURES 2 and 3 depicts alignments between a rabbit antibody light and variable heavy sequences and homologous human sequences and the humanized sequences. Framework regions are identified as FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3.

FIGURES 4A-B and 5A-B depicts alignments between light and variable heavy sequences, respectively, of different forms of Ab1. Framework regions are identified as FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Sequence differences within the CDR regions highlighted.

FIGURE 6 provides the α -2-macroglobulin (A2M) dose response curve for antibody Ab1 administered intravenously at different doses one hour after a 100 μ g/kg s.c. dose of human IL-6. See also WO 2011/066371.

FIGURE 7 provides survival data for the antibody Ab1 progression groups versus control groups. See also WO 2011/066371.

FIGURE 8 provides additional survival data for the antibody Ab1 regression groups versus control groups. See also

WO 2011/066371.

FIGURE 9 provides survival data for polyclonal human IgG at 10 mg/kg i.v. every three days (270-320 mg tumor size) versus antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size). See *also* WO 2011/066371.

FIGURE 10 provides survival data for polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) versus antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size). See *also* WO 2011/066371.

FIGURE 11 shows increased hemoglobin concentration following administration of Ab1 to patients with advanced cancer. See *also* WO 2011/066371.

FIGURE 12 depicts mean plasma lipid concentrations following administration of Ab1 to patients with advanced cancer. See *also* WO 2011/066371.

FIGURE 13 depicts mean neutrophil counts following administration of Ab1 to patients with advanced cancer. See *also* WO 2011/066371.

FIGURE 14A demonstrates suppression of serum CRP levels in healthy individuals.

FIGURE 14B demonstrates suppression of serum CRP levels in advanced cancer patients.

FIGURE 15A depicts the mean CRP values for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody in NSCLC patients.

FIGURE 15B depicts the change in median values of CRP from each dosage concentration group corresponding to **FIGURE 15A** in NSCLC patients.

FIGURE 16 depicts the mean plasma CRP concentration in patients with advanced cancer after a single I.V. infusion of 80, 160, or 320 mg of Ab1 (ALD518) (n=8).

FIGURE 17 depicts the mean serum CRP levels in patients with rheumatoid arthritis patients with an inadequate response to methotrexate after dosing at 80, 160, or 320 mg of Ab1 (ALD518).

FIGURE 18A depicts that Ab1 increases mean hemoglobin concentration (g/dL) at 80, 160 and 320 mg after 12 weeks of dosing in NSCLC patients versus placebo. See *also* WO 2011/066371.

FIGURE 18B depicts the mean change from baseline in hemoglobin concentration (g/dL) for NSCLC patients versus placebo. See *also* WO 2011/066371.

FIGURE 18C depicts the mean hemoglobin concentration (g/dL) in NSCLC patients with a baseline hemoglobin below 11 g/L at baseline versus time with Ab1 compared to placebo.

FIGURE 19 depicts the mean change from baseline in hemoglobin concentration (g/dL) for rheumatoid arthritis patients with an inadequate response to methotrexate versus placebo. The normal range of hemoglobin concentration is approximately 11.5-15.5 g/dL. See *also* WO 2011/066371.

FIGURE 20A depicts that Ab1 increases mean albumin concentration at 80, 160 and 320 mg in NSCLC patients. See *also* WO 2011/066371.

FIGURE 20B depicts the change from baseline for mean albumin concentration from each dosage concentration group corresponding to Figure 20A in NSCLC patients. See *also* WO 2011/066371.

FIGURE 20C depicts the mean albumin concentration in NSCLC patients with a baseline albumin ≤ 35 g/l at baseline versus time for Ab1 versus placebo. See *also* WO 2011/066371.

FIGURE 21A depicts the mean plasma CRP levels concentration after subcutaneous or intravenous dosing of humanized Ab1.

FIGURE 21B depicts the mean plasma CRP levels concentration after subcutaneous or intravenous dosing of humanized Ab1 at dosing of 50 mg or 100 mg through 12 weeks.

FIGURE 22 depicts percentage of mice ulcerated at any timepoint after single dose radiation.

FIGURE 23 depicts median tumor volume over time.

FIGURE 24 depicts the percentage of mice with no ulcerations versus ulcerations on Day 10.

FIGURE 25 depicts median number of days ulcerated after single dose of radiation.

FIGURE 26 depicts of patient disposition in a Phase II clinical trial for administration of ALD518 to patients with active rheumatoid arthritis (RA). An asterisk indicates that one patient did not receive treatment as randomized (the patient was randomized to receive 160 mg ALD518, but received 320 mg on Day 1 and 160 mg ALD518 at Week 8; AE=adverse event).

FIGURE 27 graphically illustrates the mean changes in SF-36 composite scores at Week 12 in a Phase II clinical trial for administration of ALD518 to patients with active RA. Data are mean and error bars represent 95% confidence intervals (for each group, the left bar shows the PCS score and the right bar shows the MCS score). Mean changes in PCS and MCS scores at Week 12 exceeded the MCID in all ALD-518 treatment groups. Greater improvements in MCS score in favor of all ALD-518 treatment groups were demonstrated at Week 12 ($p < 0.05$). MCS scores changes also exceeded the PCS scores in all ALD-518 treatment groups. SF-36=Short Form Health Survey-36; PCS=physical component score; MCS=mental component score; MCID=minimum clinically important difference.

FIGURE 28A-D presents spidergrams summarizing the changes from baseline to week 12 in SF-36 domain scores compared with age/gender matched norms for a Phase II clinical trial for administration of ALD518 to patients with active RA. The spidergrams summarize age/gender norms, average baseline scores prior to treatment, and average

scores after treatment in each of eight tested domains for patients receiving 80 mg (panel A), 160 mg (panel B), or 320 mg (panel C) ALD-518, or placebo (panel D). PF=physical function; RP=role physical; BP=bodily pain; GH=general health; VT=vitality; SF=social functioning; RE=role emotional; MH=mental health; SF-36=Short Form-36.

FIGURE 29A-B presents spydergrams summarizing the changes from baseline to weeks 12 (A) and 16 (B) in SF-36 domain scores compared with age/gender matched norms for a Phase II clinical trial for administration of ALD518 to patients with active RA. The spydergrams summarize scores in eight tested domains for age/gender norms, combined average baseline scores prior to treatment, and average scores after treatment for each treatment group (ALD-518 dosages of 80 mg, 160 mg, or 320 mg), and the placebo group. Abbreviations are as in FIG. 28.

FIGURE 30 depicts WHO oral mucositis grade versus cumulative IMRT (Gy): ALD518 160 mg intravenous at week 0 and week 4 for three patients.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0169] The invention is as defined in the claims.

Definitions

[0170] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0171] As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

[0172] *Amplification* as used herein, refers broadly to the amplification of polynucleotide sequences is the *in vitro* production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are known in the art. See, e.g., Van Brunt (1990) Bio/Technol. 8(4): 291-294. Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[0173] *Antibody*, as used herein, refers broadly to any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where at least one non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, from all sources, e.g., human, rodent, rabbit, cow, sheep, pig, dog, chicken, are considered to be "antibodies." Antibodies include but are not limited to chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (scFvs), camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments (e.g., Fabs, Fab', F(ab')₂). Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. See Streltsov, et al. (2005) Protein Sci. 14(11): 2901-9; Greenberg, et al. (1995) Nature 374(6518): 168-173; Nuttall, et al. (2001) Mol Immunol. 38(4): 313-26; Hamers-Casterman, et al. (1993) Nature 363(6428): 446-8; Gill, et al. (2006) Curr Opin Biotechnol. 17(6): 653-8.

[0174] *Antibody fragment*, as used herein, refers broadly to a fragment of an antibody which recognizes an antigen (e.g., paratopes, antigen-binding fragment.) The antibody fragment may comprise a paratope that may be a small region (e.g., 15-22 amino acids) of the antibody's Fv region and may contain parts of the antibody's heavy and light chains. See Goldsby, et al. Antigens (Chapter 3) Immunology (5th Ed.) New York: W.H. Freeman and Company, pages 57-75.

[0175] *C-Reactive Protein (CRP)*, as used herein, refers broadly to a 224 amino acid protein found in the blood that rise in response to inflammation [(e.g., GenBank Protein Accession No. NP_000558 (SEQ ID NO: 726)]. CRP also encompasses any pre-pro, pro- and mature forms of this CRP amino acid sequence, as well as mutants and variants including allelic variants of this sequence. CRP levels, e.g. in the serum, liver, or elsewhere in the body, can be readily measured using routine methods and commercially available reagents, e.g. ELISA, antibody test strip, immunoturbidimetry, rapid immunodiffusion, visual agglutination, Western blot, Northern blot As mentioned above CRP levels may in addition be measured in patients having or at risk of developing thrombosis according to the invention.

[0176] *Coding sequence*, as used herein refers broadly to an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a

DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence. A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (*i.e.*, the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[0177] *Complementarity determining region, hypervariable region, or CDR*, as used herein refer broadly to at least one of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (See Kabat, E. A. et al. (1987) Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md.). These expressions include the hypervariable regions as defined by Kabat *et al.* ("Sequences of Proteins of Immunological Interest," Kabat E., et al. (1983) US Dept. of Health and Human Services) or the hypervariable loops in 3-dimensional structures of antibodies. Chothia and Lesk (1987) J Mol. Biol. 196: 901-917. The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri (2005) Methods 36:25-34). CDRs for exemplary anti-IL-6 antibodies are provided herein.

[0178] *Disease or condition*, as used herein, refers broadly to a disease or condition that a patient has been diagnosed with or is suspected of having, particularly a disease or condition associated with elevated IL-6. A disease or condition encompasses, without limitation thereto, mucositis, as well as idiopathic conditions characterized by symptoms that include elevated IL-6.

[0179] *Effective amount*, as used herein, refers broadly to an amount of an active ingredient that is effective to relieve or reduce to some extent at least one of the symptoms of the disease in need of treatment, or to retard initiation of clinical markers or symptoms of a disease in need of prevention, when the compound is administered. Thus, an effective amount refers to an amount of the active ingredient which exhibit effects such as (i) reversing the rate of progress of a disease; (ii) inhibiting to some extent further progress of the disease; and/or, (iii) relieving to some extent (or, preferably, eliminating) at least one symptoms associated with the disease. The effective amount may be empirically determined by experimenting with the compounds concerned in known *in vivo* and *in vitro* model systems for a disease in need of treatment. The context in which the phrase "effective amount" is used may indicate a particular desired effect. For example, "an amount of an anti-IL-6 antibody effective to prevent or treat a hypercoagulable state" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable improvement in the subject's coagulation profile, or prevent, slow, delay, or arrest, a worsening of the coagulation profile for which the subject is at risk. Similarly, "an amount of an anti-IL-6 antibody effective to reduce serum CRP levels" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable decrease in serum CRP levels, or prevent, slow, delay, or arrest, an increase in serum CRP levels for which the subject is at risk. Similarly, "an amount of an anti-IL-6 antibody effective to increase serum albumin levels" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable increase in serum albumin levels, or prevent, slow, delay, or arrest, a decrease in serum albumin levels for which the subject is at risk. Similarly, "an amount of an anti-IL-6 antibody effective to reduce weakness" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable decrease in weakness as determined by the hand grip strength test. Similarly, "an amount of an anti-IL-6 antibody effective to increase weight" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable increase in a patient's weight. An effective amount will vary according to the weight, sex, age and medical history of the individual, as well as the severity of the patient's condition(s), the type of disease(s), mode of administration, and the like. An effective amount may be readily determined using routine experimentation, e.g., by titration (administration of increasing dosages until an effective dosage is found) and/or by reference to amounts that were effective for prior patients. Generally, the anti-IL-6 antibodies of the present invention will be administered in dosages ranging between about 0.1 mg/kg and about 20 mg/kg of the patient's body-weight.

[0180] *Expression Vector*, as used herein, refers broadly to a DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host (e.g., *E. coli*) and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods

for transformation of yeast are described, for example, in Burke, Dawson, & Stearns (2000) *Methods in Yeast Genetics*: a Cold Spring Harbor Laboratory course manual. Cold Spring Harbor Laboratory Press.

[0181] *Folding*, as used herein, refers broadly to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. While non-covalent interactions are important in determining structure, usually the proteins of interest will have intra- and/or intermolecular covalent disulfide bonds formed by two cysteine residues. For naturally occurring proteins and polypeptides or derivatives and variants thereof, the proper folding is typically the arrangement that results in optimal biological activity, and can conveniently be monitored by assays for activity, e.g. ligand binding, enzymatic activity.

[0182] *Framework region* or *FR*, as used herein refers broadly to at least one of the framework regions within the variable regions of the light and heavy chains of an antibody. See Kabat, et al. (1987) *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda, MD. These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody. As mentioned in the preferred embodiments, the FRs may comprise human FRs highly homologous to the parent antibody (e.g., rabbit antibody).

[0183] *Glasgow Prognostic Score (GPS)*, as used herein, refers broadly to an inflammation-based prognostic score that awards one point for a serum albumin level less than < 35 mg/L and one point for a CRP level above 10 mg/L. Thus, a GPS of 0 indicates normal albumin and CRP, a GPS of 1 indicates reduced albumin or elevated CRP, and a GPS of 2 indicates both reduced albumin and elevated CRP.

[0184] *gp130* (also called Interleukin-6 receptor subunit beta), as used herein, refers broadly to a transmembrane protein that forms one subunit of type I cytokine receptors in the IL-6 receptor family [(e.g., 918 precursor amino acid sequence available as Swiss-Prot Protein Accession No. P40189 (SEQ ID NO: 728)]. gp130 also encompasses any pre-pro, pro- and mature forms of this amino acid sequence, such as the mature form encoded by amino acids 23 through 918 of the sequence shown, as well as mutants and variants including allelic variants of this sequence.

[0185] *Heterologous region* or *domain* of a DNA construct, as used herein, refers broadly to an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[0186] *Homology*, as used herein, refers broadly to a degree of similarity between a nucleic acid sequence and a reference nucleic acid sequence or between a polypeptide sequence and a reference polypeptide sequence. Homology may be partial or complete. Complete homology indicates that the nucleic acid or amino acid sequences are identical. A partially homologous nucleic acid or amino acid sequence is one that is not identical to the reference nucleic acid or amino acid sequence. The degree of homology can be determined by sequence comparison. The term "sequence identity" may be used interchangeably with "homology."

[0187] *Host cell*, as used herein, refers broadly to a cell that contains an expression vector and supports the replication or expression of the expression vector. Host cells may be prokaryotic cells such as *E. coli*, or eukaryotic cells such as yeast, insect (e.g., SF9), amphibian, or mammalian cells such as CHO, HeLa, HEK-293 (e.g., cultured cells, explants, and cells *in vivo*).

[0188] *Isolated*, as used herein, refers broadly to material removed from its original environment in which it naturally occurs, and thus is altered by the hand of man from its natural environment. Isolated material may be, for example, exogenous nucleic acid included in a vector system, exogenous nucleic acid contained within a host cell, or any material which has been removed from its original environment and thus altered by the hand of man (e.g., "isolated antibody").

[0189] *Improved*, as used herein, refers broadly to any beneficial change resulting from a treatment. A beneficial change is any way in which a patient's condition is better than it would have been in the absence of the treatment. "Improved" includes prevention of an undesired condition, slowing the rate at which a condition worsens, delaying the development of an undesired condition, and restoration to an essentially normal condition. For example, improvement in mucositis encompasses any decrease in pain, swelling, joint stiffness, or inflammation, and/or an increase in joint mobility.

[0190] *IL-6 antagonist*, as used herein, refers broadly to any composition that prevents, inhibits, or lessens the effect(s) of IL-6 signaling. Generally, such antagonists may reduce the levels or activity of IL-6, IL-6 receptor alpha, gp130, or a molecule involved in IL-6 signal transduction, or may reduce the levels or activity complexes between the foregoing (e.g., reducing the activity of an IL-6 / IL-6 receptor complex). Antagonists include antisense nucleic acids, including DNA, RNA, or a nucleic acid analogue such as a peptide nucleic acid, locked nucleic acid, morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, or threose nucleic acid. See Heasman (2002) *Dev Biol.* 243(2): 209-14; Hannon and Rossi (2004) *Nature* 431(7006):371-8; Paul, et al. (2002) *Nat Biotechnol.* 20(5):505-8; Zhang, et al. (2005) *J Am Chem Soc.* 127(12):4174-5; Wahlestedt, et al. (2000) *Proc Natl Acad Sci USA.* 97(10):5633-8; Hanvey, et al.

(1992) Science 258 (5087):1481-5; Braasch, et al. (2002) Biochemistry 41(14): 4503-10; Schoning, et al. (2000) Science 290(5495): 1347-51. In addition IL-6 antagonists specifically include peptides that block IL-6 signaling such as those described in any of U.S. Patent Nos. 5,210,075; 6,172,042; 6,599,875; 6,841,533; and 6,838,433. Also, IL-6 antagonists according to the invention may include p38 MAP kinase inhibitors such as those reported in U.S. Patent Application No. 2007/0010529 given this kinase's role in cytokine production and more particularly IL-6 production. Further, IL-6 antagonists according to the invention include the glycoalkaloid compounds reported in U.S. Patent Application Publication No. 2005/0090453 as well as other IL-6 antagonist compounds isolatable using the IL-6 antagonist screening assays reported therein. Other IL-6 antagonists include antibodies, such as anti-IL-6 antibodies, anti-IL-6 receptor alpha antibodies, anti-gp130 antibodies, and anti-p38 MAP kinase antibodies including (but not limited to) the anti-IL-6 antibodies disclosed herein, Actemra® (Tocilizumab), Remicade®, Zenapax® (daclizumab), or any combination thereof. Other IL-6 antagonists include portions or fragments of molecules involved in IL-6 signaling, such as IL-6, IL-6 receptor alpha, and gp130, which may be native, mutant, or variant sequence, and may optionally be coupled to other moieties (such as half-life-increasing moieties, e.g. an Fc domain). For example, an IL-6 antagonist may be a soluble IL-6 receptor or fragment, a soluble IL-6 receptor:Fc fusion protein, a small molecule inhibitor of IL-6, an anti-IL-6 receptor antibody or antibody fragment or variant thereof, antisense nucleic acid. Other IL-6 antagonists include avemirs, such as C326 (Silverman, et al. (2005) Nat Biotechnol. 23(12): 1556-61) and small molecules, such as synthetic retinoid AM80 (tamibarotene) (Takeda, et al. (2006) Arterioscler Thromb Vasc Biol. 26(5): 1177-83). Such IL-6 antagonists may be administered by any means known in the art, including contacting a subject with nucleic acids which encode or cause to be expressed any of the foregoing polypeptides or antisense sequences.

[0191] *Interleukin-6 (IL-6)*, as used herein, refers broadly to interleukin-6 (IL-6) encompasses not only the following 212 amino acid sequence available as GenBank Protein Accession No. NP_000591 (e.g., SEQ ID NO: 1), but also any pre-pro, pro- and mature forms of this IL-6 amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0192] *Interleukin-6 receptor (IL-6R) (IL-6 receptor alpha (IL-6RA) [CD126]*, as used herein, refers broadly to 468 amino acid protein that binds IL-6, a potent pleiotropic cytokine that regulates cell growth and differentiation and also plays an important role in immune response (e.g., Swiss-Prot Protein Accession No. P08887 and SEQ ID NO: 727). IL-6R also includes any pre-pro, pro- and mature forms of this amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0193] *Mammal*, as used herein, refers broadly to any and all warm-blooded vertebrate animals of the class Mammalia, including humans, characterized by a covering of hair on the skin and, in the female, milk-producing mammary glands for nourishing the young. Examples of mammals include but are not limited to alpacas, armadillos, capybaras, cats, camels, chimpanzees, chinchillas, cattle, dogs, goats, gorillas, hamsters, horses, humans, lemurs, llamas, mice, non-human primates, pigs, rats, sheep, shrews, squirrels, and tapirs. Mammals include but are not limited to bovine, canine, equine, feline, murine, ovine, porcine, primate, and rodent species. Mammal also includes any and all those listed on the Mammal Species of the World maintained by the National Museum of Natural History, Smithsonian Institution in Washington DC.

[0194] *Meiosis*, as used herein, refers broadly to a process by which a diploid yeast cell undergoes reductive division to form four haploid spore products. Each spore may then germinate and form a haploid vegetatively growing cell line.

[0195] *Nucleic acid or nucleic acid sequence*, as used herein, refers broadly to a deoxyribonucleotide or ribonucleotide oligonucleotide in either single- or double-stranded form. The term encompasses nucleic acids, i.e., oligonucleotides, containing known analogs of natural nucleotides. The term also encompasses nucleic-acid-like structures with synthetic backbones. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. The term nucleic acid is used interchangeably with gene, cDNA, mRNA, oligonucleotide, and polynucleotide.

[0196] *Operatively linked*, as used herein, refers broadly to when two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

[0197] *Paratope*, as used herein, refers broadly to the part of an antibody which recognizes an antigen (e.g., the antigen-binding site of an antibody.) Paratopes may be a small region (e.g., 15-22 amino acids) of the antibody's Fv region and may contain parts of the antibody's heavy and light chains. See Goldsby, et al. Antigen (Chapter 3) Immunology (5th Ed.) New York: W.H. Freeman and Company, pages 57-75.

[0198] *Patient*, as used herein, refers broadly to any animal who is in need of treatment either to alleviate a disease state or to prevent the occurrence or reoccurrence of a disease state. Also, "Patient" as used herein, refers broadly to any animal who has risk factors, a history of disease, susceptibility, symptoms, signs, was previously diagnosed, is at risk for, or is a member of a patient population for a disease. The patient may be a clinical patient such as a human or a veterinary patient such as a companion, domesticated, livestock, exotic, or zoo animal. The term "subject" may be used interchangeably with the term "patient".

[0199] *Polyploid yeast that stably expresses or expresses a desired secreted heterologous polypeptide for prolonged*

time, as used herein, refers broadly to a yeast culture that secretes said polypeptide for at least several days to a week, more preferably at least a month, still more preferably at least about 1-6 months, and even more preferably for more than a year at threshold expression levels, typically at least about 10-25 mg/liter and preferably substantially greater.

[0200] *Polyploidal yeast culture that secretes desired amounts of recombinant polypeptide*, as used herein, refers broadly to cultures that stably or for prolonged periods secrete at least about 10-25 mg/liter of heterologous polypeptide, more preferably at least about 50-500 mg/liter, and most preferably at least about 500-1000 mg/liter or more.

[0201] *Prolonged reduction in serum CRP*, and similar phrases, as used herein refer broadly to a measurable decrease in serum CRP level relative to the initial serum CRP level (*i.e.* the serum CRP level at a time before treatment begins) that is detectable within about a week from when a treatment begins (*e.g.* administration of an anti-IL-6 antibody) and remains below the initial serum CRP level for an prolonged duration, *e.g.* at least about 14 days, at least about 21 days, at least about 28 days, at least about 35 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 11 weeks, or at least about 12 weeks from when the treatment begins.

[0202] *Promoter*, as used herein, refers broadly to an array of nucleic acid sequences that direct transcription of a nucleic acid. As used herein, a promoter includes necessary nucleic acid sequences near the start site of transcription, such as, in the case of a polymerase II type promoter, a TATA element. A promoter also optionally includes distal enhancer or repressor elements, which can be located as much as several thousand base pairs from the start site of transcription. A "constitutive" promoter is a promoter that is active under most environmental and developmental conditions. An "inducible" promoter is a promoter that is active under environmental or developmental regulation.

[0203] *Prophylactically effective amount*, as used herein, refers broadly to the amount of a compound that, when administered to a patient for prophylaxis of a disease or prevention of the reoccurrence of a disease, is sufficient to effect such prophylaxis for the disease or reoccurrence. The prophylactically effective amount may be an amount effective to prevent the incidence of signs and/or symptoms. The "prophylactically effective amount" may vary depending on the disease and its severity and the age, weight, medical history, predisposition to conditions, preexisting conditions, of the patient to be treated.

[0204] *Prophylaxis*, as used herein, refers broadly to a course of therapy where signs and/or symptoms are not present in the patient, are in remission, or were previously present in a patient. Prophylaxis includes preventing disease occurring subsequent to treatment of a disease in a patient. Further, prevention includes treating patients who may potentially develop the disease, especially patients who are susceptible to the disease (*e.g.*, members of a patent population, those with risk factors, or at risk for developing the disease).

[0205] *Recombinant* as used herein, refers broadly with reference to a product, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[0206] *Selectable Marker*, as used herein, refers broadly to a selectable marker is a gene or gene fragment that confers a growth phenotype (physical growth characteristic) on a cell receiving that gene as, for example through a transformation event. The selectable marker allows that cell to survive and grow in a selective growth medium under conditions in which cells that do not receive that selectable marker gene cannot grow. Selectable marker genes generally fall into several types, including positive selectable marker genes such as a gene that confers on a cell resistance to an antibiotic or other drug, temperature when two ts mutants are crossed or a ts mutant is transformed; negative selectable marker genes such as a biosynthetic gene that confers on a cell the ability to grow in a medium without a specific nutrient needed by all cells that do not have that biosynthetic gene, or a mutagenized biosynthetic gene that confers on a cell inability to grow by cells that do not have the wild type gene; and the like. Suitable markers include but are not limited to ZEOMYCIN® (zeocin), neomycin, G418, LYS3, MET1, MET3a, ADE1, ADE3, and URA3.

[0207] *Specifically (or selectively) binds* to an antibody or "specifically (or selectively) immunoreactive with," or "specifically interacts or binds," as used herein, refers broadly to a protein or peptide (or other epitope), refers, in some embodiments, to a binding reaction that is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. For example, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times greater than the background (non-specific signal) and do not substantially bind in a significant amount to other proteins present in the sample. Typically a specific or selective reaction will be at least twice background signal or noise and more typically more than about 10 to 100 times background.

[0208] *Signs of disease*, as used herein, refers broadly to any abnormality indicative of disease, discoverable on examination of the patient; an objective indication of disease, in contrast to a symptom, which is a subjective indication of disease.

[0209] *Solid support, support, and substrate*, as used herein, refers broadly to any material that provides a solid or semi-solid structure with which another material can be attached including but not limited to smooth supports (*e.g.*, metal, glass, plastic, silicon, and ceramic surfaces) as well as textured and porous materials.

[0210] *Subjects* as used herein, refers broadly to anyone suitable to be treated according to the present invention

include, but are not limited to, avian and mammalian subjects, and are preferably mammalian. Mammals of the present invention include, but are not limited to, canines, felines, bovines, caprines, equines, ovines, porcines, rodents (e.g., rats and mice), lagomorphs, primates, humans. Any mammalian subject in need of being treated according to the present invention is suitable. Human subjects of both genders and at any stage of development (i.e., neonate, infant, juvenile, adolescent, adult) can be treated according to the present invention. The present invention may also be carried out on animal subjects, particularly mammalian subjects such as mice, rats, dogs, cats, cattle, goats, sheep, and horses for veterinary purposes, and for drug screening and drug development purposes. "Subjects" is used interchangeably with "patients."

[0211] *Mating competent yeast species*, as used herein refers broadly encompass any diploid or tetraploid yeast which can be grown in culture. Such species of yeast may exist in a haploid, diploid, or tetraploid form. The cells of a given ploidy may, under appropriate conditions, proliferate for indefinite number of generations in that form. Diploid cells can also sporulate to form haploid cells. Sequential mating can result in tetraploid strains through further mating or fusion of diploid strains. In the present invention the diploid or polyploidal yeast cells are preferably produced by mating or spheroplast fusion.

[0212] *Haploid Yeast Cell*, as used herein, refers broadly to a cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[0213] *Polyploid Yeast Cell*, as used herein, refers broadly to a cell having more than one copy of its normal genomic (chromosomal) complement.

[0214] *Diploid Yeast Cell*, as used herein, refers broadly to a cell having two copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells.

[0215] *Tetraploid Yeast Cell*, as used herein, refers broadly to a cell having four copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells. Tetraploids may carry two, three, four, or more different expression cassettes. Such tetraploids might be obtained in *S. cerevisiae* by selective mating homozygotic heterothallic a/a and alpha/alpha diploids and in *Pichia* by sequential mating of haploids to obtain auxotrophic diploids. For example, a [met his] haploid can be mated with [ade his] haploid to obtain diploid [his]; and a [met arg] haploid can be mated with [ade arg] haploid to obtain diploid [arg]; then the diploid [his] x diploid [arg] to obtain a tetraploid prototroph. It will be understood by those of skill in the art that reference to the benefits and uses of diploid cells may also apply to tetraploid cells.

[0216] *Yeast Mating*, as used herein, refers broadly to a process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[0217] *Variable region* or VR as used herein refers broadly to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0218] *Variants*, as used herein refers broadly to single-chain antibodies, dimers, multimers, sequence variants, and domain substitution variants. Single-chain antibodies such as SMIPs, shark antibodies, nanobodies (e.g., Camelidae antibodies). Sequence variants can be specified by percentage identity (similarity, sequence homology) e.g., 99%, 95%, 90%, 85%, 80%, 70%, 60%, or by numbers of permitted conservative or non-conservative substitutions. Domain substitution variants include replacement of a domain of one protein with a similar domain of a related protein. A similar domain may be identified by similarity of sequence, structure (actual or predicted), or function. For example, domain substitution variants include the substitution of at least one CDRs and/or framework regions.

[0219] The techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Sambrook, et al. (2001) Molec. Cloning: Lab. Manual [3rd Ed] Cold Spring Harbor Laboratory Press. Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture, and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

MUCOSITIS

[0220] Mucositis is a medical term that is used to refer to mouth sores, oral mucositis, or esophagitis. It can range in severity from a red, sore mouth and/or gums to open sores that can cause a patient to be unable to eat. The lining of the entire gastrointestinal tract (e.g., mouth, throat, stomach, and bowel) is made up of epithelial cells, which divide and

replicate rapidly, and are killed by chemotherapy and radiation therapy. Thus the entire lining of the entire gastrointestinal tract from the mouth to the anus are susceptible to mucositis (e.g., alimentary tract mucositis). Mucositis can occur in areas of the alimentary tract; for example, gastrointestinal (GI) mucositis. Emesis (vomiting) and diarrhea are also common in mucositis, especially gastrointestinal mucositis. See Lalla, et al. (2008) Dent Clin North Am. 52(1): 61-viii.

[0221] Patients treated with radiation therapy for head and neck cancer typically receive an approximately 200 cGy daily dose of radiation, five days per week, for 5-7 continuous weeks. Almost all such patients will develop some degree of oral mucositis. In recent studies, severe oral mucositis occurred in 29-66% of all patients receiving radiation therapy for head and neck cancer. The incidence of oral mucositis was especially high in (A) patients with primary tumors in the oral cavity, oropharynx or nasopharynx, (B) those who also received concomitant chemotherapy, (C) those who received a total dose over 5000 cGy, and (D) those who were treated with altered fractionation radiation schedules (e.g., more than one radiation treatment per day). See Lalla, et al. (2008) Dent Clin North Am. 52(1): 61-viii.

[0222] Recent studies have indicated that the fundamental mechanisms involved in the pathogenesis of mucositis are much more complex than direct damage to epithelium alone. Mechanisms for radiation-induced and chemotherapy-induced mucositis are believed to be similar. The following five-stage model for the pathogenesis of mucositis:

1. Initiation of tissue injury: Radiation and/or chemotherapy induce cellular damage resulting in death of the basal epithelial cells. The generation of reactive oxygen species (free radicals) by radiation or chemotherapy is also believed to exert a role in the initiation of mucosal injury. These small highly reactive molecules are byproducts of oxygen metabolism and can cause significant cellular damage.

2. Upregulation of inflammation via generation of messenger signals: In addition to causing direct cell death, free radicals activate second messengers that transmit signals from receptors on the cellular surface to the inside of the cell. This leads to upregulation of pro-inflammatory cytokines, tissue injury and cell death.

3. Signaling and amplification: Upregulation of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), produced mainly by macrophages, causes injury to mucosal cells, and also activates molecular pathways that amplify mucosal injury.

4. Ulceration and inflammation: There is a significant inflammatory cell infiltrate associated with the mucosal ulcerations, based in part on metabolic byproducts of the colonizing oral microflora. Production of pro-inflammatory cytokines is also further upregulated due to this secondary infection.

5. Healing: This phase is characterized by epithelial proliferation as well as cellular and tissue differentiation, restoring the integrity of the epithelium.

[0223] The degree and extent of oral mucositis that develops in any particular patient and site appears to depend on factors such as age, gender, underlying systemic disease and race as well as tissue specific factors (e.g., epithelial types, local microbial environment and function). See Lalla, et al. (2008) Dent Clin North Am. 52(1): 61-viii.

[0224] The IL-6 antagonists described herein, include but are not limited to anti-IL-6 antibodies and antibody fragments, and may be used in methods and compositions for the treatment of mucositis (e.g., oral, esophageal, alimentary, gastrointestinal tract mucositis).

Oral Mucositis

[0225] Oral mucositis is a significant problem in patients undergoing chemotherapeutic management for solid tumors. In one study, it was reported that 303 of 599 patients (51%) receiving chemotherapy for solid tumors or lymphoma developed oral and/or GI mucositis. Oral mucositis developed in 22% of 1236 cycles of chemotherapy, GI mucositis in 7% of cycles and both oral and GI mucositis in 8% of cycles. An even higher percentage (approximately 75-80%) of patients who receive high-dose chemotherapy prior to hematopoietic cell transplantation develop clinically significant oral mucositis. See Lalla, et al. (2008) Dent Clin North Am. 52(1): 61-viii.

[0226] Oral mucositis leads to several problems, including pain, nutritional problems as a result of inability to eat, and increased risk of infection due to open sores in the mucosa. Oral mucositis has a significant effect on the patient's quality of life and can be dose-limiting (requiring a reduction in subsequent chemotherapy doses).

[0227] Signs and symptoms of mucositis include: red, shiny, or swollen mouth and gums; blood in the mouth; sores in the mouth or on the gums or tongue; soreness or pain in the mouth or throat; difficulty swallowing or talking; feeling of dryness, mild burning, or pain when eating food; soft, whitish patches or pus in the mouth or on the tongue; and Increased mucus or thicker saliva in the mouth.

[0228] Over forty percent of patients who receive chemotherapy will develop some degree of mucositis during the course of their treatment. Patients receiving radiation to the head, neck, or chest areas, and patients who undergo bone marrow or stem cell transplant, are even more likely to develop mucositis. Certain chemotherapy agents are more likely to cause this side effect (Table 1), as is total body irradiation which is often used for bone marrow transplants.

TABLE 1 Select chemotherapy agents known to cause mucositis.

[0229]

5	Alemtuzumab (Campath®)	Bleomycin (Blenoxane®)	Asparaginase (Elspar®)
	Cyclophosphamide (Cytoxan®)	Cytarabine (Cytosar-U®)	Busulfan (Myleran®, Busulfex®)
	Docetaxel (Taxotere®)	Doxorubicin (Adriamycin®)	Capecitabine (Xeloda®)
10	Fluorouracil (5-FU®)	Gemcitabine (Gemzar®)	Carboplatin (Paraplatin®)
	Gemtuzumab ozogamicin (Mylotarg®)	Hydroxyurea (Hydrea®)	Daunorubicin (Cerubidine®)
	Idarubicin (Idamycin®)	Interleukin 2 (Proleukin®)	Epirubicin (Ellence®)
	Lomustine (CeeNU®)	Melphalan (Akeran®)	Etoposide (VePesid®)
15	Mitomycin (Mutamycin®)	Mitoxantrone (Novantrone®)	Irinotecan (Camptosar®)
	Oxaliplatin (Eloxatin®)	Paclitaxel (Taxol®)	Methotrexate (Rheumatrex®)
	Pentostatin (Nipent®)	Procarbazine (Matulane®)	Mechlorethamine (Mustargen®)
20	Topotecan (Hycamtin®)	Trastuzumab (Herceptin®)	Pemetrexed (Alimta®)
	Vinblastine (Velban®)	Vincristine (Oncovin®)	Thiotepa (Thioplex®)
	Tretinoin (Vesanoid®)	Cisplatin (PLATINOL®)	

25 [0230] Poor oral or dental health, smoking, using chewing tobacco, drinking alcohol, dehydration, and diseases such as kidney disease, diabetes or HIV/AIDS can increase the likelihood of developing mucositis or worsen it.

[0231] Monitoring the development and resolution of mucositis can be difficult, given that the experience is different for every patient. The World Health Organization (WHO) oral toxicity scale is a commonly used grading systems developed to assist in evaluating the severity of mucositis:

30 TABLE 2: Oral Mucositis Severity Scale (adapted from WHO ORAL TOXICITY SCALE)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
35	None	Soreness & erythema	Erythema, ulcers; Patient can swallow solid diet	Ulcers, extensive erythema; Patients cannot swallow solid diet	Mucositis to the extent that alimentation is not possible

40 [0232] Numerous studies using many different medications and interventions have been tried to reduce the incidence and severity of oral mucositis. Unfortunately, only a few of these interventions have shown much success. Currently, good oral care regimen (Table 3) is the most effective in preventing or decreasing the severity of mucositis and help prevent the development of infection through open mouth sores. The mainstay of an oral care regimen is mouth rinses, and numerous studies have determined old salt water is an effective mouth rinse. The mouth rinse aides in removing debris and keeping the oral tissue moist and clean. Other important components include using mouth and lip moisturizers, using a soft-bristle toothbrush, maintaining adequate intake of fluids and protein, and avoiding irritating foods, alcohol and tobacco.

Table 3: Example of oral care protocol

	Oral Care Protocol Recommendations	
50	Normal saline (1 tsp of table salt to 1 quart (32 oz.) of water) [e.g., salt and soda (one-half tsp of salt and 2 tbsp of sodium bicarbonate in 1 quart of warm water)]	
	Use a soft-bristle toothbrush after meals and at bedtime. If the brush causes pain, toothettes may be used	
	Use a non-abrasive toothpaste (or mix 1 tsp baking soda in 2 cups water). Avoid toothpastes with whiteners.	
55	Keep lips moist with moisturizers. Avoid using Vaseline (the oil base can promote infection).	
	Avoid products that irritate the mouth and gums: avoid commercial mouthwashes and those with alcohol	

(continued)

	Oral Care Protocol Recommendations
5	Limit use of dental floss, DO NOT use with platelets below 40,000 Do not use lemon or glycerin swabs or toothbrushes without soft bristles
	Increase your fluid intake.
	Try to include foods high in protein in your diet.
10	Avoid hot, spicy or acidic foods, alcohol, hard or coarse foods (crusty bread, chips, crackers).
	If you wear dentures: remove whenever possible to expose gums to air Loose fitting dentures can irritate the mouth and gums and should not be worn Do not wear dentures if mouth sores are severe
15	Do not smoke cigarettes, cigars or pipes. Do not use smokeless tobacco (chewing tobacco, snuff)

[0233] Cryotherapy, which involves sucking on ice chips during chemotherapy administration, has shown some effect in alleviating mucositis caused by 5-FU (fluorouracil). Two agents, Gelclair® and Zilactin®, are mucosal protectants that work by coating the mucosa, forming a protective barrier for exposed nerve endings. These agents resulted in improved pain control, and ability to eat and speak. Amifostine (Ethyol®), a drug that protects against the damage to the mucosa caused by radiation (approved by the FDA for patients receiving radiation therapy for cancers of the head and neck).

[0234] Keratinocyte growth factor (KGF) stimulates the growth, repair, and survival of cells that protect the lining of the mouth and GI tract. Recombinant human KGF has been developed as the drug KEPIVANCE® (palifermin) and is currently used for treating oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support (HSCT). Palifermin was found to decrease the length and severity of oral mucositis in these patients. "Coping with Cancer" by Vachani of the Abramson Cancer Center of the University of Pennsylvania (2009). The IL-6 antagonists, including anti-IL-6 antibodies and antibody fragments thereof, may be used in methods and compositions for the treatment of mucositis, including oral mucositis associated with chemotherapy and radiotherapy. Emesis and diarrhea may also be seen in patients suffering from oral mucositis. The IL-6 antagonists, including anti-IL-6 antibodies may be used in methods and compositions for the treatment of emesis and diarrhea associated with chemotherapy, radiotherapy, and oral mucositis.

Alimentary tract mucositis

[0235] Mucositis is a major acute clinical problem in oncology, caused by the cytotoxic effects of chemotherapy and radiotherapy. The condition may affect the mucosa of the entire alimentary tract (AT), causing mouth and throat pain, ulceration, abdominal pain, bloating, vomiting (emesis), and diarrhea. Mucositis is extremely common, occurring in approximately 40% of patients following standard doses of chemotherapy and in almost all patients undergoing high-dose chemotherapy with stem-cell transplantation or head-and-neck radiation. Bowen, et al. (2011) Journal of Supportive Oncology 9(5): 161-168.

[0236] Alimentary tract mucositis refers to the expression of mucosal injury across the continuum of oral and gastrointestinal mucosa, from the mouth to the anus. Incidence of WHO grade 3 or 4 oral mucositis can be as high as -75% in patients undergoing hematopoietic stem-cell transplantation (HSCT), depending on the intensity of the conditioning regimen used and the use of methotrexate. For all tumor sites, chemotherapy with 5-fluorouracil (5-FU), capecitabine or tegafur leads to a high rate (e.g. 20-50%) of alimentary tract mucositis. Chemotherapy with methotrexate and other antimetabolites leads to a 20-60% rate of alimentary tract mucositis according to the drug's given dose per cycle. See Peterson, et al. (2009) Annals of Oncology 20(Supplement 4): iv174-iv177 and Logan, et al. (2008) Cancer chemotherapy and Pharmacology 62(1): 33-41. The IL-6 antagonists, including anti-IL-6 antibodies and antibody fragments thereof, may be used in methods and compositions for the treatment of alimentary tract mucositis, including alimentary tract mucositis associated with chemotherapy and radiotherapy. Emesis and diarrhea are also commonly seen in patients suffering from mucositis, especially alimentary tract mucositis. The IL-6 antagonists, including anti-IL-6 antibodies may be used in methods and compositions for the treatment of emesis and diarrhea associated with chemotherapy, radiotherapy, and alimentary tract mucositis.

Gastrointestinal tract mucositis

[0237] Gastrointestinal mucositis may result from chemotherapy and/or radiotherapy and refers to inflammatory lesions in the gastrointestinal tract. Vomiting (emesis), and diarrhea are common elements of gastrointestinal mucositis.

[0238] Basic bowel care including maintenance of adequate hydration is recommended for patients undergoing chemotherapy and radiotherapy to limit the effects of gastrointestinal mucositis. Current recommendations also include administration of 500 mg sulfasalazine orally twice daily to reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis. Amifostine is also suggested in a dose of at least 340 mg/m² to prevent radiation proctitis in those receiving standard-dose radiotherapy for rectal cancer. Additionally, octreotide at a dose of at least 100 µg s.c. twice daily when loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT as well as amifostine is suggested to reduce esophagitis induced by concomitant chemotherapy and radiotherapy in patients with non-small-cell lung cancer. See Peterson, et al. (2009) Annals of Oncology 20(Supplement 4): iv174-iv177. The IL-6 antagonists, including anti-IL-6 antibodies and antibody fragments thereof, may be used in methods and compositions for the treatment of gastrointestinal mucositis, including gastrointestinal mucositis associated with chemotherapy and radiotherapy.

[0239] Emesis and diarrhea are also commonly seen in patients suffering from mucositis, especially gastrointestinal tract mucositis. See Lalla, et al. (2008) Dent Clin North Am. 51(1): 61-viii. The IL-6 antagonists, including anti-IL-6 antibodies may be used in methods and compositions for the treatment of emesis and diarrhea associated with chemotherapy, radiotherapy, and gastrointestinal tract mucositis.

TREATMENT OF RHEUMATOID ARTHRITIS

[0240] Also described herein is the use of IL-6 antagonists including anti-IL-6 antibodies described herein, such as Ab1 or humanized forms thereof for treating or preventing rheumatoid arthritis. This application provides results of clinical studies showing safety, pharmacokinetics, and pharmacodynamics for subcutaneous and intravenous administration of an exemplary anti-IL-6 antibody, Ab1 (*also known as* ALD-518, exemplary sequences are provided in Table 4.) The clinical data demonstrates that an anti-IL-6 antibody decreases disease severity in rheumatoid arthritis patients which have been subcutaneously (SC) or intravenously (IV) administered ALD-518, including improvement in mental and physical components of disease.

[0241] The anti-IL-6 antibody (e.g., ALD518) was well tolerated when administered in a single subcutaneous (SC) dose; injection site reactions were generally mild. The bioavailability of SC ALD518 was ~60% of IV ALD518, and the half life was ~30 days. Rapid and significant reductions in CRP (C-reactive protein) were observed, which were sustained over 24 weeks of assessment. The half-life of ALD518 when administered subcutaneously (approximately 30 days) is similar to the half-life previously observed with IV administration. Additionally, subcutaneous ALD518 led to rapid and large reductions in serum CRP and the reductions in CRP observed during the first 12 weeks of the study were sustained over 24 weeks of assessment. These results are also similar to those observed with IV administration. Together, these results suggest that anti-IL-6 antibodies, such as Ab1 (ALD518) may be used for the treatment of RA, as well as prevention or treatment of other IL-6 associated conditions. These therapeutic regimens may be combined with other RA therapeutics, including methotrexate or other RA drugs identified herein and generally known in the art, including analgesics, disease-modifying antirheumatic drugs (DMARDs), anti-inflammatories, and others.

[0242] Further described are specific dosage regimens and dosage formulations for treating rheumatoid arthritis by subcutaneous or intravenous administration of anti-IL-6 antibodies or antibody fragments according to the invention such as humanized Ab1 antibodies. For example, a subject may be administered 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1).

[0243] The anti-IL-6 antibodies may be used to subcutaneously administer antibodies of the disclosure, including Ab1, for rheumatoid arthritis indications, the administration formulation comprises, or alternatively consists of, about 50 or 100 mg/mL of antibody, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80. The administration formulation may comprise, or alternatively consist of, about 20 or 100 mg/mL of antibody, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 to 280 mM sorbitol (or sorbitol in combination with sucrose), and 0.015% (w/w) Polysorbate 80, said formulation having a nitrogen headspace in the shipping vials.

[0244] Therapeutic regimens for the prevention or treatment of RA may be combined with other RA therapeutics, including analgesics, analgesics, DMARDs, anti-inflammatories, and others. For example, analgesics and anti-inflammatory drugs, including steroids, may provide relief of disease symptoms, while disease-modifying antirheumatic drugs (DMARDs), may inhibit or halt the underlying immune process and prevent further long-term damage. In exemplary embodiments, ALD518 (or another antibody of the present disclosure) may be administered to a patient at approximately the same time as another RA therapeutic (which may or may not be formulated together) or may be administered to a patient who is also undergoing another therapeutic regiment but not necessarily at the same time. A regimen may be considered to provide a combination of therapeutics as long as the patient concurrently experiences the effects of the combined therapeutics. Due to possible differences in dosing schedule, a combination may include administration of different therapeutics at different times, e.g., a patient may receive a drug such as methotrexate on a weekly schedule (e.g., at least 10 mg per week) and may receive ALD518 (or another anti-IL-6 antibody of the present disclosure) less

frequently (such as about every eight weeks, every twelve weeks, every three months). Exemplary DMARDs that may administered in combination with ALD518 (or another antibody of the present disclosure) include, but are not limited to Mycophenolate mofetil (CellCept®), calcineurin inhibitors (e.g., cyclosporine, sirolimus, everolimus), oral retinoids, azathioprine, fumeric acid esters, D-penicillamine, cyclophosphamide, immunoadsorption columns (e.g., Prosorba® columns), gold salts (e.g., Auranofin, sodium aurothiomalate (Myocrisin)), hydroxychloroquine, chloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine (SSZ), tumor necrosis factor alpha (TNF α) blockers (e.g., etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi)), Interleukin 1 (IL-1) blockers (e.g., anakinra (Kineret)), monoclonal antibodies against B cells (e.g., rituximab (Rituxan)), T cell costimulation blockers (e.g., abatacept (Orencia)), Interleukin 6 (IL-6) blockers (e.g., tocilizumab (an anti-IL-6 receptor antibody), RoActemra, Actemra). Exemplary anti-inflammatory agents that may administered in combination with ALD518 (or another antibody of the present disclosure) include, but are not limited to, anti-inflammatory steroids such as Cortisone, Glucocorticoids, prednisone, prednisolone, Hydrocortisone (Cortisol), Cortisone acetate, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone, Beclometasone, and Fludrocortisone acetate, and non-steroidal anti-inflammatory drug (NSAIDs) (which may also act as analgesics), such as ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac, tolemin, choline magnesium salicylate, diclofenac, diflunisal, indomethacin, Ketoprofen, Oxaprozin, piroxicam, and nimesulide, Salicylates, Aspirin (acetylsalicylic acid), Diflunisal, Salsalate, p-amino phenol derivatives, Paracetamol, phenacetin, Propionic acid derivatives, Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen, Acetic acid derivatives, Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone, Enolic acid (Oxicam) derivatives, Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, Fenamic acid derivatives (Fenamates), Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid, Selective COX-2 inhibitors (Coxibs), Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, Firocoxib, Sulphonanilides, Nimesulide, and Licofelone. Exemplary analgesics include that may administered in combination with ALD518 (or another antibody of the present disclosure) include, but are not limited to, NSAIDs, COX-2 inhibitors (including Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, and Firocoxib), acetaminophen, opiates (e.g., Dextropropoxyphene, Codeine, Tramadol, Anileridine, Pethidine, Hydrocodone, Morphine [e.g., oral, intravenous (IV), or intramuscular (IM)], Oxycodone, Methadone, Diacetylmorphine, Hydromorphone, Oxymorphone, Levorphanol, Buprenorphine, Fentanyl, Sufentanyl, Etorphine, Carfentanil, dihydromorphone, dihydrocodeine, Thebaine, and Papaverine), diproqualone, Flupirtine, Tricyclic antidepressants, and lidocaine (topical).

ANTI-IL-6 ANTAGONISTS

[0245] The IL-6 antagonist may comprise an antibody, or an antibody fragment. The IL-6 antagonist may be an agent that blocks signal transmission by IL-6, blocks IL-6 binding to its receptor, suppresses/interferes with IL-6 expression, and/or inhibits the biological activity of IL-6. The IL-6 antagonists may be attached directly or indirectly to immunoglobulin polypeptides or effector moieties such as therapeutic or detectable entities.

[0246] Examples of IL-6 antagonists include but are not limited to anti-IL-6 antibody, anti-IL-6R antibody, anti-gp130 antibody, IL-6 mutant, IL-6R antisense oligonucleotide, and partial peptides of IL-6 or IL-6R. An example of the IL-6 mutant used in the present invention is disclosed in Brakenhoff, et al. (1994) J. Biol. Chem. 269: 86-93 or Savino, et al. (1994) EMBO J. 13: 1357-1367. The IL-6 mutant polypeptide or fragment thereof does not possess the signal transmission effects of IL-6 but retains the binding activity with IL-6R, and is produced by introducing a mutation in the form of a substitution, deletion or insertion into the amino acid sequence of IL6. While there are no limitations on the animal species used, it is preferable to use an IL6 of human origin. Similarly, any IL-6 partial peptides or IL-6R partial peptides used in the present invention provided they prevent IL6 or IL6R (gp80) or gp130 from affecting signal transduction and thereby prevent IL-6 associated biological activity. For details regarding IL-6 partial peptides and IL-6R partial peptides, see, e.g., U.S. Patent No. 5,210,075 and EP Patent No. 617126. Additionally, a mutated soluble IL-6 receptor may be used as an IL-6 antagonist. See Salvati, et al. (1995) The Journal of Biological Chemistry 270: 12242-12249.

[0247] IL-6 signaling is mediated by the Jak-Tyk family of cytoplasmic tyrosine kinases, including JAK1, JAK2, and JAK3 (reviewed in Murray (2007) J Immunol. 178(5): 2623-9). Inhibitors of JAK1, JAK2, or JAK3 may be used as IL-6 antagonists of IL-6. Sivash, et al. (2004) British Journal of Cancer 91: 1074-1080. An inhibitor of Syk may be used as an IL-6 antagonist. Ulanova, et al. (2005) Am J Physiol Lung Cell Mol Physiol. 288(3): L497-507. Thalidomide, and derivatives thereof, such as lenalidomide, may be useful antagonists of IL-6. Kedar, et al. (2004) Int J Cancer. 110(2): 260-5.

[0248] Further, oligonucleotides capable of IL6 or IL6R RNA silencing or antisense mechanisms can be used in the method of the present invention (JP5-300338 for details regarding IL-6R antisense oligonucleotide).

[0249] Additionally, the IL-6 antagonist may target IL-6, IL-6 receptor α , gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof. For example, SANT-7 is an IL-6 receptor antagonist that interferes with the formation of IL-6/IL-6R/gp130 heteromers. See Hönnemann, et al. (2001) Int. J. Cancer 93: 674-680.

[0250] The IL-6 antagonist may comprise an anti-IL-6 receptor (e.g., TOCILIZUMAB®, ACTEMRA®), anti-IL6 (e.g.,

SILTUXIMAB®), anti-gp130, anti-p38 MAP kinase, anti-JAK1, anti-JAK2, anti-JAK3, or anti-SYK antibody or antibody fragment. See Nishimoto, et al. (2005) Blood 106(8): 2627-32; van Rhee, et al. (2010) Journal of Clinical Oncology 28(23): 3701-3708; WO 2010/056948; U.S. Patent Application Publication No. 2010/0138945.

[0251] The IL-6 antagonist may comprise a small molecule including but not limited to thalidomide, lenalidomide, aryl hydrocarbon receptor agonists (e.g., 7,12-dimethylbenz [a]anthracene (DMBA) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)) or any combination thereof. See Jensen, et al. (2003) Environmental Health: A Global Access Science Source 2:16.

[0252] IL-6 antagonist may be an IL-6 antagonist peptide. See, e.g., U.S. Patent No. 6,838,433. For example, a truncated IL-6 molecule may act as an IL-6 antagonist. See Alberti, et al. (2005) J. Cancer Res 65: 2-5.

[0253] The IL-6 antagonist may be an anti-IL-6 antibody. See also U.S. Patent Application Publication No. 2007/0292420. The IL-6 antagonist may comprise an anti-IL-6 antibody or antibody fragment as described in further detail herein. The disclosure includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth in the polypeptide sequence of SEQ ID NO: 2 or SEQ ID NO: 709 and humanized versions and variants thereof including those set forth in FIGS. 1-5, and those identified in Table 4.

ANTI-IL-6 ANTIBODIES AND ANTIBODY FRAGMENTS THEREOF

[0254] Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the Fab region; the stem portion of the "Y" configuration is designated the Fc region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[0255] The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (*i.e.*, the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ , μ , α , δ , and ϵ (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A. (1976) Structural Concepts in Immunology and Immunochemistry [2nd Ed.] pages 413-436, Holt, Rinehart, Winston), and other cellular responses (Andrews, et al. (1980) Clinical Immunobiology pages 1-18, W. B. Sanders; Kohl, et al. (1983) Immunology 48: 187); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be paired with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[0256] For example, antibodies or antigen binding fragments or variants thereof may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[0257] Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of at least one cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (e.g., a functional domain, catalytic amino acid residues). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for *in vitro* mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

[0258] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, *e.g.*, in U.S. Patent No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

[0259] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. See, *e.g.*, U.S. Patent No. 6,187,287. In a preferred embodiment, humanization may be effected as disclosed in detail *infra*. This scheme grafts CDRs onto human FRs highly homologous to the parent antibody that is being humanized.

[0260] Immunoglobulins and fragments thereof may be modified post-translationally, *e.g.* to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention.

Exemplary Anti-IL-6 Antibodies

[0261] The IL-6 antagonist antibody for use according to the present invention comprises the humanized variable light sequence of amino acid sequence of SEQ ID NO: 709 and the humanized variable heavy sequence of amino acid sequence of SEQ ID NO: 657.

[0262] Also described herein are antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth in the polypeptide sequences of SEQ ID NO: 3 and SEQ ID NO: 657 and humanized versions and variants thereof including those set forth in FIGS. 1-5, and those identified in Table 4.

[0263] Further described are antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence which is a modified version of SEQ ID NO: 3 wherein the tryptophan residue in CDR2 is changed to a serine as set forth in the polypeptide sequence of SEQ ID NO: 658 and humanized versions and variants thereof including those set forth in FIGS. 1-5, and those identified in Table 4.

[0264] The invention further contemplates antibodies comprising the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2, and the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8 or 120; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or 19. Other antibodies described herein include combinations of the CDRs and the variable heavy and light chain sequences set forth herein.

[0265] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2, and the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8 or 120; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or 19. Other antibodies described herein include combinations of the CDRs and humanized versions of the variable heavy and light chain sequences set forth above.

[0266] The invention also contemplates fragments of the antibody having binding specificity to IL-6. Antibody fragments described herein may comprise, or alternatively consist of, humanized versions of the polypeptide sequence of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709. Antibody fragments described herein may comprise, or alternatively consist of, humanized versions of the polypeptide sequence of SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708.

[0267] In a further embodiment of the disclosure, fragments of the antibody having binding specificity to IL-6 comprise, the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2 or SEQ ID NO: 709.

[0268] In a further embodiment of the disclosure, fragments of the antibody having binding specificity to IL-6 comprise, the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8 or SEQ ID NO: 120; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 and 657 or 19.

[0269] Also described are antibody fragments which include at least one of the antibody fragments described herein.

Fragments of the antibodies having binding specificity to IL-6 may comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 2; the variable heavy chain region of SEQ ID NO: 3; the complementarity-determining regions (SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6) of the variable light chain region of SEQ ID NO: 2; and the complementarity-determining regions (SEQ ID NO: 7; SEQ ID NO: 8 or SEQ ID NO: 120; and SEQ ID NO: 9) of the variable heavy chain region of SEQ ID NO: 3 and 657 or 19.

[0270] Also described are variants wherein either of the heavy chain polypeptide sequences of SEQ ID NO: 18 or SEQ ID NO: 19 is substituted for the heavy chain polypeptide sequence of SEQ ID NO: 3 or 657; the light chain polypeptide sequence of SEQ ID NO: 20 is substituted for the light chain polypeptide sequence of SEQ ID NO: 2 or SEQ ID NO: 709; and the heavy chain CDR sequence of SEQ ID NO: 120 is substituted for the heavy chain CDR sequence of SEQ ID NO: 8.

[0271] The anti-IL-6 antibody described herein may be Ab1, comprising SEQ ID NO: 2 and SEQ ID NO: 3, or more particularly an antibody comprising SEQ ID NO: 657 and SEQ ID NO: 709 (which are respectively encoded by the nucleic acid sequences in SEQ ID NO: 700 and SEQ ID NO: 723) or one comprised of the alternative SEQ ID NOs set forth in the preceding paragraph, and having at least one of the biological activities set forth herein. The anti-IL-6 antibody may comprise a humanized sequence as shown in Figures 1-5.

[0272] Sequences of anti-IL-6 antibodies are shown in Table 4. Exemplary sequence variants other alternative forms of the heavy and light chains of Ab1 through Ab36 are shown. The antibodies described encompass additional sequence variants, including conservative substitutions, substitution of at least one CDR sequences and/or FR sequences.

[0273] Exemplary Ab1 variants include an antibody comprising a variant of the light chain and/or heavy chain. Exemplary variants of the light chain of Ab1 include the sequence of any of the Ab1 light chains shown (*i.e.*, any of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709) wherein the entire CDR1 sequence is replaced or wherein at least one residues in the CDR1 sequence is substituted by the residue in the corresponding position of any of the other light chain CDR1 sequences set forth (*i.e.*, any of SEQ ID NO: 23, 39, 55, 71, 87, 103, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, 524, 540, 556, or 572); and/or wherein the entire CDR2 sequence is replaced or wherein at least one residues in the CDR2 sequence is substituted by the residue in the corresponding position of any of the other light chain CDR2 sequences set forth (*i.e.*, any of SEQ ID NO: 24, 40, 56, 72, 88, 104, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, 349, 365, 381, 397, 413, 429, 445, 461, 477, 493, 509, 525, 541, 557, or 573); and/or wherein the entire CDR3 sequence is replaced or wherein at least one residues in the CDR3 sequence is substituted by the residue in the corresponding position of any of the other light chain CDR3 sequences set forth (*i.e.*, any of SEQ ID NO: 25, 41, 57, 73, 89, 105, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 462, 478, 494, 510, 526, 542, 558, or 574).

[0274] Exemplary variants of the heavy chain of Ab1 include the sequence of any of the Ab1 heavy chains shown (*i.e.*, any of SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708) wherein the entire CDR1 sequence is replaced or wherein at least one residues in the CDR1 sequence is substituted by the residue in the corresponding position of any of the other heavy chain CDR1 sequences set forth (*i.e.*, any of SEQ ID NO: 26, 42, 58, 74, 90, 106, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, 351, 367, 383, 399, 415, 431, 447, 463, 479, 495, 511, 527, 543, 559, or 575); and/or wherein the entire CDR2 sequence is replaced or wherein at least one residues in the CDR2 sequence is substituted by the residue in the corresponding position of an Ab1 heavy chain CDR2, such as those set forth in Table 4 (*i.e.*, any of SEQ ID NO: 8, or 120) or any of the other heavy chain CDR2 sequences set forth (*i.e.*, any of SEQ ID NO: 27, 43, 59, 75, 91, 107, 121, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, 528, 544, 560, or 576); and/or wherein the entire CDR3 sequence is replaced or wherein at least one residues in the CDR3 sequence is substituted by the residue in the corresponding position of any of the other heavy chain CDR3 sequences set forth (*i.e.*, any of SEQ ID NO: 28, 44, 60, 76, 92, 108, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 369, 385, 401, 417, 433, 449, 465, 481, 497, 513, 529, 545, 561, or 577).

[0275] In another embodiment, the invention contemplates other antibodies, such as for example chimeric or humanized antibodies, comprising the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2, and the polypeptide sequences of SEQ ID NO: 7 (CDR1); SEQ ID NO: 8 (CDR2); SEQ ID NO: 120 (CDR2); and SEQ ID NO: 9 (CDR3) which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or SEQ ID NO: 19. Other antibodies described herein include combinations of the CDRs and the variable heavy and light chain sequences set forth above including those set forth in FIGS. 1-5, and those identified in Table 4.

[0276] In another aspect the anti-IL-6 antibody of the disclosure is one comprising at least one of the following: a CDR1 light chain encoded by the sequence in SEQ ID NO: 12 or SEQ ID NO: 694; a light chain CDR2 encoded by the sequence in SEQ ID NO: 13; a light chain CDR3 encoded by the sequence in SEQ ID NO: 14 or SEQ ID NO: 695; a heavy chain CDR1 encoded by the sequence in SEQ ID NO: 15, a heavy chain CDR2 encoded by SEQ ID NO: 16 or SEQ ID NO:

696 and a heavy chain CDR3 encoded by SEQ ID NO: 17 or SEQ ID NO: 697. In addition the disclosure embraces such nucleic acid sequences and variants thereof.

[0277] In another aspect, the disclosure is directed to amino acid sequences corresponding to the CDRs of said anti-IL-6 antibody which are selected from SEQ ID NO: 4 (CDR1), SEQ ID NO: 5 (CDR2), SEQ ID NO: 6 (CDR3), SEQ ID NO: 7, SEQ ID NO: 120 and SEQ ID NO: 9.

[0278] Also described is an anti-IL-6 antibody comprising a light chain nucleic acid sequence of SEQ ID NO: 10, 662, 698, 701, 705, 720, 721, 722, or 723; and/or a heavy chain nucleic acid sequence of SEQ ID NO: 11, 663, 700, 703, 707, 724, or 725. Also described are the corresponding polypeptides encoded by any of the foregoing nucleic acid sequences and combinations thereof.

[0279] Also described are anti-IL-6 antibodies or a portion thereof encoded by a nucleic acid sequence selected from those comprised in SEQ ID NO: 10, 12, 13, 14, 662, 694, 695, 698, 701, 705, 720, 721, 722, 723, 11, 15, 16, 17, 663, 696, 697, 700, 703, 707, 724, and 725. For example the CDR1 in the light chain may be encoded by SEQ ID NO: 12 or 694, the CDR2 in the light chain may be encoded by SEQ ID NO: 13, the CDR3 in the light chain may be encoded by SEQ ID NO: 14 or 695; the CDR1 in the heavy chain may be encoded by SEQ ID NO: 15, the CDR2 in the heavy chain may be encoded by SEQ ID NO: 16 or 696, the CDR3 in the heavy chain may be encoded by SEQ ID NO: 17 or 697. As discussed infra antibodies containing these CDRs may be constructed using appropriate human frameworks based on the humanization methods disclosed herein.

[0280] Also described is a variable light chain encoded by SEQ ID NO: 10, 662, 698, 701, 705, 720, 721, 722, or 723 and a variable heavy chain of the anti-IL-6 antibodies encoded by SEQ ID NO: 11, 663, 700, 703, 707, 724, or 725.

[0281] Variable light and heavy chains of the anti-IL-6 antibody respectively may be encoded by SEQ ID NO: 10 and 11, or SEQ ID NO: 698 and SEQ ID NO: 700, or SEQ ID NO: 701 and SEQ ID NO: 703 or SEQ ID NO: 705 and SEQ ID NO: 707.

[0282] Described herein are nucleic acid constructs containing any of the foregoing nucleic acid sequences and combinations thereof as well as recombinant cells containing these nucleic acid sequences and constructs containing wherein these nucleic acid sequences or constructs may be extrachromosomal or integrated into the host cell genome

[0283] Described herein are polypeptides containing any of the CDRs or combinations thereof recited in SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 120, SEQ ID NO: 9 or polypeptides comprising any of the variable light polypeptides comprised in SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709 and/or the variable heavy polypeptides comprised in SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708.

[0284] Described herein is an anti-IL-6 antibody comprising at least one of the following: a variable light chain encoded by the sequence in SEQ ID NO: 10 or SEQ ID NO: 698 or SEQ ID NO: 701 or SEQ ID NO: 705 and a variable chain encoded by the sequence in SEQ ID NO: 11 or SEQ ID NO: 700 or SEQ ID NO: 703 or SEQ ID NO: 707.

[0285] In another aspect the anti-IL-6 antibody is a variant of the foregoing sequences that includes at least one substitution in the framework and/or CDR sequences and which has at least one of the properties of Ab1 *in vitro* and/or upon *in vivo* administration.

[0286] These *in vitro* and *in vivo* properties are described in more detail in the examples below and include: competing with Ab1 for binding to IL-6 and/or peptides thereof; having a binding affinity (K_d) for IL-6 of less than about 50 picomolar, and/or a rate of dissociation (K_{off}) from IL-6 of less than or equal to 10^{-4} s^{-1} ; having an *in-vivo* half-life of at least about 22 days in a healthy human subject; ability to prevent or treat hypoalbuminemia; ability to prevent or treat elevated CRP; ability to prevent or treat abnormal coagulation; and/or ability to decrease the risk of thrombosis in an individual having a disease or condition associated with increased risk of thrombosis. Additional non-limiting examples of anti-IL-6 activity are set forth herein, for example, under the heading "Anti-IL-6 Activity."

[0287] Described herein is an anti-IL-6 antibody that includes at least one of the Ab1 light-chain and/or heavy chain CDR sequences (see Table 4) or variant(s) thereof which has at least one of the properties of Ab1 *in vitro* and/or upon *in vivo* administration (examples of such properties are discussed in the preceding paragraph). One of skill in the art would understand how to combine these CDR sequences to form an antigen-binding surface, e.g. by linkage to at least one scaffold which may comprise human or other mammalian framework sequences, or their functional orthologs derived from a SMIP (Small Modular ImmunoPharmaceutical), camelbody, nanobody, IgNAR, other immunoglobulin, or other engineered antibody. See, e.g., Robak & Robak (2011) BioDrugs 25(1): 13-25 and Wesolowski, et al. (2009) Med Microbiol Immunol 198: 157-174. For example, an antibody according to the disclosure may specifically bind to human IL-6 and include one, two, three, four, five, six, or more of the following CDR sequences or variants thereof: a polypeptide having at least 72.7% sequence identity (*i.e.*, 8 out of 11 amino acids) to the light chain CDR1 of SEQ ID NO: 4; a polypeptide having at least 81.8% (*i.e.*, 9 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4; a polypeptide having at least 90.9% (*i.e.*, 10 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4; a polypeptide having 100% (*i.e.*, 11 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4; a polypeptide having at least 85.7% sequence identity (*i.e.*, 6 out of 7 amino acids) to the light chain CDR2 of SEQ ID NO: 5; a polypeptide having 100% (*i.e.*, 7 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5; a polypeptide

having at least 50% sequence identity (*i.e.*, 6 out of 12 amino acids) to the light chain CDR3 of SEQ ID NO: 6; a polypeptide having at least 58.3% sequence identity (*i.e.*, 7 out of 12 amino acids) to the light chain CDR3 of SEQ ID NO: 6;

[0288] a polypeptide having at least 66.6% (*i.e.*, 8 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6; a polypeptide having at least 75% (*i.e.*, 9 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO:

6; a polypeptide having at least 83.3% sequence identity (*i.e.*, 10 out of 12 amino acids) to the light chain CDR3 of SEQ ID NO: 6; a polypeptide having at least 91.6% sequence identity (*i.e.*, 11 out of 12 amino acids) to the light chain CDR3

[0289] a polypeptide having at least 81.2% sequence identity (*i.e.*, 13 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; a polypeptide having at least 87.5% sequence identity (*i.e.*, 14 out of 16 amino acids) to the heavy

[0290] Other aspects of the disclosure include at least one polynucleotides encoding any of the foregoing, e.g., a

heavy chain CDR2 of SEQ ID NO: 120; a polynucleotide encoding a polypeptide having at least 68.7% sequence identity (i.e., 11 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; a polynucleotide encoding a polypeptide having at least 75% sequence identity (i.e., 12 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; a polynucleotide encoding a polypeptide having at least 81.2% sequence identity (i.e., 13 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; a polynucleotide encoding a polypeptide having at least 87.5% sequence identity (i.e., 14 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; a polynucleotide encoding a polypeptide having at least 93.7% sequence identity (i.e., 15 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; **[0292]** a polynucleotide encoding a polypeptide having 100% sequence similarity (i.e., 16 out of 16 amino acids) to the heavy chain CDR2 of SEQ ID NO: 120; a polynucleotide encoding a polypeptide having at least 50% sequence similarity (i.e., 6 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9; a polynucleotide encoding a polypeptide having at least 58.3% sequence identity (i.e., 7 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9; a polynucleotide encoding a polypeptide having at least 66.6% sequence identity (i.e., 8 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9; a polynucleotide encoding a polypeptide having at least 75% sequence identity (i.e., 9 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9; a polynucleotide encoding a polypeptide having at least 83.3% sequence identity (i.e., 10 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9; a polynucleotide encoding a polypeptide having at least 91.6% sequence identity (i.e., 11 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9; a polynucleotide encoding a polypeptide having 100% sequence similarity (i.e., 12 out of 12 amino acids) to the heavy chain CDR3 of SEQ ID NO: 9.

Table 4: Sequences of exemplary anti-IL-6 antibodies.

Antibody	Antibody chains		CDR1		CDR2		CDR3	
	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.
	2	10	4	12	5	13	6	14
	20	720	4	12	5	13	6	14
	647	721	4	12	5	13	6	14
	651		4	12	5	13	6	14
Ab1 light chains *	660	662	4	12	5	13	6	14
	666	722	4	12	5	13	6	14
	699	698	4	694	5	13	6	695
	702	701	4	694	5	13	6	695
	706	705	4	694	5	13	6	695
	709	723	4	12	5	13	6	14
Human light chains used in Ab1 humanization	648		710		713			
	649		711		714			
	650		712		715			
		11	7	15	8	16	9	17
	18		7	15	8	16	9	17
	19	724	7	15	120	696	9	17
	652	725	7	15	8	16	9	17
	656		7	15	8	16	9	17
Ab1 heavy chains	657	700	7	15	659	696	9	697
	658		7	15	120	696	9	17
	661	663	7	15	8	16	9	17
	664		7	15	8	16	9	17
	665		7	15	120	696	9	17
	704	703	7	15	120	696	9	697

(continued)

	Antibody	Antibody chains		CDR1		CDR2		CDR3	
		PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.
5		708	707	7	15	120	696	9	697
	Human heavy chains	653		716		717			
	used in Ab1 humanization	654		716		717			
10		655		74	82	718			
	Ab2 light chains	21	29	23	31	24	32	25	33
		667	669	23	31	24	32	25	33
	Ab2 heavy chains	22	30	26	34	27	35	28	36
15		668	670	26	34	27	35	28	36
	Ab3 light chains	37	45	39	47	40	48	41	49
		671	673	39	47	40	48	41	49
	Ab3 heavy chains	38	46	42	50	43	51	44	52
20		672	674	42	50	43	51	44	52
	Ab4 light chains	53	61	55	63	56	64	57	65
		675	677	55	63	56	64	57	65
25	Ab4 heavy chains	54	62	58	66	59	67	60	68
		676	678	58	66	59	67	60	68
	Ab5 light chains	69	77	71	79	72	80	73	81
30		679	681	71	79	72	80	73	81
	Ab5 heavy chains	70	78	74	82	75	83	76	84
		680	682	74	82	75	83	76	84
	Ab6 light chains	85	93	87	95	88	96	89	97
35		683	685	87	95	88	96	89	97
	Ab6 heavy chains	86	94	90	98	91	99	92	100
		684	686	90	98	91	99	92	100
40	Ab7 light chains	101	109	103	111	104	112	105	113
		119		103	111	104	112	105	113
		687	689	103	111	104	112	105	113
		693		103	111	104	112	105	113
45	Ab7 heavy chains	102	110	106	114	107	115	108	116
		117		106	114	107	115	108	116
		118		106	114	121		108	116
		688	690	106	114	107	115	108	116
50		691		106	114	107	115	108	116
		692		106	114	121		108	116
	Ab8 light chain	122	130	124	132	125	133	126	134
55	Ab8 heavy chain	123	131	127	135	128	136	129	137
	Ab9 light chain	138	146	140	148	141	149	142	150

(continued)

	Antibody	Antibody chains		CDR1		CDR2		CDR3	
		PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.
5	Ab9 heavy chain	139	147	143	151	144	152	145	153
	Ab10 light chain	154	162	156	164	157	165	158	166
	Ab10 heavy chain	155	163	159	167	160	168	161	169
10	Ab11 light chain	170	178	172	180	173	181	174	182
	Ab11 heavy chain	171	179	175	183	176	184	177	185
	Ab12 light chain	186	194	188	196	189	197	190	198
	Ab12 heavy chain	187	195	191	199	192	200	193	201
15	Ab13 light chain	202	210	204	212	205	213	206	214
	Ab13 heavy chain	203	211	207	215	208	216	209	217
	Ab14 light chain	218	226	220	228	221	229	222	230
20	Ab14 heavy chain	219	227	223	231	224	232	225	233
	Ab15 light chain	234	242	236	244	237	245	238	246
	Ab15 heavy chain	235	243	239	247	240	248	241	249
	Ab16 light chain	250	258	252	260	253	261	254	262
25	Ab16 heavy chain	251	259	255	263	256	264	257	265
	Ab17 light chain	266	274	268	276	269	277	270	278
	Ab17 heavy chain	267	275	271	279	272	280	273	281
30	Ab18 light chain	282	290	284	292	285	293	286	294
	Ab18 heavy chain	283	291	287	295	288	296	289	297
	Ab19 light chain	298	306	300	308	301	309	302	310
	Ab19 heavy chain	299	307	303	311	304	312	305	313
35	Ab20 light chain	314	322	316	324	317	325	318	326
	Ab20 heavy chain	315	323	319	327	320	328	321	329
	Ab21 light chain	330	338	332	340	333	341	334	342
40	Ab21 heavy chain	331	339	335	343	336	344	337	345
	Ab22 light chain	346	354	348	356	349	357	350	358
	Ab22 heavy chain	347	355	351	359	352	360	353	361
	Ab23 light chain	362	370	364	372	365	373	366	374
45	Ab23 heavy chain	363	371	367	375	368	376	369	377
	Ab24 light chain	378	386	380	388	381	389	382	390
	Ab24 heavy chain	379	387	383	391	384	392	385	393
50	Ab25 light chain	394	402	396	404	397	405	398	406
	Ab25 heavy chain	395	403	399	407	400	408	401	409
	Ab26 light chain	410	418	412	420	413	421	414	422
	Ab26 heavy chain	411	419	415	423	416	424	417	425
55	Ab27 light chain	426	434	428	436	429	437	430	438
	Ab27 heavy chain	427	435	431	439	432	440	433	441

(continued)

5	Antibody	Antibody chains		CDR1		CDR2		CDR3	
		PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.
	Ab28 light chain	442	450	444	452	445	453	446	454
	Ab28 heavy chain	443	451	447	455	448	456	449	457
	Ab29 light chain	458	466	460	468	461	469	462	470
10	Ab29 heavy chain	459	467	463	471	464	472	465	473
	Ab30 light chain	474	482	476	484	477	485	478	486
	Ab30 heavy chain	475	483	479	487	480	488	481	489
15	Antibody	Antibody chains		CDR1		CDR2		CDR3	
		PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.
	Ab31 light chain	490	498	492	500	493	501	494	502
	Ab31 heavy chain	491	499	495	503	496	504	497	505
20	Ab32 light chain	506	514	508	516	509	517	510	518
	Ab32 heavy chain	507	515	511	519	512	520	513	521
	Ab33 light chain	522	530	524	532	525	533	526	534
	Ab33 heavy chain	523	531	527	535	528	536	529	537
25	Ab34 light chain	538	546	540	548	541	549	542	550
	Ab34 heavy chain	539	547	543	551	544	552	545	553
	Ab35 light chain	554	562	556	564	557	565	558	566
30	Ab35 heavy chain	555	563	559	567	560	568	561	569
	Ab36 light chain	570	578	572	580	573	581	574	582
	Ab36 heavy chain	571	579	575	583	576	584	577	585
35	* Exemplary sequence variant forms of heavy and light chains are shown on separate lines. (PRT.: Polypeptide sequence Nuc.: Exemplary coding sequence)								

[0293] For reference, sequence identifiers other than those included in Table 4 are summarized in Table 5.

40	Table 5: Summary of sequence identifiers in this application.	
	SEQ ID	Description
	1	Human IL-6
	586	kappa constant light chain polypeptide sequence
45	587	kappa constant light chain polynucleotide sequence
	588	gamma-1 constant heavy chain polypeptide sequence
	589	gamma-1 constant heavy chain polynucleotide sequence
50	590-646	Human IL-6 peptides (Example 14)
	719	gamma-1 constant heavy chain polypeptide sequence (differs from SEQ ID NO: 518 at two positions)
	726	C-reactive protein polypeptide sequence
55	727	IL-6 receptor alpha
	728	IL-6 receptor beta/gp130

[0294] Such antibody fragments or variants thereof may be present in at least one of the following non-limiting forms: Fab, Fab', F(ab')₂, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-IL-6 antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth in the polypeptide sequence of SEQ ID NO: 586.

[0295] In another preferred embodiment, the anti-IL-6 antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising one of the sequences set forth in the polypeptide sequence of SEQ ID NO: 588 and SEQ ID NO: 719.

[0296] Embodiments of antibodies described herein may include a leader sequence, such as a rabbit Ig leader, albumin pre-peptide, a yeast mating factor pre pro secretion leader sequence (such as *P. pastoris* or *Saccharomyces cerevisiae* a or alpha factor), or human HAS leader. Exemplary leader sequences are shown offset from FR1 at the N-terminus of polypeptides shown in Figs. 4A-B and 5A-B as follows: rabbit Ig leader sequences in SEQ ID NOs: 2 and 660 and SEQ ID NOs: 3 and 661; and an albumin prepeptide in SEQ ID NOs: 706 and 708, which facilitates secretion. Other leader sequences known in the art to confer desired properties, such as secretion, improved stability or half-life, may also be used, either alone or in combinations with one another, on the heavy and/or light chains, which may optionally be cleaved prior to administration to a subject. For example, a polypeptide may be expressed in a cell or cell-free expression system that also expresses or includes (or is modified to express or include) a protease, e.g., a membrane-bound signal peptidase, that cleaves a leader sequence.

[0297] Described herein is an isolated anti-IL-6 antibody comprising a V_H polypeptide sequence comprising: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 661, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, or 708; and further comprising a V_L polypeptide sequence comprising: SEQ ID NO: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 or a variant thereof wherein at least one of the framework residues (FR residues) or CDR residues in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-IL-6 antibody that specifically binds IL-6. The invention contemplates humanized and chimeric forms of these antibodies wherein preferably the FR will comprise human FRs highly homologous to the parent antibody. The chimeric antibodies may include an Fc derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions and in particular a variable heavy and light chain constant region as set forth in SEQ ID NO: 588 and SEQ ID NO: 586.

[0298] In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from at least one rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0299] In another embodiment of the invention, the anti-IL-6 antibodies and fragments and variants thereof have binding specificity for primate homologs of the human IL-6 protein. Non-limiting examples of primate homologs of the human IL-6 protein are IL-6 obtained from *Macaca fascicularis* (cynomolgus monkey) and the Rhesus monkey. In another embodiment of the invention, the anti-IL-6 antibodies and fragments and variants thereof inhibits the association of IL-6 with IL-6R, and/or the production of IL-6/IL-6R/gp130 complexes and/or the production of IL-6/IL-6R/gp130 multimers and/or antagonizes the biological effects of at least one of the foregoing.

Polyclonal Antibody

[0300] Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen. Polyclonal antibodies which selectively bind the IL-6 may be made by methods well-known in the art. See, e.g., Howard & Kaser (2007) Making and Using Antibodies: A Practical Handbook CRC Press.

Monoclonal Antibody

[0301] A monoclonal antibody contains a substantially homogeneous population of antibodies specific to antigens, which population contains substantially similar epitope binding sites. Monoclonal antibodies may be obtained by methods known to those skilled in the art. See, e.g. Kohler and Milstein (1975) Nature 256: 495-497; U.S. Patent No. 4,376,110; Ausubel, et al. [Eds.] (2011) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Greene Publishing Assoc. and Wiley Interscience, NY.; and Harlow & Lane (1998) USING ANTIBODIES: A LABORATORY MANUAL Cold Spring Harbor Laboratory; Colligan, et al. (2005) [Eds.] Current Protocols in Immunology Greene Publishing Assoc. and Wiley Interscience, NY. Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, GILD, and any subclass thereof. A hybridoma producing an antibody of the present invention may be cultivated *in vitro*, *in situ*, or *in vivo*.

Chimeric Antibody

[0302] Chimeric antibodies are molecules different portions of which are derived from different animal species, such as those having variable region derived from a murine antibody and a human immunoglobulin constant region, which are primarily used to reduce immunogenicity in application and to increase yields in production, for example, where murine monoclonal antibodies have higher yields from hybridomas but higher immunogenicity in humans, such that human murine chimeric monoclonal antibodies are used. Chimeric antibodies and methods for their production are known in the art. See Cabilly, et al. (1984) Proc. Natl. Acad. Sci. USA 81: 3273-3277; Morrison, et al. (1994) Proc. Natl. Acad. Sci. USA 81: 6851-6855; Boulianne, et al. (1984) Nature 312: 643-646; Neuberger, et al. (1985) Nature 314: 268-270; European Patent Application 173494 (1986); WO 86/01533 (1986); European Patent 184187 (1992); Sahagan, et al. (1986) J Immunol. 137: 1066-1074; Liu, et al. (1987) Proc. Natl. Acad. Sci. USA 84: 3439-3443; Sun, et al. (1987) Proc. Natl. Acad. Sci. USA 84: 214-218; Better, et al. (1988) Science 240: 1041-1043; and Harlow & Lane (1998) USING ANTIBODIES: A LABORATORY MANUAL Cold Spring Harbor Laboratory; and U.S. Patent No. 5,624,659.

Humanized Antibody

[0303] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This may be accomplished by examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. See, e.g., U.S. Patent No. 6,187,287. Likewise, other methods of producing humanized antibodies are now well known in the art. See, e.g., U.S. Patent Nos. 5,225,539; 5,530,101; 5,585,089; 5,693,762; 6,054,297; 6,180,370; 6,407,213; 6,548,640; 6,632,927; and 6,639,055; Jones, et al. (1986) Nature 321: 522-525; Reichmann, et al. (1988) Nature 332: 323-327; Verhoeyen, et al. (1988) Science 239: 1534-36; and Zhiqiang An (2009) [Ed.] Therapeutic Monoclonal Antibodies: From Bench to Clinic John Wiley & Sons, Inc.

Antibody Fragments (antigen-binding fragments)

[0304] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', F(ab')₂, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, e.g. diabodies, which comprise two distinct Fv specificities. Antibody fragments of immunoglobulins include but are not limited to SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR. Further, antigen-binding fragments may comprise the epitope binding site and have the same antigen binding selectivity as the antibody.

[0305] An antigen-binding fragment (e.g., Fab fragment) may comprise at least one constant and one variable domain of each of the heavy and the light chain of the antibody from which it is derived. These domains shape the paratope - the antigen-binding site - at the amino terminal end of the monomer. The two variable domains bind the epitope on their specific antigens. Fc and Fab fragments may be generated using papain that cleaves the immunoglobulin monomer into two Fab fragments and an Fc fragment. Pepsin cleaves below hinge region, so a F(ab')₂ fragment and a pFc' fragment may be formed. Another enzyme, IdeS (Immunoglobulin degrading enzyme from *Streptococcus pyogenes*, trade name FabRICATOR®) cleaves IgG in a sequence specific manner at neutral pH. The F(ab')₂ fragment may be split into two Fab' fragments by mild reduction. Additionally, the variable regions of the heavy and light chains may be fused together to form a single-chain variable fragment (scFv), which is only half the size of the Fab fragment, but retains the original specificity of the parent antibody.

Anti-idiotypic Antibody

[0306] An anti-idiotypic (anti-Id) antibody is an antibody which recognizes unique determinants generally associated with the antigen-binding site of an antibody. An Id antibody may be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the antibody with the antibody to which an anti-Id is being prepared. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody by producing an antibody to these idiotypic determinants (the anti-Id antibody). See e.g., U.S. Patent No. 4,699,880. The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody. The anti-anti-Id may be epitopically identical to the original antibody which induced the anti-Id. Thus, by using antibodies to the idiotypic determinants of an antibody it is possible to identify other clones expressing antibodies of identical specificity.

Engineered And Modified Antibodies

[0307] An antibody of the disclosure further may be prepared using an antibody having at least one of the VH and/or VL sequences derived from an antibody starting material to engineer a modified antibody, which modified antibody may have altered properties from the starting antibody. An antibody may be engineered by modifying at least one residues within one or both variable regions (*i.e.*, VH and/or VL), for example within at least one CDR regions and/or within at least one framework regions. Additionally or alternatively, an antibody may be engineered by modifying residues within the constant region(s), for example to alter the effector function(s) of the antibody.

[0308] One type of variable region engineering that may be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties. See, *e.g.*, Riechmann, et al. (1998) *Nature* 332: 323-327; Jones, et al. (1986) *Nature* 321: 522-525; Queen, et al. (1989) *Proc. Natl. Acad. U.S.A.* 86: 10029-10033; U.S. Patent Nos. 5,225,539; 5,530,101; 5,585,089; 5,693,762; and 6,180,370.

[0309] Suitable framework sequences may be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes may be found in the "VBase" human germline sequence database (available on the Internet), as well as in Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, et al. (1992) "The Repertoire of Human Germline VH Sequences Reveals about Fifty Groups of VH Segments with Different Hypervariable Loops" *J. Mol. Biol.* 227: 776-798; and Cox, et al. (1994) *Eur. J Immunol.* 24: 827-836.

[0310] Another type of variable region modification is to mutate amino acid residues within the VH and/or VL CDR 1, CDR2 and/or CDR3 regions to thereby improve at least one binding properties (*e.g.*, affinity) of the antibody of interest. Site-directed mutagenesis or PCR-mediated mutagenesis may be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, may be evaluated in appropriate *in vitro* or *in vivo* assays. Preferably conservative modifications (as discussed herein) may be introduced. The mutations may be amino acid substitutions, additions or deletions, but are preferably substitutions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

[0311] Engineered antibodies of the disclosure include those in which modifications have been made to framework residues within VH and/or VL, *e.g.* to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" at least one framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues may be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived.

[0312] In addition or alternative to modifications made within the framework or CDR regions, antibodies of the disclosure may be engineered to include modifications within the Fc region, typically to alter at least one functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody of the disclosure may be chemically modified (*e.g.*, at least one chemical moieties may be attached to the antibody) or be modified to alter its glycosylation, again to alter at least one functional properties of the antibody. Such embodiments are described further below. The numbering of residues in the Fc region is that of the EU index of Kabat.

[0313] The hinge region of CH1 may be modified such that the number of cysteine residues in the hinge region is altered, *e.g.*, increased or decreased. See U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of CH1 may be altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody. The Fc hinge region of an antibody may be mutated to decrease the biological half life of the antibody. More specifically, at least one amino acid mutations may be introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired *Staphylococcal* protein A (SpA) binding relative to native Fc-hinge domain SpA binding. See, *e.g.*, U.S. Patent No. 6,165,745.

[0314] The antibody may be modified to increase its biological half life. Various approaches are possible. For example, at least one of the following mutations may be introduced: T252L, T254S, T256F. See U.S. Patent No. 6,277,375. Alternatively, to increase the biological half life, the antibody may be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG. See U.S. Patent Nos. 5,869,046 and 6,121,022.

[0315] The Fc region may be altered by replacing at least one amino acid residue with a different amino acid residue

to alter the effector function(s) of the antibody. For example, at least one amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322 may be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity may be altered may be, for example, an Fc receptor or the C1 component of complement. See U.S. Patent Nos. 5,624,821 and 5,648,260.

[0316] The Fc region may be modified to increase the affinity of the antibody for an Fcγ receptor by modifying at least one amino acids at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439. See WO 00/42072. Moreover, the binding sites on human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding. See Shields, et al. (2001) J. Biol. Chem. 276: 6591-6604. Specific mutations at positions 256, 290, 298, 333, 334 and 339 are shown to improve binding to FcγRIII. Additionally, the following combination mutants are shown to improve FcγRIII binding: T256A/S298A, S298A/E333A, S298A/K224A and S298A/E333A/K334A.

[0317] The glycosylation of an antibody may be modified. For example, an aglycosylated antibody may be made (*i.e.*, the antibody lacks glycosylation). Glycosylation may be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications may be accomplished by, for example, altering at least one sites of glycosylation within the antibody sequence. For example, at least one amino acid substitutions may be made that result in elimination of at least one variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. See, *e.g.*, U.S. Patent Nos. 5,714,350 and 6,350,861.

[0318] Additionally or alternatively, an antibody may be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such carbohydrate modifications may be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and may be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. See U.S. Patent Application Publication No. 2004/0110704 and Yamane-Ohnuki, et al. (2004) Biotechnol Bioeng. 87: 614-22; EP 1,176,195; WO 2003/035835; Shields, et al. (2002) J. Biol. Chem. 277: 26733-26740; WO 99/54342; Umana, et al. (1999) Nat. Biotech. 17: 176-180; and Tarentino, et al. (1975) Biochem. 14: 5516-23.

[0319] An antibody may be pegylated to, for example, increase the biological (*e.g.*, serum) half life of the antibody. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which at least one PEG groups become attached to the antibody or antibody fragment. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer).

[0320] Described herein are variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelbodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, *e.g.*, conservative substitution mutations, (*i.e.*, the substitution of at least one amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, *e.g.*, one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. Also described are the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-IL-6 activity. Non-limiting examples of anti-IL-6 activity are set forth herein, for example, under the heading "Anti-IL-6 Activity," *infra*.

[0321] Anti-IL-6 antibodies have also been disclosed in the following published and unpublished patent applications, which are co-owned by the assignee of the present application: WO 2008/144763; U.S. Patent Application Publication Nos. 2009/0028784, 2009/0297513, and 2009/0297436. Other anti-IL-6 antibodies have been disclosed in the following U.S. Patents Nos: 7,482,436; 7,291,721; 6,121,423; U.S. Patent Application Publication Nos. 2008/0075726; 2007/0178098; 2007/0154481; 2006/0257407; and 2006/0188502.

Polypeptide Sequence Variants

[0322] For any anti-IL-6 antibodies sequence described herein, further characterization or optimization may be achieved by systematically either adding or removing amino acid residues to generate longer or shorter peptides, and testing those and sequences generated by walking a window of the longer or shorter size up or down the antigen from that point. Coupling this approach to generating new candidate targets with testing for effectiveness of antigenic molecules based on those sequences in an immunogenicity assay, as known in the art or as described herein, may lead to further manipulation of the antigen. Further still, such optimized sequences may be adjusted by, *e.g.*, the addition, deletions, or other mutations as known in the art and/or discussed herein to further optimize the anti-IL-6 antibodies (*e.g.*, increasing serum stability or circulating half-life, increasing thermal stability, enhancing delivery, enhance immunogenicity, increas-

ing solubility, targeting to a particular *in vivo* location or cell type).

[0323] In another aspect, the disclosure provides polypeptide sequences having at least about 90% sequence homology to any at least one of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the disclosure provides polypeptide sequences having at least about 95% sequence homology, even
 5 more preferably at least about 98% sequence homology, and still more preferably at least about 99% sequence homology to any at least one of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[0324] The anti-IL-6 antibodies polypeptides described herein may comprise conservative substitution mutations, (*i.e.*,
 10 the substitution of at least one amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, *e.g.*, one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid.

[0325] Anti-IL-6 antibodies polypeptide sequences may have at least about 60, 65, 70, 75, 80, 81, 82, 83, 84, 85, 86,
 15 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 98.5, 99, 99.5, 99.8, 99.9, or 100% sequence homology to any at least one of the polypeptide sequences set forth herein. More preferably, the disclosure provides polypeptide sequences having at least about 95% sequence homology, even more preferably at least about 98% sequence homology, and still more preferably at least about 99% sequence homology to any at least one of the polypeptide sequences of Anti-IL-6 antibodies polypeptide sequences set forth herein. Methods for determining homology between amino acid sequences, as well as nucleic acid sequences, are well known to those of ordinary skill in the art. See, *e.g.*, Nedelkov & Nelson
 20 (2006) New and Emerging Proteomic Techniques Humana Press. Thus, an anti-IL-6 antibodies polypeptide may have at least about 60, 65, 70, 75, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 98.5, 99, 99.5, 99.8, 99.9, or 100% sequence homology with a polypeptide sequence.

[0326] The term homology, or identity, is understood as meaning the number of agreeing amino acids (identity) with
 25 other proteins, expressed in percent. The identity is preferably determined by comparing a given sequence with other proteins with the aid of computer programs. If sequences which are compared with each other are different in length, the identity is to be determined in such a way that the number of amino acids which the short sequence shares with the longer sequence determines the percentage identity. The identity can be determined routinely by means of known computer programs which are publicly available such as, for example, Clustal W. Thompson, et al. (1994) Nucleic Acids Research 22: 4673-4680. ClustalW is publicly available from the European Molecular Biology Laboratory and may be
 30 downloaded from various internet pages, *inter alia* the IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire) and the EBI and all mirrored EBI internet pages (European Bioinformatics Institute). If the ClustalW computer program Version 1.8 is used to determine the identity between, for example, the reference protein of the present application and other proteins, the following parameters are to be set: KTUPLE=1, TOPDIAG=5, WINDOW=5, PAIRGAP=3, GAP-OPEN=10, GAPEXTEND=0.05, GAPDIST=8, MAXDIV=40, MATRIX=GONNET, ENDGAPS(OFF), NOPGAP, NOH-
 35 GAP. See *also* European Bioinformatics Institute (EBI) toolbox available on-line and Smith (2002) Protein Sequencing Protocols [2nd Ed.] Humana Press.

[0327] One possibility of finding similar sequences is to carry out sequence database researches. Here, at least one
 40 sequences may be entered as what is known as a query. This query sequence is then compared with sequences present in the selected databases using statistical computer programs. Such database queries (blast searches) are known to the skilled worker and may be carried out at different suppliers. If, for example, such a database query is carried out at the NCBI (National Center for Biotechnology Information), the standard settings for the respective comparison query should be used. For protein sequence comparisons (blastp), these settings are: Limit entrez = not activated; Filter = low complexity activated; Expect value = 10; word size = 3; Matrix = BLOSUM62; Gap costs: Existence = 11, Extension = 1. The result of such a query is, among other parameters, the degree of identity between the query sequence and the
 45 similar sequences found in the databases. Methods and materials for making fragments of Anti-IL-6 antibodies polypeptides are well known in the art. See, *e.g.*, Maniatis, et al. (2001) Molecular Cloning: A Laboratory Manual [3rd Ed.] Cold Spring Harbor Laboratory Press.

[0328] Variant anti-IL-6 antibodies polypeptides may retain their antigenic specificity to bind IL-6. Fully specific variants
 50 may contain only conservative variations or variations in non-critical residues or in non-critical regions. Variants may also contain substitution of similar amino acids that result in no change or an insignificant change in their specificity. Alternatively, such substitutions may positively or negatively affect specificity to some degree. Non-specific variants typically contain at least one non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region of an epitope. Molecular biology and biochemistry techniques for modifying anti-IL-6 antibodies polypeptides while preserving specificity are well known
 55 in the art. See, *e.g.*, Ho, et al. (1989) Gene 77(1): 51-59; Landt, et al. (1990) Gene 96(1): 125-128; Hopp & Woods (1991) Proc. Natl. Acad. Sci. USA 78(6): 3824-3828; Kolaskar & Tongaonkar (1990) FEBS Letters 276(1-2): 172-174; and Welling, et al. (1985) FEBS Letters 188(2): 215-218.

[0329] Amino acids that are essential for function may be identified by methods known in the art, such as site-directed

mutagenesis or alanine-scanning mutagenesis. Cunningham, et al. (1989) Sci. 244: 1081-85. The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as epitope binding. Sites that are critical for ligand-receptor binding may also be determined by structural analysis such as crystallography, nuclear magnetic resonance, or photoaffinity labeling. Smith, et al. (1992) J. Mol. Biol. 224: 899-904; de Vos, et al. (1992) Sci. 255: 306-12.

[0330] For example, one class of substitutions is conserved amino acid substitutions. Such substitutions are those that substitute a given amino acid in a Anti-IL-6 antibodies polypeptide with another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg, replacements among the aromatic residues Phe, Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent is found in, for example, Bowie, et al. (1990) Sci. 247: 1306-10. Hence, one of ordinary skill in the art appreciates that the inventors possess peptide variants without delineation of all the specific variants. As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. See, e.g., Creighton (1992) Proteins: Structures and Molecular Properties [2nd Ed.] W.H. Freeman.

[0331] Moreover, polypeptides often contain amino acids other than the twenty "naturally occurring" amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other post-translational modifications, or by chemical modification techniques well known in the art. Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, g-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See Creighton (1992) Proteins: Structure and Molecular Properties [2nd Ed.] and Lundblad (1995) Techniques in Protein Modification [1st Ed.] Many detailed reviews are available on this subject. See, e.g., Wold (1983) Posttranslational Covalent Modification of Proteins Acad. Press, NY; Seifter, et al. (1990) Meth. Enzymol. 182: 626-46; and Rattan, et al. (1992) Ann. NY Acad. Sci. 663: 48-62.

[0332] In another aspect, the disclosure further contemplates the generation and use of anti-idiotypic antibodies that bind any of the foregoing sequences. In an exemplary aspect, such an anti-idiotypic antibody could be administered to a subject who has received an anti-IL-6 antibody to modulate, reduce, or neutralize, the effect of the anti-IL-6 antibody. A further exemplary use of such anti-idiotypic antibodies is for detection of the anti-IL-6 antibodies of the present disclosure for example to monitor the levels of the anti-IL-6 antibodies present in a subject's blood or other bodily fluids.

[0333] Anti-IL-6 antibodies or fragments or variants thereof in accordance with the claims contain a variable heavy and light sequence of SEQ ID NO: 657, and 709. **POLYNUCLEOTIDES ENCODING ANTI-IL-6 ANTIBODY POLYPEPTIDES**

[0334] Described herein are polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. Polynucleotides may comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 2 which is encoded by the polynucleotide sequence of SEQ ID NO: 10 or the polynucleotide sequence of SEQ ID NO: 662, 698, 701, or 705.

[0335] Polynucleotides may comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 3 which is encoded by the polynucleotide sequence of SEQ ID NO: 11 or the polynucleotide sequence of SEQ ID NO: 663, 700, 703, or 707.

[0336] Polynucleotides encoding fragments or variants of the antibody having binding specificity to IL-6 may comprise, or alternatively consist of, at least one of the polynucleotide sequences of SEQ ID NO: 12 or 694; SEQ ID NO: 13; and SEQ ID NO: 14 or 695 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 2.

[0337] Polynucleotides encoding fragments or variants of the antibody having binding specificity to IL-6 may comprise, or alternatively consist of, at least one of the polynucleotide sequences of SEQ ID NO: 15; SEQ ID NO: 16 or 696; and SEQ ID NO: 17 or 697 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 3 or SEQ ID NO: 661 or SEQ ID NO: 657 or others depicted in Figs. 4 or 5.

[0338] Also described are polynucleotide sequences including at least one of the polynucleotide sequences encoding

antibody fragments or variants described herein. Polynucleotides encoding fragments or variants of the antibody having binding specificity to IL-6 may comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 10 encoding the light chain variable region of SEQ ID NO: 2; the polynucleotide SEQ ID NO: 11 encoding the heavy chain variable region of SEQ ID NO: 3; the polynucleotide SEQ ID NO: 720 encoding the light chain polypeptide of SEQ ID NO: 20; the polynucleotide SEQ ID NO: 721 encoding the light chain polypeptide of SEQ ID NO: 647; the polynucleotide SEQ ID NO: 662 encoding the light chain polypeptide of SEQ ID NO: 660; the polynucleotide SEQ ID NO: 722 encoding the light chain polypeptide of SEQ ID NO: 666; the polynucleotide SEQ ID NO: 698 encoding the light chain polypeptide of SEQ ID NO: 699; the polynucleotide SEQ ID NO: 701 encoding the light chain polypeptide of SEQ ID NO: 702; the polynucleotide SEQ ID NO: 705 encoding the light chain polypeptide of SEQ ID NO: 706; the polynucleotide SEQ ID NO: 723 encoding the light chain polypeptide of SEQ ID NO: 709; the polynucleotide SEQ ID NO: 724 encoding the heavy chain polypeptide of SEQ ID NO: 19; the polynucleotide SEQ ID NO: 725 encoding the heavy chain polypeptide of SEQ ID NO: 652; the polynucleotide SEQ ID NO: 700 encoding the heavy chain polypeptide of SEQ ID NO: 657; the polynucleotide SEQ ID NO: 663 encoding the heavy chain polypeptide of SEQ ID NO: 661; the polynucleotide SEQ ID NO: 703 encoding the heavy chain polypeptide of SEQ ID NO: 704; the polynucleotide SEQ ID NO: 707 encoding the heavy chain polypeptide of SEQ ID NO: 708; the polynucleotides of SEQ ID NO: 12, 13, 14, 694 and 695 encoding the complementarity-determining regions of the aforementioned light chain polypeptides; and the polynucleotides of SEQ ID NO: 15, 16, 17, 696 and 697 encoding the complementarity-determining regions of the aforementioned heavy chain polypeptides, and polynucleotides encoding the variable heavy and light chain sequences in SEQ ID NO: 657 and SEQ ID NO: 709 respectively, e.g., the nucleic acid sequences in SEQ ID NO: 700 and SEQ ID NO: 723 and fragments or variants thereof, e.g., based on codon degeneracy. These nucleic acid sequences encoding variable heavy and light chain sequences may be expressed alone or in combination and these sequences preferably are fused to suitable variable constant sequences, e.g., those in SEQ ID NO: 589 and SEQ ID NO: 587.

[0339] Exemplary nucleotide sequences encoding anti-IL-6 antibodies are identified in Table 4. The polynucleotide sequences shown are to be understood to be illustrative, rather than limiting. One of skill in the art can readily determine the polynucleotide sequences that would encode a given polypeptide and can readily generate coding sequences suitable for expression in a given expression system, such as by adapting the polynucleotide sequences provided and/or by generating them *de novo*, and can readily produce codon-optimized expression sequences, for example as described in published U.S. Patent Application No. 2008/0120732 or using other methods known in the art.

[0340] Polynucleotides may further comprise, the following polynucleotide sequence encoding the kappa constant light chain sequence of SEQ ID NO: 586 which is encoded by the polynucleotide sequence of SEQ ID NO: 587.

[0341] Polynucleotides may further comprise, the following polynucleotide sequence encoding the gamma-1 constant heavy chain polypeptide sequence of SEQ ID NO: 588 which is encoded by the polynucleotide sequence of SEQ ID NO: 589.

[0342] Also described herein is an isolated polynucleotide comprising a polynucleotide encoding an anti-IL-6 V_H antibody amino acid sequence selected from SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, and 708 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_H polypeptide or a conservative amino acid substitution. In addition, the invention specifically encompasses humanized anti-IL-6 antibodies or humanized antibody binding fragments or variants thereof and nucleic acid sequences encoding the foregoing comprising the humanized variable heavy chain and/or light chain polypeptides depicted in the sequences contained in FIG. 1-5, or those identified in Table 4, or variants thereof wherein at least one framework or CDR residues may be modified. Preferably, if any modifications are introduced they will not affect adversely the binding affinity of the resulting anti-IL-6 antibody or fragment or variant thereof.

[0343] Also described is an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-IL-6 V_L antibody amino acid sequence selected from SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, and 709 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_L polypeptide or a conservative amino acid substitution.

[0344] Also described is at least one heterologous polynucleotides comprising a sequence encoding the polypeptides set forth in SEQ ID NO: 2 and SEQ ID NO: 3; SEQ ID NO: 2 and SEQ ID NO: 18; SEQ ID NO: 2 and SEQ ID NO: 19; SEQ ID NO: 20 and SEQ ID NO: 3; SEQ ID NO: 20 and SEQ ID NO: 18; or SEQ ID NO: 20 and SEQ ID NO: 19.

[0345] Also described is an isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said expressed polypeptide alone specifically binds IL-6 or specifically binds IL-6 when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said at least one CDR is selected from those contained in the V_L or V_H polypeptides set forth in SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, 708, 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709.

[0346] Host cells and vectors comprising said polynucleotides are also described.

[0347] Described herein are nucleic acid constructs containing any of the foregoing nucleic acid sequences and combinations thereof as well as recombinant cells containing these nucleic acid sequences and constructs containing wherein these nucleic acid sequences or constructs may be extrachromosomal or integrated into the host cell genome.

[0348] Described herein are vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity determining regions (CDRs, or hypervariable regions) set forth herein, as well as host cells comprising said sequences. The host cell may be a yeast cell. The yeast host cell may belong to the genus *Pichia*.

[0349] In some instances, more than one exemplary polynucleotide encoding a given polypeptide sequence is provided, as summarized in Table 5.

Table 5 Multiple exemplary polynucleotides encoding particular polypeptides.

Polypeptide SEQ ID NO	Exemplary coding SEQ ID NOs
4	12, 111, 694
5	13, 112, 389, 501
6	14, 113, 695
9	17, 116, 697
39	47, 260
40	48, 261
60	68, 265
72	80, 325, 565, 581
89	97, 134, 166
103	12, 111, 694
104	13, 112, 389, 501
105	14, 113, 695
108	17, 116, 697
126	97, 134, 166
158	97, 134, 166
190	198, 214
191	199, 215
205	213, 469, 485
206	198, 214
207	199, 215
252	47, 260
253	48, 261
257	68, 265
317	80, 325, 565, 581
333	341, 533
381	13, 112, 389, 501
415	423, 439
431	423, 439
461	213, 469, 485
475	483, 499

(continued)

	Polypeptide SEQ ID NO	Exemplary coding SEQ ID NOs
5	476	484, 500
	477	213, 469, 485
	478	486, 502
	479	487, 503
10	480	488, 504
	481	489, 505
	491	483, 499
15	492	484, 500
	493	13, 112, 389, 501
	494	486, 502
	495	487, 503
20	496	488, 504
	497	489, 505
	525	341, 533
25	545	553, 585
	554	562, 578
	556	564, 580
	557	80, 325, 565, 581
30	558	566, 582
	570	562, 578
	572	564, 580
35	573	80, 325, 565, 581
	574	566, 582
	577	553, 585

40 **[0350]** In some instances, multiple sequence identifiers refer to the same polypeptide or polynucleotide sequence, as summarized in Table 3. References to these sequence identifiers are understood to be interchangeable, except where context indicates otherwise.

Table 6 Repeated sequences. Each cell lists a group of repeated sequences included in the sequence listing.

45	SEQ ID NOs of repeated sequences
	4, 103
	5, 104, 381, 493
50	6, 105
	9, 108
	12, 111
	13, 112
55	14, 113
	17, 116

(continued)

SEQ ID NOs of repeated sequences	
5	39, 252
	40, 253
	48, 261
	60, 257
10	68, 265
	72, 317, 557, 573
	80, 325, 565, 581
	89, 126, 158
15	97, 134, 166
	120, 659
	190, 206
	191, 207
20	198, 214
	199, 215
	205, 461, 477
	213, 469
25	333, 525
	415, 431
	423, 439
	475, 491
30	476, 492
	478, 494
	479, 495
	480, 496
35	481, 497
	483, 499
	484, 500
	486, 502
40	487, 503
	488, 504
	489, 505
	545, 577
45	554, 570
	556, 572
	558, 574
	562, 578
50	564, 580
	566, 582

[0351] Certain examples include polynucleotides that hybridize under moderately or highly stringent hybridization conditions to a polynucleotide having one of the exemplary coding sequences recited in Table 4, and also include polynucleotides that hybridize under moderately or highly stringent hybridization conditions to a polynucleotide encoding the same polypeptide as a polynucleotide having one of the exemplary coding sequences recited in Table 4, or polypeptide encoded by any of the foregoing polynucleotides.

[0352] The phrase "high stringency hybridization conditions" refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of nucleic acid, but to no other sequences. High stringency conditions are sequence dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Techniques in Biochemistry and Molecular Biology- Hybridization with Nucleic Probes, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993). Generally, high stringency conditions are selected to be about 5-10°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength pH. The T_m is the temperature (under defined ionic strength, pH, and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at T_m , 50% of the probes are occupied at equilibrium). High stringency conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50 nucleotides). High stringency conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal is at least two times background, optionally 10 times background hybridization. Exemplary high stringency hybridization conditions can be as following: 50% formamide, 5xSSC, and 1% SDS, incubating at 42 °C, or, 5xSSC, 1% SDS, incubating at 65°C, with wash in 0.2xSSC, and 0.1% SDS at 65°C. Such hybridizations and wash steps can be carried out for, e.g., 1, 2, 5, 10, 15, 30, 60; or more minutes.

[0353] Nucleic acids that do not hybridize to each other under high stringency conditions are still substantially related if the polypeptides that they encode are substantially related. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic acids typically hybridize under moderate stringency hybridization conditions. Exemplary "moderate stringency hybridization conditions" include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 1×SSC at 45°C. Such hybridizations and wash steps can be carried out for, e.g., 1, 2, 5, 10, 15, 30, 60, or more minutes. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency.

[0354] Expression vectors for use in the methods of the invention will further include yeast specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains. A drug marker may further be used to amplify copy number of the vector in a yeast host cell.

[0355] The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in yeast cells. These vector components may include, but are not limited to, at least one of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence. A yeast origin of replication is optional, as expression vectors are often integrated into the yeast genome.

[0356] In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[0357] Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway® Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0358] Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, e.g., the presence or absence of a nutrient or a change in temperature.

[0359] The yeast promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the yeast genome; alternatively a selectable marker is used as the site for homologous recombination. *Pichia* transformation is described in Cregg, et al. (1985) Mol. Cell. Biol. 5:3376-3385.

[0360] Examples of suitable promoters from *Pichia* include the AOX1 and promoter (Cregg, et al. (1989) Mol. Cell. Biol. 9:1316-1323); ICL1 promoter (Menendez, et al. (2003) Yeast 20(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham, et al. (1997) Gene 186(1):37-44); and FLD1 promoter (Shen, et al. (1998) Gene 216(1):93-102). The GAP promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

[0361] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile, amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[0362] The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, e.g. a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Other secretion signals of interest also include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, e.g., K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. See Hashimoto, et al. (1998) Protein Eng 11(2): 75; and Kobayashi, et al. (1998) Therapeutic Apheresis 2(4): 257.

[0363] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

[0364] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[0365] Construction of suitable vectors containing at least one of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and religated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin® (phleomycin)) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[0366] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) Ann. Rev. Biochem. 58: 913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli*-encoded recombination proteins. Recombination occurs between specific attachment (*att*) sites on the interacting DNA molecules. For a description of att sites See Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda Cold Spring Harbor, NY: Cold Spring Harbor Press), pages 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the *att* sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

[0367] *Att* sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing *att* B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites.

[0368] The expression host may be further modified by the introduction of sequences encoding at least one enzymes that enhance folding and disulfide bond formation, i.e. foldases, chaperonins. Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, are known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

[0369] For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond

isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, e.g. one strain may express BIP, and the other strain may express PDI or combinations thereof.

[0370] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes or other lipid aggregates (for polypeptides and/or polynucleotides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell.

This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence. Exemplary expression vectors and techniques for their use are described in the following publications: Old, et al. (1989) Principles of Gene Manipulation: An Introduction to Genetic Engineering, Blackwell Scientific Publications [4th Ed.]; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory Press; Sambrook, et al. (2001) Molecular Cloning: A Laboratory Manual [3rd Ed.] Cold Spring Harbor Laboratory Press; Gorman, "High Efficiency Gene Transfer into Mammalian Cells," in DNA Cloning, Volume II, Glover, D. M., Ed., IRL Press, Washington, D.C., pages 143-190.

[0371] For example, a liposomes or other lipid aggregate may comprise a lipid such as phosphatidylcholines (lecithins) (PC), phosphatidylethanolamines (PE), lysolecithins, lysophosphatidylethanolamines, phosphatidylserines (PS), phosphatidylglycerols (PG), phosphatidylinositol (PI), sphingomyelins, cardiolipin, phosphatidic acids (PA), fatty acids, gangliosides, glucolipids, glycolipids, mono-, di or triglycerides, ceramides, cerebrosides and combinations thereof; a cationic lipid (or other cationic amphiphile) such as 1,2-dioleoyloxy-3-(trimethylamino) propane (DOTAP); N-cholesteryloxycarbaryl-3,7,12-triazapentadecane-1,15-diamine (CTAP); N-[1-(2,3,-ditetradecyloxy)propyl]-N,N-dimethyl-N-hydroxyethylammonium bromide (DMRIE); N-[1-(2,3,-dioleoyloxy)propyl]-N,N-dimethyl-N-hydroxy ethylammonium bromide (DORIE); N-[1-(2,3-dioleoyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA); 3 beta [N-(N',N'-dimethylaminoethane)carbamoyl] cholesterol (DC-Choi); and dimethyldioctadecylammonium (DDAB); dioleoylphosphatidyl ethanolamine (DOPE), cholesterol-containing DOPC; and combinations thereof; and/or a hydrophilic polymer such as polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, polyaspartamide and combinations thereof. Other suitable cationic lipids are described in Miller (1998) Angewandte Chemie International Edition 37(13-14): 1768-1785 and Cooper, et al. (1998) Chem. Eur. J. 4(1): 137-151. Liposomes can be crosslinked, partially crosslinked, or free from crosslinking. Crosslinked liposomes can include crosslinked as well as non-crosslinked components. Suitable cationic liposomes or cytofectins are commercially available and can also be prepared as described in Sipkins, et al. (1998) Nature Medicine 4(5): 623-626 or as described in Miller, *supra*. Exemplary liposomes include a polymerizable zwitterionic or neutral lipid, a polymerizable integrin targeting lipid and a polymerizable cationic lipid suitable for binding a nucleic acid. Liposomes can optionally include peptides that provide increased efficiency, for example as described in U.S. Patent No. 7,297,759. Additional exemplary liposomes and other lipid aggregates are described in U.S. Patent No. 7,166,298.

Methods of Producing Antibodies and Fragments thereof

[0372] Also described herein is the production of the antibodies described herein or fragments thereof. Recombinant polypeptides corresponding to the antibodies described herein or fragments thereof are secreted from polyploid, preferably diploid or tetraploid strains of mating competent yeast. Described are methods for producing these recombinant polypeptides in secreted form for prolonged periods using cultures comprising polyploid yeast, *i.e.*, at least several days to a week, more preferably at least a month or several months, and even more preferably at least 6 months to a year or longer. These polyploid yeast cultures will express at least 10-25 mg/liter of the polypeptide, more preferably at least 50-250 mg/liter, still more preferably at least 500-1000 mg/liter, and most preferably a gram per liter or more of the recombinant polypeptide(s).

[0373] A pair of genetically marked yeast haploid cells are transformed with expression vectors comprising subunits of a desired heteromultimeric protein. One haploid cell comprises a first expression vector, and a second haploid cell comprises a second expression vector. Diploid yeast cells will be transformed with at least one expression vectors that provide for the expression and secretion of at least one of the recombinant polypeptides. A single haploid cell may be transformed with at least one vectors and used to produce a polyploid yeast by fusion or mating strategies. A diploid yeast culture may be transformed with at least one vectors providing for the expression and secretion of a desired

polypeptide or polypeptides. These vectors may comprise vectors e.g., linearized plasmids or other linear DNA products that integrate into the yeast cell's genome randomly, through homologous recombination, or using a recombinase such as Cre/Lox or Flp/Frt. Optionally, additional expression vectors may be introduced into the haploid or diploid cells; or the first or second expression vectors may comprise additional coding sequences; for the synthesis of heterotrimers; heterotetramers. The expression levels of the non-identical polypeptides may be individually calibrated, and adjusted through appropriate selection, vector copy number, promoter strength and/or induction and the like. The transformed haploid cells are genetically crossed or fused. The resulting diploid or tetraploid strains are utilized to produce and secrete fully assembled and biologically functional proteins, humanized antibodies described herein or fragments thereof.

[0374] The use of diploid or tetraploid cells for protein production provides for unexpected benefits. The cells can be grown for production purposes, *i.e.* scaled up, and for extended periods of time, in conditions that can be deleterious to the growth of haploid cells, which conditions may include high cell density; growth in minimal media; growth at low temperatures; stable growth in the absence of selective pressure; and which may provide for maintenance of heterologous gene sequence integrity and maintenance of high level expression over time. Without wishing to be bound thereby, the inventors theorize that these benefits may arise, at least in part, from the creation of diploid strains from two distinct parental haploid strains. Such haploid strains can comprise numerous minor autotrophic mutations, which mutations are complemented in the diploid or tetraploid, enabling growth and enhanced production under highly selective conditions.

[0375] Transformed mating competent haploid yeast cells provide a genetic method that enables subunit pairing of a desired protein. Haploid yeast strains are transformed with each of two expression vectors, a first vector to direct the synthesis of one polypeptide chain and a second vector to direct the synthesis of a second, non-identical polypeptide chain. The two haploid strains are mated to provide a diploid host where optimized target protein production can be obtained.

[0376] Optionally, additional non-identical coding sequence(s) are provided. Such sequences may be present on additional expression vectors or in the first or the second expression vectors. As is known in the art, multiple coding sequences may be independently expressed from individual promoters; or may be coordinately expressed through the inclusion of an "internal ribosome entry site" or "IRES", which is an element that promotes direct internal ribosome entry to the initiation codon, such as ATG, of a cistron (a protein encoding region), thereby leading to the cap-independent translation of the gene. IRES elements functional in yeast are described by Thompson, et al. (2001) PNAS 98: 12866-12868.

[0377] Antibody sequences are produced in combination with a secretory J chain, which provides for enhanced stability of IgA. See U.S. Patent Nos. 5,959,177 and 5,202,422.

[0378] The two haploid yeast strains are each auxotrophic, and require supplementation of media for growth of the haploid cells. The pair of auxotrophs are complementary, such that the diploid product will grow in the absence of the supplements required for the haploid cells. Many such genetic markers are known in yeast, including requirements for amino acids (e.g. met, lys, his, arg), nucleosides (e.g. ura3, ade1); and the like. Amino acid markers may be preferred for the methods of the invention. Alternatively diploid cells which contain the desired vectors can be selected by other means, e.g., by use of other markers, such as green fluorescent protein, antibiotic resistance genes, various dominant selectable markers, and the like.

[0379] Two transformed haploid cells may be genetically crossed and diploid strains arising from this mating event selected by their hybrid nutritional requirements and/or antibiotic resistance spectra. Alternatively, populations of the two transformed haploid strains are spheroplasted and fused, and diploid progeny regenerated and selected. By either method, diploid strains can be identified and selectively grown based on their ability to grow in different media than their parents. For example, the diploid cells may be grown in minimal medium that may include antibiotics. The diploid synthesis strategy has certain advantages. Diploid strains have the potential to produce enhanced levels of heterologous protein through broader complementation to underlying mutations, which may impact the production and/or secretion of recombinant protein. Furthermore, once stable strains have been obtained, any antibiotics used to select those strains do not necessarily need to be continuously present in the growth media.

[0380] As noted above, a haploid yeast may be transformed with a single or multiple vectors and mated or fused with a non-transformed cell to produce a diploid cell containing the vector or vectors. In other embodiments, a diploid yeast cell may be transformed with at least one vectors that provide for the expression and secretion of a desired heterologous polypeptide by the diploid yeast cell.

[0381] Two haploid strains are transformed with a library of polypeptides, e.g. a library of antibody heavy or light chains. Transformed haploid cells that synthesize the polypeptides are mated with the complementary haploid cells. The resulting diploid cells are screened for functional protein. The diploid cells provide a means of rapidly, conveniently and inexpensively bringing together a large number of combinations of polypeptides for functional testing. This technology is especially applicable for the generation of heterodimeric protein products, where optimized subunit synthesis levels are critical for functional protein expression and secretion.

[0382] The expression level ratio of the two subunits is regulated in order to maximize product generation. Heterodimer subunit protein levels have been shown previously to impact the final product generation. Simmons (2002) J Immunol

Methods. 263(1-2): 133-47. Regulation can be achieved prior to the mating step by selection for a marker present on the expression vector. By stably increasing the copy number of the vector, the expression level can be increased. In some cases, it may be desirable to increase the level of one chain relative to the other, so as to reach a balanced proportion between the subunits of the polypeptide. Antibiotic resistance markers are useful for this purpose, e.g. Zeocin® (phleomycin) resistance marker, G418 resistance and provide a means of enrichment for strains that contain multiple integrated copies of an expression vector in a strain by selecting for transformants that are resistant to higher levels of Zeocin® (phleomycin) or G418. The proper ratio (e.g. 1:1; 1:2) of the subunit genes may be important for efficient protein production. Even when the same promoter is used to transcribe both subunits, many other factors contribute to the final level of protein expressed and therefore, it can be useful to increase the number of copies of one encoded gene relative to the other. Alternatively, diploid strains that produce higher levels of a polypeptide, relative to single copy vector strains, are created by mating two haploid strains, both of which have multiple copies of the expression vectors.

[0383] Host cells are transformed with the above-described expression vectors, mated to form diploid strains, and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants or amplifying the genes encoding the desired sequences. A number of minimal media suitable for the growth of yeast are known in the art. Any of these media may be supplemented as necessary with salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as phosphate, HEPES), nucleosides (such as adenosine and thymidine), antibiotics, trace elements, and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[0384] Secreted proteins are recovered from the culture medium. A protease inhibitor, such as phenyl methyl sulfonyl fluoride (PMSF) may be useful to inhibit proteolytic degradation during purification, and antibiotics may be included to prevent the growth of adventitious contaminants. The composition may be concentrated, filtered, dialyzed, using methods known in the art.

[0385] The diploid cells of the invention are grown for production purposes. Such production purposes desirably include growth in minimal media, which media lacks pre-formed amino acids and other complex biomolecules, e.g., media comprising ammonia as a nitrogen source, and glucose as an energy and carbon source, and salts as a source of phosphate, calcium and the like. Preferably such production media lacks selective agents such as antibiotics, amino acids, purines, pyrimidines. The diploid cells can be grown to high cell density, for example at least about 50 g/L; more usually at least about 100 g/L; and may be at least about 300, about 400, about 500 g/L or more.

[0386] The growth of the subject cells for production purposes is performed at low temperatures, which temperatures may be lowered during log phase, during stationary phase, or both. The term "low temperature" refers to temperatures of at least about 15°C, more usually at least about 17°C, and may be about 20°C, and is usually not more than about 25°C, more usually not more than about 22°C. In another embodiment of the invention, the low temperature is usually not more than about 28°C. Growth temperature can impact the production of full-length secreted proteins in production cultures, and decreasing the culture growth temperature can strongly enhance the intact product yield. The decreased temperature appears to assist intracellular trafficking through the folding and post-translational processing pathways used by the host to generate the target product, along with reduction of cellular protease degradation.

[0387] The methods provide for expression of secreted, active protein, preferably a mammalian protein. Secreted, "active antibodies", as used herein, refers to a correctly folded multimer of at least two properly paired chains, which accurately binds to its cognate antigen. Expression levels of active protein are usually at least about 10-50 mg/liter culture, more usually at least about 100 mg/liter, preferably at least about 500 mg/liter, and may be 1000 mg/liter or more.

[0388] The methods can provide for increased stability of the host and heterologous coding sequences during production. The stability is evidenced, for example, by maintenance of high levels of expression of time, where the starting level of expression is decreased by not more than about 20%, usually not more than 10%, and may be decreased by not more than about 5% over about 20 doublings, 50 doublings, 100 doublings, or more.

[0389] The strain stability also provides for maintenance of heterologous gene sequence integrity over time, where the sequence of the active coding sequence and requisite transcriptional regulatory elements are maintained in at least about 99% of the diploid cells, usually in at least about 99.9% of the diploid cells, and preferably in at least about 99.99% of the diploid cells over about 20 doublings, 50 doublings, 100 doublings, or more. Preferably, substantially all of the diploid cells maintain the sequence of the active coding sequence and requisite transcriptional regulatory elements.

[0390] Other methods of producing antibodies are well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art. See, e.g., U.S. Patent No. 4,816,567; Morrison, et al. (1984) PNAS USA 81: 8651-55; Neuberger, et al. (1985) Nature 314: 268-270; Boulianne, et al. (1984) Nature 312: 643-46.

[0391] Likewise, other methods of producing humanized antibodies are now well known in the art. See, e.g., U.S. Patent Nos. 5,225,539; 5,530,101; 5,585,089; 5,693,762; 6,054,297; 6,180,370; 6,407,213; 6,548,640; 6,632,927; and 6,639,055; Jones, et al. (1986) Nature 321: 522-525; Reichmann, et al. (1988) Nature 332: 323-327; Verhoeyen, et al. (1988) Science 239: 1534-36.

[0392] Antibody polypeptides of the disclosure having IL-6 binding specificity may also be produced by constructing, using conventional techniques well known to those of ordinary skill in the art, an expression vector containing an operon and a DNA sequence encoding an antibody heavy chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[0393] A second expression vector is produced using the same conventional means well known to those of ordinary skill in the art, said expression vector containing an operon and a DNA sequence encoding an antibody light chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[0394] The expression vectors are transfected into a host cell by convention techniques well known to those of ordinary skill in the art to produce a transfected host cell, said transfected host cell cultured by conventional techniques well known to those of ordinary skill in the art to produce said antibody polypeptides.

[0395] The host cell may be co-transfected with the two expression vectors described above, the first expression vector containing DNA encoding an operon and a light chain-derived polypeptide and the second vector containing DNA encoding an operon and a heavy chain-derived polypeptide. The two vectors contain different selectable markers, but preferably achieve substantially equal expression of the heavy and light chain polypeptides. Alternatively, a single vector may be used, the vector including DNA encoding both the heavy and light chain polypeptides. The coding sequences for the heavy and light chains may comprise cDNA.

[0396] The host cells used to express the antibody polypeptides may be either a bacterial cell such as *E. coli*, or a eukaryotic cell. In a particularly preferred embodiment of the invention, a mammalian cell of a well-defined type for this purpose, such as a myeloma cell or a Chinese hamster ovary (CHO) cell line may be used.

[0397] The general methods by which the vectors may be constructed, transfection methods required to produce the host cell and culturing methods required to produce the antibody polypeptides from said host cells all include conventional techniques. Although preferably the cell line used to produce the antibody is a mammalian cell line, any other suitable cell line, such as a bacterial cell line such as an *E. coli*-derived bacterial strain, or a yeast cell line, may alternatively be used.

[0398] Similarly, once produced the antibody polypeptides may be purified according to standard procedures in the art, such as for example cross-flow filtration, ammonium sulphate precipitation, affinity column chromatography and the like.

[0399] The antibody polypeptides described herein may also be used for the design and synthesis of either peptide or non-peptide mimetics that would be useful for the same therapeutic applications as the antibody polypeptides of the invention. See, e.g., Saragobi et al. (1991) Science 253: 792-795.

B-Cell Screening and Isolation

[0400] Also described herein are methods of isolating a clonal population of antigen-specific B cells that may be used for isolating at least one antigen-specific cell. As described and exemplified infra, these methods contain a series of culture and selection steps that can be used separately, in combination, sequentially, repetitively, or periodically. Preferably, these methods are used for isolating at least one antigen-specific cell, which can be used to produce a monoclonal antibody, which is specific to a desired antigen, or a nucleic acid sequence corresponding to such an antibody.

[0401] Described is a method comprising the steps of:

- (a) preparing a cell population comprising at least one antigen-specific B cell;
- (b) enriching the cell population, e.g., by chromatography, to form an enriched cell population comprising at least one antigen-specific B cell;
- (c) isolating a single B cell from the enriched B cell population; and
- (d) determining whether the single B cell produces an antibody specific to the antigen.

[0402] Described herein is an improvement to a method of isolating a single, antibody-producing B cell, the improvement comprising enriching a B cell population obtained from a host that has been immunized or naturally exposed to an antigen, wherein the enriching step precedes any selection steps, comprises at least one culturing step, and results in a clonal population of B cells that produces a single monoclonal antibody specific to said antigen.

[0403] Throughout this application, a "clonal population of B cells" refers to a population of B cells that only secrete a single antibody specific to a desired antigen. That is to say that these cells produce only one type of monoclonal antibody specific to the desired antigen.

[0404] In the present application, "enriching" a cell population cells means increasing the frequency of desired cells, typically antigen-specific cells, contained in a mixed cell population, e.g., a B cell-containing isolate derived from a host that is immunized against a desired antigen. Thus, an enriched cell population encompasses a cell population having

a higher frequency of antigen-specific cells as a result of an enrichment step, but this population of cells may contain and produce different antibodies.

[0405] The general term "cell population" encompasses pre- and a post-enrichment cell populations, keeping in mind that when multiple enrichment steps are performed, a cell population can be both pre- and post-enrichment. For example, described herein is a method comprising:

- (a) harvesting a cell population from an immunized host to obtain a harvested cell population;
- (b) creating at least one single cell suspension from the harvested cell population;
- (c) enriching at least one single cell suspension to form a first enriched cell population;
- (d) enriching the first enriched cell population to form a second enriched cell population;
- (e) enriching the second enriched cell population to form a third enriched cell population; and
- (f) selecting an antibody produced by an antigen-specific cell of the third enriched cell population.

[0406] Each cell population may be used directly in the next step, or it can be partially or wholly frozen for long- or short- term storage or for later steps. Also, cells from a cell population can be individually suspended to yield single cell suspensions. The single cell suspension can be enriched, such that a single cell suspension serves as the pre-enrichment cell population. Then, at least one antigen-specific single cell suspensions together form the enriched cell population; the antigen-specific single cell suspensions can be grouped together, e.g., re-plated for further analysis and/or antibody production.

[0407] Described herein is a method of enriching a cell population to yield an enriched cell population having an antigen-specific cell frequency that is about 50% to about 100%, or increments therein. Preferably, the enriched cell population has an antigen-specific cell frequency at least about 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or 100%.

[0408] Described herein is a method of enriching a cell population whereby the frequency of antigen-specific cells is increased by at least about 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or increments therein.

[0409] Throughout this application, the term "increment" is used to define a numerical value in varying degrees of precision, e.g., to the nearest 10, 1, 0.1, 0.01. The increment can be rounded to any measurable degree of precision, and the increment need not be rounded to the same degree of precision on both sides of a range. For example, the range 1 to 100 or increments therein includes ranges such as 20 to 80, 5 to 50, and 0.4 to 98. When a range is open-ended, e.g., a range of less than 100, increments therein means increments between 100 and the measurable limit. For example, less than 100 or increments therein means 0 to 100 or increments therein unless the feature, e.g., temperature, is not limited by 0.

[0410] Antigen-specificity can be measured with respect to any antigen. The antigen can be any substance to which an antibody can bind including, but not limited to, peptides, proteins or fragments thereof; carbohydrates; organic and inorganic molecules; receptors produced by animal cells, bacterial cells, and viruses; enzymes; agonists and antagonists of biological pathways; hormones; and cytokines. Exemplary antigens include, but are not limited to, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN- α , IFN- γ , BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF) and Hepcidin. Preferred antigens include IL-6, IL-13, TNF- α , VEGF- α , Hepatocyte Growth Factor (HGF) and Hepcidin. In a method utilizing more than one enrichment step, the antigen used in each enrichment step can be the same as or different from one another. Multiple enrichment steps with the same antigen may yield a large and/or diverse population of antigen-specific cells; multiple enrichment steps with different antigens may yield an enriched cell population with cross-specificity to the different antigens.

[0411] Enriching a cell population can be performed by any cell-selection means known in the art for isolating antigen-specific cells. For example, a cell population can be enriched by chromatographic techniques, e.g., Miltenyi bead or magnetic bead technology. The beads can be directly or indirectly attached to the antigen of interest. In a preferred embodiment, the method of enriching a cell population includes at least one chromatographic enrichment step.

[0412] A cell population can also be enriched by performed by any antigen-specificity assay technique known in the art, e.g., an ELISA assay or a halo assay. ELISA assays include, but are not limited to, selective antigen immobilization (e.g., biotinylated antigen capture by streptavidin, avidin, or neutravidin coated plate), non-specific antigen plate coating, and through an antigen build-up strategy (e.g., selective antigen capture followed by binding partner addition to generate a heteromeric protein-antigen complex). The antigen can be directly or indirectly attached to a solid matrix or support, e.g., a column. A halo assay comprises contacting the cells with antigen-loaded beads and labeled anti-host antibody specific to the host used to harvest the B cells. The label can be, e.g., a fluorophore. In one embodiment, at least one assay enrichment step is performed on at least one single cell suspension. In another embodiment, the method of enriching a cell population includes at least one chromatographic enrichment step and at least one assay enrichment step.

[0413] Methods of "enriching" a cell population by size or density are known in the art. See, e.g., U.S. Patent 5,627,052. These steps can be used in the present method in addition to enriching the cell population by antigen-specificity.

[0414] The cell populations contain at least one cell capable of recognizing an antigen. Antigen-recognizing cells include, but are not limited to, B cells, plasma cells, and progeny thereof. In one embodiment, the present invention

provides a clonal cell population containing a single type of antigen-specific B-cell, *i.e.*, the cell population produces a single monoclonal antibody specific to a desired antigen.

[0415] It is believed that the clonal antigen-specific population of B cells consists predominantly of antigen-specific, antibody-secreting cells, which are obtained by the novel culture and selection protocol provided herein. Accordingly, described herein are methods for obtaining an enriched cell population containing at least one antigen-specific, antibody-secreting cell. Described herein is an enriched cell population containing about 50% to about 100%, or increments therein, at least about 60%, 70%, 80%, 90%, or 100% of antigen-specific, antibody-secreting cells.

[0416] Described herein is a method of isolating a single B cell by enriching a cell population obtained from a host before any selection steps, *e.g.*, selecting a particular B cell from a cell population and/or selecting an antibody produced by a particular cell. The enrichment step can be performed as one, two, three, or more steps. A single B cell is isolated from an enriched cell population before confirming whether the single B cell secretes an antibody with antigen-specificity and/or a desired property.

[0417] A method of enriching a cell population is used in a method for antibody production and/or selection. Thus, described herein is a method comprising enriching a cell population before selecting an antibody. The method can include the steps of: preparing a cell population comprising at least one antigen-specific cell, enriching the cell population by isolating at least one antigen-specific cell to form an enriched cell population, and inducing antibody production from at least one antigen-specific cell. The enriched cell population contains more than one antigen-specific cell. Each antigen-specific cell of the enriched population is cultured under conditions that yield a clonal antigen-specific B cell population before isolating an antibody producing cell therefrom and/or producing an antibody using said B cell, or a nucleic acid sequence corresponding to such an antibody. In contrast to prior techniques where antibodies are produced from a cell population with a low frequency of antigen-specific cells, the present invention allows antibody selection from among a high frequency of antigen-specific cells. Because an enrichment step is used prior to antibody selection, the majority of the cells, preferably virtually all of the cells, used for antibody production are antigen-specific. By producing antibodies from a population of cells with an increased frequency of antigen specificity, the quantity and variety of antibodies are increased.

[0418] In the antibody selection methods described herein, an antibody is preferably selected after an enrichment step and a culture step that results in a clonal population of antigen-specific B cells. The methods can further comprise a step of sequencing a selected antibody or portions thereof from at least one isolated, antigen-specific cells. Any method known in the art for sequencing can be employed and can include sequencing the heavy chain, light chain, variable region(s), and/or complementarity determining region(s) (CDR).

[0419] In addition to the enrichment step, the method for antibody selection can also include at least one steps of screening a cell population for antigen recognition and/or antibody functionality. For example, the desired antibodies may have specific structural features, such as binding to a particular epitope or mimicry of a particular structure; antagonist or agonist activity; or neutralizing activity, *e.g.*, inhibiting binding between the antigen and a ligand. The antibody functionality screen may be ligand-dependent. Screening for antibody functionality includes, but is not limited to, an *in vitro* protein-protein interaction assay that recreates the natural interaction of the antigen ligand with recombinant receptor protein; and a cell-based response that is ligand dependent and easily monitored (*e.g.*, proliferation response). The method for antibody selection may include a step of screening the cell population for antibody functionality by measuring the inhibitory concentration (IC₅₀). At least one of the isolated, antigen-specific cells produces an antibody having an IC₅₀ of less than about 100, 50, 30, 25, 10 $\mu\text{g/mL}$, or increments therein.

[0420] In addition to the enrichment step, the method for antibody selection can also include at least one steps of screening a cell population for antibody binding strength. Antibody binding strength can be measured by any method known in the art (*e.g.*, Biacore®). At least one of the isolated, antigen-specific cells produces an antibody having a high antigen affinity, *e.g.*, a dissociation constant (K_d) of less than about 5×10^{-10} M⁻¹, preferably about 1×10^{-13} to 5×10^{-10} , 1×10^{-12} to 1×10^{-10} , 1×10^{-12} to 7.5×10^{-11} , 1×10^{-11} to 2×10^{-11} , about 1.5×10^{-11} or less, or increments therein. The antibodies are said to be affinity mature. The affinity of the antibodies is comparable to or higher than the affinity of any one of Panorex® (edrecolomab), Rituxan® (rituximab), Herceptin® (trastuzumab), Mylotarg® (gentuzumab), Campath® (alemtuzumab), Zevalin® (ibritumomab), Erbitux® (cetuximab), Avastin® (bevacizumab), Raptiva® (efalizumab), Remicade® (infliximab), Humira® (adalimumab), or Xolair® (omalizumab). Preferably, the affinity of the antibodies is comparable to or higher than the affinity of Humira®. The affinity of an antibody can also be increased by known affinity maturation techniques. At least one cell population is screened for at least one of, preferably both, antibody functionality and antibody binding strength.

[0421] In addition to the enrichment step, the method for antibody selection can also include at least one steps of screening a cell population for antibody sequence homology, especially human homology. At least one of the isolated, antigen-specific cells produces an antibody that has a homology to a human antibody of at least about 50% to about 100%, or increments therein, or at least about 60%, 70%, 80%, 85%, 90%, or 95% homologous. The antibodies can be humanized to increase the homology to a human sequence by techniques known in the art such as CDR grafting or selectivity determining residue grafting (SDR).

[0422] Also described herein are the antibodies themselves according to any of the embodiments described above in terms of IC50, Kd, and/or homology.

Methods of Humanizing Antibodies

[0423] Described herein is a method for humanizing antibody heavy and light chains. The following method may be followed for the humanization of the heavy and light chains:

Light Chain

[0424]

1. Identify the amino acid that is the first one following the signal peptide sequence. This is the start of Framework 1. The signal peptide starts at the first initiation methionine and is typically, but not necessarily 22 amino acids in length for rabbit light chain protein sequences. The start of the mature polypeptide can also be determined experimentally by N-terminal protein sequencing, or can be predicted using a prediction algorithm. This is also the start of Framework 1 as classically defined by those in the field.

Example: RbtVL Amino acid residue 1 in Fig. 1, starting 'AYDM...' (SEQ ID NO: 733)

2. Identify the end of Framework

3. This is typically 86-90 amino acids following the start of Framework 1 and is typically a cysteine residue preceded by two tyrosine residues. This is the end of the Framework 3 as classically defined by those in the field.

Example: RbtVL amino acid residue 88 in Fig. 1, ending as 'TYYC' (SEQ ID NO: 733)

3. Use the rabbit light chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be a search against human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be found from various sources such as NCBI (National Center for Biotechnology Information).

Example: RbtVL amino acid sequence from residues numbered 1 through 88 in Fig. 1 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Fig. 1 as L12A (SEQ ID NO: 734), V1 (SEQ ID NO: 735), and Vx02 (SEQ ID NO: 736).

4. Generally the most homologous human germline variable light chain sequence is then used as the basis for humanization. However those skilled in the art may decide to use another sequence that wasn't the highest homology as determined by the homology algorithm, based on other factors including sequence gaps and framework similarities.

Example: In Fig. 1, L12A (SEQ ID NO: 734) was the most homologous human germline variable light chain sequence and is used as the basis for the humanization of RbtVL.

5. Determine the framework and CDR arrangement (FR1, FR2, FR3, CDR1 & CDR2) for the human homolog being used for the light chain humanization. This is using the traditional layout as described in the field. Align the rabbit variable light chain sequence with the human homolog, while maintaining the layout of the framework and CDR regions.

Example: In Fig. 1, the RbtVL sequence is aligned with the human homologous sequence L12A, and the framework and CDR domains are indicated.

6. Replace the human homologous light chain sequence CDR1 and CDR2 regions with the CDR1 and CDR2 sequences from the rabbit sequence. If there are differences in length between the rabbit and human CDR sequences then use the entire rabbit CDR sequences and their lengths. It is possible that the specificity, affinity and/or immunogenicity of the resulting humanized antibody may be unaltered if smaller or larger sequence exchanges are performed, or if specific residue(s) are altered, however the exchanges as described have been used successfully, but do not exclude the possibility that other changes may be permitted.

Example: In Fig. 1, the CDR1 and CDR2 amino acid residues of the human homologous variable light chain L12A are replaced with the CDR1 and CDR2 amino acid sequences from the RbtVL rabbit antibody light chain sequence. The human L12A frameworks 1, 2 and 3 are unaltered. The resulting humanized sequence is shown below as VLh from residues numbered 1 through 88. Note that the only residues that are different from the L12A human sequence are underlined, and are thus rabbit-derived amino acid residues. In this example only 8 of the 88 residues are different than the human sequence.

7. After framework 3 of the new hybrid sequence created in Step 6, attach the entire CDR3 of the rabbit light chain antibody sequence. The CDR3 sequence can be of various lengths, but is typically 9 to 15 amino acid residues in length. The CDR3 region and the beginning of the following framework 4 region are defined classically and identifiable

by those skilled in the art. Typically the beginning of Framework 4, and thus after the end of CDR3 consists of the sequence 'FGGG...' (SEQ ID NO: 743), however some variation may exist in these residues.

Example: In Fig. 1, the CDR3 of RbtVL (amino acid residues numbered 89-100) is added after the end of framework 3 in the humanized sequence indicated as VLh.

8. The rabbit light chain framework 4, which is typically the final 11 amino acid residues of the variable light chain and begins as indicated in Step 7 above and typically ends with the amino acid sequence '...VVKR' (SEQ ID NO: 744) is replaced with the nearest human light chain framework 4 homolog, usually from germline sequence. Frequently this human light chain framework 4 is of the sequence 'FGGGTKVEIKR' (SEQ ID NO: 745). It is possible that other human light chain framework 4 sequences that are not the most homologous or otherwise different may be used without affecting the specificity, affinity and/or immunogenicity of the resulting humanized antibody. This human light chain framework 4 sequence is added to the end of the variable light chain humanized sequence immediately following the CDR3 sequence from Step 7 above. This is now the end of the variable light chain humanized amino acid sequence.

[0425] Example: In Fig. 1, Framework 4 (FR4) of the RbtVL rabbit light chain sequence is shown above a homologous human FR4 sequence. The human FR4 sequence is added to the humanized variable light chain sequence (VLh) right after the end of the CD3 region added in Step 7 above.

[0426] In addition, Figs. 4 and 5 depict preferred humanized anti-IL-6 variable heavy and variable light chain sequences humanized from the variable heavy and light regions in Ab1 according to the invention. These humanized light and heavy chain regions are respectively contained in the polypeptides set forth in SEQ ID NO: 647, or 651 and in SEQ ID NO: 652, 656, 657 or 658. The CDR2 of the humanized variable heavy region in SEQ ID NO: 657 (containing a serine substitution in CDR2) is set forth in SEQ ID NO: 658. Alignments illustrating variants of the light and heavy chains are shown in Figs. 2 and 3, respectively, with sequence differences within the CDR regions highlighted. Sequence identifiers of CDR sequences and of exemplary coding sequences are summarized in Table 4, above.

Heavy Chain

[0427]

1. Identify the amino acid that is the first one following the signal peptide sequence. This is the start of Framework 1. The signal peptide starts at the first initiation methionine and is typically 19 amino acids in length for rabbit heavy chain protein sequences. Typically, but not necessarily always, the final 3 amino acid residues of a rabbit heavy chain signal peptide are '...VQC', followed by the start of Framework 1. The start of the mature polypeptide can also be determined experimentally by N-terminal protein sequencing, or can be predicted using a prediction algorithm.

This is also the start of Framework 1 as classically defined by those in the field.

Example: RbtVH Amino acid residue 1 in Fig. 1, starting 'QEQL...' (SEQ ID NO: 738)

2. Identify the end of Framework 3. This is typically 95-100 amino acids following the start of Framework 1 and typically has the final sequence of '...CAR' (although the alanine can also be a valine). This is the end of the Framework 3 as classically defined by those in the field.

Example: RbtVH amino acid residue 98 in Fig. 1, ending as '...FCVR' (SEQ ID NO: 738).

3. Use the rabbit heavy chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be against a database of human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be found from various sources such as NCBI (National Center for Biotechnology Information).

Example: RbtVH amino acid sequence from residues numbered 1 through 98 in Fig. 1 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Fig. 1 as 3-64-04 (SEQ ID NO: 739), 3-66-04 (SEQ ID NO: 740), and 3-53-02 (SEQ ID NO: 741).

4. Generally the most homologous human germline variable heavy chain sequence is then used as the basis for humanization. However those skilled in the art may decide to use another sequence that wasn't the most homologous as determined by the homology algorithm, based on other factors including sequence gaps and framework similarities.

Example: 3-64-04 in Fig. 1 was the most homologous human germline variable heavy chain sequence and is used as the basis for the humanization of RbtVH.

5. Determine the framework and CDR arrangement (FR1, FR2, FR3, CDR1 & CDR2) for the human homolog being used for the heavy chain humanization. This is using the traditional layout as described in the field. Align the rabbit variable heavy chain sequence with the human homolog, while maintaining the layout of the framework and CDR

regions.

Example: In Fig. 1, the RbtVH sequence is aligned with the human homologous sequence 3-64-04, and the framework and CDR domains are indicated.

6. Replace the human homologous heavy chain sequence CDR1 and CDR2 regions with the CDR1 and CDR2 sequences from the rabbit sequence. If there are differences in length between the rabbit and human CDR sequences then use the entire rabbit CDR sequences and their lengths. In addition, it may be necessary to replace the final three amino acids of the human heavy chain Framework 1 region with the final three amino acids of the rabbit heavy chain Framework 1. Typically but not always, in rabbit heavy chain Framework 1 these three residues follow a Glycine residue preceded by a Serine residue. In addition, it may be necessary replace the final amino acid of the human heavy chain Framework 2 region with the final amino acid of the rabbit heavy chain Framework 2. Typically, but not necessarily always, this is a Glycine residue preceded by an Isoleucine residue in the rabbit heavy chain Framework 2. It is possible that the specificity, affinity and/or immunogenicity of the resulting humanized antibody may be unaltered if smaller or larger sequence exchanges are performed, or if specific residue(s) are altered, however the exchanges as described have been used successfully, but do not exclude the possibility that other changes may be permitted. For example, a tryptophan amino acid residue typically occurs four residues prior to the end of the rabbit heavy chain CDR2 region, whereas in human heavy chain CDR2 this residue is typically a Serine residue. Changing this rabbit tryptophan residue to a the human Serine residue at this position has been demonstrated to have minimal to no effect on the humanized antibody's specificity or affinity, and thus further minimizes the content of rabbit sequence-derived amino acid residues in the humanized sequence.

Example: In Fig. 1, The CDR1 and CDR2 amino acid residues of the human homologous variable heavy chain are replaced with the CDR1 and CDR2 amino acid sequences from the RbtVH rabbit antibody light chain sequence, except for the boxed residue, which is tryptophan in the rabbit sequence (position number 63) and Serine at the same position in the human sequence, and is kept as the human Serine residue. In addition to the CDR1 and CDR2 changes, the final three amino acids of Framework 1 (positions 28-30) as well as the final residue of Framework 2 (position 49) are retained as rabbit amino acid residues instead of human. The resulting humanized sequence is shown below as VHh from residues numbered 1 through 98. Note that the only residues that are different from the 3-64-04 human sequence are underlined, and are thus rabbit-derived amino acid residues. In this example only 15 of the 98 residues are different than the human sequence.

7. After framework 3 of the new hybrid sequence created in Step 6, attach the entire CDR3 of the rabbit heavy chain antibody sequence. The CDR3 sequence can be of various lengths, but is typically 5 to 19 amino acid residues in length. The CDR3 region and the beginning of the following framework 4 region are defined classically and are identifiable by those skilled in the art. Typically the beginning of framework 4, and thus after the end of CDR3 consists of the sequence WGXXG... (where X is usually Q or P) (SEQ ID NO: 746), however some variation may exist in these residues.

Example: The CDR3 of RbtVH (amino acid residues numbered 99-110) is added after the end of framework 3 in the humanized sequence indicated as VHh.

8. The rabbit heavy chain framework 4, which is typically the final 11 amino acid residues of the variable heavy chain and begins as indicated in Step 7 above and typically ends with the amino acid sequence '...TVSS' (SEQ ID NO: 747) is replaced with the nearest human heavy chain framework 4 homolog, usually from germline sequence. Frequently this human heavy chain framework 4 is of the sequence 'WGQGTSLTVSS' (SEQ ID NO: 748). It is possible that other human heavy chain framework 4 sequences that are not the most homologous or otherwise different may be used without affecting the specificity, affinity and/or immunogenicity of the resulting humanized antibody. This human heavy chain framework 4 sequence is added to the end of the variable heavy chain humanized sequence immediately following the CDR3 sequence from Step 7 above. This is now the end of the variable heavy chain humanized amino acid sequence.

[0428] Example: In Fig. 1, framework 4 (FR4) of the RbtVH rabbit heavy chain sequence is shown above a homologous human heavy FR4 sequence. The human FR4 sequence is added to the humanized variable heavy chain sequence (VHh) right after the end of the CD3 region added in Step 7 above.

Additional Exemplary Embodiments of the Invention

[0429] Also described herein are anti-IL-6 antibodies or antibody fragments or variants thereof which may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Ab1 and chimeric, humanized, single chain antibodies and fragments thereof (containing at least one CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated. The anti-IL-6 antibody or fragment or variant thereof may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or con-

formational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as Ab1 and chimeric, humanized, single chain antibodies and fragments thereof (containing at least one CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated.

[0430] The anti-IL-6 antibody which may specifically bind to the same linear or conformational epitopes on an intact IL-6 polypeptide or fragment thereof that is (are) specifically bound by Ab1 may bind to an IL-6 epitope(s) ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide. The IL-6 epitope comprises, or alternatively consists of, at least one residues comprised in IL-6 fragments selected from those respectively encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72.

[0431] Described herein is an anti-IL-6 antibody that binds with the same IL-6 epitope and/or competes with an anti-IL-6 antibody for binding to IL-6 as an antibody or antibody fragment disclosed herein, including but not limited to an anti-IL-6 antibody selected from Ab1 and chimeric, humanized, single chain antibodies and fragments thereof (containing at least one CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated.

[0432] Also described is an isolated anti-IL-6 antibody or antibody fragment or variant thereof comprising at least one of the CDRs contained in the V_H polypeptide sequences comprising: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 652, 656, 657, 658, 661, 664, 665, 668, 672, 676, 680, 684, 688, 691, 692, 704, or 708 and/or at least one of the CDRs contained in the V_L polypeptide sequence consisting of: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 and the VH and VL sequences depicted in the antibody alignments comprised in Figures 1-5 of this application.

[0433] The anti-IL-6 antibody described herein may comprise at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-IL-6 antibody comprising Ab1 and chimeric, humanized, single chain antibodies and fragments thereof (containing at least one CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated.

[0434] The anti-IL-6 antibody described herein may comprise at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in Ab1. In another embodiment, all of the CDRs of the anti-IL-6 antibody discussed above are identical to the CDRs contained in an anti-IL-6 antibody comprising Ab1 and chimeric, humanized, single chain antibodies and fragments thereof (containing at least one CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated. In a preferred embodiment of the invention, all of the CDRs of the anti-IL-6 antibody discussed above are identical to the CDRs contained in Ab1, e.g., an antibody comprised of the VH and VL sequences comprised in SEQ ID NO: 657 and SEQ ID NO: 709 respectively.

[0435] The invention further contemplates that the one or more anti-IL-6 antibodies discussed above are aglycosylated or substantially non-glycosylated (e.g., may contain one or more, e.g., 1-5 mannose residues); that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody. Exemplary constant regions that provide for the production of aglycosylated antibodies in *Pichia* are comprised in SEQ ID NO: 588 and SEQ ID NO: 586 which respectively are encoded by the nucleic acid sequences in SEQ ID NO: 589 and SEQ ID NO: 587.

[0436] The invention further contemplates at least one anti-IL-6 antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of at most 2 or 3 human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

[0437] In one embodiment of the invention, the anti-IL-6 antibody or fragment or variant thereof may specifically bind to IL-6 expressing human cells and/or to circulating soluble IL-6 molecules *in vivo*, including IL-6 expressed on or by human cells in a patient with a disease associated with cells that express IL-6.

[0438] The invention further contemplates anti-IL-6 antibodies or fragments or variants thereof directly or indirectly attached to a detectable label or therapeutic agent.

[0439] Also described are nucleic acid sequences which result in the expression of an anti-IL-6 antibody or antibody fragment or variant thereof as set forth above, including those comprising, or alternatively consisting of, yeast or human preferred codons. Further described are vectors (including plasmids or recombinant viral vectors) comprising said nucleic acid sequence(s). Also described are host cells or recombinant host cells expressing at least one of the antibodies set forth above, including a mammalian, yeast, bacterial, and insect cells. The host cell may be a yeast cell. The yeast cell may be a diploidal yeast cell. The yeast cell may be a *Pichia* yeast.

[0440] Described herein is a method of treatment comprising administering to a patient with a disease or condition

associated with mucositis a therapeutically effective amount of at least one anti-IL-6 antibody or antibody fragment or variant thereof. The diseases that may be treated are presented in the non-limiting list set forth above. The treatment further includes the administration of another therapeutic agent or regimen selected from chemotherapy, radiotherapy, cytokine administration or gene therapy agent. For example, TNF- α inhibitors including but not limited to glyococorticoids, triamcinolone, dexamethasone, prednisone, may also be administered sequentially or subsequently with at least one anti-IL-6 antibody or antibody fragment or variant thereof described herein. Further examples of drugs that may be included with the IL-6 antagonists include but are not limited to ARISTOCORT® (triamcinolone), BAYCADROM® (dexamethasone), DECADRON® (dexamethasone), DELTASONE® (prednisone), DEXAMETHASONE INTENSOL® (dexamethasone), ENBREL® (etanercept), HUMIRA® (adalimumab), REMICADE® (infliximab), RIDUARA® (aruaofin), and SIMPONI® (golimumab).

Exemplary Embodiments of Heavy and Light Chain Polypeptides and Polynucleotides

[0441] This section recites exemplary embodiments of heavy and light chain polypeptides, as well as exemplary polynucleotides encoding such polypeptides. These exemplary polynucleotides are suitable for expression in the disclosed *Pichia* expression system.

[0442] Described herein are polynucleotides having at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity (sequence homology) to the polynucleotides recited in this application or that encode polypeptides recited in this application, or that hybridize to said polynucleotides under conditions of low-stringency, moderate-stringency, or high-stringency conditions, preferably those that encode polypeptides (e.g. an immunoglobulin heavy and light chain, a single-chain antibody, an antibody fragment) that have at least one of the biological activities set forth herein, including without limitation thereto specific binding to an IL-6 polypeptide. Described herein is a composition comprising such a polynucleotide and/or a polypeptide encoded by such a polynucleotide. Also described herein is a method of treatment of a disease or condition associated with IL-6 or that may be prevented, treated, or ameliorated with an IL-6 antagonist such as Ab1 (e.g. mucositis) comprising administration of a composition comprising such a polynucleotide and/or polypeptide.

[0443] Described herein is a heavy chain polypeptide that comprises at least one of the CDR sequences of the heavy and/or light chain polypeptides recited herein (including those contained in the heavy and light chain polypeptides recited herein) and at least one of the framework region polypeptides recited herein, including those depicted in FIGS. 1-5 or Table 4, and contained in the heavy and light chain polypeptide sequences recited herein. A heavy chain polypeptide may comprise at least one Framework 4 region sequences as depicted in FIGS. 1-5 or Table 4, or as contained in a heavy or light chain polypeptide recited herein.

[0444] A light chain polypeptide may comprise at least one of the CDR sequences of the heavy and/or light chain polypeptides recited herein (including those contained in the heavy and light chain polypeptides recited herein) and at least one of the Framework region polypeptides recited herein, including those depicted in FIGS. 1-5 or Table 4, and contained in the heavy and light chain polypeptide sequences recited herein. A light chain polypeptide may comprise at least one Framework 4 region sequences as depicted in FIGS. 1-5 or Table 4, or as contained in a heavy or light chain polypeptide recited herein.

[0445] Certain sequences recited may be substituted for each other, unless the context indicates otherwise. The recitation that particular sequences may be substituted for one another, where such recitations are made, are understood to be illustrative rather than limiting, and it is also understood that such substitutions are encompassed even when no illustrative examples of substitutions are recited. For example, wherever at least one of the Ab1 light chain polypeptides is recited, e.g. any of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709, another Ab1 light chain polypeptide may be substituted unless the context indicates otherwise. Similarly, wherever one of the Ab1 heavy chain polypeptides is recited, e.g. any of SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708, another Ab1 heavy chain polypeptide may be substituted unless the context indicates otherwise. Likewise, wherever one of the Ab1 light chain polynucleotides is recited, e.g. any of SEQ ID NO: 10, 662, 698, 701, or 705, another Ab1 light chain polynucleotide may be substituted unless the context indicates otherwise. Similarly, wherever one of the Ab1 heavy chain polynucleotides is recited, e.g. any of SEQ ID NO: 11, 663, 700, 703, or 707, another Ab1 heavy chain polynucleotide may be substituted unless the context indicates otherwise.

[0446] Additionally, recitation of any member of any of the following groups is understood to encompass substitution by any other member of the group, as follows: Ab2 Light chain polypeptides (SEQ ID NO: 21 and 667); Ab2 Light chain polynucleotides (SEQ ID NO: 29 and 669); Ab2 Heavy chain polypeptides (SEQ ID NO: 22 and 668); Ab2 Heavy chain polynucleotides (SEQ ID NO: 30 and 670); Ab3 Light chain polypeptides (SEQ ID NO: 37 and 671); Ab3 Light chain polynucleotides (SEQ ID NO: 45 and 673); Ab3 Heavy chain polypeptides (SEQ ID NO: 38 and 672); Ab3 Heavy chain polynucleotides (SEQ ID NO: 46 and 674); Ab4 Light chain polypeptides (SEQ ID NO: 53 and 675); Ab4 Light chain polynucleotides (SEQ ID NO: 61 and 677); Ab4 Heavy chain polypeptides (SEQ ID NO: 54 and 676); Ab4 Heavy chain polynucleotides (SEQ ID NO: 62 and 678); Ab5 Light chain polypeptides (SEQ ID NO: 69 and 679); Ab5 Light chain

polynucleotides (SEQ ID NO: 77 and 681); Ab5 Heavy chain polypeptides (SEQ ID NO: 70 and 680); Ab5 Heavy chain polynucleotides (SEQ ID NO: 78 and 682); Ab6 Light chain polypeptides (SEQ ID NO: 85 and 683); Ab6 Light chain polynucleotides (SEQ ID NO: 93 and 685); Ab6 Heavy chain polypeptides (SEQ ID NO: 86 and 684); Ab6 Heavy chain polynucleotides (SEQ ID NO: 94 and 686); Ab7 Light chain polypeptides (SEQ ID NO: 101, 119, 687, 693); Ab7 Light chain polynucleotides (SEQ ID NO: 109 and 689); Ab7 Heavy chain polypeptides (SEQ ID NO: 102, 117, 118, 688, 691, and 692); Ab7 Heavy chain polynucleotides (SEQ ID NO: 110 and 690); Ab1 Light Chain CDR1 polynucleotides (SEQ ID NO: 12 and 694); Ab1 Light Chain CDR3 polynucleotides (SEQ ID NO: 14 and 695); Ab1 Heavy Chain CDR2 polynucleotides (SEQ ID NO: 16 and 696) and Ab1 Heavy Chain CDR3 polynucleotides (SEQ ID NO: 17 and 697). Exemplary Ab1-encoding polynucleotide sequences include but are not limited to SEQ ID NO: 662, 663, 698, 700, 701, 703, 705, 707, 720, 721, 722, 723, 724, and 725.

ANTI-IL-6 ACTIVITY

[0447] As stated previously, IL-6 is a member of a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 and the IL-6 receptor (IL-6R). The IL-6R may also be present in a soluble form (sIL-6R). IL-6 binds to IL-6R, which then dimerizes the signal-transducing receptor gp130.

[0448] It is believed that the anti-IL-6 antibodies for use according to the invention, or IL-6 binding fragments or variants thereof, are useful by exhibiting anti-IL-6 activity. In one non-limiting embodiment of the invention, the anti-IL-6 antibodies for use according to the invention, or IL-6 binding fragments or variants thereof, exhibit anti-IL-6 activity by binding to IL-6 which may be soluble IL-6 or cell surface expressed IL-6 and/or may prevent or inhibit the binding of IL-6 to IL-6R and/or activation (dimerization) of the gp130 signal-transducing glycoprotein and the formation of IL-6/IL-6R/gp130 multimers and the biological effects of any of the foregoing. The subject anti-IL-6 antibodies may possess different antagonistic activities based on where (*i.e.*, epitope) the particular antibody binds IL-6 and/or how it affects the formation of the foregoing IL-6 complexes and/or multimers and the biological effects thereof. Consequently, different anti-IL-6 antibodies for use according to the invention *e.g.*, may be better suited for preventing or treating conditions involving the formation and accumulation of substantial soluble IL-6 such as rheumatoid arthritis whereas other antibodies may be favored in treatments wherein the prevention of IL-6/IL-6R/gp130 or IL-6/IL-6R/gp130 multimers is a desired therapeutic outcome. This can be determined in binding and other assays.

[0449] The anti-IL-6 activity of the anti-IL-6 antibody for use according to the present invention, and fragments and variants thereof having binding specificity to IL-6, may also be described by their strength of binding or their affinity for IL-6. This also may affect their therapeutic properties. In one embodiment of the invention, the anti-IL-6 antibodies and fragments thereof having binding specificity to IL-6, bind to IL-6 with a dissociation constant (K_D) of less than or equal to 5×10^{-7} , 10^{-7} , 5×10^{-8} , 10^{-8} , 5×10^{-9} , 10^{-9} , 5×10^{-10} , 10^{-10} , 5×10^{-11} , 10^{-11} , 5×10^{-12} , 10^{-12} , 5×10^{-13} , 10^{-13} , 5×10^{-14} , 10^{-14} , 5×10^{-15} or 10^{-15} . Preferably, the anti-IL-6 antibodies and fragments and variants thereof bind IL-6 with a dissociation constant of less than or equal to 5×10^{-10} .

[0450] In another embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies and fragments and variants thereof having binding specificity to IL-6, bind to IL-6 with an off-rate of less than or equal to 10^{-4} s^{-1} , $5 \times 10^{-5} \text{ s}^{-1}$, 10^{-5} s^{-1} , $5 \times 10^{-6} \text{ s}^{-1}$, 10^{-6} s^{-1} , $5 \times 10^{-7} \text{ s}^{-1}$, or 10^{-7} s^{-1} . In one embodiment of the invention, the anti-IL-6 antibodies and fragments and variants thereof having binding specificity to IL-6, bind to a linear or conformational IL-6 epitope.

[0451] In a further embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies and fragments and variants thereof having binding specificity to IL-6, exhibit anti-IL-6 activity by ameliorating or reducing the symptoms of, or alternatively treating, or preventing, diseases and disorders associated with IL-6. Non-limiting examples of diseases and disorders associated with IL-6 are set forth *infra*. In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments and variants thereof, do not have binding specificity for IL-6R or the gp-130 signal-transducing glycoprotein.

SCREENING ASSAYS

[0452] Also described herein are screening assays designed to assist in the identification of diseases and disorders associated with IL-6 in patients exhibiting symptoms of an IL-6 associated disease or disorder, especially mucositis.

[0453] The anti-IL-6 antibodies or IL-6 binding fragments or variants thereof, are used to detect the presence of IL-6 in a biological sample obtained from a patient exhibiting symptoms of a disease or disorder associated with IL-6. The presence of IL-6, or elevated levels thereof when compared to pre-disease levels of IL-6 in a comparable biological sample, may be beneficial in diagnosing a disease or disorder associated with IL-6.

[0454] Also described is a diagnostic or screening assay to assist in diagnosis of diseases or disorders associated with IL-6 in patients exhibiting symptoms of an IL-6 associated disease or disorder identified herein, comprising assaying the level of IL-6 expression in a biological sample from said patient using a post-translationally modified anti-IL-6 antibody

or binding fragment or variant thereof. The anti-IL-6 antibody or binding fragment or variant thereof may be post-translationally modified to include a detectable moiety such as set forth previously in the disclosure.

[0455] The IL-6 level in the biological sample is determined using a modified anti-IL-6 antibody or binding fragment or variant thereof as set forth herein, and comparing the level of IL-6 in the biological sample against a standard level of IL-6 (e.g., the level in normal biological samples). The skilled clinician would understand that some variability may exist between normal biological samples, and would take that into consideration when evaluating results.

[0456] The above-recited assay may also be useful in monitoring a disease or disorder, where the level of IL-6 obtained in a biological sample from a patient believed to have an IL-6 associated disease or disorder is compared with the level of IL-6 in prior biological samples from the same patient, in order to ascertain whether the IL-6 level in said patient has changed with, for example, a treatment regimen. A skilled clinician would understand that a biological sample includes, but is not limited to, sera, plasma, urine, saliva, mucous, pleural fluid, synovial fluid and spinal fluid.

[0457] The IL-6 antagonists described herein, including the anti-IL-6 antibodies (e.g., Ab1 antibody) may be used in methods of studying mucositis. For example, the IL-6 antagonists described herein, including the anti-IL-6 antibodies (e.g., Ab1 antibody), may be compared to other therapeutic agents, both known and experimental, to test for effectiveness in treating mucositis. See Bowen, et al. (2011) J Support Oncol. 9(5): 161-8.

FUSION PROTEINS

[0458] Fusion proteins comprising IL-6 antagonists are also described herein. Fusions comprising the anti-IL-6 antibodies polypeptides are also within the scope of the present disclosure. For example, the fusion protein may be linked to a GST fusion protein in which the anti-IL-6 antibodies polypeptide sequences are fused to the C-terminus of the GST sequences. Such fusion proteins may facilitate the purification of the recombinant Anti-IL-6 antibodies polypeptides. Alternatively, anti-IL-6 antibodies polypeptides may be fused with a protein that binds B-cell follicles, thus initiating both a humoral immune response and activation of T cells. Berney, et al. (1999) J. Exp. Med. 190: 851-60. Alternatively, for example, the Anti-IL-6 antibodies polypeptides may be genetically coupled with and anti-dendritic cell antibody to deliver the antigen to the immune system and stimulate a cellular immune response. He, et al. (2004) Clin. Cancer Res. 10: 1920-27. A chimeric or fusion protein of the invention may be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, e.g., by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. The fusion gene may be synthesized by conventional techniques including automated DNA synthesizers.

[0459] Fusion proteins may include C-terminal or N-terminal translocation sequences. Further, fusion proteins can comprise additional elements, e.g., for protein detection, purification, or other applications. Detection and purification facilitating domains including but not limited to metal chelating peptides such as polyhistidine tracts, histidine-tryptophan modules, or other domains that allow purification on immobilized metals; maltose binding protein; protein A domains that allow purification on immobilized immunoglobulin; or the domain utilized in the FLAG extension/affinity purification system (Immunex Corp, Seattle WA.)

[0460] A fusion protein may be prepared from a protein of the disclosure by fusion with a portion of an immunoglobulin comprising a constant region of an immunoglobulin. More preferably, the portion of the immunoglobulin comprises a heavy chain constant region which is optionally and more preferably a human heavy chain constant region. The heavy chain constant region is most preferably an IgG heavy chain constant region, and optionally and most preferably is an Fc chain, most preferably an IgG Fc fragment that comprises CH2 and CH3 domains. Although any IgG subtype may optionally be used, the IgG1 subtype is preferred. The Fc chain may optionally be a known or "wild type" Fc chain, or alternatively may be mutated. See, e.g., U.S. Patent Application Publication No. 2006/0034852. The term "Fc chain" also optionally comprises any type of Fc fragment. Several of the specific amino acid residues that are involved in antibody constant region-mediated activity in the IgG subclass have been identified. Inclusion, substitution or exclusion of these specific amino acids therefore allows for inclusion or exclusion of specific immunoglobulin constant region-mediated activity. Furthermore, specific changes may result in aglycosylation for example and/or other desired changes to the Fc chain. At least some changes may optionally be made to block a function of Fc which is considered to be undesirable, such as an undesirable immune system effect. See McCafferty, et al. (2002) Antibody Engineering: A Practical Approach (Eds.) Oxford University Press.

[0461] The inclusion of a cleavable linker sequences such as Factor Xa (see, e.g., Ottavi, (1998) Biochimie 80: 289-93), subtilisin protease recognition motif (see, e.g., Polyak (1997) Protein Eng. 10: 615-19); enterokinase (Invitrogen, San Diego, CA.), between the translocation domain (for efficient plasma membrane expression) and the rest of the newly translated polypeptide may be useful to facilitate purification. For example, one construct can include a polypeptide encoding a nucleic acid sequence linked to six histidine residues followed by a thioredoxin, an enterokinase cleavage site (see, e.g., Williams (1995) Biochemistry 34: 1787-97), and an C-terminal translocation domain. The histidine residues

facilitate detection and purification while the enterokinase cleavage site provides a means for purifying the desired protein(s) from the remainder of the fusion protein. Technology pertaining to vectors encoding fusion proteins and application of fusion proteins are well described in the art. See, e.g., Kroll (1993) DNA Cell. Biol. 12: 441-53.

5 CONJUGATES

[0462] IL-6 antagonists may be conjugated to other moieties (e.g., conjugates). Further, the anti-IL-6 antibodies, antibodies that bind the Anti-IL-6 antibodies and fragments thereof, may be conjugated to other moieties. Such conjugates are often used in the preparation of vaccines. The anti-IL-6 antibodies polypeptide may be conjugated to a carbohydrate (e.g., mannose, fucose, glucose, GlcNAs, maltose), which is recognized by the mannose receptor present on dendritic cells and macrophages. The ensuing binding, aggregation, and receptor-mediated endocytosis and phagocytosis functions provide enhanced innate and adaptive immunity. See Mahnke, et al. (2000) J. Cell Biol. 151: 673-84; Dong, et al. (1999) J. Immunol. 163: 5427-34. Other moieties suitable for conjugation to elicit an immune response includes but not limited to Keyhole Limpet Hemocyanin (KLH), diphtheria toxoid, cholera toxoid, Pseudomonas exoprotein A, and microbial outer membrane proteins (OMPS).

LABELS

[0463] As stated above, antibodies and fragments and variants thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0464] The anti-IL-6 antibodies and antibody fragments thereof described herein may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties, a cytotoxic agent, radioactive materials, or functional moieties.

[0465] A wide variety of entities, e.g., ligands, may be coupled to the oligonucleotides as known in the art. Ligands may include naturally occurring molecules, or recombinant or synthetic molecules. Exemplary ligands include, but are not limited to, avadin, biotin, peptides, peptidomimetics, polylysine (PLL), polyethylene glycol (PEG), mPEG, cationic groups, spermine, spermidine, polyamine, thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, mucin, glycosylated polyaminoacids, transferrin, aptamer, immunoglobulins (e.g., antibodies), insulin, transferrin, albumin, sugar, lipophilic molecules (e.g., steroids, bile acids, cholesterol, cholic acid, and fatty acids), vitamin A, vitamin E, vitamin K, vitamin B, folic acid, B12, riboflavin, biotin, pyridoxal, vitamin cofactors, lipopolysaccharide, hormones and hormone receptors, lectins, carbohydrates, multivalent carbohydrates, radiolabeled markers, fluorescent dyes, and derivatives thereof. See, e.g., U.S. Patent Nos. 6,153, 737; 6,172,208; 6,300,319; 6,335,434; 6,335,437; 6,395,437; 6,444,806; 6,486,308; 6,525,031; 6,528,631; and 6,559, 279.

[0466] Additionally, moieties may be added to the antigen or epitope to increase half-life *in vivo* (e.g., by lengthening the time to clearance from the blood stream. Such techniques include, for example, adding PEG moieties (also termed pegylation), and are well-known in the art. See U.S. Patent Application Publication No. 2003/0031671.

[0467] An anti-IL-6 antibody or antigen binding fragment thereof, described herein may be "attached" to a substrate when it is associated with the solid label through a non-random chemical or physical interaction. The attachment may be through a covalent bond. However, attachments need not be covalent or permanent. Materials may be attached to a label through a "spacer molecule" or "linker group." Such spacer molecules are molecules that have a first portion that attaches to the biological material and a second portion that attaches to the label. Thus, when attached to the label, the spacer molecule separates the label and the biological materials, but is attached to both. Methods of attaching biological material (e.g., label) to a label are well known in the art, and include but are not limited to chemical coupling.

Detectable Labels

[0468] The anti-IL-6 antibody or antibody fragments described herein may be modified post-translationally to add effector labels such as chemical linkers, detectable labels such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent labels, or functional labels such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials. Further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, β -galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent labels include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, bismuth-213 (^{213}Bs),

carbon-14 (^{14}C), carbon-11 (^{11}C), chlorine-18 (^{18}Cl), chromium-51 (^{51}Cr), cobalt-57 (^{57}Co), cobalt-60 (^{60}Co), copper-64 (^{64}Cu), copper-67 (^{67}Cu), dysprosium-165 (^{165}Dy), erbium-169 (^{169}Er), fluorine-18 (^{18}F), gallium-67 (^{67}Ga), gallium-68 (^{68}Ga), germanium-68 (^{68}Ge), holmium-166 (^{166}Ho), indium-111 (^{111}In), iodine-125 (^{125}I), iodine-123 (^{124}I), iodine-124 (^{124}I), iodine-131 (^{131}I), iridium-192 (^{192}Ir), iron-59 (^{59}Fe), krypton-81 (^{81}Kr), lead-212 (^{212}Pb), lutetium-177 (^{177}Lu), molybdenum-99 (^{99}Mo), nitrogen-13 (^{13}N), oxygen-15 (^{15}O), palladium-103 (^{103}Pd), phosphorus-32 (^{32}P), potassium-42 (^{42}K), rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), rubidium-81 (^{81}Rb), rubidium-82 (^{82}Rb), samarium-153 (^{153}Sm), selenium-75 (^{75}Se), sodium-24 (^{24}Na), strontium-82 (^{82}Sr), strontium-89 (^{89}Sr), sulfur 35 (^{35}S), technetium-99m (^{99}Tc), thallium-201 (^{201}Tl), tritium (^3H), xenon-133 (^{133}Xe), ytterbium-169 (^{169}Yb), ytterbium-177 (^{177}Yb), and yttrium-90 (^{90}Y).

Cytotoxic Agents

[0469] The anti-IL-6 antibodies and antibody fragments described herein may be conjugated to cytotoxic agents including, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclophosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimetabolic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (TAXOL®), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, teniposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytostane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0470] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine, bleomycin, VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcitabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids (e.g., vinblastine, vincristine, vindesine and vinorelbine), mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1 antagonists, interleukins (e.g. IL-12 or IL-2), IL-12R antagonists, Erbitux®, Avastin®, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and Pseudomonas toxin may be conjugated to the humanized antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents. Youle, et al. (1980) Proc. Nat'l Acad. Sci. USA 77: 5483; Gilliland, et al. (1980) Proc. Nat'l Acad. Sci. USA 77: 4539; Krolick, et al. (1980) Proc. Nat'l Acad. Sci. USA 77: 5419. Other cytotoxic agents include cytotoxic ribonucleases. See U.S. Patent No. 6,653,104.

[0471] The anti-IL-6 antibodies and antibody fragments described herein may be conjugated to a radionuclide that emits alpha or beta particles (e.g., radioimmunoconjugates). Such radioactive isotopes include but are not limited to beta-emitters such as phosphorus-32 (^{32}P), scandium-47 (^{47}Sc), copper-67 (^{67}Cu), gallium-67 (^{67}Ga), yttrium-88 (^{88}Y), yttrium-90 (^{90}Y), iodine-125 (^{125}I), iodine-131 (^{131}I), samarium-153 (^{153}Sm), lutetium-177 (^{177}Lu), rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), and alpha-emitters such as astatine-211 (^{211}At), lead-212 (^{212}Pb), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi) or actinium-225 (^{225}Ac).

[0472] Methods are known in the art for conjugating an anti-IL-6 antibody described herein to a label, such as those methods described by Hunter, et al. (1962) Nature 144: 945; David, et al. (1974) Biochemistry 13: 1014; Pain, et al. (1981) J. Immunol. Meth. 40: 219; and Nygren (1982) Histochem and Cytochem 30: 407.

SUBSTRATES

[0473] The anti-IL-6 antibodies and antibody fragments thereof described herein may be attached to a substrate. A number of substrates (e.g., solid supports) known in the art are suitable for use with the anti-IL-6 antibody described herein. The substrate may be modified to contain channels or other configurations. See Fung (2004) [Ed.] Protein Arrays: Methods and Protocols Humana Press and Kambhampati (2004) [Ed.] Protein Microarray Technology John Wiley & Sons.

[0474] Substrate materials include, but are not limited to acrylics, agarose, borosilicate glass, carbon (e.g., carbon nanofiber sheets or pellets), cellulose acetate, cellulose, ceramics, gels, glass (e.g., inorganic, controlled-pore, modified, soda-lime, or functionalized glass), latex, magnetic beads, membranes, metal, metalloids, nitrocellulose, NYLON®, optical fiber bundles, organic polymers, paper, plastics, polyacryloylmorpholide, poly(4-methylbutene), poly(ethylene terephthalate), poly(vinyl butyrate), polyacrylamide, polybutylene, polycarbonate, polyethylene, polyethyleneglycol terephthalate, polyformaldehyde, polymethacrylate, polymethylmethacrylate, polypropylene, polysaccharides, polystyrene, polyurethanes, polyvinylacetate, polyvinylchloride, polyvinylidene difluoride (PVDF), polyvinylpyrrolidinone, rayon,

resins, rubbers, semiconductor materials, sepharose®, silica, silicon, styrene copolymers, TEFLON®, and variety of other polymers.

[0475] Substrates need not be flat and can include any type of shape including spherical shapes (e.g., beads) or cylindrical shapes (e.g., fibers). Materials attached to solid supports may be attached to any portion of the solid support (e.g., may be attached to an interior portion of a porous solid support material).

[0476] The substrate body may be in the form of a bead, box, column, cylinder, disc, dish (e.g., glass dish, PETRI dish), fiber, film, filter, microtiter plate (e.g., 96-well microtiter plate), multi-bladed stick, net, pellet, plate, ring, rod, roll, sheet, slide, stick, tray, tube, or vial. The substrate may be a singular discrete body (e.g., a single tube, a single bead), any number of a plurality of substrate bodies (e.g., a rack of 10 tubes, several beads), or combinations thereof (e.g., a tray comprises a plurality of microtiter plates, a column filled with beads, a microtiter plate filled with beads).

[0477] An anti-IL-6 antibody or antibody fragment thereof may be "attached" to a substrate when it is associated with the solid substrate through a non-random chemical or physical interaction. The attachment may be through a covalent bond. However, attachments need not be covalent or permanent. Materials may be attached to a substrate through a "spacer molecule" or "linker group." Such spacer molecules are molecules that have a first portion that attaches to the biological material and a second portion that attaches to the substrate. Thus, when attached to the substrate, the spacer molecule separates the substrate and the biological materials, but is attached to both. Methods of attaching biological material (e.g., label) to a substrate are well known in the art, and include but are not limited to chemical coupling.

[0478] Plates, such as microtiter plates, which support and contain the solid-phase for solid-phase synthetic reactions may be used. Microtiter plates may house beads that are used as the solid-phase. By "particle" or "microparticle" or "nanoparticle" or "bead" or "microbead" or "microsphere" herein is meant microparticulate matter having any of a variety of shapes or sizes. The shape may be generally spherical but need not be spherical, being, for example, cylindrical or polyhedral. As will be appreciated by those in the art, the particles may comprise a wide variety of materials depending on their use, including, but not limited to, cross-linked starch, dextrans, cellulose, proteins, organic polymers including styrene polymers such as polystyrene and methylstyrene as well as other styrene co-polymers, plastics, glass, ceramics, acrylic polymers, magnetically responsive materials, colloids, thoriasol, carbon graphite, titanium dioxide, nylon, latex, and TEFLON®. See e.g., "Microsphere Detection Guide" from Bangs Laboratories, Fishers, IN.

[0479] The anti-IL-6 antibody or antibody fragment may be attached to on any of the forms of substrates described herein (e.g., bead, box, column, cylinder, disc, dish (e.g., glass dish, PETRI dish), fiber, film, filter, microtiter plate (e.g., 96-well microtiter plate), multi-bladed stick, net, pellet, plate, ring, rod, roll, sheet, slide, stick, tray, tube, or vial). In particular, particles or beads may be a component of a gelling material or may be separate components such as latex beads made of a variety of synthetic plastics (e.g., polystyrene). The label (e.g., streptavidin) may be bound to a substrate (e.g., bead).

ASSESSMENT OF INFLAMMATORY MARKERS

[0480] Known inflammatory markers (e.g., IL-6) may be measured to assess the risk for mucositis or the severity of mucositis. These markers may be measured from serum, synovial fluid, or skin biopsies using known methods in the art (e.g., immunassays).

IL-6 Serum Levels

[0481] Serum IL-6 levels may be measured as a pharmacodynamic marker evaluate the effect of neutralization of IL-6 levels. Serum IL-6 levels may be measured using an immunoassay (e.g., ELISA assay). A decrease of serum IL-6 levels may be indicative of a lessening of inflammation.

Serum Inflammatory Biomarkers

[0482] Serum biomarkers may be measured to determine the expression of pro-inflammatory cytokines and other soluble biomarkers that may correlate with mucositis (e.g., oral, alimeniary, or gastrointestinal tract mucositis) disease activity including but not limited to acute phase reactants, serum pro-inflammatory cytokines (e.g., IL-1, TNF- α , IFN- γ , IL-12p40, IL-17), chemokines (e.g., RANTES, MIP-1 α , MCP-1), matrix metalloproteinases (e.g., MMP-2, MMP-3, MMP-9) and other biomarkers associated with inflammation and autoimmune pathways that are known in the art. Soluble biomarkers of bone and cartilage metabolism (e.g., osteocalcin and other collagen degradation products) may also be assessed by an immunoassay (e.g., ELISA). A decrease in a serum inflammatory biomark may be indicative of a lessening of inflammation.

Immunohistochemistry of Skin Biopsies

[0483] Skin biopsies may be collected for biomarker analysis including whole genome array analysis and immunohistochemistry (IHC). Immunohistochemical analysis may include the measurement of epidermal thickness, frequency of resident and inflammatory cell populations (e.g., T cells, macrophages, keratinocytes) and other inflammatory markers related to the IL-6 pathway known in the art. Specifically, the following specific antigens may be assessed per standard IHC procedure using the formalin-fixed samples: CD3, CD68, keratin 16, FoxP3, IL-6R and MMP-3. A decrease in an inflammatory biomarker in a skin biopsy may be indicative of a lessening of inflammation.

ADMINISTRATION

[0484] The anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, may be administered to a subject at a concentration of between about 0.1 and 20 mg/kg, such as about 0.4 mg/kg, about 0.8 mg/kg, about 1.6 mg/kg, or about 4 mg/kg, of body weight of recipient subject. For example, compositions comprising the IL-6 antagonists described herein may comprise at least about 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, or 500 mg. For example, compositions comprising the anti-IL-6 antibodies described herein may comprise at least about 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, or 500 mg.

[0485] For example, a composition for treating mucositis may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating oral mucositis may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating mucositis associated with chemotherapy may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating oral mucositis associated with chemotherapy may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating mucositis associated with radiotherapy may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating oral mucositis associated with radiotherapy may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating mucositis associated with cancer may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). A composition for treating oral mucositis associated with cancer may comprise 80, 160, or 320 mg of an anti-IL-6 antibody (e.g., Ab1). For example, compositions comprising the anti-IL-6 antibodies described herein may comprise at least about 0.5-10 mg/kg of the anti-IL-6 antibody. The anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, may be administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject. The anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, may be administered to a recipient subject with a frequency of once every twenty-six weeks or less, such as once every sixteen weeks or less, once every eight weeks or less, or once every four weeks, or less. The anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations thereof, may be administered to a recipient subject with a frequency at most once per period of approximately one week, such as at most once per period of approximately two weeks, such as at most once per period of approximately four weeks, such as at most once per period of approximately eight weeks, such as at most once per period of approximately twelve weeks, such as at most once per period of approximately sixteen weeks, such as at most once per period of approximately twenty-four weeks.

[0486] The compositions described herein may be administered in any of the following routes: buccal, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. The preferred routes of administration are intravenous injection or infusion. The administration can be local, where the composition is administered directly, close to, in the locality, near, at, about, or in the vicinity of, the site(s) of disease, e.g., local (joint) or systemic, wherein the composition is given to the patient and passes through the body widely, thereby reaching the site(s) of disease. Local administration (e.g., subcutaneous injection) may be accomplished by administration to the cell, tissue, organ, and/or organ system, which encompasses and/or is affected by the disease, and/or where the disease signs and/or symptoms are active or are likely to occur (e.g., swollen joint). Administration can be topical with a local effect, composition is applied directly where its action is desired (e.g., joint). Further, administration of a composition comprising an effective amount of an anti-IL-6 antibody selected from the group consisting of Ab1-Ab36 or an antibody fragment thereof, may be subcutaneous.

[0487] The compounds can be administered by a variety of dosage forms as known in the art. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, chewable tablets, quick dissolve tablets, effervescent tablets,

reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, tablets, multi-layer tablets, bi-layer tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, beads, powders, gum, granules, particles, microparticles, dispersible granules, cachets, douches, suppositories, creams, topicals, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, ingestibles, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0488] Other compounds which can be included by admixture are, for example, medically inert ingredients (e.g., solid and liquid diluent), such as lactose, dextrose, saccharose, cellulose, starch or calcium phosphate for tablets or capsules, olive oil or ethyl oleate for soft capsules and water or vegetable oil for suspensions or emulsions; lubricating agents such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate, binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinylpyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescent mixtures; dyestuff; sweeteners; wetting agents such as lecithin, polysorbates or laurylsulphates; and other therapeutically acceptable accessory ingredients, such as humectants, preservatives, buffers and antioxidants, which are known additives for such formulations.

[0489] Liquid dispersions for oral administration can be syrups, emulsions, solutions, or suspensions. The syrups can contain as a carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. The suspensions and the emulsions can contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

[0490] Also described are kits including at least one containers comprising pharmaceutical dosage units comprising an effective amount of at least one antibodies and fragments thereof of the present invention. Kits may include instructions, directions, labels, marketing information, warnings, or information pamphlets.

Dosages

[0491] The amount of anti-IL-6 antibodies in a therapeutic composition according to any embodiments of this invention may vary according to factors such as the disease state, age, gender, weight, patient history, risk factors, predisposition to disease, administration route, pre-existing treatment regime (e.g., possible interactions with other medications), and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of therapeutic situation.

[0492] For example, for the treatment of mucositis (e.g., oral, esophageal, alimentary, and gastrointestinal tract mucositis) a composition may comprise at least about 80, 160, or 320 mg IL-6 antagonists may be administered to a patient in need thereof. In another embodiment, for the treatment of oral mucositis a composition may comprise at least about 80, 160, or 320 mg IL-6 antagonists may be administered to a patient in need thereof. Further, for the treatment of mucositis a composition may comprise at least about 80, 160, or 320 mg anti-IL-6 antibody (e.g., Ab1) may be administered to a patient in need thereof. In another embodiment, for the treatment of oral mucositis a composition may comprise at least about 80, 160, or 320 mg anti-IL-6 antibody (e.g., Ab1) may be administered to a patient in need thereof. The dosage of IL-6 antagonist, may depend upon the mode of administration. For example, for subcutaneous administration of a composition may comprise an IL-6 antagonist, the composition may comprise at least about 1-500 mg/mL, 10-250 mg/mL, 10-100 mg/mL, or 40-100 mg/mL of an IL-antagonist. For example, a composition for subcutaneous administration may comprise at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/mL of an IL-6 antagonist. Thus, a composition for subcutaneous administration may comprise at least about at least about 1-500 mg/mL, 10-250 mg/mL, 10-100 mg/mL, or 40-100 mg/mL of an anti-IL-6 antibody (e.g., Ab1). or at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/mL of an anti-IL-6 antibody (e.g., Ab1). For intravenous administration of a composition may comprise an IL-6 antagonist, the composition may comprise at least about 1-500 mg/mL, 10-250 mg/mL, 10-100 mg/mL, or 40-100 mg/mL of an IL-antagonist. For example, a composition for intravenous administration may comprise at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/mL of an IL-6 antagonist. Thus, a composition for intravenous administration may comprise at least about at least about 1-500 mg/mL, 10-250 mg/mL, 10-100 mg/mL, or 40-100 mg/mL of an anti-IL-6 antibody (e.g., Ab1) or at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/mL of an anti-IL-6 antibody (e.g., Ab1). The mucositis may be associated with chemotherapy, radiotherapy, cancer, or hematopoietic stem cell transplants. For example, the oral mucositis may be associated with chemotherapy, radiotherapy, cancer, or hematopoietic stem cell transplants.

[0493] For example, a composition for the treatment of alimentary tract mucositis may comprise at least about 80, 160, or 320 mg IL-6 antagonists may be administered to a patient in need thereof. Further, a composition for the treatment of alimentary tract mucositis may comprise at least about 80, 160, or 320 mg anti-IL-6 antibody (e.g., Ab1) may be administered to a patient in need thereof. For example, a composition for the treatment of alimentary tract mucositis formulated for subcutaneous administration may comprise at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/mL of an IL-6 antagonist. Thus, a composition for the treatment of alimentary tract mucositis formulated for subcutaneous

of an IL-6 antagonist. Thus, a composition for the treatment of diarrhea formulated for intravenous administration may comprise at least about 1-500 mg/mL, 10-250 mg/mL, 10-100 mg/mL, or 40-100 mg/mL of an anti-IL-6 antibody (e.g., Ab1) or at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/mL of an anti-IL-6 antibody (e.g., Ab1). The diarrhea may be associated with chemotherapy, radiotherapy, cancer, or hematopoietic stem cell transplants.

[0498] It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of antibodies, or antibody fragments thereof, calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the antibodies, and fragments thereof, and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an antibodies, and fragments thereof, for the treatment of sensitivity in individuals. In therapeutic use for treatment of conditions in mammals (e.g., humans) for which the antibodies and fragments thereof of the present invention or an appropriate pharmaceutical composition thereof are effective, the antibodies and fragments thereof of the present invention may be administered in an effective amount. The dosages as suitable for this invention may be a composition, a pharmaceutical composition or any other compositions described herein.

[0499] The dosage may be administered as a single dose, a double dose, a triple dose, a quadruple dose, and/or a quintuple dose. The dosages may be administered singularly, simultaneously, and sequentially. For example, two doses may be administered on the same day followed by subsequent two doses four weeks later.

[0500] The dosage form may be any form of release known to persons of ordinary skill in the art. The compositions of the present invention may be formulated to provide immediate release of the active ingredient or sustained or controlled release of the active ingredient. In a sustained release or controlled release preparation, release of the active ingredient may occur at a rate such that blood levels are maintained within a therapeutic range but below toxic levels over an extended period of time (e.g., 4 to 24 hours). The preferred dosage forms include immediate release, extended release, pulse release, variable release, controlled release, timed release, sustained release, delayed release, long acting, and combinations thereof, and are known in the art.

[0501] It will be appreciated that the pharmacological activity of the compositions may be monitored using standard pharmacological models that are known in the art. Furthermore, it will be appreciated that the compositions comprising an anti-IL-6 antibodies or antibody fragments thereof may be incorporated or encapsulated in a suitable polymer matrix or membrane for site-specific delivery, or may be functionalized with specific targeting agents capable of effecting site specific delivery. These techniques, as well as other drug delivery techniques are well known in the art. Determination of optimal dosages for a particular situation is within the capabilities of those skilled in the art. See, e.g., Grennaro (2005) [Ed.] Remington: The Science and Practice of Pharmacy [21st Ed.]

[0502] The anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, may be administered to a subject in a pharmaceutical formulation.

[0503] A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via at least one of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration. Further, a pharmaceutical composition comprising an anti-IL-6 antibody described herein (e.g., ALD518) may be administered subcutaneously.

[0504] The anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, may be optionally administered in combination with at least one active agents. Such active agents include analgesic, antipyretic, anti-inflammatory, antibiotic, antiviral, and anti-cytokine agents. Active agents include agonists, antagonists, and modulators of TNF-*alpha*, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-*alpha*, IFN-*gamma*, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, including antibodies reactive against any of the foregoing, and antibodies reactive against any of their receptors. Active agents also include 2-Arylpropionic acids, Aceclofenac, Acemetacin, Acetylsalicylic acid (Aspirin), Alclofenac, Alminoprofen, Amoxiprin, Ampyrone, Arylalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxaprofen, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofezone, COX-2 inhibitors, Dexibuprofen, Dextketoprofen, Diclofenac, Diflunisal, Droxicam, Ethenzamide, Etodolac, Etoricoxib, Faislamine, fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuprofen, Ibuprofen, Indometacin, Indoprofen, Kebuzone, Ketoprofen, Ketorolac, Lornoxicam, Loxoprofen, Lumiracoxib, Magnesium salicylate, Meclofenamic acid, Mefenamic acid, Meloxicam, Metamizole, Methyl salicylate, Mofebutazone, Nabumetone, Naproxen, N-Arylanthranilic acids, Oxametacin, Oxaprozin, Oxams, Oxyphenbutazone, Parecoxib, Phenazone, Phenylbutazone, Phenylbutazone, Piroxicam, Pirprofen, profens, Proglumetacin, Pyrazolidine derivatives, Rofecoxib, Salicyl salicylate, Salicylamide, Salicylates, Sulfinpyrazone, Sulin-

dac, Suprofen, Tenoxicam, Tiaprofenic acid, Tolfenamic acid, Tolmetin, and Valdecoxib. Antibiotics include Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ansamycins, Arsphenamine, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenems, Carbenicillin, Cefaclor, Cefadroxil, Cefalexin, Cefalothin, Cefalotin, Cefamandole, Cefazolin, Cefdinir, Cefditoren, Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefoxitin, Cefpodoxime, Cefprozil, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftobiprole, Ceftriaxone, Cefuroxime, Cephalosporins, Chloramphenicol, Cilastatin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacillin, Colistin, Co-trimoxazole, Dalfopristin, Demeclocycline, Dicloxacillin, Dirithromycin, Doripenem, Doxycycline, Enoxacin, Ertapenem, Erythromycin, Ethambutol, Flucloxacillin, Fosfomycin, Furazolidone, Fusidic acid, Gatifloxacin, Geldanamycin, Gentamicin, Glycopeptides, Herbimycin, Imipenem, Isoniazid, Kanamycin, Levofloxacin, Lincomycin, Linezolid, Lomefloxacin, Loracarbef, Macrolides, Mafenide, Meropenem, Meti-
 cillin, Metronidazole, Mezlocillin, Minocycline, Monobactams, Moxifloxacin, Mupirocin, Nafcillin, Neomycin, Netilmicin, Nitrofurantoin, Norfloxacin, Ofloxacin, Oxacillin, Oxytetracycline, Paromomycin, Penicillin, Penicillins, Piperacillin, Plat-
 ensimycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxi-
 thromycin, Spectinomycin, Streptomycin, Sulfacetamide, Sulfamethizole, Sulfanilimide, Sulfasalazine, Sulfisoxazole, Sulfonamides, Teicoplanin, Telithromycin, Tetracycline, Tetracyclines, Ticarcillin, Tinidazole, Tobramycin, Trimethoprim,
 Trimethoprim-Sulfamethoxazole, Troleandomycin, Trovafloxacin, and Vancomycin. Active agents also include Aldos-
 terone, Beclometasone, Betamethasone, Corticosteroids, Cortisol, Cortisone acetate, Deoxycorticosterone acetate, Dexamethasone, Fludrocortisone acetate, Glucocorticoids, Hydrocortisone, Methylprednisolone, Prednisolone, Pred-
 nisone, Steroids, and Triamcinolone. Antiviral agents include but are not limited to abacavir, aciclovir, acyclovir, adefovir, amantadine, amprenavir, an antiretroviral fixed dose combination, an antiretroviral synergistic enhancer, arbidol, ata-
 zanavir, atripla, brivudine, cidofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, em-
 tricitabine, enfuvirtide, entecavir, entry inhibitors, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, fusion in-
 hibitor, ganciclovir, gardasil, ibacitabine, idoxuridine, imiquimod, imunovir, indinavir, inosine, integrase inhibitor, inter-
 feron, interferon type I, interferon type II, interferon type III, lamivudine, lopinavir, loviride, maraviroc, MK-0518, morox-
 ydine, nelfinavir, nevirapine, nexavir, nucleoside analogues, oseltamivir, penciclovir, peramivir, pleconaril, podophyllo-
 toxin, protease inhibitor, reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, saquinavir, stavudine, tenofovir,
 tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine,
 viramidine, zalcitabine, zanamivir, and zidovudine. Any suitable combination of these active agents is also contemplated.

[0505] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or at least one fragments or variants thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Grennaro (2005) [Ed.] Remington: The Science and Practice of Pharmacy [21st Ed.]

[0506] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0507] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition may be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition.

[0508] The antibodies and fragments thereof, for use according to the present invention thereof may be formulated into pharmaceutical compositions of various dosage forms. For example, the antibody may be ALD518, a humanized anti-interleukin-6 (anti-IL-6) monoclonal immunoglobulin 1 (IgG1) antibody manufactured in the yeast *Pichia pastoris*. ALD518 may be supplied as a pH 6.0 frozen injection in single-use vials (80 mg or 160 mg) for intravenous administration. Exemplary non-active excipients include but are not limited to histidine (e.g., 25 mM) and sorbitol (e.g., 250 mM). For example, a 160 mg formulation may comprise as non-active excipients, 25 mM histidine, 250 mM sorbitol, and 0.015% polysorbate 80. To prepare the pharmaceutical compositions for use according to the invention, at least one anti-IL-6 antibodies or binding fragments thereof, as the active ingredient may be intimately mixed with appropriate carriers and additives according to techniques well known to those skilled in the art of pharmaceutical formulations. See Grennaro (2005) [Ed.] Remington: The Science and Practice of Pharmacy [21st Ed.] For example, the antibodies described herein

may be formulated in phosphate buffered saline pH 7.2 and supplied as a 5.0 mg/mL clear colorless liquid solution.

[0509] Similarly, compositions for liquid preparations include solutions, emulsions, dispersions, suspensions, syrups, and elixirs, with suitable carriers and additives including but not limited to water, alcohols, oils, glycols, preservatives, flavoring agents, coloring agents, and suspending agents. Typical preparations for parenteral administration comprise the active ingredient with a carrier such as sterile water or parenterally acceptable oil including but not limited to polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil, with other additives for aiding solubility or preservation may also be included. In the case of a solution, it may be lyophilized to a powder and then reconstituted immediately prior to use. For dispersions and suspensions, appropriate carriers and additives include aqueous gums, celluloses, silicates, or oils.

[0510] The anti-IL-6 antibodies or binding fragments thereof, may be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0511] In many cases, it will be preferable to include isotonic agents, e.g., sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent which delays absorption, e.g., monostearate salts and gelatin. Moreover, the compounds described herein may be formulated in a time release formulation, e.g. in a composition that includes a slow release polymer. The anti-IL-6 antibodies may be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0512] In one embodiment of the invention that may be used to intravenously administer antibodies according to the invention, including ALD518, for mucositis indications, the administration formulation comprises, or alternatively consists of, about 10.5 mg/mL of antibody, 25 mM Histidine base, Phosphoric acid q.s. to pH 6, and 250 mM sorbitol.

[0513] In another embodiment of the invention that may be used to intravenously administer antibodies according to the invention, including ALD581, for mucositis indications, the administration formulation comprises, or alternatively consists of, about 10.5 mg/mL of antibody, 12.5 mM Histidine base, 12.5 mM Histidine HCl (or 25 mM Histidine base and Hydrochloric acid q.s. to pH 6), 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80.

[0514] In one embodiment of the invention that may be used to subcutaneously administer antibodies according to the invention, including ALD518, for mucositis indications, the administration formulation comprises, or alternatively consists of, about 50 or 100 mg/mL of antibody, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 mM sorbitol, and 0.015% (w/w) Polysorbate 80. In another embodiment of the invention that may be used to subcutaneously administer antibodies according to the invention, including Ab1, for mucositis indications, the administration formulation comprises, or alternatively consists of, about 20 or 100 mg/mL of antibody, about 5 mM Histidine base, about 5 mM Histidine HCl to make final pH 6, 250 to 280 mM sorbitol (or sorbitol in combination with sucrose), and 0.015% (w/w) Polysorbate 80, said formulation having a nitrogen headspace in the shipping vials.

[0515] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition.

[0516] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0517] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol

inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0518] A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, et al. (2011) Goodman & Gilman's The Pharmacological Basis of Therapeutics [12th Ed.]; Howland, et al. (2005) Lippincott's Illustrated Reviews: Pharmacology [2nd Ed.]; and Golan, (2008) Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy [2nd Ed.] See, also, Grennaro (2005) [Ed.] Remington: The Science and Practice of Pharmacy [21st Ed.]

[0519] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Certain teachings related to methods for obtaining a clonal population of antigen-specific B cells were disclosed in U.S. Patent Application Publication No. 2007/0269868.

[0520] Certain teachings related to humanization of rabbit-derived monoclonal antibodies and preferred sequence modifications to maintain antigen binding affinity were disclosed in U.S. Patent Application Publication No. 2009/0104187.

[0521] Certain teachings related to producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. Patent Application Publication No. 2006/0270045.

[0522] Certain teachings related to anti-IL-6 antibodies, methods of producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. Patent Application Publication No. 2009/0104187.

[0523] Certain teachings related to anti-IL-6 antibodies and methods of using those antibodies or fragments thereof to address certain diseases and/or disorders were disclosed in U.S. Patent Application Publication No. 2010/0150829.

[0524] Certain anti-IL-6 antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

[0525] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g., amounts, temperature, concentrations) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

EXAMPLES

[0526] The following examples describing an anti-IL6 antibody comprising a variable light sequence of SeqIdNo.709 and a variable heavy sequence of SeqIdNo.657 for use in the treatment or prevention of mucositis associated with radiotherapy are illustrative of the invention. The other examples are preparatory examples or examples non-illustrative of the invention.

[0527] In the following examples, the term "Ab1" refers to an antibody comprising the light chain sequence of SEQ ID NO: 702 and the heavy chain sequence of SEQ ID NO: 704, except where the context indicates otherwise. The laboratory designation "Ab1" also encompasses an anti-IL-6 antibody also known as "ALD518" and "BMS-945429" comprising the light chain sequence of SEQ ID NO: 19 and the heavy chain sequence of SEQ ID NO: 20.

Example 1

Production of Enriched Antigen-Specific B Cell Antibody Culture

[0528] Panels of antibodies are derived by immunizing traditional antibody host animals to exploit the native immune response to a target antigen of interest. Typically, the host used for immunization is a rabbit or other host that produces antibodies using a similar maturation process and provides for a population of antigen-specific B cells producing antibodies of comparable diversity, e.g., epitopic diversity. The initial antigen immunization can be conducted using complete Freund's adjuvant (CFA), and the subsequent boosts effected with incomplete adjuvant. At about 50-60 days after immunization, preferably at day 55, antibody titers are tested, and the Antibody Selection (ABS) process is initiated if appropriate titers are established. The two key criteria for ABS initiation are potent antigen recognition and function-modifying activity in the polyclonal sera.

[0529] At the time positive antibody titers are established, animals are sacrificed and B cell sources isolated. These sources include: the spleen, lymph nodes, bone marrow, and peripheral blood mononuclear cells (PBMCs). Single cell suspensions are generated, and the cell suspensions are washed to make them compatible for low temperature long term storage. The cells are then typically frozen.

[0530] To initiate the antibody identification process, a small fraction of the frozen cell suspensions are thawed, washed, and placed in tissue culture media. These suspensions are then mixed with a biotinylated form of the antigen that was

used to generate the animal immune response, and antigen-specific cells are recovered using the Miltenyi magnetic bead cell selection methodology. Specific enrichment is conducted using streptavidin beads. The enriched population is recovered and progressed in the next phase of specific B cell isolation.

5 Example 2

Production of Clonal, Antigen-Specific B Cell-Containing Culture

10 [0531] Enriched B cells produced according to Example 1 are then plated at varying cell densities per well in a 96 well microtiter plate. Generally, this is at 50, 100, 250, or 500 cells per well with 10 plates per group. The media is supplemented with 4% activated rabbit T cell conditioned media along with 50K frozen irradiated EL4B feeder cells. These cultures are left undisturbed for 5-7 days at which time supernatant-containing secreted antibody is collected and evaluated for target properties in a separate assay setting. The remaining supernatant is left intact, and the plate is frozen at -70°C. Under these conditions, the culture process typically results in wells containing a mixed cell population that comprises 15 a clonal population of antigen-specific B cells, *i.e.*, a single well will only contain a single monoclonal antibody specific to the desired antigen.

Example 3

20 Screening of Antibody Supernatants for Monoclonal Antibody of Desired Specificity and/or Functional Properties

[0532] Antibody-containing supernatants derived from the well containing a clonal antigen-specific B cell population produced according to Example 2 are initially screened for antigen recognition using ELISA methods. This includes 25 selective antigen immobilization (*e.g.*, biotinylated antigen capture by streptavidin coated plate), non-specific antigen plate coating, or alternatively, through an antigen build-up strategy (*e.g.*, selective antigen capture followed by binding partner addition to generate a heteromeric protein-antigen complex). Antigen-positive well supernatants are then optionally tested in a function-modifying assay that is strictly dependant on the ligand. One such example is an *in vitro* protein-protein interaction assay that recreates the natural interaction of the antigen ligand with recombinant receptor protein. Alternatively, a cell-based response that is ligand dependent and easily monitored (*e.g.*, proliferation response) is utilized. Supernatant that displays significant antigen recognition and potency is deemed a positive well. Cells derived from the original positive well are then transitioned to the antibody recovery phase.

35 Example 4

Recovery of Single, Antibody-Producing B Cell of Desired Antigen Specificity

[0533] Cells are isolated from a well that contains a clonal population of antigen-specific B cells (produced according to Example 2 or 3), which secrete a single antibody sequence. The isolated cells are then assayed to isolate a single, 40 antibody-secreting cell. Dynal® (magnetic beads) streptavidin beads are coated with biotinylated target antigen under buffered medium to prepare antigen-containing microbeads compatible with cell viability. Next antigen-loaded beads, antibody-producing cells from the positive well, and a fluorescein isothiocyanate (FITC)-labeled anti-host H&L IgG antibody (as noted, the host can be any mammalian host, *e.g.*, rabbit, mouse, rat) are incubated together at 37°C. This mixture is then re-pipetted in aliquots onto a glass slide such that each aliquot has on average a single, antibody-producing B-cell. The antigen-specific, antibody-secreting cells are then detected through fluorescence microscopy. Secreted antibody is locally concentrated onto the adjacent beads due to the bound antigen and provides localization information based on the strong fluorescent signal. Antibody-secreting cells are identified via FITC detection of antibody-antigen complexes formed adjacent to the secreting cell. The single cell found in the center of this complex is then recovered using a micromanipulator. The cell is snap-frozen in an eppendorf PCR tube for storage at -80°C until antibody 50 sequence recovery is initiated.

Example 5

Isolation of Antibody Sequences From Antigen-Specific B Cell

55 [0534] Antibody sequences are recovered using a combined RT-PCR based method from a single isolated B-cell produced according to Example 4 or an antigenic specific B cell isolated from the clonal B cell population obtained according to Example 2. Primers are designed to anneal in conserved and constant regions of the target immunoglobulin

genes (heavy and light), such as rabbit immunoglobulin sequences, and a two-step nested PCR recovery step is used to obtain the antibody sequence. Amplicons from each well are analyzed for recovery and size integrity. The resulting fragments are then digested with AluI to fingerprint the sequence clonality. Identical sequences display a common fragmentation pattern in their electrophoretic analysis. Significantly, this common fragmentation pattern which proves cell clonality is generally observed even in the wells originally plated up to 1000 cells/well. The original heavy and light chain amplicon fragments are then restriction enzyme digested with HindIII and XhoI or HindIII and BsiWI to prepare the respective pieces of DNA for cloning. The resulting digestions are then ligated into an expression vector and transformed into bacteria for plasmid propagation and production. Colonies are selected for sequence characterization.

Example 6

Recombinant Production of Monoclonal Antibody of Desired Antigen Specificity and/or Functional Properties

[0535] Correct full-length antibody sequences for each well containing a single monoclonal antibody is established and miniprep DNA is prepared using Qiagen solid-phase methodology. This DNA is then used to transfect mammalian cells to produce recombinant full-length antibody. Crude antibody product is tested for antigen recognition and functional properties to confirm the original characteristics are found in the recombinant antibody protein. Where appropriate, large-scale transient mammalian transfections are completed, and antibody is purified through Protein A affinity chromatography. Kd is assessed using standard methods (e.g., Biacore®) as well as IC50 in a potency assay.

Example 7

Preparation of Antibodies that Bind Human IL-6

[0536] By using the antibody selection protocol described herein, one can generate an extensive panel of antibodies. The antibodies have high affinity towards IL-6 (single to double digit pM Kd) and demonstrate potent antagonism of IL-6 in multiple cell-based screening systems (T1165 and HepG2). Furthermore, the collection of antibodies displays distinct modes of antagonism toward IL-6-driven processes.

Immunization Strategy

[0537] Rabbits were immunized with huIL-6 (R&R). Immunization consisted of a first subcutaneous (sc) injection of 100 µg in complete Freund's adjuvant (CFA) (Sigma) followed by two boosts, two weeks apart, of 50 µg each in incomplete Freund's adjuvant (IFA) (Sigma). Animals were bled on day 55, and serum titers were determined by ELISA (antigen recognition) and by non-radioactive proliferation assay (Promega) using the T1165 cell line.

Antibody Selection Titer Assessment

[0538] Antigen recognition was determined by coating Immulon 4 plates (Thermo) with 1 µg/mL of huIL-6 (50 µL/well) in phosphate buffered saline (PBS, Hyclone) overnight at 4 °C. On the day of the assay, plates were washed 3 times with PBS /Tween 20 (PBST tablets, Calbiochem). Plates were then blocked with 200 µL/well of 0.5% fish skin gelatin (FSG, Sigma) in PBS for 30 minutes at 37°C. Blocking solution was removed, and plates were blotted. Serum samples were made (bleeds and pre-bleeds) at a starting dilution of 1:100 (all dilutions were made in FSG 50 µL/well) followed by 1:10 dilutions across the plate (column 12 was left blank for background control). Plates were incubated for 30 minutes at 37°C. Plates were washed 3 times with PBS/Tween 20. Goat anti-rabbit Fc-HRP (Pierce) diluted 1:5000 was added to all wells (50 µL/well), and plates were incubated for 30 minutes at 37°C. Plates were washed as described above. 50 µL/well of TMB-Stable stop (Fitzgerald Industries) was added to plates, and color was allowed to develop, generally for 3 to 5 minutes. The development reaction was stopped with 50 µL/well 0.5 M HCl. Plates were read at 450 nm. Optical density (OD) versus dilution was plotted using Graph Pad Prism software, and titers were determined.

Functional Titer Assessment

[0539] The functional activity of the samples was determined by a T1165 proliferation assay. T1165 cells were routinely maintained in modified RPMI medium (Hyclone) supplemented with HEPES, sodium pyruvate, sodium bicarbonate, L-glutamine, high glucose, penicillin/streptomycin, 10% heat inactivated fetal bovine serum (FBS) (all supplements from Hyclone), 2-mercaptoethanol (Sigma), and 10 ng/mL of huIL-6 (R&D). On the day of the assay, cell viability was determined by trypan blue (Invitrogen), and cells were seeded at a fixed density of 20,000 cells/well. Prior to seeding, cells were washed twice in the medium described above without human-IL-6 (by centrifuging at 13000 rpm for 5 minutes and

discarding the supernatant). After the last wash, cells were resuspended in the same medium used for washing in a volume equivalent to 50 μL /well. Cells were set aside at room temperature.

[0540] In a round-bottom, 96-well plate (Costar), serum samples were added starting at 1:100, followed by a 1:10 dilution across the plate (columns 2 to 10) at 30 μL /well in replicates of 5 (rows B to F: dilution made in the medium described above with no hUL-6). Column 11 was medium only for IL-6 control. 30 μL /well of hUL-6 at 4x concentration of the final EC50 (concentration previously determined) were added to all wells (hUL-6 was diluted in the medium described above). Wells were incubated for 1 hour at 37°C to allow antibody binding to occur. After 1 hour, 50 μL /well of antibody-antigen (Ab-Ag) complex were transferred to a flat-bottom, 96-well plate (Costar) following the plate map format laid out in the round-bottom plate. On Row G, 50 μL /well of medium were added to all wells (columns 2 to 11) for background control. 50 μL /well of the cell suspension set aside were added to all wells (columns 2 to 11, rows B to G). On Columns 1 and 12 and on rows A and H, 200 μL /well of medium was added to prevent evaporation of test wells and to minimize edge effect. Plates were incubated for 72 hours at 37°C in 4% CO₂. At 72 hours, 20 μL /well of CellTiter96 (Promega) reagents was added to all test wells per manufacturer protocol, and plates were incubated for 2 hours at 37°C. At 2 hours, plates were gently mixed on an orbital shaker to disperse cells and to allow homogeneity in the test wells. Plates were read at 490 nm wavelength. Optical density (OD) versus dilution was plotted using Graph Pad Prizm software, and functional titer was determined. A positive assay control plate was conducted as described above using MAB2061 (R&D Systems) at a starting concentration of 1 $\mu\text{g}/\text{mL}$ (final concentration) followed by 1:3 dilutions across the plate.

Tissue Harvesting

[0541] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[0542] Spleen and lymph nodes were processed into a single cell suspension by disassociating the tissue and pushing through sterile wire mesh at 70 μm (Fisher) with a plunger of a 20 cc syringe. Cells were collected in the modified RPMI medium described above without hUL-6, but with low glucose. Cells were washed twice by centrifugation. After the last wash, cell density was determined by trypan blue. Cells were centrifuged at 1500 rpm for 10 minutes; the supernatant was discarded. Cells were resuspended in the appropriate volume of 10% dimethyl sulfoxide (DMSO, Sigma) in FBS (Hyclone) and dispensed at 1 mL/vial. Vials were then stored at -70 °C for 24 h prior to being placed in a liquid nitrogen (LN2) tank for long-term storage.

[0543] Peripheral blood mononuclear cells (PBMCs) were isolated by mixing whole blood with equal parts of the low glucose medium described above without FBS. 35 mL of the whole blood mixture was carefully layered onto 8 mL of Lympholyte Rabbit (Cedarlane) into a 45 mL conical tube (Corning) and centrifuged 30 minutes at 2500 rpm at room temperature without brakes. After centrifugation, the PBMC layers were carefully removed using a glass Pasteur pipette (VWR), combined, and placed into a clean 50 mL vial. Cells were washed twice with the modified medium described above by centrifugation at 1500 rpm for 10 minutes at room temperature, and cell density was determined by trypan blue staining. After the last wash, cells were resuspended in an appropriate volume of 10% DMSO/FBS medium and frozen as described herein.

B cell culture

[0544] On the day of setting up B cell culture, PBMC, splenocyte, or lymph node vials were thawed for use. Vials were removed from LN2 tank and placed in a 37°C water bath until thawed. Contents of vials were transferred into 15 mL conical centrifuge tube (Corning) and 10 mL of modified RPMI described above was slowly added to the tube. Cells were centrifuged for 5 minutes at 1.5K RPM, and the supernatant was discarded. Cells were resuspended in 10 mL of fresh media. Cell density and viability was determined by trypan blue. Cells were washed again and resuspended at 1E07 cells/80 μL medium. Biotinylated hUL-6 (B hUL-6) was added to the cell suspension at the final concentration of 3 $\mu\text{g}/\text{mL}$ and incubated for 30 minutes at 4°C. Unbound B hUL-6 was removed with two 10 mL washes of phosphate-buffered (PBF):Ca/Mg free PBS (Hyclone), 2 mM ethylenediamine tetraacetic acid (EDTA), 0.5% bovine serum albumin (BSA) (Sigma-biotin free). After the second wash, cells were resuspended at 1E07 cells/80 μL PBF. 20 μL of MACS® streptavidin beads (Miltenei)/10E7 cells were added to the cell suspension. Cells were incubated at 4°C for 15 minutes. Cells were washed once with 2 mL of PBF/10E7 cells. After washing, the cells were resuspended at 1E08 cells/500 μL of PBF and set aside. A MACS® MS column (Miltenei) was pre-rinsed with 500 mL of PBF on a magnetic stand (Miltenei). Cell suspension was applied to the column through a pre-filter, and unbound fraction was collected. The column was washed with 1.5 mL of PBF buffer. The column was removed from the magnet stand and placed onto a clean, sterile 5 mL Polypropylene Falcon tube. 1 mL of PBF buffer was added to the top of the column, and positive selected cells were collected. The yield and viability of positive and negative cell fraction was determined by trypan blue staining. Positive selection yielded an average of 1% of the starting cell concentration.

[0545] A pilot cell screen was established to provide information on seeding levels for the culture. Three 10-plate groups (a total of 30 plates) were seeded at 50, 100, and 200 enriched B cells/well. In addition, each well contained 50K cells/well of irradiated EL-4.B5 cells (5,000 Rads) and an appropriate level of T cell supernatant (ranging from 1-5% depending on preparation) in high glucose modified RPMI medium at a final volume of 250 μ L/well. Cultures were incubated for 5 to 7 days at 37 °C in 4% CO₂.

Identification of Selective Antibody Secreting B Cells

[0546] Cultures were tested for antigen recognition and functional activity between days 5 and 7.

Antigen Recognition Screening

[0547] The ELISA format used is as described above except 50 μ L of supernatant from the B cell cultures (BCC) wells (all 30 plates) was used as the source of the antibody. The conditioned medium was transferred to antigen-coated plates. After positive wells were identified, the supernatant was removed and transferred to a 96-well master plate(s). The original culture plates were then frozen by removing all the supernatant except 40 μ L/well and adding 60 μ L/well of 16% DMSO in FBS. Plates were wrapped in paper towels to slow freezing and placed at -70 °C.

Functional Activity Screening

[0548] Master plates were then screened for functional activity in the T1165 proliferation assay as described before, except row B was media only for background control, row C was media + IL-6 for positive proliferation control, and rows D-G and columns 2-11 were the wells from the BCC (50 μ L/well, single points). 40 μ L of IL-6 was added to all wells except the media row at 2.5 times the EC50 concentration determined for the assay. After 1 hour incubation, the Ab/Ag complex was transferred to a tissue culture (TC) treated, 96-well, flat-bottom plate. 20 μ L of cell suspension in modified RPMI medium without hIL-6 (T1165 at 20,000 cells/well) was added to all wells (100 μ L final volume per well). Background was subtracted, and observed OD values were transformed into % of inhibition.

B cell recovery

[0549] Plates containing wells of interest were removed from -70°C, and the cells from each well were recovered with 5-200 μ L washes of medium/well. The washes were pooled in a 1.5 mL sterile centrifuge tube, and cells were pelleted for 2 minutes at 1500 rpm.

[0550] The tube was inverted, the spin repeated, and the supernatant carefully removed. Cells were resuspended in 100 μ L/tube of medium. 100 μ L biotinylated IL-6 coated streptavidin M280 dynabeads (Invitrogen) and 16 μ L of goat anti-rabbit H&L IgG-FITC diluted 1:100 in medium was added to the cell suspension.

[0551] 20 μ L of cell/beads/FITC suspension was removed, and 5 μ L droplets were prepared on a glass slide (Corning) previously treated with Sigmacote (Sigma), 35 to 40 droplets/slide. An impermeable barrier of paraffin oil (JT Baker) was added to submerge the droplets, and the slide was incubated for 90 minutes at 37°C, 4% CO₂ in the dark.

[0552] Specific B cells that produce antibody can be identified by the fluorescent ring around them due to antibody secretion, recognition of the bead-associated biotinylated antigen, and subsequent detection by the fluorescent-IgG detection reagent. Once a cell of interest was identified, the cell in the center of the fluorescent ring was recovered via a micromanipulator (Eppendorf). The single cell synthesizing and exporting the antibody was transferred into a 250 μ L microcentrifuge tube and placed in dry ice. After recovering all cells of interest, these were transferred to -70°C for long-term storage.

Example 8

Yeast Cell Expression

[0553] Antibody genes: Genes were cloned and constructed that directed the synthesis of a chimeric humanized rabbit monoclonal antibody.

[0554] Expression vector: The vector contains the following functional components: 1) a mutant ColE1 origin of replication, which facilitates the replication of the plasmid vector in cells of the bacterium *Escherichia coli*; 2) a bacterial Sh ble gene, which confers resistance to the antibiotic Zeocin® (phleomycin) and serves as the selectable marker for transformations of both *E. coli* and *P. pastoris*; 3) an expression cassette composed of the glyceraldehyde dehydrogenase gene (GAP gene) promoter, fused to sequences encoding the *Saccharomyces cerevisiae* alpha mating factor pre pro secretion leader sequence, followed by sequences encoding a *P. pastoris* transcriptional termination signal from the P.

pastoris alcohol oxidase I gene (AOX1). The Zeocin® (phleomycin) resistance marker gene provides a means of enrichment for strains that contain multiple integrated copies of an expression vector in a strain by selecting for transformants that are resistant to higher levels of Zeocin® (phleomycin).

[0555] *Pichia pastoris* strains: *Pichia pastoris* strains *met1*, *lys3*, *ura3* and *ade1* may be used. Although any two complementing sets of auxotrophic strains could be used for the construction and maintenance of diploid strains, these two strains are especially suited for this method for two reasons. First, they grow more slowly than diploid strains that are the result of their mating or fusion. Thus, if a small number of haploid *ade1* or *ura3* cells remain present in a culture or arise through meiosis or other mechanism, the diploid strain should outgrow them in culture.

[0556] The second is that it is easy to monitor the sexual state of these strains since diploid Ade⁺ colonies arising from their mating are a normal white or cream color, whereas cells of any strains that are haploid *ade1* mutants will form a colony with a distinct pink color. In addition, any strains that are haploid *ura3* mutants are resistant to the drug 5-fluoroorotic acid (FOA) and can be sensitively identified by plating samples of a culture on minimal medium + uracil plates with FOA. On these plates, only uracil-requiring *ura3* mutant (presumably haploid) strains can grow and form colonies. Thus, with haploid parent strains marked with *ade1* and *ura3*, one can readily monitor the sexual state of the resulting antibody-producing diploid strains (haploid versus diploid).

Methods

[0557] Construction of pGAPZ-alpha expression vectors for transcription of light and heavy chain antibody genes. The humanized light and heavy chain fragments were cloned into the pGAPZ expression vectors through a PCR directed process. The recovered humanized constructs were subjected to amplification under standard KOD polymerase (Novagen) kit conditions ((1) 94°C, 2 minutes; (2) 94°C, 30 seconds (3) 55°C, 30 seconds; (4) 72°C, 30 seconds-cycling through steps 2-4 for 35 times; (5) 72°C 2 minutes) employing the following primers (1) light chain forward AGCGCT-TATTCCGCTATCCAGATGACCCAGTC-the Afel site is single underlined (SEQ ID NO: 729). The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable light chain (not underlined); the reverse CGTACGTTTGATTTCACCTTG (SEQ ID NO: 730).

[0558] Variable light chain reverse primer. BsiWI site is underlined, followed by the reverse complement for the 3' end of the variable light chain. Upon restriction enzyme digest with Afel and BsiWI this enable insertion in-frame with the pGAPZ vector using the human HAS leader sequence in frame with the human kappa light chain constant region for export. (2) A similar strategy is performed for the heavy chain. The forward primer employed is AGCGCTTATTCCGAG-GTGCAGCTGGTGGAGTC (SEQ ID NO: 731). The Afel site is single underlined. The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable heavy chain (not underlined). The reverse heavy chain primer is CTCGAGACGGTGACGAGGGT (SEQ ID NO: 732). The XhoI site is underlined, followed by the reverse complement for the 3' end of the variable heavy chain. This enables cloning of the heavy chain in-frame with IgG-γ1 CH1-CH2-CH3 region previous inserted within pGAPZ using a comparable directional cloning strategy.

[0559] Transformation of expression vectors into haploid *ade1 ura3*, *met1* and *lys3* host strains of *P. pastoris*. All methods used for transformation of haploid *P. pastoris* strains and genetic manipulation of the *P. pastoris* sexual cycle are as described in Higgins, D. R., and Cregg, J. M., Eds. 1998. *Pichia* Protocols. Methods in Molecular Biology. Humana Press, Totowa, NJ.

[0560] Prior to transformation, each expression vector is linearized within the *GAP* promoter sequences with AvrII to direct the integration of the vectors into the *GAP* promoter locus of the *P. pastoris* genome. Samples of each vector are then individually transformed into electrocompetent cultures of the *ade1*, *ura3*, *met1* and *lys3* strains by electroporation and successful transformants are selected on YPD Zeocin® (phleomycin) plates by their resistance to this antibiotic. Resulting colonies are selected, streaked for single colonies on YPD Zeocin® (phleomycin) plates and then examined for the presence of the antibody gene insert by a PCR assay on genomic DNA extracted from each strain for the proper antibody gene insert and/or by the ability of each strain to synthesize an antibody chain by a colony lift/immunoblot method. Wung, et al. (1996) *Biotechniques* 21: 808-812. Haploid *ade1*, *met1* and *lys3* strains expressing one of the three heavy chain constructs are collected for diploid constructions along with haploid *ura3* strain expressing light chain gene. The haploid expressing heavy chain genes are mated with the appropriate light chain haploid *ura3* to generate diploid secreting protein.

[0561] Mating of haploid strains synthesizing a single antibody chain and selection of diploid derivatives synthesizing tetrameric functional antibodies. To mate *P. pastoris* haploid strains, each *ade1* (or *met1* or *lys3*) heavy chain producing strain to be crossed is streaked across a rich YPD plate and the *ura3* light chain producing strain is streaked across a second YPD plate (~10 streaks per plate). After one or two days incubation at 30°C, cells from one plate containing heavy chain strains and one plate containing *ura3* light chain strains are transferred to a sterile velvet cloth on a replica-plating block in a cross hatched pattern so that each heavy chain strain contain a patch of cells mixed with each light chain strain. The cross-streaked replica plated cells are then transferred to a mating plate and incubated at 25°C to stimulate the initiation of mating between strains. After two days, the cells on the mating plates are transferred again to

a sterile velvet on a replica-plating block and then transferred to minimal medium plates. These plates are incubated at 30°C for three days to allow for the selective growth of colonies of prototrophic diploid strains. Colonies that arose are picked and streaked onto a second minimal medium plate to single colony isolate and purify each diploid strain. The resulting diploid cell lines are then examined for antibody production.

[0562] Putative diploid strains are tested to demonstrate that they are diploid and contain both expression vectors for antibody production. For diploidy, samples of a strain are spread on mating plates to stimulate them to go through meiosis and form spores. Haploid spore products are collected and tested for phenotype. If a significant percentage of the resulting spore products are single or double auxotrophs it may be concluded that the original strain must have been diploid. Diploid strains are examined for the presence of both antibody genes by extracting genomic DNA from each and utilizing this DNA in PCR reactions specific for each gene.

[0563] Fusion of haploid strains synthesizing a single antibody chain and selection of diploid derivatives synthesizing tetrameric functional antibodies. As an alternative to the mating procedure described above, individual cultures of single-chain antibody producing haploid *ade1* and *ura3* strains are spheroplasted and their resulting spheroplasts fused using polyethylene glycol/CaCl₂. The fused haploid strains are then embedded in agar containing 1 M sorbitol and minimal medium to allow diploid strains to regenerate their cell wall and grow into visible colonies. Resulting colonies are picked from the agar, streaked onto a minimal medium plate, and the plates are incubated for two days at 30°C to generate colonies from single cells of diploid cell lines. The resulting putative diploid cell lines are then examined for diploidy and antibody production as described above.

[0564] Purification and analysis of antibodies. A diploid strain for the production of full length antibody is derived through the mating of *met1* light chain and *lys3* heavy chain using the methods described above. Culture media from shake-flask or fermenter cultures of diploid *P. pastoris* expression strains are collected and examined for the presence of antibody protein via SDS-PAGE and immunoblotting using antibodies directed against heavy and light chains of human IgG, or specifically against the heavy chain of IgG.

[0565] To purify the yeast secreted antibodies, clarified media from antibody producing cultures are passed through a protein A column and after washing with 20 mM sodium phosphate, pH 7.0, binding buffer, protein A bound protein is eluted using 0.1 M glycine HCl buffer, pH 3.0. Fractions containing the most total protein are examined by Coomassie blue stained SDS-PAGE and immunoblotting for antibody protein. Antibody is characterized using the ELISA described above for IL-6 recognition.

[0566] *Assay for antibody activity.* The recombinant yeast-derived humanized antibody is evaluated for functional activity through the IL-6 driven T1165 cell proliferation assay and IL-6 stimulated HepG2 haptoglobin assay described above.

Example 9

Acute Phase Response Neutralization by Intravenous Administration of Anti-IL-6 Antibody Ab1

[0567] Human IL-6 can provoke an acute phase response in rats, and one of the major acute phase proteins that is stimulated in the rat is alpha-2 macroglobulin (A2M). A study was designed to assess the dose of antibody Ab1 required to ablate the A2M response to a single subcutaneous injection of 100 µg of human IL-6 given one hour after different doses (0.03, 0.1, 0.3, 1, and 3 mg/kg) of antibody Ab1 administered intravenously (n=10 rats/dose level) or polyclonal human IgG1 as the control (n=10 rats). Plasma was recovered and the A2M was quantitated via a commercial sandwich ELISA kit (ICL Inc., Newberg OR; cat. no.- E-25A2M). The endpoint was the difference in the plasma concentration of A2M at the 24 hour time point (post-Ab1).

[0568] The ID50 for antibody Ab1 was 0.1 mg/kg with complete suppression of the A2M response at the 0.3 mg/kg. See Figure 6. This demonstrates that the IL-6 may be neutralized *in vivo* by anti-IL-6 antibodies described herein.

Example 10

RXF393 Cachexia Model Study 1

Introduction

[0569] The human renal cell cancer cell line, RXF393 produces profound weight loss when transplanted into athymic nude mice. Weight loss begins around day 15 after transplantation with 80% of all animals losing at least 30% of their total body weight by day 18-20 after transplantation. RXF393 secretes human IL-6 and the plasma concentration of human IL-6 in these animals is very high at around 10ng/ml. Human IL-6 can bind murine soluble IL-6 receptor and activate IL-6 responses in the mouse. Human IL-6 is approximately 10 times less potent than murine IL-6 at activating IL-6 responses in the mouse. The objectives of this study were to determine the effect of antibody Ab1, on survival, body

weight, serum amyloid A protein, hematology parameters, and tumor growth in athymic nude mice transplanted with the human renal cell cancer cell line, RXF393.

Methods

[0570] Eighty, 6 week old, male athymic nude mice were implanted with RXF393 tumor fragments (30-40 mg) subcutaneously in the right flank. Animals were then divided into eight groups of ten mice. Three groups were given either antibody Ab1 at 3 mg/kg, 10 mg/kg, or 30 mg/kg intravenously weekly on day 1, day 8, day 15 and day 22 after transplantation (progression groups). Another three groups were given either antibody Ab1 at 3 mg/kg, or 10 mg/kg, or 30 mg/kg intravenously weekly on day 8, day 15 and day 22 after transplantation (regression groups). Finally, one control group was given polyclonal human IgG 30 mg/kg and a second control group was given phosphate buffered saline intravenously weekly on day 1, day 8, day 15 and day 22 after transplantation.

[0571] Animals were euthanized at either day 28, when the tumor reached 4,000 mm³ or if they became debilitated (>30% loss of body weight). Animals were weighed on days 1, 6 and then daily from days 9 to 28 after transplantation. Mean Percent Body Weight (MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows: (Body Weight - Tumor Weight)/Baseline Body Weight x 100. Tumor weight was measured on days 1, 6, 9, 12, 15, 18, 22, 25 and 28 after transplantation. Blood was taken under anesthesia from five mice in each group on days 5 and 13 and all ten mice in each group when euthanized (day 28 in most cases). Blood was analyzed for hematology and serum amyloid A protein (SAA) concentration. An additional group of 10 non-tumor bearing 6 week old, athymic nude male mice had blood samples taken for hematology and SAA concentration estimation to act as a baseline set of values.

Results - Survival

[0572] No animals were euthanized or died in any of the antibody Ab1 groups prior to the study termination date of day 28. In the two control groups, 15 animals (7/9 in the polyclonal human IgG group and 8/10 in the phosphate buffered saline group) were found dead or were euthanized because they were very debilitated (>30% loss of body weight). Median survival time in both control groups was 20 days.

[0573] The survival curves for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) groups are presented in **FIGURE 7**.

[0574] The survival curves for the two control groups and the antibody Ab1 regression (dosed from day 8 of the study) groups are presented in **FIGURE 8**.

[0575] There was a statistically significant difference between the survival curves for the polyclonal human IgG ($p=0.0038$) and phosphate buffered saline ($p=0.0003$) control groups and the survival curve for the six antibody Ab1 groups. There was no statistically significant difference between the two control groups ($p=0.97$).

Results - Tumor Size

[0576] Tumor size in surviving mice was estimated by palpation. For the first 15 days of the study, none of the mice in any group were found dead or were euthanized, and so comparison of tumor sizes between groups on these days was free from sampling bias. No difference in tumor size was observed between the antibody Ab1 progression or regression groups and the control groups through day 15. Comparison of the tumor size between surviving mice in the control and treatment groups subsequent to the onset of mortality in the controls (on day 15) was not undertaken because tumor size the surviving control mice was presumed to be biased and accordingly the results of such comparison would not be meaningful.

[0577] As administration of antibody Ab1 promoted survival without any apparent reduction in tumor size, elevated serum IL-6 may contribute to mortality through mechanisms independent of tumor growth. These observations supports the hypothesis that antibody Ab1 can promote cancer patient survivability without directly affecting tumor growth, possibly by enhancing general patient well-being.

Results - Weight Loss

[0578] Compared to controls, mice dosed with Ab1 were protected from weight loss. On day 18, MPBW in control mice was 75%, corresponding to an average weight loss of 25%. In contrast, on the same day, MPBW in Ab-1 treatment groups was minimally changed (between 97% and 103%). There was a statistically significant difference between the MPBW curves for the controls (receiving polyclonal human IgG or PBS) and the 10 mg/kg dosage group ($p<0.0001$) or 3 mg/kg and 30 mg/kg dosage groups ($p<0.0005$). There was no statistically significant difference between the two control groups.

[0579] Control mice are emaciated compared to the normal appearance of the Ab1-treated mouse. These results suggest that Ab1 may be useful to prevent or treat cachexia caused by elevated IL-6 in humans.

Results - Plasma Serum Amyloid A

[0580] The mean ($\pm$ SEM) plasma serum amyloid A concentration versus time for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) and regression (dosed from day 8 of the study) groups are presented in Table 7.

Table 7 Mean Plasma SAA-antibody Ab1, all groups versus control groups

	Mean Plasma SAA $\pm$ SEM Day 5 (μ g/ml)	Mean Plasma SAA $\pm$ SEM Day 13 (μ g/ml)	Mean Plasma SAA $\pm$ SEM Terminal Bleed (μ g/ml)
Polyclonal IgG 30 mg/kg iv weekly from day 1	675 $\pm$ 240 (n=5)	3198 $\pm$ 628 (n=4)	13371 $\pm$ 2413 (n=4)
PBS iv weekly from day 1	355 $\pm$ 207 (n=5)	4844 $\pm$ 1126 (n=5)	15826 $\pm$ 802 (n=3)
Ab 1 30 mg/kg iv weekly from day 1	246 $\pm$ 100 (n=5)	2979 $\pm$ 170 (n=5)	841 $\pm$ 469 (n=10)
Abl 10 mg/kg iv weekly from day 1	3629 $\pm$ 624 (n=5)	3096 $\pm$ 690 (n=5)	996 $\pm$ 348 (n=10)
Abl 3 mg/kg iv weekly from day 1	106 $\pm$ 9 (n=5)	1623 $\pm$ 595 (n=4)	435 $\pm$ 70 (n=9)
Ab 1 30 mg/kg iv weekly from day 8	375 $\pm$ 177 (n=5)	1492 $\pm$ 418 (n=4)	498 $\pm$ 83 (n=9)
Abl 10 mg/kg iv weekly from day 8	487 $\pm$ 170 (n=5)	1403 $\pm$ 187 (n=5)	396 $\pm$ 58 (n=10)
Abl 3 mg/kg iv weekly from day 8	1255 $\pm$ 516 (n=5)	466 $\pm$ 157 (n=5)	685 $\pm$ 350 (n=5)

[0581] SAA is up-regulated via the stimulation of hIL-6 and this response is directly correlated with circulating levels of hIL-6 derived from the implanted tumor. The surrogate marker provides an indirect readout for active hIL-6. Thus in the two treatment groups described above there are significantly decreased levels of SAA due to the neutralization of tumor-derived hIL-6. This further supports the contention that antibody Ab1 displays *in vivo* efficacy.

Example 11

RXF393 Cachexia Model Study 2

Introduction

[0582] A second study was performed in the RXF-393 cachexia model where treatment with antibody Ab1 was started at a later stage (days 10 and 13 post-transplantation) and with a more prolonged treatment phase (out to 49 days post transplantation). The dosing interval with antibody Ab1 was shortened to 3 days from 7 and also daily food consumption was measured. There was also an attempt to standardize the tumor sizes at the time of initiating dosing with antibody Ab1.

Methods

[0583] Eighty, 6 week old, male athymic nude mice were implanted with RXF393 tumor fragments (30-40 mg) subcutaneously in the right flank. 20 mice were selected whose tumors had reached between 270-320 mg in size and divided into two groups. One group received antibody Ab1 at 10 mg/kg i.v. every three days and the other group received polyclonal human IgG 10 mg/kg every 3 days from that time-point (day 10 after transplantation). Another 20 mice were selected when their tumor size had reached 400-527 mg in size and divided into two groups. One group received antibody Ab1 at 10 mg/kg i.v. every three days and the other group received polyclonal human IgG 10 mg/kg every 3 days from

that time-point (day 13 after transplantation). The remaining 40 mice took no further part in the study and were euthanized at either day 49, when the tumor reached 4,000 mm³ or if they became very debilitated (>30% loss of body weight).

[0584] Animals were weighed every 3-4 days from day 1 to day 49 after transplantation. Mean Percent Body Weight (MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows: ((Body Weight - Tumor Weight)/Baseline Body Weight) x 100. Tumor weight was measured every 3-4 days from day 5 to day 49 after transplantation. Food consumption was measured (amount consumed in 24 hours by weight (g) by each treatment group) every day from day 10 for the 270-320 mg tumor groups and day 13 for the 400-527 mg tumor groups.

Results -survival

[0585] The survival curves for antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size) and for the polyclonal human IgG 10 mg/kg i.v. every three days (270-320 mg tumor size) are presented in Figure 9.

[0586] Median survival for the antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size) was 46 days and for the polyclonal human IgG at 10 mg/kg i.v. every three days (270-320 mg tumor size) was 32.5 days (p=0.0071).

[0587] The survival curves for the antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size) and for the polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) are presented in Figure 10. Median survival for the antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size) was 46.5 days and for the polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) was 27 days (p=0.0481).

Example 12

Multi-dose Pharmacokinetic Evaluation of Antibody Ab1 in Non-human Primates

[0588] Antibody Ab1 was dosed in a single bolus infusion to a single male and single female cynomolgus monkey in phosphate buffered saline. Plasma samples were removed at fixed time intervals and the level of antibody Ab1 was quantitated through the use of an antigen capture ELISA assay. Biotinylated IL-6 (50 µl of 3 µg/mL) was captured on Streptavidin coated 96 well microtiter plates. The plates were washed and blocked with 0.5% Fish skin gelatin. Appropriately diluted plasma samples were added and incubated for 1 hour at room temperature. The supernatants removed and an anti-hFc-HRP conjugated secondary antibody applied and left at room temperature.

[0589] The plates were then aspirated and TMB added to visualize the amount of antibody. The specific levels were then determined through the use of a standard curve. A second dose of antibody Ab1 was administered at day 35 to the same two cynomolgus monkeys and the experiment replicated using an identical sampling plan.

[0590] This humanized full length aglycosylated antibody expressed and purified *Pichia pastoris* displays comparable characteristics to mammalian expressed protein. In addition, multiple doses of this product display reproducible half-lives inferring that this production platform does not generate products that display enhanced immunogenicity.

Example 13

Octet Mechanistic Characterization of Antibody Proteins

[0591] IL-6 signaling is dependent upon interactions between IL-6 and two receptors, IL-6R1 (CD126) and gp130 (IL-6 signal transducer). To determine the antibody mechanism of action, mechanistic studies were performed using bio-layer interferometry with an Octet QK instrument (ForteBio; Menlo Park, CA). Studies were performed in two different configurations. In the first orientation, biotinylated IL-6 (R&D systems part number 206-IL-001MG/CF, biotinylated using Pierce EZ-link sulfo-NHS-LC-LC-biotin product number 21338 according to manufacturer's protocols) was initially bound to a streptavidin coated biosensor (ForteBio part number 18-5006). Binding is monitored as an increase in signal.

[0592] The IL-6 bound to the sensor was then incubated either with the antibody in question or diluent solution alone. The sensor was then incubated with soluble IL-6R1 (R&D systems product number 227-SR-025/CF) molecule. If the IL-6R1 molecule failed to bind, the antibody was deemed to block IL-6/IL-6R1 interactions. These complexes were incubated with gp130 (R&D systems 228-GP-010/CF) in the presence of IL-6R1 for stability purposes. If gp130 did not bind, it was concluded that the antibody blocked gp130 interactions with IL-6.

[0593] In the second orientation, the antibody was bound to a biosensor coated with an anti-human IgG1 Fc-specific reagent (ForteBio part number 18-5001). The IL-6 was bound to the immobilized antibody and the sensor was incubated with IL-6R1. If the IL-6R1 did not interact with the IL-6, then it was concluded that the IL-6 binding antibody blocked IL-6/IL-6R1 interactions. In those situations where antibody/IL-6/IL-6R1 was observed, the complex was incubated with gp130 in the presence of IL-6R1. If gp130 did not interact, then it was concluded that the antibody blocked IL-6/gp130 interactions. All studies were performed in a 200 µL final volume, at 30°C and 1000 rpm. For these studies, all proteins were diluted using ForteBio's sample diluent buffer (part number 18-5028). Results are presented in TABLE 8.

TABLE 8 Anti-IL6 Antibodies binding to R1 or GP130

Antibody	Blocks IL6 binding to R1	Blocks IL6 Binding to GP130
Ab1	Yes	Yes
Ab2	No	Partial
Ab3	No	Yes
Ab4	No	Yes
Ab6	Yes	Yes
Ab7	Yes	Yes
Ab8	No	Yes

Example 14

Peptide Mapping

[0594] In order to determine the epitope recognized by Ab1 on human IL-6, the antibody was employed in a western-blot based assay. The form of human IL-6 utilized in this example had a sequence of 183 amino acids in length. A 57-member library of overlapping 15 amino acid peptides encompassing this sequence was commercially synthesized and covalently bound to a PepSpots nitrocellulose membrane (JPT Peptide technologies, Berlin, Germany). The sequences of the overlapping 15 amino acid peptides is in SEQ ID NOs: 590-646. Blots were prepared and probed according to the manufacturer's recommendations.

[0595] Briefly, blots were pre-wet in methanol, rinsed in PBS, and blocked for over 2 hours in 10% non-fat milk in PBS/0.05% Tween (Blocking Solution). The Ab1 antibody was used at 1 mg/mL final dilution, and the HRP-conjugated Mouse Anti-Human-Kappa secondary antibody (Southern BioTech #9220-05) was used at a 1:5000 dilution. Antibody dilutions/incubations were performed in blocking solution. Blots were developed using Amersham ECL advance reagents (GE# RPN2135) and chemiluminescent signal documented using a CCD camera (AlphaInnotec). The sequence of the form of human IL-6 utilized to generate peptide library is set forth in SEQ ID NO: 1.

Example 15

Ab1 has high affinity for IL-6

[0596] Surface plasmon resonance was used to measure association rate (K_a), dissociation rate (K_d) and dissociation constant (K_D) for Ab1 to IL-6 from rat, mouse, dog, human, and cynomolgus monkey at 25°C (TABLE 5). The dissociation constant for human IL-6 was 4 pM, indicating very high affinity. As expected, affinity generally decreased with phylogenetic distance from human. The dissociation constants of Ab1 for IL-6 of cynomolgus monkey, rat, and mouse were 31 pM, 1.4 nM, and 0.4 nM, respectively. Ab1 affinity for dog IL-6 below the limit of quantitation of the experiment.

[0597] The high affinity of Ab1 for mouse, rat, and cynomolgus monkey IL-6 suggest that Ab1 may be used to inhibit IL-6 of these species. This hypothesis was tested using a cell proliferation assay. In brief, each species's IL-6 was used to stimulate proliferation of T1165 cells, and the concentration at which Ab1 could inhibit 50% of proliferation (IC_{50}) was measured. Inhibition was consistent with the measured dissociation constants (TABLE 6). These results demonstrate that Ab1 can inhibit the native IL-6 of these species, and suggest the use of these organisms for *in vitro* or *in vivo* modeling of IL-6 inhibition by Ab1. Further, other IL-6 antibodies described herein may have similar properties.

Table 9 Surface Plasmon Resonance: Averaged binding constants determined at 25°C for Ab1 to IL-6.

Species (IL-6)	K_a ($M^{-1}s^{-1}$)	K_d (s^{-1})	K_p
Rat	1.6e ⁶	2.2e ⁻³	1.4nM
Mouse	1.1e ⁶	4.0e ⁻⁴	0.4nM
Dog	Below LOQ ^a	Below LOQ ^a	Below LOQ ^a
Human	1.6e ⁵	5e ⁻⁷	4 pM

(continued)

Species (IL-6)	K_a ($M^{-1}s^{-1}$)	K_d (s^{-1})	K_p
Cynomolgus monkey	9.6e4	3e-6	31 pM
a. Below Limit of Quantitation			

Table 10 IC50 values for Ab1 against human, cynomolgus monkey, mouse, rat and dog IL-6 in the T1165 assay.

IL-6 Species	IC50 (pM)
Human	13
Cynomolgus monkey	12
Mouse	1840
Rat	2060
Dog	No inhibition of cell proliferation

Example 16

Multi-dose Pharmacokinetic Evaluation of Antibody Ab1 in Healthy Human Volunteers

[0598] Antibody Ab1 was dosed in a single bolus infusion in histidine and sorbitol to healthy human volunteers. Dosages of 1 mg, 3 mg, 10 mg, 30 mg or 100 mg were administered to each individual in dosage groups containing five to six individuals. Plasma samples were removed at fixed time intervals for up to twelve weeks. Human plasma was collected via venipuncture into a vacuum collection tube containing EDTA. Plasma was separated and used to assess the circulating levels of Ab1 using a monoclonal antibody specific for Ab1, as follows. A 96 well microtiter plate was coated overnight with the monoclonal antibody specific for Ab1 in 1X PBS overnight at 4°C. The remaining steps were conducted at room temperature. The wells were aspirated and subsequently blocked using 0.5% Fish Skin Gelatin (FSG) (Sigma) in 1X PBS for 60 minutes. Human plasma samples were then added and incubated for 60 minutes, then aspirated, then 50 µL of 1 µg/mL biotinylated IL-6 was then added to each well and incubated for 60 minutes. The wells were aspirated, and 50 µL streptavidin-HRP (Pharmingen), diluted 1:5,000 in 0.5% FSG/PBS, was added and incubated for 45 minutes. Development was conducted using standard methods employing TMB for detection. Levels were then determined via comparison to a standard curve prepared in a comparable format.

[0599] Average plasma concentration of Ab1 for each dosage group was examined. Mean AUC and Cmax increased linearly with dosage. For dosages of 30 mg and above, the average Ab1 half-life in each dosage group was between approximately 25 and 30 days. The pharmacokinetics is shown in Table 11.

Table 11 Summary of Ab1 Pharmacokinetics in Health Human Volunteers

Dose of Ab1	$T_{1/2}$ (days)	AUC ($\mu g \cdot h / mL$)	C_{max} ($\mu g / mL$)	T_{max}
1mg	10.3	35	0.1	8
3mg	11.6	229	0.7	4
10mg	22.4	1473	4.0	4
30mg	25.1	9076	19.7	4
100mg	30.3	26128	48.0	12
300mg	26.2	92891	188.0	12
640mg	30.2	175684	306.0	12

Example 17

Pharmacokinetics of Ab1 in patients with advanced cancer

[0600] Antibody Ab1 was dosed in a single bolus infusion in phosphate buffered saline to five individuals with advanced cancer. Each individual received a dosage of 80 mg (n=2) or 160 mg (n=3) of Ab1. Plasma samples were drawn weekly, and the level of antibody Ab1 was quantitated as in Example 16. Average plasma concentration of Ab1 in these individuals as a function of time was examined. The average Ab1 half-life was approximately 31 days. The anti-IL-6 antibodies described herein may have similarly long half-lives.

Example 18

Ab1 has an unexpectedly long half-life

[0601] Overall, the average half-life of Ab1 was approximately 31 days in humans (for dosages of 10 mg and above), and approximately 15-21 days in cynomolgus monkey. The Ab1 half-life in humans and cynomolgus monkeys are unprecedented when compared with the half-lives of other anti-IL-6 antibodies (TABLE 11). As described above, Ab1 was derived from humanization of a rabbit antibody, and is produced from *Pichia pastoris* in an aglycosylated form. These characteristics results in an antibody with very low immunogenicity in humans. Moreover, the lack of glycosylation prevents Ab1 from interacting with the Fc receptor or complement. Without intent to be limited by theory, it is believed that the unexpectedly long half-life of Ab1 is at least partially attributable to the humanization and/or the lack of glycosylation. The particular sequence and/or structure of the antigen binding surfaces may also contribute to Ab1's half-life. See also WO 2011/066369.

TABLE 12 Elimination Half-life of Ab1

Dose of AB1	Cynomolgus Monkey (days)	Human (days)
Ab1	15-21	~31
Acemra (Tocilizumab)	7	6
Remicade	5	8-9.5
Synagis	8.6	20
Erbitux	3-7	5
Zenapax	7	20
A vastin	10	20
Pertuzumab	10	18-22

Example 19

Ab1 Effect on Hemoglobin Concentration, Plasma Lipid Concentration, and Neutrophil Counts in Patients with Advanced Cancer.

[0602] Antibody Ab1 was dosed in a single bolus infusion in phosphate buffered saline to eight individuals with advanced cancer (NSCLC, colorectal cancer, cholangiocarcinoma, or mesothelioma). Each individual received a dosage of 80 mg, 160 mg, or 320 mg of Ab1. Blood samples were removed just prior to infusion and at fixed time intervals for six weeks, and the hemoglobin concentration, plasma lipid concentration, and neutrophil counts were determined. Average hemoglobin concentration rose slightly (Figure 11), as did total cholesterol and triglycerides (Figure 12), while mean neutrophil counts fell slightly (Figure 13).

[0603] These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration in these individuals. Similarly, as IL-6 is centrally important in increasing neutrophil counts in inflammation, the observed slight reduction in neutrophil counts further confirms that Ab1 inhibits IL-6. Finally, IL-6 causes anorexia as well as cachexia in these patients; neutralization of IL-6 by Ab1 results in the return of appetite and reversal of cachexia. The increase in plasma lipid concentrations reflects the improved nutritional status of the patients. Taken together, these results further demonstrate that Ab1 effec-

tively reverses these adverse consequences of IL-6 in these patients.

Example 20 Ab1 Suppresses Serum CRP in Healthy Volunteers and in Patients with Advanced Cancer

Introduction

[0604] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto *et al.* performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence. Hashimoto, et al. (2005) Cancer 103(9): 1856-1864. Patients were classified into two groups, those with serum CRP levels > 1.0 mg/dL ("the CRP positive group") and those with serum CRP levels < 1.0 mg/dL ("the CRP negative group"). The authors identified "a significant correlation between preoperative serum CRP level and tumor size." *Id.* Furthermore, the authors found that "[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group." *Id.* The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[0605] Similar correlations have been identified by other investigators. For example, Karakiewicz *et al.* determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality. Karakiewicz, et al. (2007) Cancer. 110(6):1241-1247. Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[0606] Healthy volunteers received a single 1-hour intravenous (IV) infusion of either 100 mg (5 patients), 30 mg (5 patients), 10 mg (6 patients), 3 mg (6 patients) or 1 mg (6 patients) of the Ab1 monoclonal antibody, while another 14 healthy volunteers received intravenous placebo. Comparatively, 2 patients with advanced forms of colorectal cancer received a single 1-hour intravenous (IV) infusion of 80 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[0607] Patients were evaluated prior to administration of the dosage, and thereafter on a weekly basis for at least 5 weeks post dose. At the time of each evaluation, patients were screened for serum CRP concentration.

Results- Healthy Volunteers

[0608] As noted above, serum CRP levels are a marker of inflammation; accordingly, baseline CRP levels are typically low in healthy individuals. The low baseline CRP levels can make a further reduction in CRP levels difficult to detect. Nonetheless, a substantial reduction in serum CRP concentrations was detectable in healthy volunteers receiving all concentrations of the Ab1 monoclonal antibody, compared to controls (Figure 14A). The reduction in serum CRP levels was rapid, occurring within one week of antibody administration, and prolonged, continuing at least through the final measurement was taken (8 or 12 weeks from antibody administration).

Results- Cancer Patients

[0609] Five advanced cancer patients (colorectal cancer, cholangiocarcinoma, or NSCLC) having elevated serum CRP levels were dosed with 80 mg or 160 mg of Ab1. Serum CRP levels were greatly reduced in these patients (Figure 14B). The reduction in serum CRP levels was rapid, with 90% of the decrease occurring within one week of Ab1 administration, and prolonged, continuing at least until the final measurement was taken (up to twelve weeks). In two representative individuals, the CRP levels were lowered to below the normal reference range (less than 5-6 mg/l) within one week. Thus, administration of Ab1 to patients can cause a rapid and sustained suppression of serum CRP levels.

Example 21

Ab1 Improved Muscular Strength, Improved Weight, and Reduced Fatigue in Patients with Advanced Cancer

Introduction

[0610] Weight loss and fatigue (and accompanying muscular weakness) are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue, weight loss and muscular weakness can have significant negative effects on the recovery of patients with advanced forms of cancer,

for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue, weight loss and muscular weakness include regular routines of fitness and exercise, methods of conserving the patient's energy, and treatments that address anemia-induced fatigue and muscular weakness. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue, weight loss and muscular weakness in cancer patients.

Methods

[0611] Four patients with advanced forms of cancer [(colorectal cancer (2), NSCLC (1), cholangiocarcinoma (1))] received a single 1-hour intravenous (IV) infusion of either 80 mg or 160 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[0612] Patients were evaluated prior to administration of the dosage, and thereafter for at least 6 weeks post dose. At the time of each evaluation, patients were screened for the following: a.) any change in weight; b.) fatigue as measured using the Facit-F Fatigue Subscale questionnaire a medically recognized test for evaluating fatigue. See, e.g., Cella, et al. (2002) Cancer 94(2): 528-538; Cella, et al. (2002) Journal of Pain & Symptom Management 24(6): 547-561); and hand-grip strength (a medically recognized test for evaluating muscle strength, typically employing a handgrip dynamometer).

Results-Weight Change

[0613] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase of about 2 kilograms of weight per patient over the period of 6 weeks.

Fatigue

[0614] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase in the mean Facit-F FS subscale score of at least about 10 points in the patient population over the period of 6 weeks.

Hand-Grip Strength

[0615] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase in the mean hand-grip strength of at least about 10 percent in the patient population over the period of 6 weeks. See, e.g., WO 2011/066371.

Example 22

Ab1 For Prevention of Thrombosis

[0616] Prior studies have shown that administration of an anti-IL-6 antibody can cause decreased platelet counts. Emilie, et al. (1994) Blood 84(8): 2472-9; Blay, et al. (1997) Int J Cancer 72(3): 424-30. These results have apparently been viewed as an indicator of potential danger, because further decreases in platelet counts could cause complications such as bleeding. However, Applicants have now discerned that inhibiting IL-6 restores a normal coagulation profile, which Applicants predict will prevent thrombosis. Decreased platelet counts resulting from inhibition of IL-6 is not a sign of potential danger but rather reflects the beneficial restoration of normal coagulation.

[0617] The mechanism by which normal coagulation is restored is believed to result from the interplay between IL-6 and the acute phase reaction. In response to elevated IL-6 levels, as for example in a cancer patient, the liver produces acute phase proteins. These acute phase proteins include coagulation factors, such as Factor II, Factor V, Factor VIII, Factor IX, Factor XI, Factor XII, F/fibrin degradation products, thrombin-antithrombin III complex, fibrinogen, plasminogen, prothrombin, and von Willebrand factor. This increase in coagulation factors may be measured directly, or may be inferred from functional measurements of clotting ability. Antagonists of IL-6, such as Ab1, suppresses acute phase proteins, e.g., Serum Amyloid (Example 10). Applicants now predict that this suppression of acute phase proteins will restore the normal coagulation profile, and thereby prevent thrombosis. The restoration of normal coagulation may cause a slight drop in platelet counts, but the patient will nonetheless retain normal coagulation ability and thus will not have an increased risk of bleeding. Such a treatment will represent a vast improvement over the available anticoagulation therapies whose usefulness is limited by the risk of adverse side-effects, such as major bleeding. See, e.g., WO 2011/066371.

[0618] Applicants contemplate that the same beneficial effects of inhibiting IL-6 will be obtained regardless of the method of inhibition. Suitable methods of inhibiting IL-6 include administration of anti-IL-6 antibodies, antisense therapy,

soluble IL-6 receptor, either individually or in combinations.

Example 23

5 Ab1 Increases Plasma Albumin Concentration in Patients with Advanced Cancer

Introduction

10 **[0619]** Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbumenia correlates strongly with poor patient performance in numerous forms of cancer. For example, in one study no patients undergoing systemic chemotherapy for metastatic pancreatic adenocarcinoma and having serum albumin levels less than 3.5 g/dL successfully responded to systemic chemotherapy. Fujishiro, et al. (2000) Hepatogastroenterology 47(36): 1744-46 and Senior and Maroni (1999) Am. Soc. Nutr. Sci. 129: 313S-314S. In at least one study, attempts to rectify hypoalbuminemia in 27 patients with metastatic cancer by daily intravenous albumin
15 infusion of 20 g until normal serum albumin levels (>3.5 g/dL) were achieved had little success. Demirkazik, et al. (2002) Proc. Am. Soc. Clin. Oncol. 21:Abstr 2892. Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

20 Methods

[0620] Four patients with advanced forms of cancer [(colorectal cancer (2), NSCLC (1), cholangiocarcinoma (1)] received a single 1-hour intravenous (IV) infusion of either 80 mg or 160 mg of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

25 **[0621]** Patients were evaluated prior to administration of the dosage, and thereafter for at least 6 weeks post dose. At the time of each evaluation, patients were screened for plasma albumin concentration.

Results

30 **[0622]** The averaged data for both dosage concentrations (80 mg and 160 mg) of the Ab1 monoclonal antibody demonstrated an increase of about 5 g/L of plasma albumin concentration per patient over the period of 6 weeks. See, e.g., WO 2011/066371.

Example 24

35

Ab1 Suppresses Serum CRP in Patients with Advanced Cancer

Introduction

40 **[0623]** Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto *et al.* performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence. Hashimoto, et al. (2005) Cancer 103(9): 1856-1864. Patients were classified into two groups, those with serum CRP levels > 1.0 mg/dL ("the CRP positive group") and those with serum CRP levels < 1.0 mg/dL ("the CRP negative group"). The authors identified "a significant correlation between preoperative serum CRP level and tumor size." *Id.*
45 Furthermore, the authors found that "[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group." *Id.* The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

50 **[0624]** Similar correlations have been identified by other investigators. For example, Karakiewicz *et al.* determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality. Karakiewicz, et al. (2007) Cancer 110(6):1241-1247. Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

55 Methods

[0625] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160

mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (*i.e.* Roche CRP Tinaquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer.

[0626] Patients were evaluated prior to administration of the dosage, and thereafter at weeks 2, 4, 8, and 12. At the time of each evaluation, patients were screened for serum CRP concentration.

Results

[0627] The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody are plotted in Figure 15A. All dosage levels of Ab1 antibody demonstrated an immediate drop in CRP concentrations relative to placebo over the period of 12 weeks. CRP levels displayed breakthrough at 8 weeks post-dosing. The CRP levels fell below 5 mg/L by week 12. Median values of CRP demonstrated rapid and sustained decreases for all dosage concentrations relative to placebo (Fig. 15B). Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 25

Ab1 Suppresses Serum CRP in Patients with Advanced Cancers

Introduction

[0628] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with certain forms of cancer. For example, Hashimoto *et al.* performed univariate and multivariate analysis of preoperative serum CRP concentrations in patients with hepatocellular carcinoma in order to identify factors affecting survival and disease recurrence. Hashimoto, et al. (2005) Cancer 103(9): 1856-1864. Patients were classified into two groups, those with serum CRP levels > 1.0 mg/dL ("the CRP positive group") and those with serum CRP levels < 1.0 mg/dL ("the CRP negative group"). The authors identified "a significant correlation between preoperative serum CRP level and tumor size." *Id.* Furthermore, the authors found that "[t]he overall survival and recurrence-free survival rates in the CRP-positive group were significantly lower compared with the rates in the CRP-negative group." *Id.* The authors concluded that the preoperative CRP level of patients is an independent and significant predictive indicator of poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[0629] Similar correlations have been identified by other investigators. For example, Karakiewicz *et al.* determined that serum CRP was an independent and informative predictor of renal cell carcinoma-specific mortality. Karakiewicz, et al. (2007) Cancer 110(6): 1241-1247. Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in cancer patients, and particularly those with advanced cancers.

Methods

[0630] Eight patients with various forms of advanced cancer [(colorectal (3), NSCLC (1), cholangio (1), and mesothelioma (2))] received a single 1-hour intravenous infusion of either 80 mg (2 patients), 160 mg (3 patients) or 320 mg (3 patients) of the Ab1 monoclonal antibody. No further dosages of the Ab1 monoclonal antibody were administered to the test population.

[0631] Patients were evaluated prior to administration of the dosage and thereafter on a weekly basis for at least 8 weeks post dose. At the time of each evaluation, patients were screened for serum CRP concentration. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (*i.e.* Roche CRP Tinaquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer.

Results

[0632] Serum CRP levels were greatly reduced in all patients studied (Fig. 16). The reduction in serum CRP levels

was rapid, with approximately 90% of the decrease occurring within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to twelve weeks). In all cases except one patient with colorectal cancer, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. The colorectal cancer patient achieved similar normal levels by week 4 of the study. Thus, administration of Ab1 to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 26

Ab1 Suppresses Serum CRP in Patients with Rheumatoid Arthritis.

Introduction

[0633] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with rheumatoid arthritis. Patients suffering from rheumatoid arthritis with high levels of CRP demonstrated almost universal deterioration. Amos, et al. (1977) Br. Med. J. 1: 195-97. Conversely, patients with low CRP levels showed no disease progression, suggesting that sustaining low levels of CRP is necessary for effectively treating rheumatoid arthritis. *Id.* Tracking of CRP during rheumatoid arthritis treatment regimes of gold, D-penicillamine, chloroquine, or dapsone indicated that radiological deterioration was impeded after the first 6 months of treatment when CRP levels were consistently controlled. Dawes et al., (1986) Rheumatology 25: 44-49. A highly significant correlation between CRP production and radiological progression was identified. van Leeuwen, et al. (1997) Rheumatology 32 (Supp. 3): 9-13. Another study revealed that for patients with active rheumatoid arthritis, suppression of abnormally elevated CRP led to improvement in functional testing metrics, whereas sustained CRP elevation associated with deterioration in the same metrics. Devlin, et al. (1997) J. Rheumatol. 24: 9-13. No further deterioration was observed without CRP re-elevation, indicating CRP suppression as a viable candidate for rheumatoid arthritis treatment. *Id.* Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in rheumatoid arthritis patients.

Methods

[0634] One-hundred twenty-seven patients with active rheumatoid arthritis and CRP ≥ 10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (*i.e.*, Roche CRP Tinaquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analyzer. Data on CRP concentration was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16.

Results

[0635] Serum CRP levels were greatly reduced in all patients studied (Fig. 17). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Ab1 to rheumatoid arthritis patients can cause a rapid and sustained suppression of serum CRP levels and presents an effective treatment regime.

Example 27

Ab1 Increases Hemoglobin in Patients with Advanced Cancer

[0636] Antibody Ab1 was dosed at 80 mg, 160 mg, or 320 mg of Ab1 in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Ab1, while mean hemoglobin concentration of those receiving placebo did not rise after twelve

weeks when compared to the concentration just prior to dosing (zero week) (Figs. 18A and 18B).

[0637] A subset of the study population began the study with low levels of hemoglobin, defined as a baseline hemoglobin concentration below 11 g/l. Mean hemoglobin concentration rose above 11 g/l after eight weeks for those receiving antibody Ab1 at dosages of 160 mg and 320 mg, while mean hemoglobin concentration of those receiving antibody Ab1 at dosages of 80 mg or placebo did not rise above 11 g/l after eight weeks (Fig. 18C).

[0638] These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration in these individuals.

Example 28

Ab1 Increases Hemoglobin in Patients with Rheumatoid Arthritis

[0639] Hemoglobin levels were analyzed in patients with rheumatoid arthritis during treatment with Ab1 antibody. Ab1 antibody was dosed at 80 mg, 160 mg, or 320 mg in phosphate buffered saline to 94 individuals with rheumatoid arthritis. The placebo group of 33 individuals with rheumatoid arthritis was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at one, two, three, four, six, eight, ten, twelve, and sixteen weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Ab1, while mean hemoglobin concentration of those receiving placebo did not appreciably rise after sixteen weeks when compared to the concentration just prior to dosing (zero week) (Fig. 19).

[0640] These results further demonstrate some of the beneficial effects of administration of Ab1 to chronically ill individuals. Because IL-6 is the main cytokine responsible for the anemia of chronic disease (including cancer-related anemia), neutralization of IL-6 by Ab1 increases hemoglobin concentration.

Example 29

Ab1 Increases Albumin in Patients with Advanced Cancer

Introduction

[0641] Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbumenia correlates strongly with poor patient performance in numerous forms of cancer. For example, in one study no patients undergoing systemic chemotherapy for metastatic pancreatic adenocarcinoma and having serum albumin levels less than 3.5 g/dL successfully responded to systemic chemotherapy. Fujishiro, et al. (2000) Hepatogastroenterology 47(36): 1744-46. The authors conclude that "[p]atients with ... hypoalbuminemia ... might be inappropriate candidates for systemic chemotherapy and might be treated with other experimental approaches or supportive care." *Id.*

[0642] Similarly, Senior and Maroni state that "[t]he recent appreciation that hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease highlights the critical importance of ensuring adequate protein intake in this patient population." Senior & Maroni (1999) Am. Soc. Nutr. Sci. 129: 313S-314S.

[0643] In at least one study, attempts to rectify hypoalbuminemia in 27 patients with metastatic cancer by daily intravenous albumin infusion of 20 g until normal serum albumin levels (>3.5 g/dL) were achieved had little success. The authors note that "[a]lbumin infusion for the advanced stage cancer patients has limited value in clinical practice. Patients with PS 4 and hypoalbuminemia have poorer prognosis." Demirkazik, et al. (2002) Proc. Am. Soc. Clin. Oncol. 21: Abstr 2892.

[0644] Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

[0645] Antibody Ab1 was dosed at 80 mg, 160 mg, or 320 mg of Ab1 in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. Each individual received a dosage of. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the albumin concentration was determined.

Results

[0646] Mean albumin concentration rose for those receiving antibody Ab1, while mean albumin concentration of those receiving placebo did not rise after twelve weeks when compared to the concentration just prior to dosing (zero week) (Fig. 20A). The change from baseline albumin values for all dosage concentration groups is plotted in Figure 20B.

[0647] A subset of the study population began the study with low levels of albumin, defined as a baseline albumin concentration less than or equal to 35 g/L. Mean albumin concentration initially rose with all dosages of antibody Ab1 over placebo, but only patients receiving 160 mg or 320 mg demonstrated sustained albumin levels above 35 g/L over 8 weeks of the study (Fig. 20C). The 80 mg dosage group demonstrated an initial increase, but gradually declined after week 2 and never rose above 35 g/L during the 8 weeks where data was available. *Id.*

Example 30

Ab1 Improved Weight and Reduced Fatigue in Patients with Advanced Cancer

Introduction

[0648] Weight loss and fatigue are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue and weight loss can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue and weight loss include regular routines of fitness and exercise, methods of conserving the patient's energy, and treatments that address anemia-induced fatigue. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue and weight loss in cancer patients.

Methods

[0649] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses.

[0650] Patients were evaluated prior to administration of the dosage, and thereafter for at least 12 weeks post dose. At the time of each evaluation, patients were screened for the following: any change in weight; and fatigue as measured using the Facit-F Fatigue Subscale questionnaire a medically recognized test for evaluating fatigue. See, e.g., Cella, et al. (2002) Cancer 94(2): 528-538; Cella, et al. (2002) Journal of Pain & Symptom Management 24(6): 547-561.

Results

Weight Change

[0651] The averaged weight change data from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody over 12 weeks. The average percent change in body weight from each dosage concentration. The averaged lean body mass data for the dosage concentration groups.

Fatigue

[0652] The averaged fatigue from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody demonstrated increases in the mean Facit-F FS subscale score for some of the dosage concentration groups in the patient population over the period of 8 weeks.

Example 31

Ab1 Decreases D-dimer Levels in Patients with Advanced Cancer

Introduction

[0653] D-dimer concentrations are recognized as useful diagnostic tools in predicting risks of thrombotic events in patients. Adam, et al. (2009) Blood 113: 2878-87. Patients that are negative for D-dimer have a low probability for thrombosis. For example, D-dimer analysis can rule out suspected lower-extremity deep-vein thrombosis in patients.

Wells, et al. (2003) N. Engl. J. Med. 349: 1227-35. Clinical evaluation in combination with negative D-dimer test can effectively lower the instance of pulmonary embolism to 0.5%. Van Belle, et al. (2006) JAMA 295: 172-79; Kruip, et al. (2002) Arch. Intern. Med. 162: 1631-35; Wells, et al. (2001) Ann. Intern. Med. 135: 98-107.

[0654] D-dimer analysis may have utility in tracking the progress of treating coagulation disorders. One study indicated that anticoagulation treatment for acute venous thromboembolism resulted in a gradual decline in D-dimer concentrations. Adam, et al. (2009) Blood 113: 2878-87; Schutgens, et al. (2004) J. Lab. Clin. Med. 144: 100-107. This discovery led to the conclusion that D-dimer levels monitoring could be used to assess treatment responsiveness. Adam, at 2883.

[0655] For patients with cancer, D-dimer analysis may have additional significance, as cancer increases the prevalence of thrombosis. Adam, et al. (2009) Blood 113: 2878-87. One study with oncology patients indicated that D-dimer concentrations have a high negative predictive value and high sensitivity in diagnosing pulmonary embolism. King, et al. (2008) Radiology 247: 854-61. Deep-vein thrombosis can similarly be excluded for cancer patients with low probability of developing deep-vein thrombosis and a negative test for D-dimer, although such a combination is less likely for oncology patients. Lee, et al. (2008) Thromb. Res. 123: 177-83. A higher threshold for a negative D-dimer result may be necessary in cancer patients. Righini, et al. (2006) Haemost. 95: 715-19.

[0656] Accordingly, there remains a need in the art for methods and/or treatments of thrombosis that improve D-dimer concentrations in cancer patients and address elevated D-dimer states in cancer patients, particularly those with advanced cancers.

Methods

[0657] One-hundred twenty-four patients with non-small cell lung cancer (NSCLC) were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=31), 80 mg (n=29), 160 mg (n=32), or 320 mg (n=32) of the Ab1 monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses. Data on D-dimer concentration was collected for the first 8 weeks of treatment. D-dimer data concentration was quantitated by a D-dimer immunoturbidimetric assay. Briefly, the assay is based on the change in turbidity of a micro-particle suspension that is measured by photometry. About 1.5 mL of patient sample sodium citrate plasma was collected and stored in a plastic collection tube. A suspension of latex microparticles, coated by covalent bonding with monoclonal antibodies specific for D-dimer, was mixed with the test plasma whose D-dimer level was to be assayed. Antigen-antibody reactions leading to an agglutination of the latex microparticles induced an increase in turbidity of the reaction medium. This increase in turbidity was reflected by an increase in absorbance, the latter being measured photometrically using a STAGO STA analyzer. The increase in absorbance was a function of the D-dimer level present in the test sample.

Results

[0658] The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody. All dosage levels of Ab1 antibody demonstrated a drop in D-dimer levels over placebo over the period of 8 weeks. See WO 2011/066371.

Example 32

Ab1 Efficacy and Safety in Patients with Advanced NSCLC

[0659] The primary objective of this study was to determine the efficacy and safety of ALD518 or humanized Ab1 in patients with advanced NSCLC.

Methods

[0660] 124 patients (pts) with NSCLC, ECOG 0-3, weight loss in the preceding 3 months of >5% body weight, hemoglobin (Hb) >7g/dL, and C-reactive protein (CRP) > 10mg/L were dosed. Pts were randomized to 1 of 4 groups (n~30/group). Placebo or ALD518 80mg, 160mg, or 320mg was administered intravenously every 8 weeks. Pts were followed up for 24 weeks. Data included hematology, clinical chemistry, CRP and adverse events (AEs).

Results

[0661] 29 pts completed the study treatments and evaluations, 38 failed to complete every visit, 52 died of progressive disease, and 5 withdrew because of adverse events. There were no dose limiting toxicities (DLTs) or infusion reactions. 84 pts had serious AEs of which 1 was deemed to be possibly related to administration of ALD518 (rectal hemorrhage). The mean ($\pm$ SD) values for Hb, hematocrit (Hct), mean corpuscular Hb (MCH), and albumin are below:

TABLE 13: Clinical Parameters measured for ALD518 (Abl) versus Placebo

		n	Hb (g/dL)	Hct (%)	MCH (pg)	Albumin (g/L)
ALD518 (pooled)	Pre-dose	93	11.5 (±2.1)	37.9 (±6.2)	28.4 (±2.8)	37.3 (±5.3)
	Week 4	69	13.1 (± 1.6) ^a	42.5 (±5.0) ^a	29.2 (±2.5) ^a	43.6 (±4.7) ^a
	Week 12	39	13.4 (±1.6) ^a	42.5 (±4.7) ^b	29.8 (±2.8) ^a	45.2 (±4.5) ^a
Placebo	Pre-dose	31	12.2 (± 1.8)	39.0 (±5.9)	29.0 (±2.8)	37.5 (±5.7)
	Week 4	29	11.8 (±2.0)	39.5 (±6.4)	28.0 (±2.8) ^c	37.3 (±6.8)
	Week 12	21	12.0 (±2.5)	39.6 (±7.4)	27.8 (±3.0) ^c	37.0 (±7.5)
^a p<0.0001 ^b p=0.0002 ^c p≤0.001 (paired t-test compared to pre-dose)						

[0662] 38/93 pts treated ALD518 and 10/31 given placebo has a pre-dose Hb ≤ 11g/dL. 24 of these pts on ALD518 and 7 of these pts on placebo remained in the study at week 4. 14/24 pts on ALD518 and 0/7 on placebo had raised their Hb from ≤ 11g/dL to ≥ 12g/dL.

Conclusion

[0663] ALD518 increased Hb, Hct, MCH and albumin in NSCLC pts and raised Hb to ≥ 12g/dL in 58% of pts with a Hb ≤ 11g/dL at baseline. This further indicates that ALD518 can be administered as a non-erythropoietic stimulating agent for treating cancer-related anemia.

Example 33

Ab1 achieved ACR 20/50/70 in Patients with Rheumatoid Arthritis.

Introduction

[0664] Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology ("ACR") released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement of the disease in clinical trials. Felson, et al. (1993) Arthritis & Rheumatism 36: 729-40.

Methods

[0665] One-hundred twenty-seven patients with active rheumatoid arthritis and CRP ≥10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. Data on CRP concentration was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16.

[0666] Assessment under the standardized protocols from the American College of Rheumatology were employed in determining the percentage of improvement of patients during the clinical trial and conducted by a person trained in the ordinary art of evaluating rheumatoid arthritis. The evaluation was based upon activity measures, including tender joint count, swollen joint count, the patient's assessment of pain, the patient's and physician's global assessments of disease activity, and laboratory evaluation of either erythrocyte sedimentation rate or CRP level. *Id.* The patient's assessment of pain was based upon the Stanford Health Assessment Questionnaire Disability Index (HAQ DI). Patients that achieve a 20% increase in activity measures for rheumatoid arthritis during a clinical trial are categorized as achieving ACR 20. Similarly, patients achieving 50% and 70% improvements are categorized as ACR 50 and ACR 70, respectively.

Results

[0667] A significant portion of patients suffering from rheumatoid arthritis achieved ACR 20 or greater during the course of the study. See Table 13. Patients observed rapid improvement in systems within the first 4 weeks of the study, as well as continued, steady improvement throughout the course of the 16 week evaluation. The greatest results where

exhibited by patients receiving the 320 mg dosage level, with 43% achieving ACR 70 status during the study.

TABLE 14: Percentage patients achieving ACR 20/50/70 at week 16 - MITT non responder imputation

	Placebo (n=33)	Ab1 80mg (n=32)	Ab1 160mg (n=34)	Ab1 320mg (n=28)	Ab1 Pooled (n=94)
ACR 20	36%	75% (p=0.0026)	65% (p=0.0283)	82% (p=0.0005)	73% (p=0.0002)
ACR 50	15%	41% (p=0.0281)	41% (p=0.0291)	50% (p=0.0052)	44% (p=0.0032)
ACR 70	6%	22%	18%	43%	27%
		(p=0.0824)	(p=0.2585)	(p=0.0015)	(p=0.0130)

[0668] Analysis of the individual components of the ACR evaluation demonstrated gains in every component. HAQ DI scores demonstrated clinically meaningful change over placebo during the course of the evaluation. Serum CRP levels were greatly reduced in all patients studied. The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Ab1 administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Ab1 can cause a rapid and sustained improvement rheumatoid arthritis patients, as evidenced by the significant improvement in ACR scores during clinical evaluation, and presents an effective treatment regime. See also WO 2011/066371.

Example 34

Ab1 Achieved Improved DAS28 and EULAR Scores in Patients with Rheumatoid Arthritis

Introduction

[0669] Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology ("ACR") released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement of the disease in clinical trials. Felson, et al. (1993) Arthritis & Rheumatism 36: 729-40.

[0670] Inflammatory activity associated with rheumatoid arthritis is measured using numerous variables through validated response criteria such as Disease Activity Score (DAS), DAS28 and EULAR. The DAS is a clinical index of rheumatoid arthritis disease activity that combines information from swollen joints, tender joints, the acute phase response, and general health. Fransen, et al. (2005) Clin. Exp. Rheumatol. 23(Suppl. 39): S93-S99. The DAS 28 is an index similar to the original DAS, but utilizes a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR (erythrocyte sedimentation rate), and an optional general health assessment on a visual analogue scale (range 0-100). *Id.* The European League against Rheumatism (EULAR) response criteria classify patients using the individual amount of change in the DAS and the DAS value (low, moderate, high) reached into one of the following classifications: Good; Moderate; or Non-Responders. *Id.*

Methods

[0671] One-hundred twenty-seven patients with active rheumatoid arthritis were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Ab1 monoclonal antibody, once at the start of the 16 week trial and again at week 8. Data on the DAS28 and EULAR scores was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16. Assessment under the standardized DAS28 and EULAR protocols were employed in determining the respective scores of patients during the clinical trial and conducted by a person trained in the ordinary art of evaluating rheumatoid arthritis.

Results

[0672] Patients receiving 80 mg, 160 mg or 320 mg of Ab1 demonstrated improved DAS28 scores relative to those patients receiving placebo over the course of 16 weeks, as presented in Fig. 62 as a mean change from the baseline DAS28 score. Furthermore, a significant percentage of patients receiving 80 mg, 160 mg or 320 mg of Ab1 achieved

"Good" or "Moderate" classifications relative to those patients receiving placebo over the course of 16 weeks. Thus, administration of Ab1 can result in improved DAS28 and EULAR scores in rheumatoid arthritis when compared to those patients receiving placebo. See WO 2011/066371.

5 EXAMPLE 35

Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Ab1 in Human Subjects

Background

10 **[0673]** A humanized antibody derived from Ab1 (humanized Ab1 or ALD518) containing the variable heavy and light sequences in SEQ ID NO: 19 and 20 was administered to rheumatoid arthritis patients. This antibody is a humanized, asialated, IgG1 monoclonal antibody against IL-6 which has been shown to have a half-life ($t_{1/2}$) of approximately 30 days in humans. In studies in patients with RA, intravenous (IV) with this antibody (humanized Ab1) has demonstrated:

15 efficacy over 16 weeks with rapid American College of Rheumatology (ACR) responses; Complete and durable suppression of C-reactive protein (CRP); Good tolerability, and a safety profile consistent with the biology of IL-6 blockade. This humanized antibody binds to IL-6 with high affinity, preventing interaction and signaling mediated via IL-6R. Rapid and significant treatment responses have been demonstrated with intravenous (IV) administration of humanized Ab1 in patients with RA. In this example we study the safety, pharmacokinetics and pharmacodynamics of subcutaneous (SC)

20 administration of humanized Ab1 in healthy subjects.

[0674] The objective of this study was to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of a single SC injection of this humanized antibody in healthy male subjects.

Methods

25 **[0675]** In this Phase I, double-blind, placebo-controlled study, 27 subjects were randomized 2:1 to receive a single dose of humanized Ab1 or placebo in the following groups: humanized Ab1 50 mg SC, humanized Ab1 100 mg SC or humanized Ab1 100 mg IV (n=6 active and n=3 placebo per group). The primary objective was to assess safety of SC humanized Ab1 versus placebo over 12 weeks. Plasma concentrations of humanized Ab1 and serum concentrations of

30 C-reactive protein (CRP) were assessed as secondary objectives. Assessments were performed daily in Week 1 and then on Day 10, Weeks 2, 4, 6 and 8, and then monthly to Week 12. The study was unblinded at Week 12, and humanized Ab1 subjects were monitored to Week 24.

Study design and population

35 **[0676]** The study included 27 healthy male subjects (aged 18-65 years). Subjects were dosed in three treatment groups of nine subjects each, randomized 2:1 to receive a single dose of humanized Ab1 or placebo on Day 1. Humanized Ab1 treatments per group were: humanized Ab1 IV 100 mg infusion over 60 minutes; humanized Ab1 SC 50 mg injection (1 mL); or humanized Ab1 100 mg injection (1 mL). The study was unblinded at Week 12, after which placebo subjects

40 discontinued the trial and ALD518 subjects were monitored to Week 24.

Safety and immunogenicity assessments

45 **[0677]** The primary objective of the study was to assess the safety of SC humanized Ab1 compared with placebo over 12 weeks. Safety was monitored over 12 weeks for all subjects. The study was unblinded at Week 12, and Humanized AB1 subjects were monitored to Week 24. Laboratory safety tests were performed pre-dose at screening and Day -1, and post dose on Days 2 and 7, Weeks 2, 4, 6, 8 and 12 for all subjects, and Weeks 16, 20 and 24 post-dose for those randomized to Humanized Ab1. Anti-Humanized AB1 antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Blood samples were collected at Day 1 (pre-dose) and Week 12 post-dose for all subjects, and Week

50 24 post-dose for those randomized to Humanized Ab1.

Pharmacokinetic and pharmacodynamic assessments

55 **[0678]** Plasma Humanized AB1 and serum CRP concentrations were assessed by ELISA. For all subjects, samples were collected at screening, pre-dose on Day 1, and post-dose on Days 2 and 7 and Weeks 2, 4, 6, 8 and 12. For subjects randomized to Humanized AB1, further samples were collected at Weeks 16, 20 and 24 post-dose.

Statistical analysis

[0679] All subjects who received a dose of Humanized AB 1 or placebo were included in the safety analysis. All subjects who received a dose of Humanized AB 1 or placebo were included in PD and immunogenicity analyses. All subjects who received a dose of Humanized AB 1 were included in PK analyses (n=18). All PK samples for placebo subjects were confirmed as below quantification. Descriptive statistics were generated for baseline demographics, safety data, plasma Humanized AB 1 parameters and serum CRP concentrations. Wilcoxon Rank Sum test was used to compare CRP concentrations for Humanized AB 1 treatments versus placebo.

Results- Summary

[0680] Over 24 weeks, there were no deaths or serious AEs, and no withdrawals due to AEs. Nearly all subjects (89%) experienced AEs, which were mild or moderate except one event of severe gastroenteritis in the Humanized ab1 SC 50 mg group. Injection site reactions occurred in 5/12 Humanized Ab1 SC subjects, 1/6 placebo SC subjects and 1/3 placebo IV subjects (none were reported in Humanized Ab1 IV subjects). These were mild except one case of moderate erythema and pruritis in the Humanized Ab1 100 mg SC group. Increases in direct bilirubin and neutrophil counts below the limit of normal were more common in subjects receiving Humanized Ab1 than placebo; all were CTC Grade 1 or 2. The half life of Humanized Ab1 was similar across all groups (mean range: 30.7-33.6 days). The median Tmax of Humanized Ab1 was longer after SC (~1 week) than after IV administration (~end of infusion). The PK of SC Humanized Ab1 was dose-proportional in terms of AUC and Cmax at doses of 50 mg and 100 mg. Based on AUC0-∞ (day*µg/mL) of 237, 452 and 764 for the Humanized Ab1 50 mg SC, 100 mg SC and 100 mg IV groups, respectively, the bioavailability of Humanized Ab1 was ~60% for the SC versus IV groups. Subjects receiving Humanized Ab1 experienced rapid and sustained reductions in serum CRP (Fig. 21A), similar results were seen when the antibody was administered either intravenous or subcutaneously (Fig. 21B).

Subject disposition and baseline demographics

[0681] A total of 27 subjects were enrolled and completed the study (n=18 Humanized Ab1 and n=9 placebo). No subjects were withdrawn for any reason. All subjects were male; 23/27 subjects were Caucasian and 4/27 were Asian. Mean age was 29 (range 20-59) and was similar across the groups. Mean height and weight were also generally comparable across groups, although the IV placebo group were slightly lighter.

Safety and immunogenicity to Week 12 for Humanized AB1 and placebo

[0682] A summary of safety is presented in TABLE 9. For the SC Humanized AB1 groups, a total of 11/12 (91%) patients experienced an adverse event (AE) compared with: 6/6 (100%) for the IV Humanized AB1 group; 4/6 (66.6%) for the SC placebo group; and 3/3 (100%) for the IV placebo group.

TABLE 15 Adverse Events

	Up to Week 12					Week 12 - Week 24*		
MedRA Preferred Term	SC 50 mg n=6	SC 100 mg n=6	IV 100 mg n=6	Placebo SC n=6	Placebo IV n=6	SC 100 mg n=6	SC 100 mg n=6	IV 100 mg n=6
Subjects with an AE	6	5	6	4	3	3	5	5
AE severity								
Mild	2	2	5	1	2	3	5	7
Moderate	3	3	1	3	1	1	1	0
Severe	1	0	0	0	0	0	0	0
Discontinuations Due to AEs	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0

(continued)

	Up to Week 12					Week 12 - Week 24*		
MedRA Preferred Term	SC 50 mg n=6	SC 100 mg n=6	IV 100 mg n=6	Placebo SC n=6	Placebo IV n=6	SC 100 mg n=6	SC 100 mg n=6	IV 100 mg n=6
AEs reported in ≥ 2 subjects in any group								
Injection site erythema	1	2	0	0	0	0	0	0
Injection site pruritis	1	2	0	0	1	0	0	0
Gastroenteritis	1	0	2	0	0	0	0	0
URTI	4	4	4	2	2	0	1	2
Skin laceration	2	1	2	0	0	0	0	0
Myalgia	0	0	0	2	0	0	0	0
Headache	5	2	1	1	0	0	1	1
Nasal congestion	0	0	2	0	0	0	0	0
*Patients randomized to placebo (IV or SC) discontinued at Week 12 and are not included in Week 24 analyses; AE=adverse event; SC=subcutaneous; IV=intravenous; URTI=upper respiratory tract infection.								

[0683] Across groups: No deaths or serious AEs were reported and there were no withdrawals due to AEs. Most AEs were mild or moderate in intensity. One case of gastroenteritis in a SC Humanized AB1 50 mg subject was considered severe, but not serious, and not related to study medication. No anti-Humanized AB1 antibodies were detected in any subject during this period.

Injection site reactions

[0684] Injection site reactions were reported in 26% (7/27) of subjects, and all occurred prior to Week 12 (TABLE 40). Injection site reactions occurred in 5/12 SC Humanized AB1 subjects and 1/6 SC placebo subjects. In the IV groups, 0/6 Humanized AB1 subjects and 1/3 placebo subjects experienced injection site reactions. All injection site reactions were mild except in one SC Humanized AB1 100 mg subject with moderate injection site erythema and pruritis. No injection site reactions occurred after Week 12 in any of the Humanized AB1 groups. Infusion site reactions were reported in 0/6 subjects receiving IV Humanized AB1 and 1/3 IV placebo subjects (infusion site pruritis)

TABLE 16 Ab1 Injection Site Reactions to Week 12*

	50 mg n=6	100 mg n=6	100 mg n=6	Placebo SC n=6	Placebo IV n=3
Total subjects with injection site reaction	2	3	0	1	1
Injection site erythema	1	2	0	0	0
Injection site pain	1	1	0	1	0
Injection site pruritis	1	2	0	0	1
Injection site rash	1	0	0	0	0
*All injection site reactions were reported in the first 12 weeks of the study. SC=subcutaneous; IV=intravenous					

Clinical laboratory evaluations

[0685] TABLE 43 shows incidences of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and bilirubin levels across the Humanized AB1 and placebo groups. All ALT and AST levels were Grade 1 by the

Common Terminology Criteria for Adverse Events (CTCAE), and no levels were ≥ 3 times the upper limit of normal (ULN). All increases in total and direct bilirubin were CTCAE Grade 1 or 2 and no subject met criteria for drug-induced liver damage. Only one subject (SC Humanized AB1 100 mg group) had total bilirubin out of range (26 $\mu\text{mol/L}$, range 0-24 $\mu\text{mol/L}$), at Week 24.

TABLE 16 Clinical Laboratory Evaluations Over 24 Weeks (Ab1)

	SC 50 mg n=6	SC 100 mg n=6	IV 100mg n=6	Placebo* n=9
Elevated ALT	0	1	3	2
Elevated AST	0	1	1	1
Elevated total bilirubin	0	1	1	0
Elevated direct bilirubin	2	4	5	2
Low neutrophil count [†]	4	1	2	3
Low platelet count [†]	2	0	0	1
*SC and IV groups combined up to Week 12 only, after which placebo-treated patients discontinued; [†] Below the lower limit of normal; SC=subcutaneous; IV=intravenous; ALT=alanine aminotransferase; AST=aspartate aminotransferase				

[0686] Sporadic decreases in neutrophil and platelet counts were also observed in the Humanized AB1 and placebo groups. Neutrophil counts below the lower limit of normal were more common in subjects receiving Humanized AB1 than placebo but all decreases were CTCAE Grade 1 or 2. Only one subject (SC Humanized AB1 50 mg group) had consistent mild neutropenia to Week 24 ($1.6 \times 10^9/\text{L}$ at Week 24). Reductions in platelet counts were all CTCAE Grade 1 (lowest level $134 \times 10^9/\text{L}$) and no subject had a low platelet count past Week 8.

Pharmacokinetics

[0687] Bioavailability of Humanized AB1 was 60% for SC Humanized AB1 50 and 100 mg versus IV Humanized AB1 100 mg groups based on the mean $\text{AUC}_{0-\infty}$ (TABLE 44). The half-life of Humanized AB1 was similar across all groups (mean range: 30.7-33.6 days) (Table 17). Peak plasma concentration (C_{max}) of SC Humanized AB 1 was reduced as compared to IV (Fig. 15). Median time to maximum plasma concentration (T_{max}) of Humanized Ab1 was longer after SC Humanized AB1 (at approximately one week) than after IV Humanized Ab1 administration (at approximately the end of infusion).

TABLE 17 Ab1 Plasma Pharmacokinetic Parameters to Week 24

	SC 50 mg n=6	SC 100 mg n=6	IV 100mg n=6
C_{max} ($\mu\text{g/mL}$) (CV)*	5.57 (24%)	9.19 (34%)	33.6 (30%)
T_{max} (days) (min, max) [†]	6 (6, 14)	5.5 (2, 28)	0.17 (0, 17, 0.34)
AUC_{5-24} (day $\cdot\mu\text{g/mL}$) (CV)*	218 (34%)	435 (19%)	732 (22%)
$\text{AUC}_{8-\infty}$ (day $\cdot\mu\text{g/mL}$) (CV)*	224 (39%)	444 (20%)	746 (22%)
$t_{1/2}$ (days $\pm\text{SD}$) [‡]	33.6 ± 21.7	31.1 ± 9.0	30.7 ± 5.9
CL (mL/day) (CV)*	223 (32%)	225 (21%)	134 (27%)
*Data are geometric mean (coefficient of variation %, CV%). [†] Data are median (minimum, maximum). [‡] Data are mean ($\pm\text{SD}$). CV=coefficient of variation; C_{max} =maximum plasma concentration; AUC=area under curve; SD=standard deviation; CL=apparent total body clearance for IV and apparent total body clearance divided by bioavailability for SC; IV=intravenous; SC=subcutaneous; T_{max} =time to maximum plasma concentration; $t_{1/2}$ =terminal plasma half-life			

Pharmacodynamics

[0688] CRP levels were reduced in all subjects who received Humanized AB1 irrespective of dose or administration route. From Weeks 4 to 12, CRP levels were significantly lower in subjects who received Humanized Ab1 compared

with placebo (unadjusted p-value <0.05). A high correlation between the IgG produced and antigen specificity for an exemplary IL-6 protocol was observed with 9 of 11 wells showed specific IgG correlation with antigen recognition. In Humanized AB1 subjects, CRP levels were lowered to <20% of pre-dose levels in: 72% (13/18) of subjects at Week 1; 73% (11/15) of subjects at Week 12; and 56% (10/18) of subjects at Week 24.

Conclusions

[0689] In this Phase I study, the anti-IL-6 antibody Humanized Ab1 was generally well tolerated when administered in a single SC dose in healthy male subjects. Injection site reactions were generally mild. No anti-Humanized Ab1 antibodies were detected. Changes in liver enzymes, neutrophil and platelet counts were reversible. The bioavailability of SC Humanized AB1 was approximately 60% of that observed with IV Humanized Ab1. The half-life of Humanized AB1 was approximately 30 days, irrespective of route of administration. These data concur with previous data using IV Humanized Ab12. Subcutaneous Humanized AB 1 led to rapid and large reductions in serum CRP. Reductions in CRP observed during the first 12 weeks of the study were sustained over 24 weeks of assessment. These preliminary data support the continued development and evaluation of subcutaneous Humanized Ab1 for the treatment of patients with mucositis.

[0690] In summary, in this Phase I study, the anti-IL-6 antibody Humanized Ab1 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC Humanized Ab1 was ~60% of IV Humanized Ab1, and the half life was ~30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

Example 36

Effect of Ab1 on DAS28-Assessed Disease Activity

[0691] ALD518* is an asialated, humanized anti-IL-6 monoclonal antibody with a half-life of ~30 days containing the humanized variable heavy and light sequences contained in SEQ ID NO:19 and 20. These humanized heavy and light sequences are derived from a parent rabbit antibody that specifically binds human IL-6 which antibody is referred to in said incorporated application as Ab1. ALD518 binds to IL-6 with high affinity, preventing interaction and signalling mediated via soluble and membrane-bound IL-6R. Rapid and significant ACR responses have been demonstrated with ALD518* in patients with RA. In this example we report the impact of ALD518 on DAS28-assessed disease activity over 16 weeks.

Methods

[0692] Patients with active RA and an inadequate response to methotrexate (MTX) were randomized 1:1:1:1 to intravenous ALD518* 80, 160 or 320 mg or placebo during this 16-week, double-blind, placebo-controlled Phase II study. Patients received two IV infusions of ALD518 (Day 1 and Week 8), while continuing on stable doses of methotrexate (MTX). The primary efficacy endpoint was the proportion of patients achieving ACR20 at Week 12; disease activity was assessed via Disease Activity Score (DAS28) based on C-reactive protein (CRP) as a secondary endpoint. The proportion of patients achieving DAS28-defined remission (score <2.6), low disease activity state (LDAS; score ≤3.2) and good EULAR responses (current DAS28 ≤3.2 and improvement from baseline >1.2) were assessed for the modified intent-to-treat population, and are presented for patients with available data (as observed). P-values are based on Chi-square tests.

Results

[0693] Of 127 randomized and treated patients, 116 completed the trial. At baseline, mean age was 52.3 years and RA duration was 6.8 years. At Weeks 4, 12 and 16, the proportion of patients achieving LDAS and remission was greater than placebo for all ALD518* doses; differences were significant versus placebo (p<0.05) for all assessments except ALD518* 80 mg at Week 4 (p=0.056). Similarly, EULAR responses were significantly better for all ALD518* doses versus placebo (p<0.01) at Weeks 4, 12 and 16. There was a trend toward greater responses with higher ALD518* doses.

TABLE 18 Proportion of patients achieving DAS28-defined remission, LDAS and good EULAR responses

	ALD518* 80 mg (N=32)	ALD518* 160 mg (N=34)	ALD518* 320 mg (N=28)	Placebo - (N=33)
DAS28-defined remission				
Week 4	10.0	8.8	17.9	0
Week 12	17.2	21.2	34.6	3.3
Week 16	13.8	28.1	44.0	0
LDAS				
Week 4	10.0	23.5	28.6	0
Week 12	20.6	33.3	46.1	6.6
Week 16	20.7	50.0	52.0	3.4
Good EULAR response				
Week 4	10.0	23.5	28.6	0
Week 12	20.7	33.3	46.2	6.7
Week 16	20.7	50.0	52.0	3.4
DAS28=Disease Activity Score 28; LDAS=low disease activity state				

[0694] SAEs were reported in two ALD518 patients (both had significant increases in liver enzymes, and discontinued treatment). Overall, elevations in liver enzymes >2xULN occurred in 17% of ALD518*- versus 0% placebo-treated patients; the frequency was highest in the 320 mg dose group. Modest increases in total cholesterol were observed (mean increase by Week 16=1.1 mmol/L for ALD518* versus 0.2 mmol/L for placebo). Nine ALD518 patients had transient Grade II and two had transient Grade III neutropenias. There were no serious infections or infusion reactions in any treatment group, and no evident immunogenicity.

Conclusions

[0695] In this Phase II study, the novel IL-6 inhibitor ALD518 resulted in rapid and significant improvements in disease activity sustained over 16 weeks of assessment in patients with RA and an inadequate response to methotrexate (MTX). ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

EXAMPLE 37

Ab1 Administration

Methods

[0696] Patients with active RA were randomized into a 16 week, double-blind, placebo-controlled trial comparing multiple iv infusions of ALD518 (80, 160 or 320mg). Patients received an infusion every 8 weeks and were maintained on a stable dose of MTX throughout the trial. Assessments included ACR 20/50/70 responses and DAS28. All patients were evaluated for safety. For early withdrawals, LOCF analysis was used for continuous variables and non-responder imputation for categorical variables.

Results

[0697] 132 patients were randomized; 127 were dosed. Mean disease duration was 6.6 years; mean DAS28 score was 6.2 and mean HAQ-DI was 1.72. 11 patients did not complete the 16-week trial: 320mg-3, 160mg-1, 80mg-3, placebo-4: 4 discontinued due to adverse events (80mg-2, 320mg-2), with 2 SAEs (80mg-1, 320mg-1). Elevations in liver enzymes (LFTs) >2xULN were observed in 17% ALD518 versus 0% placebo. There were modest increases in total cholesterol (mean increase by week 16 = 1.1 mmol/L ALD518 versus 0.2 mmol/L placebo). 9 patients on ALD518 had transient grade 2 neutropenias; 2 pts transient grade 3 neutropenias. There were no serious infections reported in any treatment group. Infusions of ALD518 were well tolerated without infusion reactions or evident immunogenicity. At weeks

4 and 16, ACR responses (non responder imputation analysis) and improvements in DAS28 scores were:

TABLE 19: Week 4 DAS28 Scores for Ab1 80, 160, and 320 dosages

Week 4	80mg (n=32)	160mg (n=34)	320mg (n=28)	PBO+MTX (n=33)
ACR20	50% (16)*	56% (19)*	71% (20)*	23% (8)
ACR50	9% (3)	15% (5)	29% (8)†	3% (1)
ACR70	6% (2)	0% (0)	11% (3)	0% (0)
Mean Δ DAS28	-1.8	-2.1	-2	-0.6
*p£0.04; †p=0.009				

TABLE 20: Week 16 DAS28 Scores for Ab1 80, 160, and 320 dosages

Week 16	80mg (n=32)	160mg (n=34)	320mg (n=28)	PBO+MTX (n=33)
ACR20	75% (24)*	65% (22)*	82% (23)*	36% (12)
ACR50	41% (13)*	41% (14)*	50% (14)*	15% (5)
ACR70	22% (7)†	18% (6)‡	43% (12)*	6% (2)
Mean Δ DAS28	-2.7	-2.7	-3.2	-1.1
*p£0.03 †p=0.08 ‡p=0.26				

Conclusion

[0698] ALD518 is the first mAb to IL-6, as opposed to an anti-IL-6 receptor mAb, to show a significant, rapid and sustained improvement in disease activity in RA. ALD518 in doses ranging from 80 to 320 mg given as 2 IV infusions to pts with active RA was well tolerated with increases in LFTs and total cholesterol and transient neutropenia observed in some patients. There were no infusion reactions associated with administration of ALD518 and no detectable immunogenicity.

EXAMPLE 38

Treatment of oral mucositis with head and neck cancer receiving concurrent chemotherapy and radiotherapy.

[0699] Subjects suffering from oral mucositis with head and neck cancer receiving concurrent chemotherapy and radiotherapy may receive a regimen of a 160 mg or 320 mg doses of a composition comprising a humanized monoclonal antibody that selectively binds IL-6.

[0700] Subjects will be assessed using tumor staging (standard TNM system) during the screening period, which may occur within 30 days prior to radiotherapy (RT) start. The RT treatment period will be approximately 7 weeks, depending on the subject's prescribed radiation plan. Post-RT treatment period visits will be at Weeks 1, 2, 3, and 4 following the treatment period. Long term follow-up visits will occur at 3, 6, 9, and 12 months following the end of RT to determine if there is an effect of ALD518 on the tumor response to CRT.

[0701] Subjects may have recently diagnosed, pathologically confirmed, non-metastatic SCC of the oral cavity, oropharynx, hypopharynx or larynx. Subjects may be scheduled to receive a continuous course of intensity-modulated radiotherapy (IMRT), with a minimum cumulative dose of 55 Gy and maximum dose of 72 Gy. Planned radiation treatment fields may include at least 2 oral sites (e.g., buccal mucosa, floor of oral cavity, tongue or soft palate) with each site receiving a total dose of ≥ 55 Gy. The treatment plan may include monotherapy with cisplatin administered in standard weekly (30 to 40 mg/m²) or tri-weekly (80 to 100 mg/m², given on Days 0, 21 and 42) regimens or monotherapy with carboplatin administered weekly (100 mg/m²).

[0702] A composition comprising a humanized monoclonal antibody that selectively binds IL-6 may be given within 2 hours prior to the subjects' radiation every 4 weeks for a total of 2 doses. A *baseline* visit will occur on the first day of ALD518 and RT. Safety, PK, PD, and markers of IL-6 biology (e.g., total IL-6, sIL-6r, soluble gp130, sIL-6 Complex) will be monitored during the RT treatment and Post-RT treatment period. The *long term follow-up period* of the treatment may include long term follow-up visits, primarily for the assessment of tumor response and survival. These assessments

will take place at Months 3, 6, 9 and 12 following the last dose of RT. At Months 3, 6, 9, and 12 tumors will be assessed clinically. At the Month 6 and Month 12 follow-up visits, tumor status will be assessed using RECIST criteria and the same imaging modality (CAT, PET or MRI) that was used to evaluate tumor status prior to RT start (at the time of staging) may be used.

[0703] Following a treatment regimen comprising the administration of a humanized monoclonal antibody that selectively binds IL-6, patients may show improvement in their oral mucositis (e.g., a reduction in symptoms).

EXAMPLE 39

Oral Mucositis Study 1: Single Acute Radiation Dose (40 Gy) Study

[0704] Introduction: The efficacy of treatment with a rodent anti-IL-6 antibody (monoclonal rat IgG1 clone MP5-20F3, R&D Systems) was studied in an established mouse model of radiation-induced oral mucositis. Dorr & Kummermehr (1991) Virchows Arch B Cell Pathol Incl Mol Pathol 60(5): 287-94. Study endpoints included oral mucositis duration and severity, body weight, and survival in normal C3H mice.

[0705] Methods: 36 male C3H mice were exposed to a single dose of 40 Gy radiation directed to the underside of the tongue on Day 0. Animals were dosed with a rodent anti-IL-6 antibody (monoclonal rat IgG1 clone MP5-20F3, R&D Systems), control antibody (monoclonal rat IgG1 clone 43414, R&D Systems), or vehicle on Days -1, 2, 6, 9, and 13, via intravenous injection at 10 mg/kg into the tail vein. Animals were weighed daily, and food and water consumption were monitored in each treatment group.

[0706] Images of the tongue were captured daily from Days 4 to 16. An oral mucositis score was assigned to each animal based on a defined scoring scale per protocol design. The scoring scale is presented in Table 21. Following completion of the study, the tongue images were scored by blinded observers to establish the values used to determine the degree and duration of oral mucositis and any treatment effects. A score of 1-2 is considered to represent a mild stage of disease, whereas a score of 3-5 is considered to indicate moderate to severe mucositis.

Table 21: Rodent Model Oral Mucositis Scoring Scale

Score	Description
0	Tongue completely healthy. No erythema or vasodilation.
1	Light to severe erythema and vasodilation. No erosion of mucosa.
2	Severe erythema and vasodilation. Erosion of superficial aspects of mucosa leaving denuded areas. Decreased stippling of mucosa.
3	Formation of off-white ulcers in at least one places. Ulcers may have a yellow/gray appearance due to pseudomembrane. Cumulative size of ulcers should equal about ¼ of the tongue. Severe erythema and vasodilation.
4	Cumulative size of ulcers should equal ¼ to ½ of the tongue. Loss of pliability. Severe erythema and vasodilation.
5	Virtually all of tongue is ulcerated.

[0707] Results: The onset of mucositis was the same for all 3 groups with peak mucositis scores occurring on Day 10. An analysis of the number of days mice presented with scores of 3+ during the study demonstrated no statistical difference among the 3 groups (mean days of 3.3, 4 and 3.6 for vehicle, isotype control and anti-IL-6, respectively).

[0708] On Day 10, 100% of the mice in the vehicle and control antibody groups developed ulcers while 67% of the anti-IL-6 group developed ulcers (Figure 22). There was no statistical difference in ulceration scores at Day 10 between the anti-IL-6 antibody and control antibody or vehicle groups. On Days 12 and 13, a numerically larger (not statistically different) number of mice in the anti-IL-6 group had ulceration compared to the mice in the vehicle or control groups.

[0709] Weight loss was seen in all 3 groups with peak weight loss occurring between Days 11 and 12. There were no statistically significant differences in weight change between the three groups. No general toxicities were noted in this study that could be attributed to treatment with the control or anti-IL-6 antibodies or the vehicle. No treatment-related deaths occurred during the study.

EXAMPLE 40**Ascending Radiation Dose Levels Study in Mouse Model of Radition-Induced Oral Mucositis****5 Introduction**

[0710] The efficacy of treatment with a rodent anti-IL-6 antibody (monoclonal rat IgG1 clone MP5-20F3, R&D Systems) was studied in an established mouse model of radiation-induced oral mucositis. Dorr & Kummermehr J. Proliferation kinetics of mouse tongue epithelium under normal conditions and following single dose irradiation. Virchows (1991) Arch B Cell Pathol Incl Mol Pathol. 60(5): 287-294. Study endpoints included oral mucositis duration and severity, body weight, and survival in normal C3H mice.

Methods

[0711] 120 male C3H mice (12 per treatment group per radiation dose) were exposed to a single dose of radiation, totaling 25, 30, 35, 40, or 45 Gy directed to the underside of the tongue on Day 0. Animals were dosed with a rodent anti-IL-6 antibody (monoclonal rat IgG1 clone MP5-20F3, R&D Systems) or control antibody (monoclonal rat IgG1 clone 42414, R&D Systems) on Days -1, 2, 6, 9, and 13, via intravenous injection at 10 mg/kg into the tail vein. Animals were weighed daily; and food and water consumption was monitored in each treatment group.

[0712] Images of the tongue were captured daily from Days 4 to 16. An oral mucositis score was assigned to each animal based on a defined scoring scale per protocol design. The scoring scale is presented in Table 21. Following completion of the study, the tongue images were scored by blinded observers to establish the values used to determine the degree and duration of oral mucositis and any treatment effects. A score of 1-2 is considered to represent a mild stage of disease, whereas a score of 3-5 is considered to indicate moderate to severe mucositis.

Conclusions

[0713] Mice treated with the anti-IL-6 antibody at 25 Gy showed a statistically significant decrease in the median number of days with ulceration compared to mice treated with the control antibody ($p=0.0134$). There was no difference between the treatment groups at 30 and 35 Gy. Mice treated with the anti-IL-6 antibody at 40 and 45 Gy showed a statistically significant increase in the median number of days with ulceration compared to mice treated with the control antibody ($p=0.0237$ and 0.0037 , respectively). These data are shown in Figure 23.

[0714] The anti-IL-6 treated group had a numerically lower percentage of mice that were ulcerated at any timepoint over the course of the study compared to control antibody treated group at the 25 and 30 Gy radiation levels (45% vs. 82%; 67% vs. 92%). See Figure 24. At higher radiation dose levels the percentage of mice that were ulcerated over the course of the study in the two treatment groups were similar.

[0715] Over the course of the study, the anti-IL-6 treatment group receiving 25 Gy had statistically significant positive median percentage changes from baseline body weight compared to the control antibody group at all timepoints. Additionally, at Day 4, the anti-IL-6 group at 30 and 35 Gy radiation dose levels had statistically significant positive median percentage changes from baseline body weight compared to the control antibody group. At the 40 and 45 Gy radiation dose levels, there were no differences in median percent change from baseline between the anti-IL-6 and control antibody groups.

[0716] No general toxicities were noted in this study that could be attributed to treatment with the anti-IL-6 antibody or control antibody. No treatment-related deaths were observed during the study.

Conclusions

[0717] In conclusion, at the lowest dose (25 Gy) of radiation there was a lower incidence and duration of ulcerated oral mucositis (scores 3-5) in the anti-IL-6 treated group compared to controls. Additionally, the mice treated with the anti-IL-6 antibody did not lose body weight compared to controls. At the 30 Gy radiation dose level, there was lower incidence of ulcerated oral mucositis in the anti-IL-6 treated group compared to controls. Mice receiving higher single doses of radiation (40 Gy and 45 Gy) had a longer duration of ulcerated oral mucositis in the anti-IL-6 antibody treated group compared to controls. The radiation dose levels administered as single doses in this study are much higher than the daily doses (approximately 2 Gy) given in IMRT for the treatment of head and neck cancer. These data support with the use of a humanized monoclonal antibody (e.g., ALD518) in the prevention of CRT-induced oral mucositis in head and neck cancer patients.

EXAMPLE 41**Effect of Anti-IL-6 Treatment on Tumor Growth in a Xenograft Model**5 **Introduction**

[0718] The human pharynx squamous cell carcinoma cell line (FaDu) has been utilized as a model for head and neck cancers in mouse xenograft studies. Alderson, et al (2002) Cancer Chemother. Pharmacol. 50: 202-212. FaDu expresses both IL-6 and the IL-6 receptor and IL-6 levels are induced in response to radiation treatment. Chen, et al. (2010) Int. J. Radiation Oncology Biol. Phys. 76:1214-1224 The effect of anti-IL-6 treatment on the growth of FaDu tumors in the presence or absence of radiation treatment was studied in an established mouse xenograft model. Study endpoints included tumor volume and body weights.

15 **Methods**

[0719] 120, six week old, female athymic nude mice were implanted with ten million FaDu tumor cells subcutaneously. When tumors reached the weight range of 125-250mg (Day 10), animals were divided into 3 groups of 40 mice. One group was given vehicle twice weekly via intravenous injection into the tail vein. The second group was given 10mg/kg each of ALD518 and an anti-mouse IL-6 antibody (monoclonal rat IgG1, R&D Systems). The third treatment group was given 10mg/kg each of isotype control antibodies (monoclonal human IgG1, R&D Systems). In each of the treatment groups, half of the animals (N=20) were irradiated with 2Gy/day for 5 days and the other 20 animals were not irradiated. Animals were euthanized when tumor volume reached 4,000 mm³ or ulceration of the tumor occurred. All animals were weighed and tumor volumes measured three times a week for the duration of the study.

25 **Results**

[0720] The tumor volumes for each animal were measured three times a week starting on the first day of treatment (Day 10). The study was completed on Day 29. FaDu tumors have a high rate of ulceration; in this study, between 9 and 13 animals were sacrificed in each group by Day 29 due to tumor ulceration. No animals were euthanized due to tumor burden. The median tumor volume for each group is presented in Figure 25. All groups had median tumor volumes between 162-167 mm³ at the start of treatment (Day 10). Groups treated with vehicle, isotype control antibodies or anti-IL-6 antibodies but not irradiated displayed very similar median tumor volumes throughout the study. These groups were not statistically different. Groups treated with vehicle, isotype control antibodies or anti-IL-6 antibodies plus radiation had reduced median tumor volumes of roughly 50% compared to the non-irradiated groups post Day 22. Median tumor volumes of the irradiated groups were similar and not statistically different. Thus, treatment with anti-IL-6 antibodies had no effect on tumor growth in either the non-irradiated or irradiated groups.

[0721] Additional conclusions from the study include: no differences in weight were observed between the six groups; no general toxicities were noted that could be attributed to treatment with the vehicle, control antibodies or anti-IL-6 antibodies; and there were no treatment-related deaths.

40

EXAMPLE 43**Clinical Trial Design**

[0722] A phase 2, double-blind, placebo-controlled trial evaluating the safety, efficacy, pharmacokinetics and pharmacodynamics of ALD518, and the health and economic outcomes in subjects receiving CRT for the treatment of squamous cell carcinomas (SCCs) of the oral cavity, oropharynx, hypopharynx or larynx may be conducted. Up to 96 subjects may be enrolled into this trial. Initially 3 open-label subjects will be enrolled into a safety run-in of the 160 mg dose. Approximately 90 subjects will be randomized (1:1:1) into 1 of 2 dose levels of ALD518 (160 mg and 320 mg) or placebo during the double-blind portion of the trial. Safety, PK, PD, and markers of IL-6 biology (e.g., total IL-6, sIL-6r, soluble gp130, sIL-6 Complex) will be monitored during the RT treatment and Post-RT treatment period. Additionally, exploratory analyses of IL-6 biology including cytokine biomarkers may be performed in a subset of subjects and will require separate consent.

[0723] Subject eligibility, including tumor staging (standard TNM system), will be assessed during the screening period, which may occur within 30 days prior to radiotherapy (RT) start. The RT treatment period will be approximately 7 weeks, depending on the subject's prescribed radiation plan. Post-RT follow-up visits will be at Weeks 1, 2, 3, and 4. Long term follow-up visits will occur at 3, 6, 9, and 12 months following the end of RT to determine if there is an effect of ALD518 on the tumor response to CRT.

[0724] Eligible subjects will have recently diagnosed, pathologically confirmed, non-metastatic SCC of the oral cavity, oropharynx, hypopharynx or larynx. Subjects must be scheduled to receive a continuous course of intensity-modulated radiotherapy (IMRT), with a minimum cumulative dose of 55 Gy and maximum dose of 72 Gy. Planned radiation treatment fields must include at least 2 oral sites (e.g., buccal mucosa, floor of oral cavity, tongue or soft palate) with each site receiving a total dose of ≥ 55 Gy. The treatment plan must include monotherapy with cisplatin administered in standard weekly (30 to 40 mg/m²) or tri-weekly (80 to 100 mg/m², given on Days 0, 21 and 42) regimens or monotherapy with carboplatin administered weekly (100 mg/m²).

[0725] ALD518 or placebo will be given every 4 weeks within 2 hours prior to the subjects' radiation for a total of 2 doses. A *baseline* visit will occur on the first day of RT. During the RT treatment period, subjects will be assessed twice weekly for the presence and severity of OM by treatment-blinded, trained evaluators using the World Health Organization (WHO) grading scale for OM. Subjects will also complete a daily diary, containing the Oral Mucositis Daily Questionnaire (OMDQ) and a listing of analgesic use, and on a weekly basis the FACT-HN and FACIT-F subscale PRO instruments.

[0726] All subjects will return to the clinic for 4 weekly visits after RT completion for assessment of OM. During this time, subjects will also continue to complete the OMDQ and the FACT-HN and FACIT-F subscale PRO instruments. The *long term follow-up period* of the clinical trial will include quarterly visits, primarily for the assessment of tumor response. These assessments will take place at Months 3, 6, 9 and 12 following the last dose of RT. At Months 3, 6, 9, and 12 tumors will be assessed clinically. At the Month 6 and Month 12 follow-up visits, tumor status will be assessed using RECIST criteria and the same imaging modality (CAT, PET, or MRI) that was used to evaluate tumor status prior to RT start (at the time of staging).

Example 44

Additional Evaluation of ALD518 in RA Clinical Trials

[0727] This example describes further Phase II clinical trial results for administration of ALD518 to patients with active RA. For purposes of inclusion in this study, a patient was considered to have active RA if the patient exhibited at least 6 swollen/6 tender joints, CRP ≥ 10 mg/dL, and had been treated with a stable dose of methotrexate (MTX) (>10 mg/week) for at least 3 months and stable use of NSAIDs or steroids (if any).

[0728] ALD518 was administered in a double-blind, placebo-controlled study in which patients with active RA were randomized 1:1:1:1 to receive either 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) ALD518, or placebo (n=33). ALD518 or placebo were given as an intravenous infusion over 60 minutes on Day 1 and then again 8 weeks later. Patients were maintained on stable doses of methotrexate (MTX) (at least 10 mg/week). Disease-modifying antirheumatic drugs (DMARDs) other than MTX were discontinued at least 4 months prior to study entry. Efficacy endpoints were assessed at weeks 12 (primary endpoint) and week 16. HRQoL was evaluated by the Medical Outcomes Survey Short Form-36 (SF-36). Analyses were performed on the modified intent-to-treat population for patients with data available at the visit of interest (as observed).

[0729] 127 active RA patients were randomized and treated, and 116 completed the trial (80 mg, 29/32; 160 mg, 33/34; 320 mg, 25/28; placebo, 29/33). Patient disposition is summarized in FIG. 26.

[0730] At baseline, mean age was 52.3 years; mean RA duration was 6.8 years; mean tender and swollen joint counts were 26.1 and 16.7, and mean Physical (PCS) and Mental component summary (MCS) scores were 31.0 and 35.0, respectively. Mean changes from baseline to week 12 in MCS were significantly greater in each ALD518 dose group vs placebo, and mean changes in both PCS and MCS scores exceeded MCID in each ALD518 group. At week 12, mean changes from baseline in one or more SF-36 domains were significantly greater in ALD518 dose groups vs placebo. Changes $>MCID$ were observed in all domains and in SF-6D in patients receiving ALD518. Improvements at week 12 were sustained at week 16.

Results

[0731] Short Form-36 Component Summary Scores: HRQoL was assessed by the patient-reported Short Form-36 (SF-36) questionnaire. The SF-36 includes 36 questions divided into eight domains and summarized into the physical and mental component summary scores (PCS and MCS, respectively). Scores range from 0 to 100, with higher scores indicating better health. The observed Minimum Clinically Important Differences (MCID) are 2.5-5.0 for the PCS and MCS, and 5.0-10.0 for domain scores.

[0732] Short Form-6D: The SF-6D is a validated preference-based measure of health utilities. The SF-6D was calculated using mean changes within treatment groups across all eight SF-36 domains to yield a single utility measure. The Minimum Important Difference (MID) is 0.041.

Analysis

[0733] Analysis was performed on the modified intent-to-treat population for patients with available data at the visit of interest (as observed). Changes from baseline in SF-36 PCS, MCS and domain scores were summarized as descriptive statistics by treatment group and visit. ALD518 treatment groups were also compared with placebo at Week 12 using a two-sample t-test.

[0734] For Weeks 12 and 16, spydergrams were used to present results across all domains of the SF-36 in a single figure, and to compare with age- and gender-matched normative data from a US population. Demarcations along the domain axes of the spydergrams represent changes of 10 in domain score, and patient disposition and baseline demographics and characteristics.

[0735] As shown in FIG. 26, a total of 127 patients were randomized and received ≥1 dose of ALD518; 91.3% of patients completed the study and eleven (8.7%) patients discontinued the study.

[0736] The individual SF-36 domain scores at Baseline and Week 12 are shown in Table 22 and illustrated graphically in FIG. 27. Baseline domain scores were generally well balanced across the treatment groups At baseline, patients had impaired HRQoL. Combined mean baseline PCS and MCS scores were 31.0 and 35.0, respectively, and 1.5-2.0 standard deviations less than normative values of 50. Scores for each of the individual subscales of the SF-36 were also considerably lower than age- and gender-matched US norms.

[0737] For all ALD518 treatment groups, mean improvements from baseline to Week 12 were large across the eight domains of the SF-36 and exceeded those observed with placebo (See the Table 22 and FIG. 27). Mean improvements were significantly greater than those observed with placebo (p<0.05; Table 22) at Week 12 in the following domains: Role physical (ALD518 320 mg group); bodily pain, general health, social functioning and mental health (ALD518 80 and 320 mg treatment groups); vitality (all ALD518 groups) ; role emotional (ALD518 80 mg group).

[0738] At all doses of ALD518, mean improvements in all eight SF-36 domains exceeded the MCID at Week 12. See Table 22. After adjustment for the change from baseline in the placebo group, improvements from baseline observed with ALD518 were greater than, and in some cases at least twice, that observed in the placebo group. There was observed dose-dependent changes (improvements) in the domains of role physical, bodily pain and mental health . Treatment with ALD518 resulted in improvements in SF-36 scores toward those observed in the 'normal' comparative population. See FIG. 29.

TABLE 22: SF-36 PCS and MCS Domains at Baseline and at Week 12

Domain* (+age/ gender norm)	Time point	ALD518 80 mg (n=32)	ALD518 160 mg (n=34)	ALD518 320 mg (n=28)	Placebo (n=33)
PCS Domains					
Physical functioning (79.6)	Baseline	48.3	42.1	49.3	42.8
	Mean at Week 12	61.0	61.6	70.4	55.0
Role physical (80.1)	Baseline	27.9	26.0	36.7	33.5
	Mean at Week 12	50.0	53.5	59.7†	47.1
Bodily pain (68.3)	Baseline	26.4	22.1	33.6	30.7
	Mean at Week 12	47.8†	50.5	56.9†	39.5
General health (69.5)	Baseline	36.5	33.4	38.7	38.9
	Mean at Week 12	45.1†	45.6	49.5†	39.4
Vitality (58.2)	Baseline	32.5	26.2	38.8	41.5
	Mean at Week 12	50.9†	50.8†	60.9†	46.3
Social functioning (83.6)	Baseline	47.7	31.6	42.1	48.8
	Mean at Week 12	66.8†	59.4	73.1†	57.5

(continued)

Domain* (+age/ gender norm)	Time point	ALD518 80 mg (n=32)	ALD518 160 mg (n=34)	ALD518 320 mg (n=28)	Placebo (n=33)
PCS Domains					
Role emotional (86.8)	Baseline	44.5	40.8	37.3	43.1
	Mean at Week 12	60.3†	63.0	61.7	51.9
Mental health (74.9)	Baseline	48.4	34.7	51.1	52.7
	Mean at Week 12	61.0†	61.6	70.4†	55.0
*0-100 scores are presented for each domain to enable interpretation within the context of the MCIDs; shading highlights changes ≥MCID in domain scores; Baseline scores are mean, based on patients with available data at visit of interest; PCS=Physical Component Score; MCS=Mental Component Score; MCID=Minimum Clinically Important Differences; †represents p<0.05 associated with comparison of changes from baseline between a ALD518 arm versus placebo based on an ANCOVA model, adjusted for age at baseline and sex					

[0739] Result Summary: 127 active RA patients were randomized and treated, and 116 completed the trial (80 mg, 29/32; 160 mg, 33/34; 320 mg, 25/28; placebo, 29/33). At baseline, mean age was 52.3 years; mean RA duration was 6.8 years; mean tender and swollen joint counts were 26.1 and 16.7, and mean Physical (PCS) and Mental component summary (MCS) scores were 31.0 and 35.0, respectively. Mean changes from baseline to week 12 in MCS were significantly greater in each ALD518 dose group vs placebo, and mean changes in both PCS and MCS scores exceeded MCID in each ALD518 group. At week 12, mean changes from baseline in one or more SF-36 domains were significantly greater in ALD518 dose groups than the placebo group (Table 23). Improvements in SF-6D were 3-4 times the MID in the ALD-518 groups compared with less than 2 times the MID in the placebo group (as noted above, the MID is 0.041). Changes exceeding the MCID were observed in all domains and in SF-6D in patients receiving ALD518. Improvements at week 12 were sustained at week 16.

Table 23. SF-6D Scores at Baseline and Weeks 12 and 16. Shading highlights changes that exceeded the MID (minimum important difference).

SF-6D(+age/gender norm)			ALD518 80 mg (n=32)	ALD518 160 mg (n=34)	ALD518 320 mg (n=28)	Placebo (n=33)
SF-6D (0.831)	Week 12	n =	32	33	29	32
		Baseline	0.582	0.522	0.612	0.603
		Mean at Week 12	0.714	0.715	0.785	0.664
		Mean change to Week 12	0.132	0.193	0.172	0.062
	Week 16	n =	32	33	29	32
		Baseline	0.556	0.584	0.579	0.592
		Mean at Week 16	0.692	0.736	0.751	0.662
		Mean change to Week 16	0.140	0.150	0.170	0.070

[0740] Conclusions: Treatment with the IL-6 inhibitor ALD518 resulted in statistically significant and clinically meaningful improvements in physical and mental aspects of HRQoL. These data further support the clinical efficacy of ALD518 for treatment of patients with active RA and inadequate responses to methotrexate (MTX).

EXAMPLE 45

ORAL MUCOSITIS CLINICAL TRIAL IN PROGRESS

5 **[0741]** Subjects suffering from oral mucositis with head and neck cancer receiving concurrent chemotherapy and radiotherapy are being treated with regimen of a 160 mg doses of a composition comprising a humanized monoclonal antibody that selectively binds IL-6 (ALD518, *also known as* Ab1 which contains the variable sequences in SEQ ID NO:19 and SEQ ID NO:20).

10 **[0742]** Subjects are being assessed using tumor staging (standard TNM system) during the screening period, which occurs within 30 days prior to radiotherapy (RT) start. The RT treatment period is approximately 7 weeks, depending on the subject's prescribed radiation plan. Post-RT treatment period visits are scheduled at weeks 1, 2, 3, and 4 following the treatment period. Long term follow-up visits are scheduled at 3, 6, 9, and 12 months following the end of RT to determine if there is an effect of ALD518 on the tumor response to CRT.

15 **[0743]** Subjects were recently diagnosed and pathologically confirmed with non-metastatic SCC of the oral cavity, oropharynx, hypopharynx or larynx. Subjects are scheduled to receive a continuous course of intensity-modulated radiotherapy (IMRT) with a minimum cumulative dose of 55 Gy and maximum dose of 72 Gy. Planned radiation treatment fields include at least 2 oral sites (*e.g.*, buccal mucosa, floor of oral cavity, tongue or soft palate) with each site receiving a total dose of ≥ 55 Gy. The treatment plan include monotherapy with cisplatin administered in standard weekly (30 to 40 mg/m²) or tri-weekly (80 to 100 mg/m², given on Days 0, 21 and 42) regimens or monotherapy with carboplatin administered weekly (100 mg/m²).

20 **[0744]** A composition comprising a humanized monoclonal antibody that selectively binds IL-6 (ALD518 *also known as* Ab1) is being given within 2 hours prior to the subjects' radiation every 4 weeks for a total of 2 doses. A *baseline* visit occurred on the first day of ALD518 and RT. Safety, PK, PD, and markers of IL-6 biology (*e.g.*, total IL-6, sIL-6r, soluble gp130, sIL-6 Complex) are being monitored during the RT treatment and Post-RT treatment period. The *long term follow-up period* of the treatment includes scheduled long term follow-up visits, primarily for the assessment of tumor response and survival. These assessments are scheduled at months 3, 6, 9 and 12 following the last dose of RT. At months 3, 6, 9, and 12 tumors will be assessed clinically. At the Month 6 and Month 12 follow-up visits, tumor status will be assessed using RECIST criteria and the same imaging modality (CAT, PET or MRI) that was used to evaluate tumor status prior to RT start (at the time of staging) may be used.

30 **[0745]** Following a treatment regimen comprising the administration of a humanized monoclonal antibody that selectively binds IL-6 ALD-518 (Ab1) the patients show improvement in their oral mucositis (*e.g.*, a reduction in symptoms) after only 4 weeks of treatment.

35 **[0746]** As assessed using the WHO (World Health Organization) oral mucositis scale (Table 2) 3 patients receiving 160 mg intravenous administration of ALD518 (Ab1) were assessed. The first subject (circles) has not shown any signs of developing oral mucositis, maintaining a Grade 0 for the entire 4 weeks. This is indicative of ALD518 acting to prevent the development of oral mucositis. The second patient (squares) developed Grade 2 oral mucositis, but this appears to have lessened in severity. This is indicative of ALD518 acting to prevent the development of severe oral mucositis (*e.g.*, Grade 4) and even lessen the severity of oral mucositis. The third patient (triangles) developed Grade 2/3 oral mucositis. This is indicative of ALD518 acting to prevent the development of severe oral mucositis (*e.g.*, Grade 4). In this patient population, it is expected that about 60% of patients to develop at least Grade 3 or Grade 4 oral mucositis with this type of IMRT + chemotherapy and over 80% of the patients to develop at least Grade 2 and above oral mucositis. Thus, this data suggests that a humanized monoclonal antibody that selectively binds IL-6 (*e.g.*, ALD518 *also known as* Ab1) is effective in treating and preventing oral mucositis resulting from the combination of chemotherapy and radiotherapy.

45 **[0747]** We further conclude based on these results that other IL-6 antagonists, including those identified in this application, *e.g.*, the exemplified anti-IL-6 antibodies and antibody fragments, as well as the identified non-antibody IL-6 antagonists, will have clinical application in treating and preventing mucositis, *e.g.*, oral and gastrointestinal or alimentary mucositis.

EXAMPLE 46

ONGOING ANEMIA CLINICAL TRIAL

50 **[0748]** Three cancer patients which were to be treated with cisplatin were treated with ALD-518 prior to cisplatin chemotherapy in order to prevent or lessen anemia, and in particular to prevent the onset of severe anemia which is a very common side effect of cisplatin therapy, *i.e.*, when administered alone or in conjunction with radiotherapy.

55 **[0749]** All three patients received cisplatin every 3 weeks at a dosage of 100mg/m². Particularly, said dosage of chemo was administered at week 0, at week 3 and in one patient another dose was administered at week 6. In these same patients, 160 mg of ALD518 (Ab1), a humanized anti-IL-6 monoclonal antibody containing the variable sequences in

SEQ ID NO:19 and SEQ ID NO:20, was administered intravenously at week 0 and week 4. Radiotherapy (RT) was also administered to these patients at a dosage of 2-2.2 Gray per day from week 0 and will continue until the end of the planned RT for each patient every day 5 days a week.

[0750] All 3 patients are now post-therapy (between week 8 and week 12 of the treatment regimen). The last blood count was at the end of RT about week 8. None of these patients as of week 8 after treatment shows signs of severe anemia. All three patients will be monitored at least until week 12 and are expected to show no or less severe anemia resulting from the combination of cisplatin and radiotherapy as compared to the severe anemia typically seen in patients receiving cisplatin alone or when administered in a clinical regimen also including radiation. This will be confirmed by assaying hemoglobin and/or RBC counts and other clinical indicators of anemia in these patients.

SEQUENCE LISTING

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Smith, Jeffrey T.L.

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Gln Asn Ile Tyr Arg Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
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Pro Pro Lys Phe Leu Ile Tyr Leu Ala Ser Thr Leu Ala Ser Gly Val
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Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
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	65					70					75					80
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Val Ser Ala Ala Val Gly Ala Thr Val Thr Ile Asn Cys Gln Ser Ser
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Gln Ser Val Tyr Asn Asp Met Asp Leu Ala Trp Phe Gln Gln Lys Pro
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Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser
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Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
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Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
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Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln Met Ser
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55	Gly	Thr	Val	Thr	Ile	Lys	Cys	Gln	Ala	Ser	Gln	Ser	Ile	Asn	Asn
															Glu

				20					25					30			
5		Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Arg	Pro	Lys	Leu	Leu	Ile
				35					40					45			
		Tyr	Arg	Ala	Ser	Thr	Leu	Ala	Ser	Gly	Val	Ser	Ser	Arg	Phe	Lys	Gly
10			50					55					60				
		Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Asp	Leu	Glu	Cys
		65					70					75				80	
15		Ala	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Tyr	Ser	Leu	Arg	Asn
						85					90					95	
		Ile	Asp	Asn	Ala	Phe	Gly	Gly	Gly	Thr	Glu	Val	Val	Val	Lys	Arg	
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		1				5					10					15	
		Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Arg	Asn	Asp
35					20					25					30		
		Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
				35					40					45			
40		Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50					55					60				
		Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
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		Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys								
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				20					25					30		
	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Val	Pro	Lys	Leu	Leu	Ile
10			35					40					45			
	Tyr	Ala	Ala	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
15	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65					70					75					80
	Glu	Asp	Val	Ala	Thr	Tyr	Tyr	Cys								
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				20					25					30		
35	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45			
	Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
40		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
45	65					70					75					80
	Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys								
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<400> 651

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	Asp	Arg	Val	Thr	Ile	Thr	Cys	Gln	Ala	Ser	Gln	Ser	Ile	Asn	Asn	Glu
				20					25					30		
10	Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45			
	Tyr	Arg	Ala	Ser	Thr	Leu	Ala	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
15		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
20	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Tyr	Ser	Leu	Arg	Asn
					85					90					95	
25	Ile	Asp	Asn	Ala	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	
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<400> 652

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35 <400> 653

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

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

20

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

25

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

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

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Ala Lys

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<400> 656

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

50

55

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

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<400> 658

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Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
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Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40 45

Asn Tyr Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser
65 70 75 80

Ala Ile Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
130 135 140

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
145 150 155 160

Leu Gly Cys Leu Val Lys
165

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<400> 659

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

<210> 676
<211> 126
<212> PRT
<213> Oryctolagus cuniculus

<400> 676

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

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<212> DNA
<213> Oryctolagus cuniculus

<400> 677

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	gtcagcatca	gttgccaggc	cagtcagagt	gtttatgaga	acaactat	atcctggttt	180
45	cagcagaaac	cagggcagcc	tcccaagctc	ctgatctatg	gtgcatccac	tctggattct	240
	ggggtcccat	cgcggttcaa	aggcagtgga	tctgggacac	agttcactct	caccattaca	300
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50	gatgatgcc						369

<210> 678
<211> 378
<212> DNA
<213> Oryctolagus cuniculus

<400> 678

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5 tgcacagcct ctggattctc cctcaatgcc tactacatga actgggtccg ccaggctcca 180
gggaaggggc tggaatggat cggattcatt actctgaata ataatgtagc ttacgcgaac 240
tgggcgaaag gccgattcac cttctccaaa acctcgacca cgggtggatct gaaaatgacc 300
10 agtccgacac ccgaggacac ggccacctat ttctgtgcca ggagtcgtgg ctgggggtgca 360
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15 <210> 679
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

20 <400> 679

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

50 <210> 680
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

55 <400> 680

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5	Val	Gln	Cys	Gln	Ser	Val	Glu	Glu	Ser	Gly	Gly	Arg	Leu	Val	Thr	Pro	
				20					25					30			
10	Gly	Thr	Pro	Leu	Thr	Leu	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Ser	
			35					40					45				
15	Ser	Tyr	Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	
		50					55					60					
20	Trp	Ile	Gly	Ile	Ile	Gly	Gly	Phe	Gly	Thr	Thr	Tyr	Tyr	Ala	Thr	Trp	
	65					70					75					80	
25	Ala	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Lys	Thr	Ser	Thr	Thr	Val	Asp	Leu	
					85					90					95		
30	Arg	Ile	Thr	Ser	Pro	Thr	Thr	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala	
				100					105						110		
35	Arg	Gly	Gly	Pro	Gly	Asn	Gly	Gly	Asp	Ile							
			115					120									
40	<210> 681																
	<211> 366																
	<212> DNA																
	<213> Oryctolagus cuniculus																
45	<400> 681																
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50	acatttgccc	aagtgctgac	ccagactcca	tcgcctgtgt	ctgcagctgt	gggaggcaca											120
	gtcaccatca	actgccaggc	cagtcagagt	gttgatgata	acaactgggt	aggctggtat											180
55	cagcagaaac	gagggcagcc	tcccaagtac	ctgatctatt	ctgcatccac	tctggcatct											240
	ggggtcccat	cgcggttcaa	aggcagtgga	tctgggacac	agttcactct	caccatcagc											300
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60	tttgct																366
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65	<400> 682																

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5 acagtctctg gcttctccct cagtagctat gcaatgagct ggggccgcca ggctccagga 180
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gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgag aatcaccagt 300
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15 <210> 683
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

20 <400> 683

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

50 <210> 684
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

55 <400> 684

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

30	<210> 685	
	<211> 366	
	<212> DNA	
	<213> Oryctolagus cuniculus	
35	<400> 685	
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40	acatttgcag ccgtgctgac ccagacacca tcgcccgtgt ctgtacctgt gggaggcaca	120
	gtcaccatca agtgccagtc cagtcagagt gtttataata atttcttatac gtggtatcag	180
	cagaaaccag ggcagcctcc caagctcctg atctaccagg catccaaact ggcacatctggg	240
45	gtcccagata gggttcagcgg cagtggatct gggacacagt tcactctcac catcagcggc	300
	gtgcagtgctg acgatgctgc cacttactac tgtctaggcg gttatgatga tgatgctgat	360
50	aatgct	366
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	<211> 384	
55	<212> DNA	
	<213> Oryctolagus cuniculus	
	<400> 686	

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5 acagtctctg gaatcgacct cagtgactat gcaatgagct ggggccgcca ggctccaggg 180
aaggggctgg aatggatcgg aatcatttat gctggtagtg gtagcacatg gtacgcgagc 240
tgggcgaaag gccgattcac catctccaaa acctcgacca cggcggatct gaaaatcacc 300
10 agtccgacaa ccgaggacac ggccacctat ttctgtgcca gagatggata cgatgactat 360
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15 <210> 687
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

20 <400> 687

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

<210> 688
<211> 125
<212> PRT
55 <213> Oryctolagus cuniculus

<400> 688

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

30	<210> 689	
	<211> 366	
	<212> DNA	
	<213> Oryctolagus cuniculus	
35	<400> 689	
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	gtcaccatca aatgccaggc cagtcagagc attaacaatg aattatcctg gtatcagcag	180
	aaatcagggc agcgtcccaa gctcctgata tatagggcat ccactctggc atctggggtc	240
45	tcatcgcggt tcaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg	300
	gagtgtgccg atgctgccac ttactactgt caacagggtt atagtctgag gaatattgat	360
50	aatgct	366
	<210> 690	
	<211> 375	
	<212> DNA	
55	<213> Oryctolagus cuniculus	
	<400> 690	

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acagcctctg gattctccct cagtaactac tacatgacct ggggccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatgatttat ggtagtgatg aaacagccta cgcgaactgg 240

gcgataggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ctgacagccg cggacacggc cacctatttc tgtgccagag atgatagtag tgactgggat 360

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<210> 691

<211> 450

<212> PRT

<213> Oryctolagus cuniculus

20

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55

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

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

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

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

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

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln 100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser 145 150 155 160

	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
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5	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180						185					190		
10	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
		195					200					205				
15	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
	210						215					220				
20	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
	225				230						235				240	
25	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				245					250					255		
30	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
			260						265					270		
35	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		275					280					285				
40	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg
	290						295					300				
45	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
	305				310					315					320	
50	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
			325						330					335		
55	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
			340					345					350			
60	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu
		355					360					365				
65	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
	370					375					380					
70	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
	385				390					395					400	
75	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp

				405					410					415			
5		Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
					420					425					430		
		Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro
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	1				5					10					15		
5	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Ser	Leu	Ser	Asn	Tyr	
				20					25					30			
10	Tyr	Met	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
			35					40					45				
15	Gly	Met	Ile	Tyr	Gly	Ser	Asp	Glu	Thr	Ala	Tyr	Ala	Asn	Ser	Ala	Ile	
		50					55					60					
20	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	
	65					70					75					80	
25	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
					85					90					95		
30	Arg	Asp	Asp	Ser	Ser	Asp	Trp	Asp	Ala	Lys	Phe	Asn	Leu	Trp	Gly	Gln	
				100					105					110			
35	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
			115					120					125				
40	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
		130					135					140					
45	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
	145					150					155					160	
50	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
55																	

	165							170					175			
5	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
				180					185					190		
	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
10			195					200					205			
	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
		210					215					220				
15	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
	225					230					235					240
	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
20				245						250					255	
	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
				260					265					270		
25	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
			275					280					285			
30	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg
		290					295					300				
	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
35	305					310					315					320
	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
				325						330					335	
40	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
				340					345					350		
	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu
45			355					360					365			
	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
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<400> 708

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		210					215					220					
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50	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	
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<400> 709

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10	Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
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20	Arg	Gly	Tyr	Ser	Ile	Phe	Ser	Tyr	Ala	Thr	Lys	Arg	Gln	Asp	Asn	Glu
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25	Ile	Leu	Ile	Phe	Trp	Ser	Lys	Asp	Ile	Gly	Tyr	Ser	Phe	Thr	Val	Gly
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				100					105					110		
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40	Val	Asp	Gly	Lys	Pro	Arg	Val	Arg	Lys	Ser	Leu	Lys	Lys	Gly	Tyr	Thr
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50	Gly	Gly	Asn	Phe	Glu	Gly	Ser	Gln	Ser	Leu	Val	Gly	Asp	Ile	Gly	Asn
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10	Gly	Val	Leu	Thr	Ser	Leu	Pro	Gly	Asp	Ser	Val	Thr	Leu	Thr	Cys	Pro
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55	Lys	Thr	Ser	Met	His	Pro	Pro	Tyr	Ser	Leu	Gly	Gln	Leu	Val	Pro	Glu					
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REFERENCES CITED IN THE DESCRIPTION

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PATENTKRAV

1. En sammensætning til anvendelse til behandling eller forebyggelse af mucositis associeret med strålebehandling, omfattende en effektiv mængde af et IL-6-antagonistantistof, hvor nævnte anti-IL-6-antistof omfatter den humaniserede variable
5 let sekvens af aminosyresekvensen ifølge SEQ ID NO: 709 og den humaniserede variable tunge sekvens af aminosyresekvensen ifølge SEQ ID NO: 657.
2. Sammensætning til anvendelse ifølge krav 1, hvor mucositis er udvalgt blandt
10 gruppen bestående af: oral mucositis associeret med strålebehandling; tractus digestorius mucositis associeret med strålebehandling, gastrointestinalkanal mucositis associeret med strålebehandling.
3. Sammensætning til anvendelse ifølge krav 1 eller krav 2, hvor nævnte anti-IL-6-antistof omfatter polypeptiderne ifølge SEQ ID NO: 702 og SEQ ID NO: 704.
15
4. Sammensætning til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor nævnte antistof er et enkeltkædet eller kimært antistof.
- 20 5. Sammensætning til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor nævnte antistof omfatter et Fab, Fab', F(ab')₂, Fv, scFv, IgNAR eller lille modulært immunfarmaceutisk middel (SMIP).
6. Sammensætning til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor nævnte antistof indeholder en Fc-region, hvor nævnte Fc-region eventuelt er blevet modificeret til at ændre effektorfunktion, halveringstid, proteolyse og/eller glycosylering.
25
7. Sammensætning til anvendelse ifølge et hvilket som helst af kravene 1-6, yderligere
30 omfattende en farmaceutisk acceptabel bærer, excipients eller fortyndingsmiddel.

FIGURE 2 – PREFERRED ANTI-IL-6 ANTIBODY HUMANIZATION

	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO: 647	AYDMTQTPASVSAVGGTVTIKC	<u>QASQSINNELS</u>	WYQQKPGQRPKLLIY	<u>RASILAS</u>	GVSSRFKGGSGGTEFTLTISDLECAATAYYC
SEQ ID NO: 648	AIQMTQSPSSLSASVGDRTVITC	RASQGRNDLG	WYQQKPGKAPKLLIY	AASSLOS	GVPSRFSGSGGIDFTILTISLQPEDFATYYC
SEQ ID NO: 649	DIQMTQSPSSLSASVGDRTVITC	<u>RASQGISNYLA</u>	WYQQKPGKVPKLLIY	<u>AASILOS</u>	<u>GVPSRFSGSGGIDFTILTISLQPEDVATYYC</u>
SEQ ID NO: 650	DIQMTQSPSTLSASVGDRTVITC	<u>RSQSISSWLA</u>	<u>WYQQKPGKAPKLLIY</u>	<u>KASSILES</u>	<u>GVPSRFSGSGGTEFTLTISLQPDFAYYC</u>
SEQ ID NO: 651	AIQMTQSPSSLSASVGDRTVITC	<u>QASQSINNELS</u>	WYQQKPGKAPKLLIY	<u>RASILAS</u>	GVPSRFSGSGGTDFTLTISLQPEDFATYYC
SEQ ID NO: 651	AIQMTQSPSSLSASVGDRTVITC	<u>QASQSINNELS</u>	WYQQKPGKAPKLLIY	<u>RASILAS</u>	GVPSRFSGSGGTDFTLTISLQPEDFATYYC
CDR3					
FR4					
SEQ ID NO: 647	<u>QQGYSLRNIDNA</u>	FGGGTEVWVKR			
SEQ ID NO: 648					
SEQ ID NO: 649		<u>EGGGTKVEIKR</u>			
SEQ ID NO: 650		FGGGTKVEIKR			
SEQ ID NO: 651	<u>QQGYSLRNIDNA</u>	FGGGTKVEIKR			
SEQ ID NO: 651	<u>QQGYSLRNIDNA</u>	FGGGTKVEIKR			
FR1					
SEQ ID NO: 652	QSLEESGGRVTPGTPLTCTASGFSL	<u>NIYYVI</u>	FR2 WVROAPGKGLEWVG	CDR2 <u>IYGG-SDETAYATWAIG</u>	FR3 RFTISKSTST-TVDLKMTSLTAADTATYFCAR
SEQ ID NO: 653	EVQLVESGGGLVQPGGSLRLSCAASGETVS	SNYMS	WVROAPGKGLEWVS	VYIS-GGSTYYADSVKG	RFTISRDNISKNTLYLQMNISLRAEDTAVYYCAR
SEQ ID NO: 654	EVQLVESGGGLVQPGGSLRLSCAASGETVS	SNYMS	WVROAPGKGLEWVS	VYIS-GGSTYYADSVKG	RFTISRDNISKNTLYLQMNISLRAEDTAVYYCAR
SEQ ID NO: 655	EVQLLESGGGLVQPGGSLRLSCAASGETFS	SYAMS	WVROAPGKGLEWVS	VYISGGSSITYYADSVKG	RFTISRDNISKNTLYLQMNISLRAEDTAVYYCAR
SEQ ID NO: 656	EVQLVESGGGLVQPGGSLRLSCAASGFSL	<u>NIYYVI</u>	WVROAPGKGLEWVG	<u>IYGG-SDETAYATWAIG</u>	RFTISRDNISKNTLYLQMNISLRAEDTAVYYCAR
SEQ ID NO: 657	EVQLVESGGGLVQPGGSLRLSCAASGFSL	<u>NIYYVI</u>	WVROAPGKGLEWVG	<u>IYGG-SDETAYATSAIG</u>	RFTISRDNISKNTLYLQMNISLRAEDTAVYYCAR
CDR3					
FR4					
SEQ ID NO: 652	<u>DDSSDWDAKFNL</u>	WGQGTLLVTVSS			
SEQ ID NO: 653					
SEQ ID NO: 654		<u>WGQGTLLVTVSS</u>			
SEQ ID NO: 655		WGQGTLLVTVSS			
SEQ ID NO: 656	<u>DDSSDWDAKFNL</u>	WGQGTLLVTVSS			
SEQ ID NO: 657	<u>DDSSDWDAKFNL</u>	WGQGTLLVTVSS			

FIGURE 3 – PREFERRED ANTI-IL-6 ANTIBODY HUMANIZATION

	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO: 647	AYDMTQTPTASVSAAVGGTVTIKC	QASQSINNELS	WYQOKPGQRPKLLIY	RASILAS	GVSSRFKGSQSGTEFTLTISDLECAATAYYC
SEQ ID NO: 648	ΔIQMTQSPSSLSASVGD ~~RV~~ TIIC	RASQGI ~~RND~~ LG	WYQOKPGKAPKLLIY	AASSLQS	GVPSRFSGSGSGTD ~~FT~~ LTISSLQPEDFATYYC
SEQ ID NO: 649	DIQMTQSPSSLSASVGD ~~RV~~ TIIC	RASQGISNYLA	WYQOKPGKVPKLLIY	AASILQS	GVPSRFSGSGSGTD ~~FT~~ LTISSLQPEDVATYYC
SEQ ID NO: 650	DIQMTQSPSTLSASVGD ~~RV~~ TIIC	RASQSISSWLA	WYQOKPGKAPKLLIY	KASSLES	GVPSRFSGSGSGTE ~~FT~~ LTISSLQPD ~~D~~ FATYYC
SEQ ID NO: 709	ΔIQMTQSPSSLSASVGD ~~RV~~ TIIC	QASQSINNELS	WYQOKPGKAPKLLIY	RASILAS	GVPSRFSGSGSGTD ~~FT~~ LTISSLQPD ~~D~~ FATYYC
SEQ ID NO: 709	ΔIQMTQSPSSLSASVGD ~~RV~~ TIIC	QASQSINNELS	WYQOKPGKAPKLLIY	RASILAS	GVPSRFSGSGSGTD ~~FT~~ LTISSLQPD ~~D~~ FATYYC
	CDR3	FR4			
SEQ ID NO: 647	QOQGYSLRNIDNA	FGGGTEV ~~V~~ VVKR			
SEQ ID NO: 648					
SEQ ID NO: 649		EGGGTKV ~~E~~ IKR			
SEQ ID NO: 650					
SEQ ID NO: 709	QOQGYSLRNIDNA	FGGGTKV ~~E~~ IKR			
SEQ ID NO: 709	QOQGYSLRNIDNA	FGGGTKV ~~E~~ IKR			
	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO: 652	-QSL ~~E~~ ESGGRLVTPGTPLTICTASGFSL	NY ~~Y~~ VI	WVRQAPGKGLEWIG	IY ~~Y~~ G-SDEIAYATWAI ~~G~~	RFTISK ~~T~~ ST--TVDLKMTSLTAADTATYFCAR
SEQ ID NO: 653	EVQLVESGGGLVQPGGSLRLS ~~CA~~ ASGFTVS	SN ~~Y~~ MS	WVRQAPGKGLEWVS	VLYS-GGS ~~T~~ YYADSVK ~~G~~	RETISRDN ~~S~~ KN ~~T~~ LYLQMN ~~S~~ LRAEDTAVYYCAR
SEQ ID NO: 654	EVQLVESGGGLVQPGGSLRLS ~~CA~~ ASGFTVS	SN ~~Y~~ MS	WVRQAPGKGLEWVS	VLYS-GGS ~~T~~ YYADSVK ~~G~~	RETISRDN ~~S~~ KN ~~T~~ LYLQMN ~~S~~ LRA ~~H~~ DTAVYYCAR
SEQ ID NO: 655	EVQLVESGGGLVQPGGSLRLS ~~CA~~ ASGFTFS	SY ~~Y~~ AMS	WVRQAPGKGLEWVS	VLYSGGS ~~T~~ YYADSVK ~~G~~	RETISRDN ~~S~~ KN ~~T~~ LYLQMN ~~S~~ LRAEDTAVYYCAK
SEQ ID NO: 656	EVQLVESGGGLVQPGGSLRLS ~~CA~~ ASGFSL	NY ~~Y~~ VI	WVRQAPGKGLEWVG	IY ~~Y~~ G-SDEIAYATWAI ~~G~~	RFTISRDN ~~S~~ KN ~~T~~ LYLQMN ~~S~~ LRAEDTAVYYCAR
SEQ ID NO: 657	EVQLVESGGGLVQPGGSLRLS ~~CA~~ ASGFSL	NY ~~Y~~ VI	WVRQAPGKGLEWVG	IY ~~Y~~ G-SDEIAYATSAI ~~G~~	RFTISRDN ~~S~~ KN ~~T~~ LYLQMN ~~S~~ LRAEDTAVYYCAR
	CDR3	FR4			
SEQ ID NO: 652	DDSSDWD ~~A~~ KFN ~~L~~	WGQGT ~~L~~ VTVSS			
SEQ ID NO: 653					
SEQ ID NO: 654		WGQGT ~~L~~ VTVSS			
SEQ ID NO: 655					
SEQ ID NO: 656	DDSSDWD ~~A~~ KFN ~~L~~	WGQGT ~~L~~ VTVSS			
SEQ ID NO: 657	DDSSDWD ~~A~~ KFN ~~L~~	WGQGT ~~L~~ VTVSS			

FIGURE 4A – Alignment of Ab1 light chains

SEQ ID NO:2	MDTRAPTQLLGLLLLWLP	GARC	AYDMTQTPASVSA	AVGGTVTIKC	QASQSINNELS	FR2
SEQ ID NO:20			IQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	
SEQ ID NO:647			AYDMTQTPASVSA	AVGGTVTIKC	QASQSINNELS	
SEQ ID NO:651			AIQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	
SEQ ID NO:660	MDTRAPTQLLGLLLLWLP	GARC	AYDMTQTPASVSA	AVGGTVTIKC	QASQSINNELS	
SEQ ID NO:666			IQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	
SEQ ID NO:699			AIQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	
SEQ ID NO:702			AIQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	
SEQ ID NO:706		MKWVTFISLLFLFSSAYS	AIQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	
SEQ ID NO:709			AIQMTQSPSSLSASVGD	RVITIC	QASQSINNELS	

SEQ ID NO:2	RASTLAS	CVSSRFKSGSGTEFTLTISD	LECA	DAATYYC	QQGYSLRNIDNA	CDR3
SEQ ID NO:20	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPD	DFATYYC	QQGYSLRNIDNA	
SEQ ID NO:647	RASTLAS	GVSSRFKSGSGTEFTLTISD	LECA	DAATYYC	QQGYSLRNIDNA	
SEQ ID NO:651	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPE	DFATYYC	QQGYSLRNIDNA	
SEQ ID NO:660	RASTLAS	GVSSRFKSGSGTEFTLTISD	LECA	DAATYYC	QQGYSLRNIDNA	
SEQ ID NO:666	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPD	DFATYYC	QQGYSLRNIDNA	
SEQ ID NO:699	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPD	DFATYYC	QQGYSLRNIDNA	
SEQ ID NO:702	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPD	DFATYYC	QQGYSLRNIDNA	
SEQ ID NO:706	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPD	DFATYYC	QQGYSLRNIDNA	
SEQ ID NO:709	RASTLAS	GVPSRFSGSGGTFTLTIS	SLQPD	DFATYYC	QQGYSLRNIDNA	

FIGURE 4B – Alignment of Ab1 light chains (continued)

		FR4	kappa constant light chain
SEQ ID NO: 2	FGGGTEVVVKKR	T	VAAPSVFIFPPSDEQLKSGTASVVCLLNN
SEQ ID NO: 20			
SEQ ID NO: 647	FGGGTEVVVKKR		
SEQ ID NO: 651	FGGGTKVEIKR		
SEQ ID NO: 660			
SEQ ID NO: 666	FGGGTKVEIKR	T	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYBREAKVQWKVDNALQSGN
SEQ ID NO: 699	FGGGTKVEIKR	T	
SEQ ID NO: 702	FGGGTKVEIKR	T	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYBREAKVQWKVDNALQSGN
SEQ ID NO: 706	FGGGTKVEIKR	T	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYBREAKVQWKVDNALQSGN
SEQ ID NO: 709	FGGGTKVEIKR		

		kappa constant light chain (continued)
SEQ ID NO: 2		
SEQ ID NO: 20		
SEQ ID NO: 647		
SEQ ID NO: 651		
SEQ ID NO: 660		
SEQ ID NO: 666		SOESVTEQDSKDYSLSSSTLTLSKADYEKKHKVYACEVTHQGI,SSPVTKSFNRGEC
SEQ ID NO: 699		
SEQ ID NO: 702		SOESVTEQDSKDYSLSSSTLTLSKADYEKKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 706		SOESVTEQDSKDYSLSSSTLTLSKADYEKKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 709		

FIGURE 5B – Alignment of Ab1 heavy chains, continued

		gamma-1 constant heavy chain polypeptide	
SEQ ID NO:3		ASTKGPSVFPLAPSSKSTSGGTAALGCLVK	
SEQ ID NO:658		ASTKGPSVFPLAPSSKSTSGGTAALGCLVK	
SEQ ID NO:664		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS	
SEQ ID NO:665		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS	
SEQ ID NO:704		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS	
SEQ ID NO:708		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS	
		gamma-1 constant heavy chain polypeptide, continued	
SEQ ID NO:664		TGTQTYICNVNHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVS	
SEQ ID NO:665		LGTQTYICNVNHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVS	
SEQ ID NO:704		LGTQTYICNVNHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVS	
SEQ ID NO:708		LGTQTYICNVNHNKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVS	
		gamma-1 constant heavy chain polypeptide, continued	
SEQ ID NO:664		HEDPEVKFNWYVDGVEVHNAKIKPREEQYASTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQ	
SEQ ID NO:665		HEDPEVKFNWYVDGVEVHNAKIKPREEQYASTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQ	
SEQ ID NO:704		HEDPEVKFNWYVDGVEVHNAKIKPREEQYASTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQ	
SEQ ID NO:708		HEDPEVKFNWYVDGVEVHNAKIKPREEQYASTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQ	
		gamma-1 constant heavy chain polypeptide, continued	
SEQ ID NO:664		PREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGOPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW	
SEQ ID NO:665		PREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGOPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW	
SEQ ID NO:704		PREPQVYITLPPSRDEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW	
SEQ ID NO:708		PREPQVYITLPPSRDEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW	
		gamma-1 constant heavy chain polypeptide, continued	
SEQ ID NO:664		QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
SEQ ID NO:665		QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
SEQ ID NO:704		QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
SEQ ID NO:708		QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	

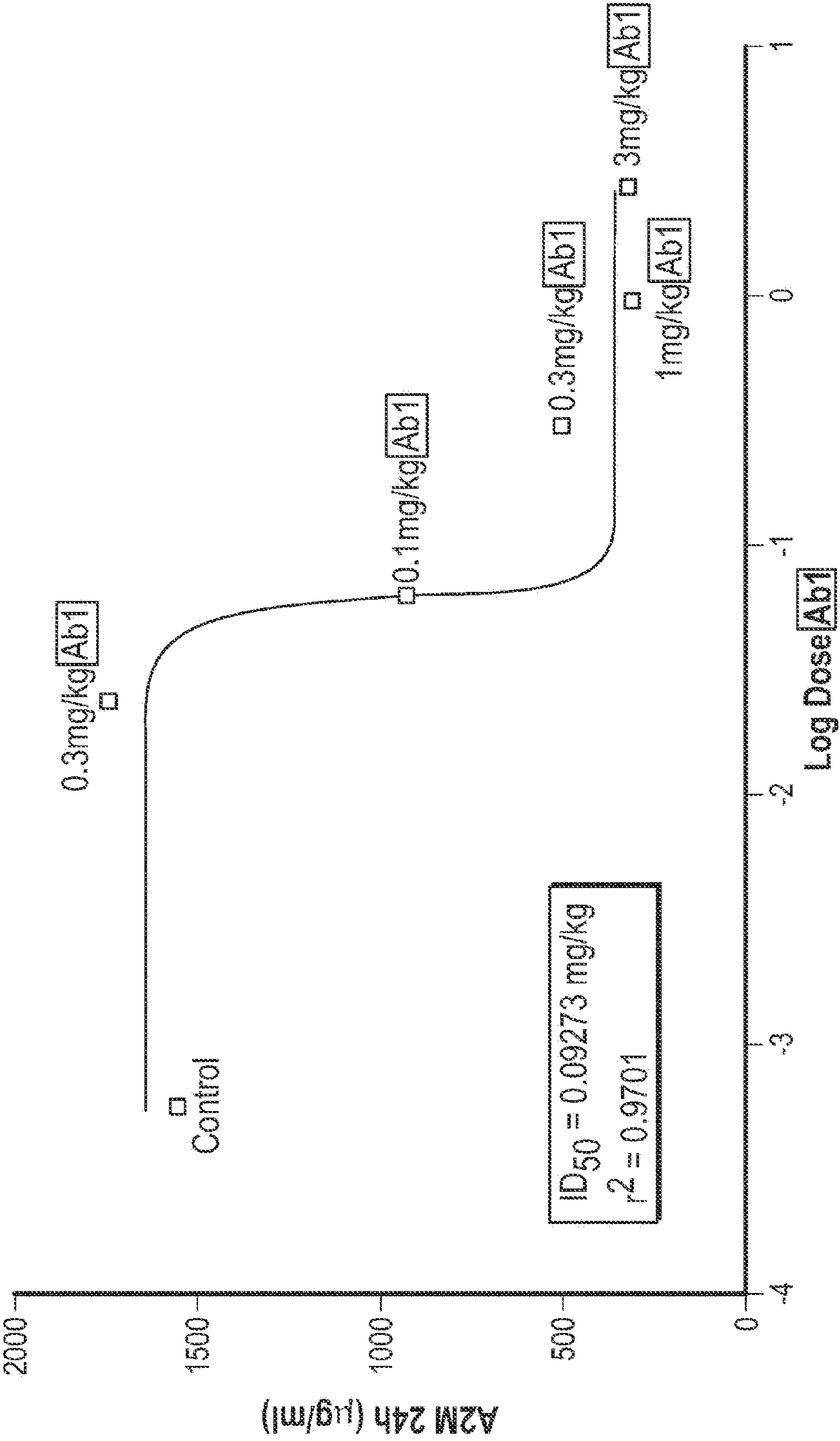


FIG. 6

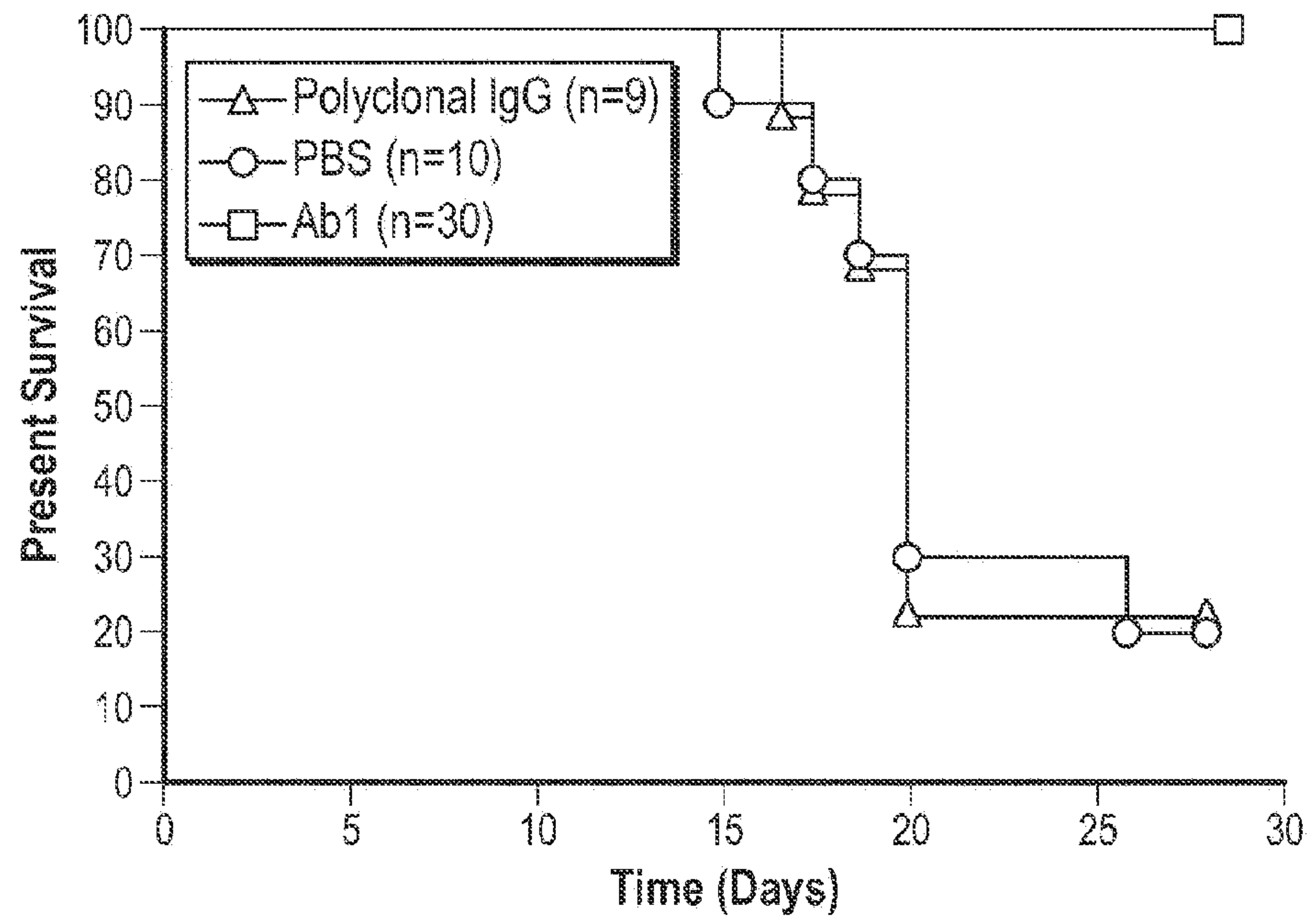


FIG. 7

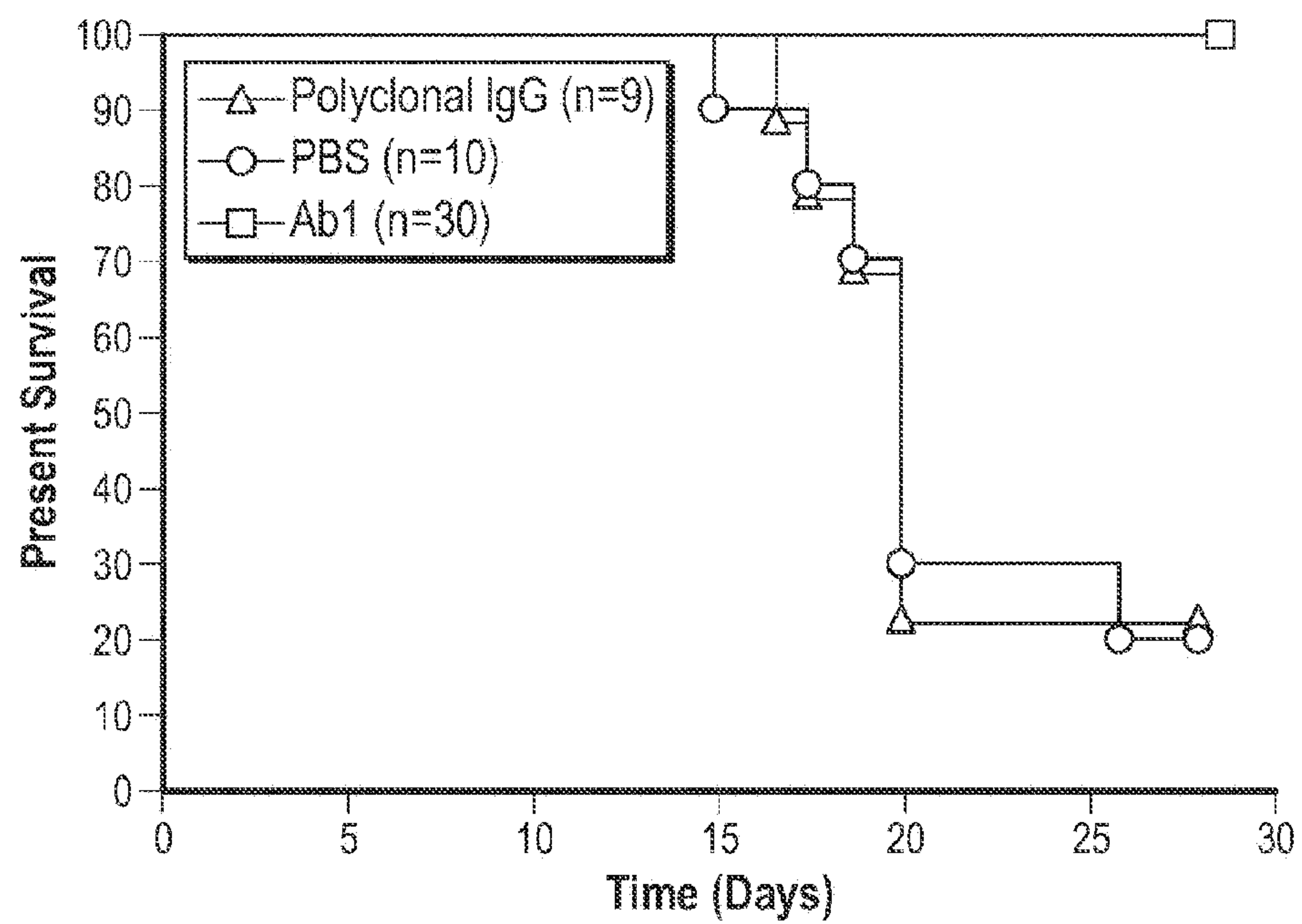


FIG. 8

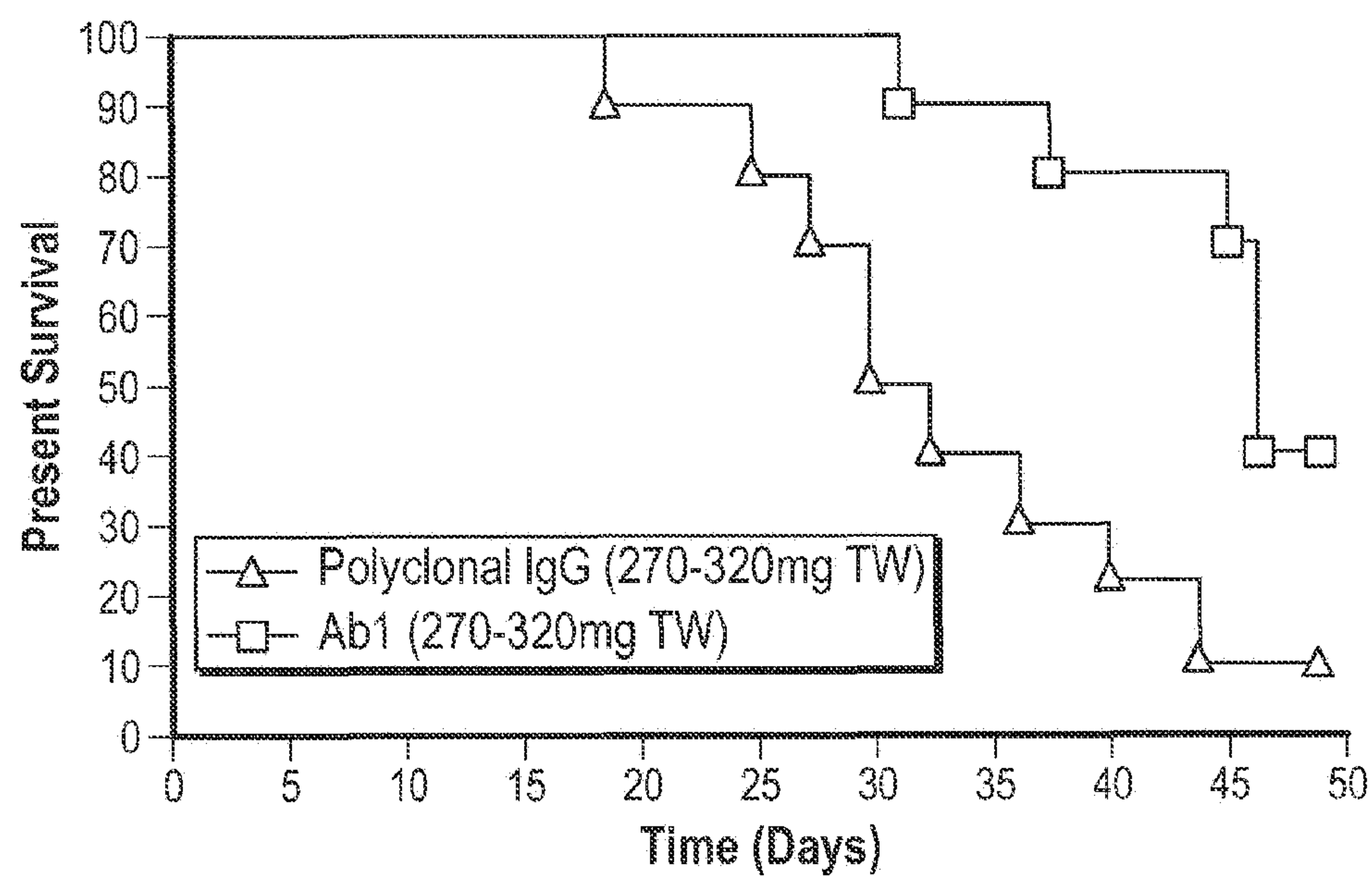


FIG. 9

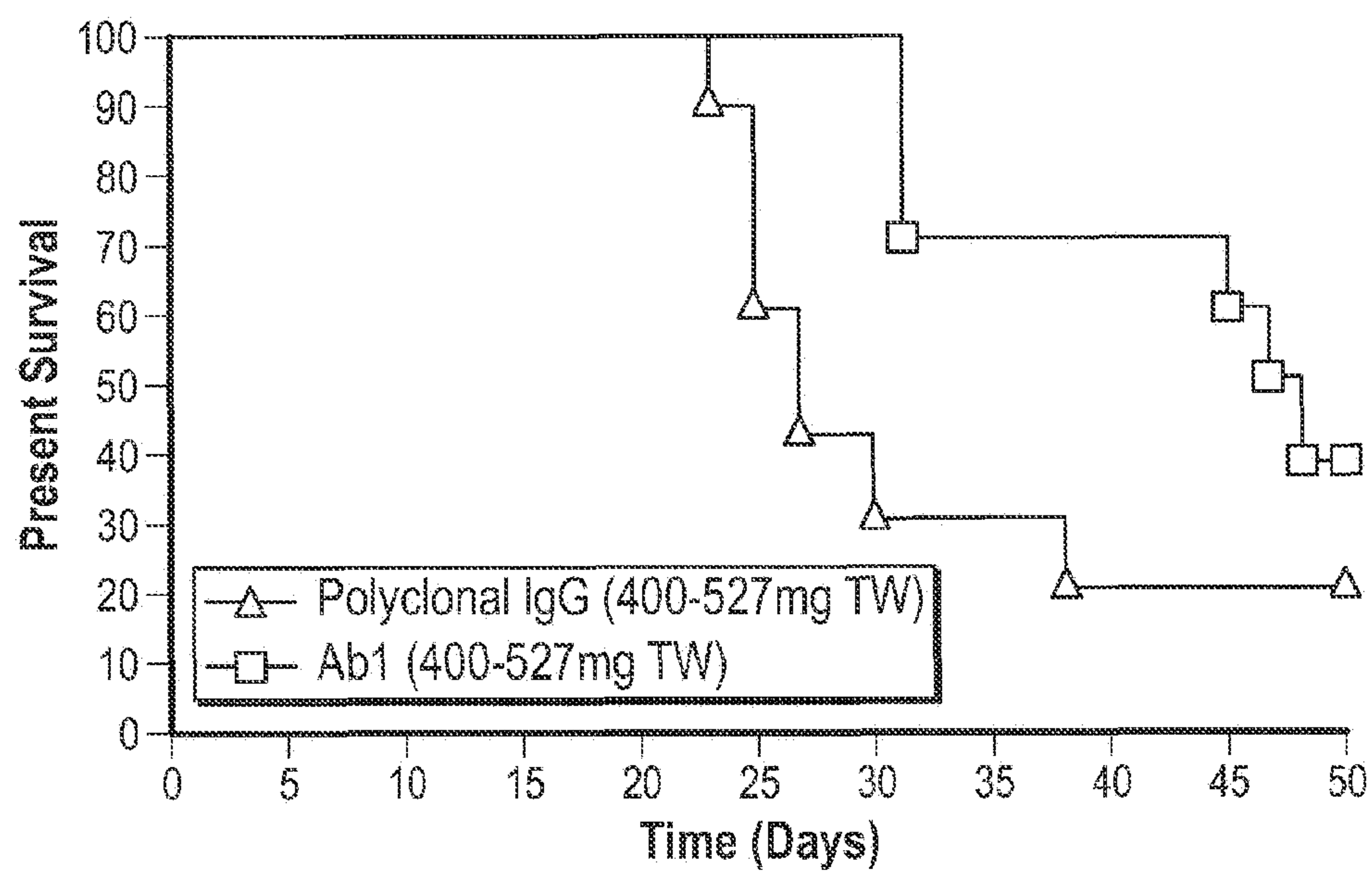


FIG. 10

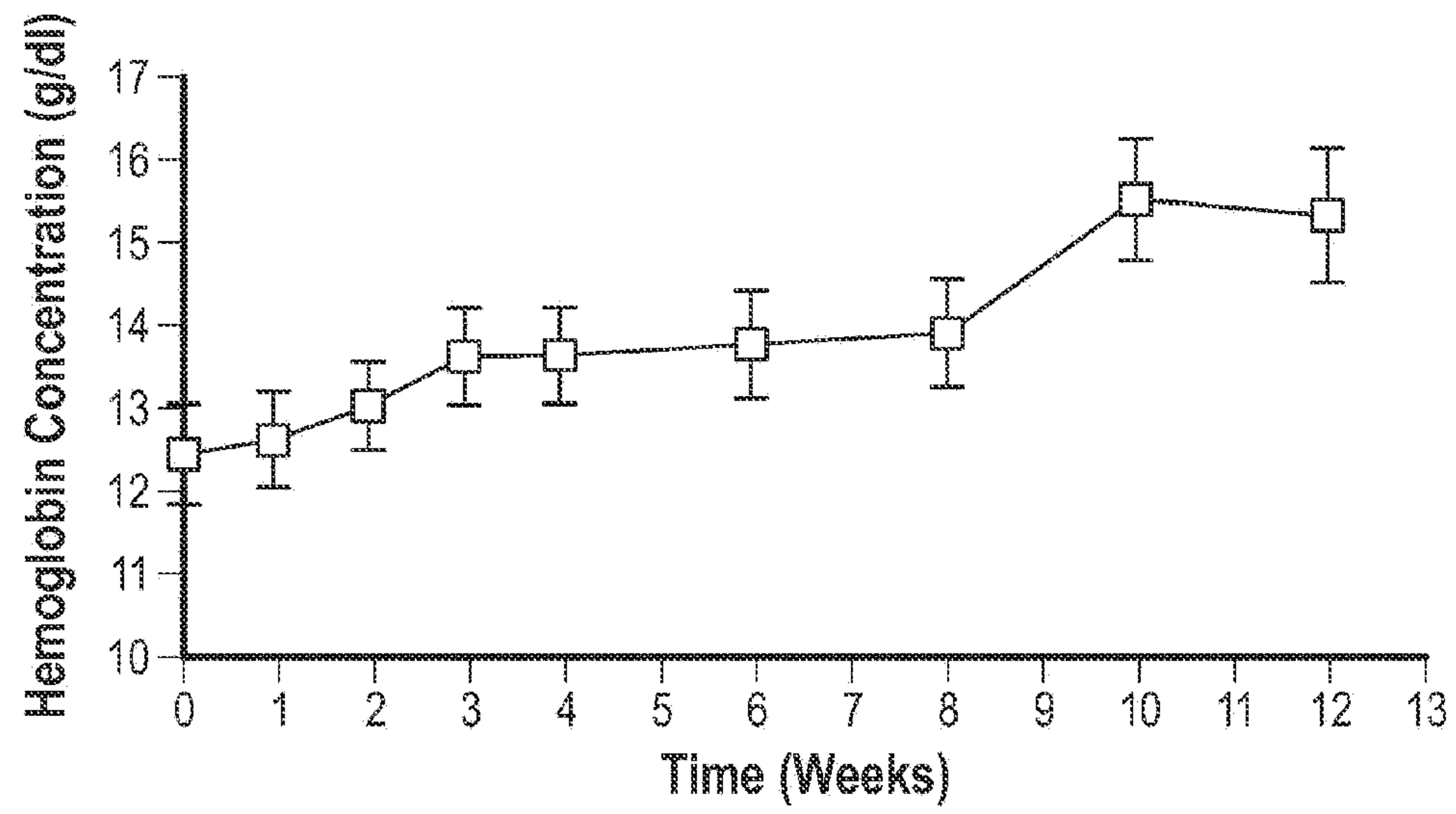


FIG. 11

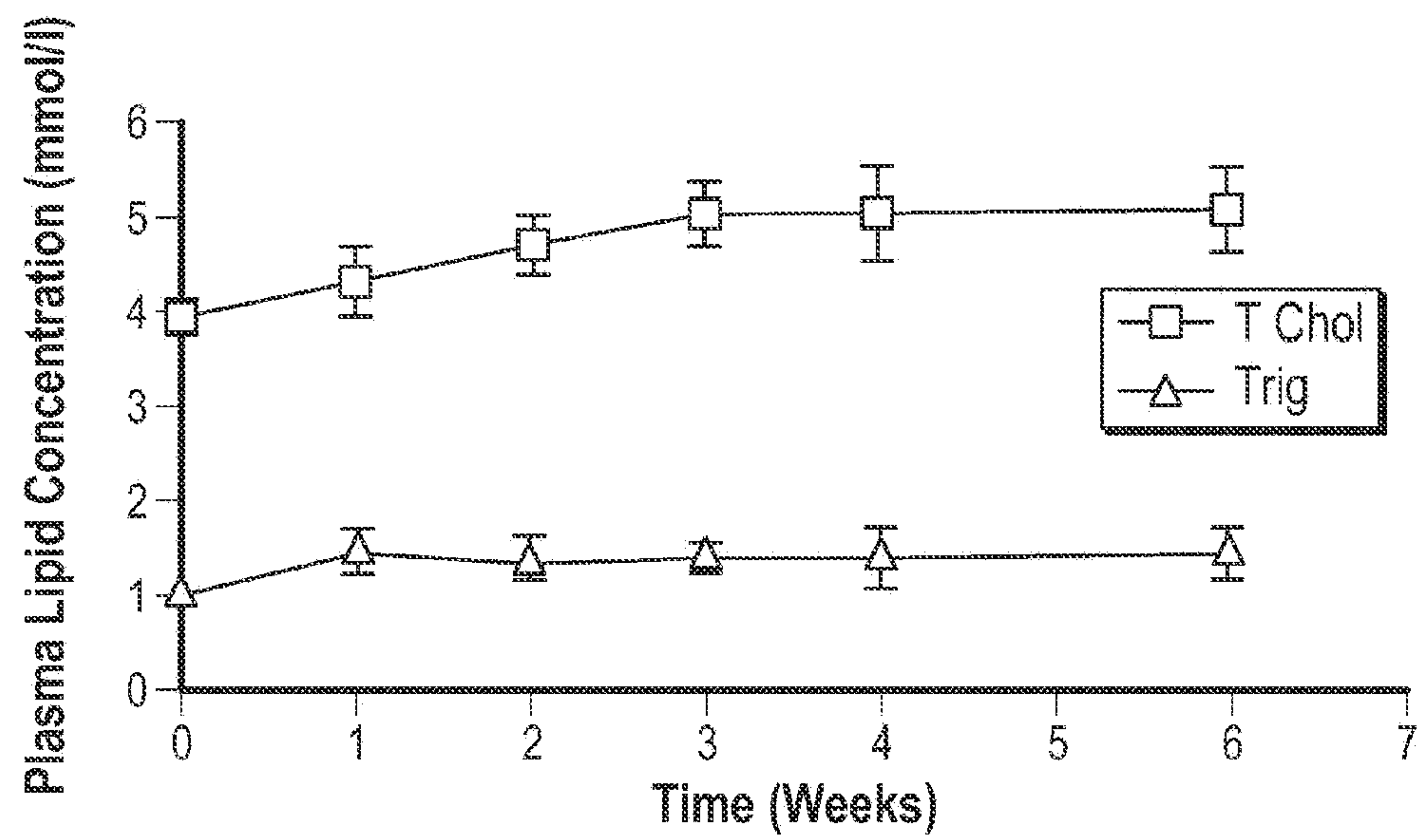


FIG. 12

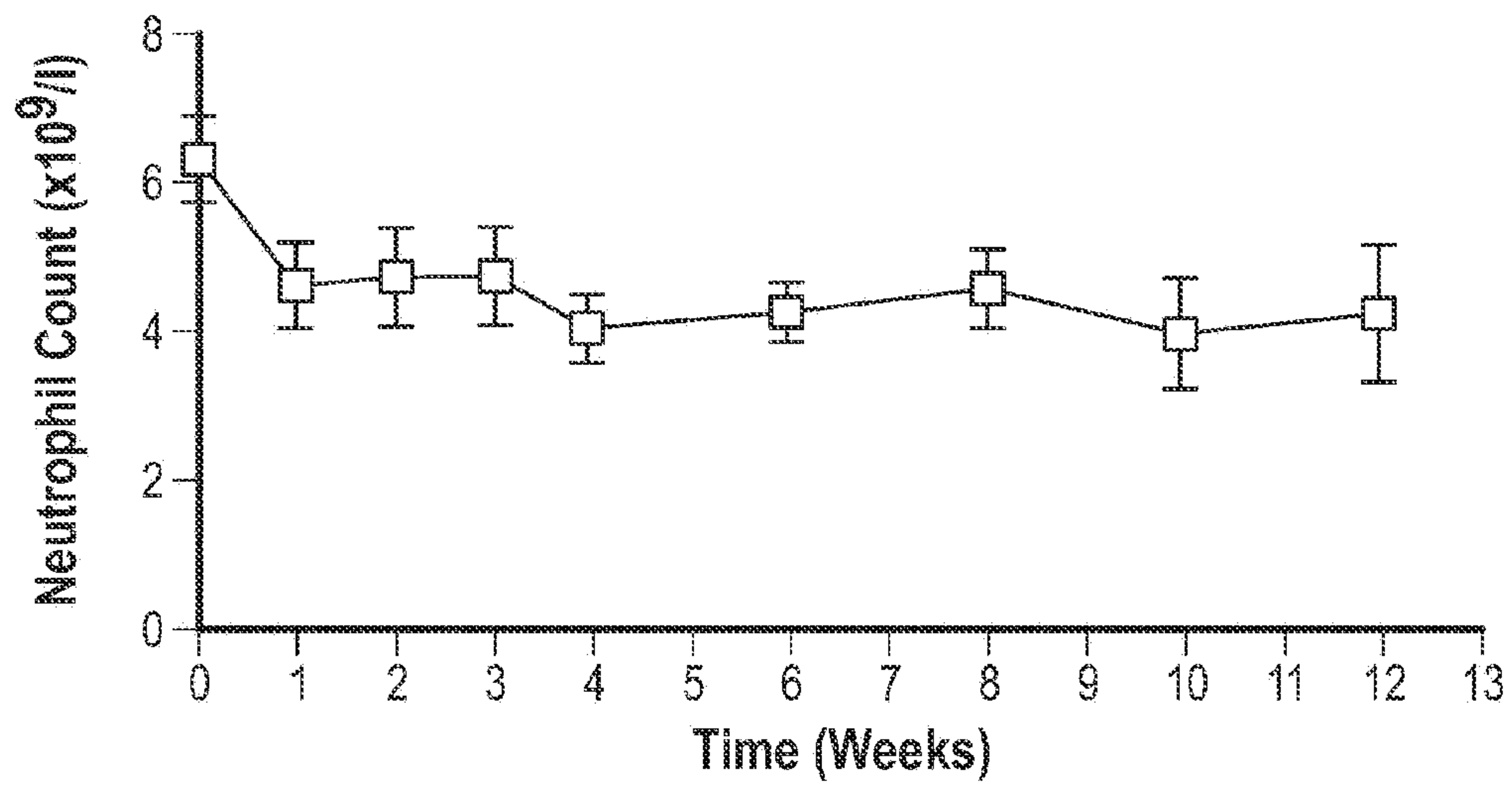


FIG. 13

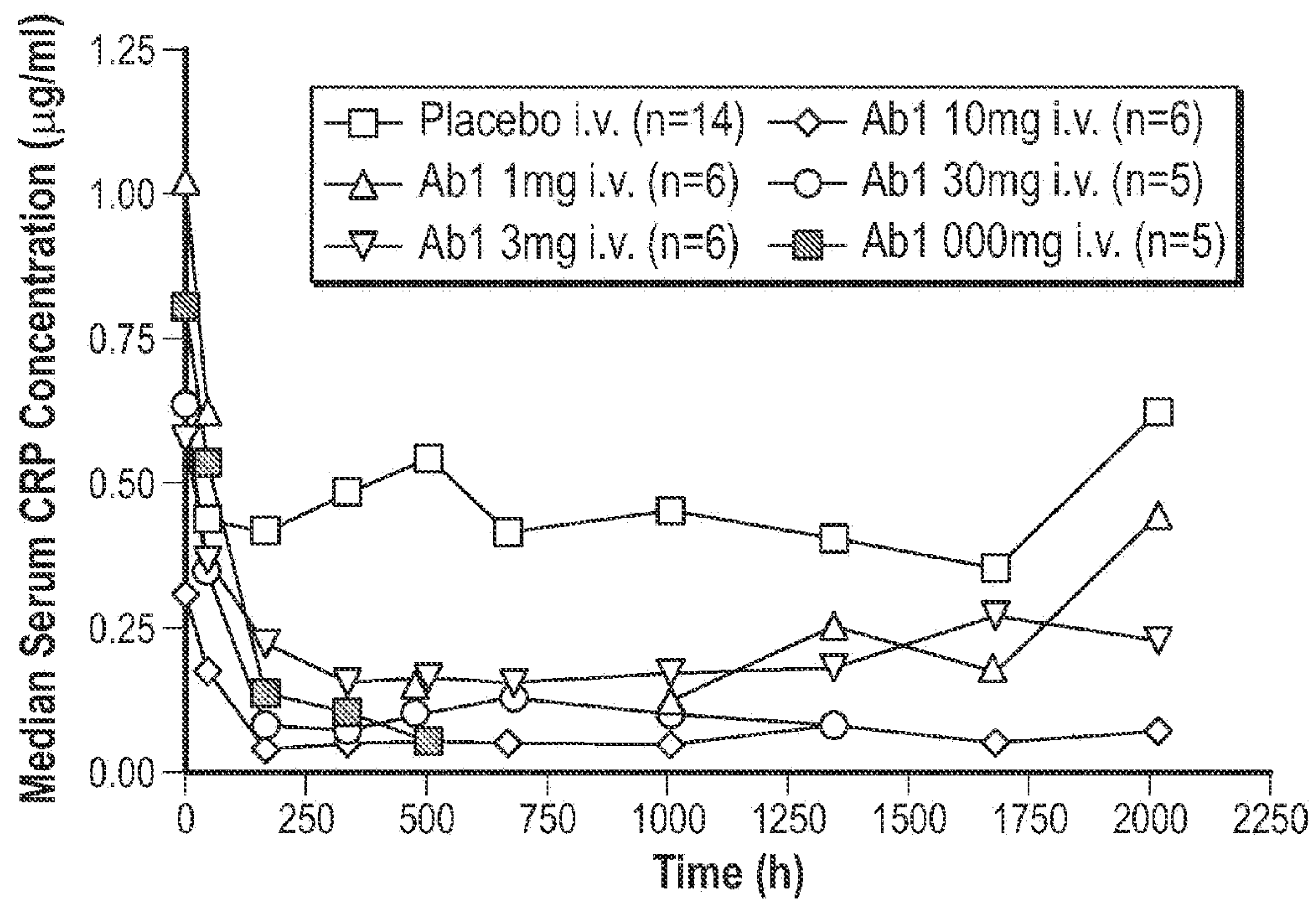


FIG. 14A

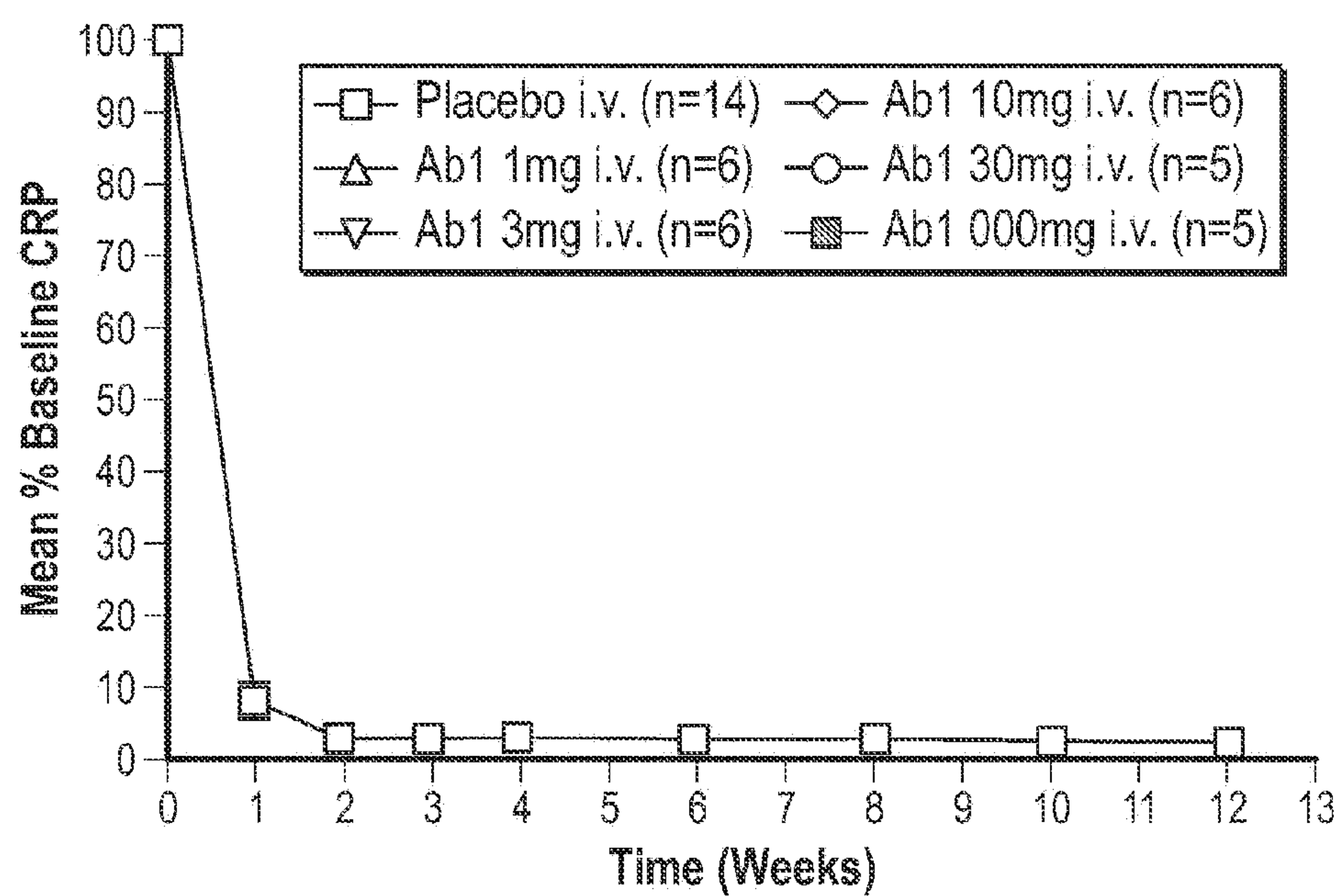


FIG. 14B

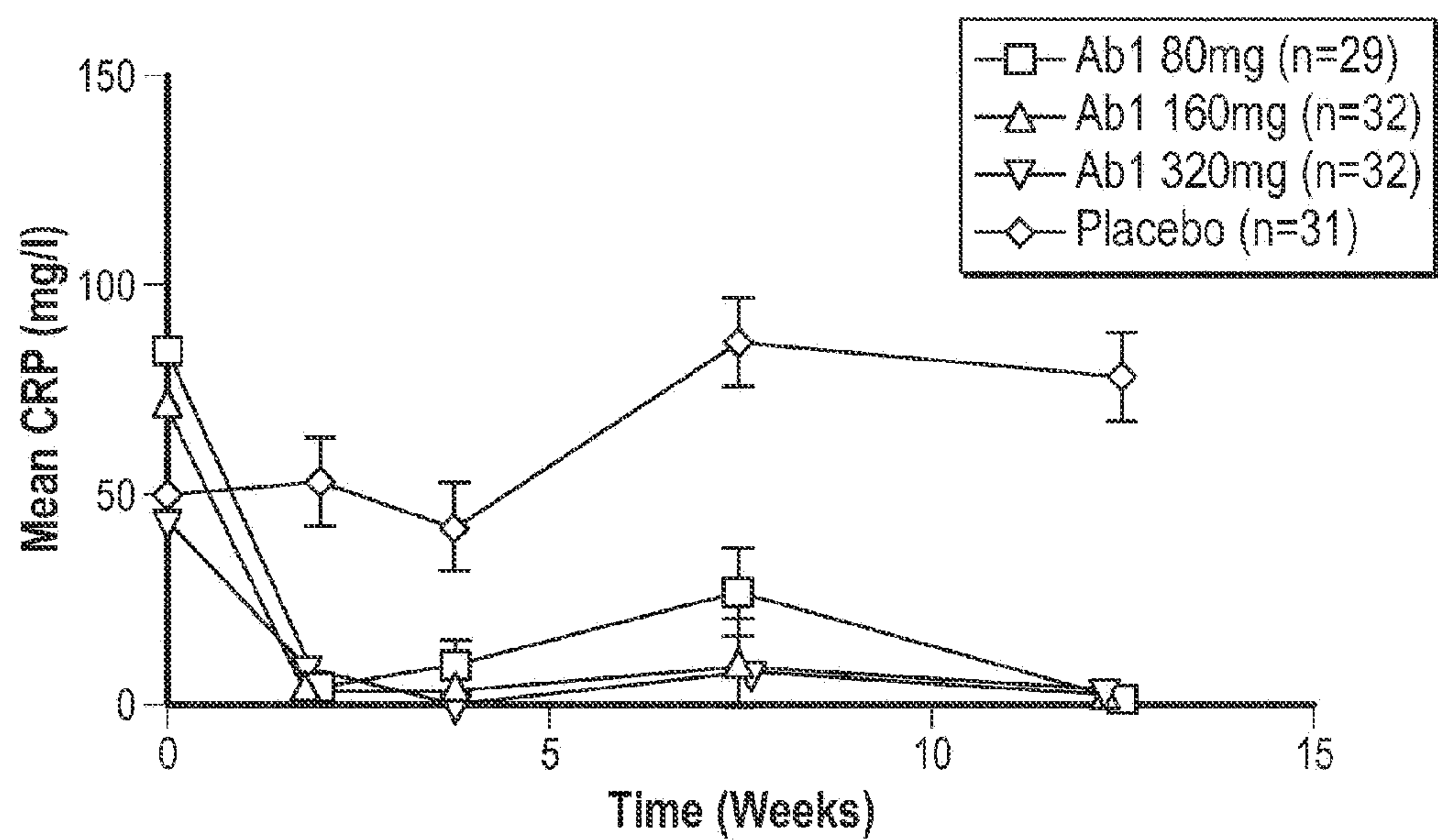


FIG. 15A

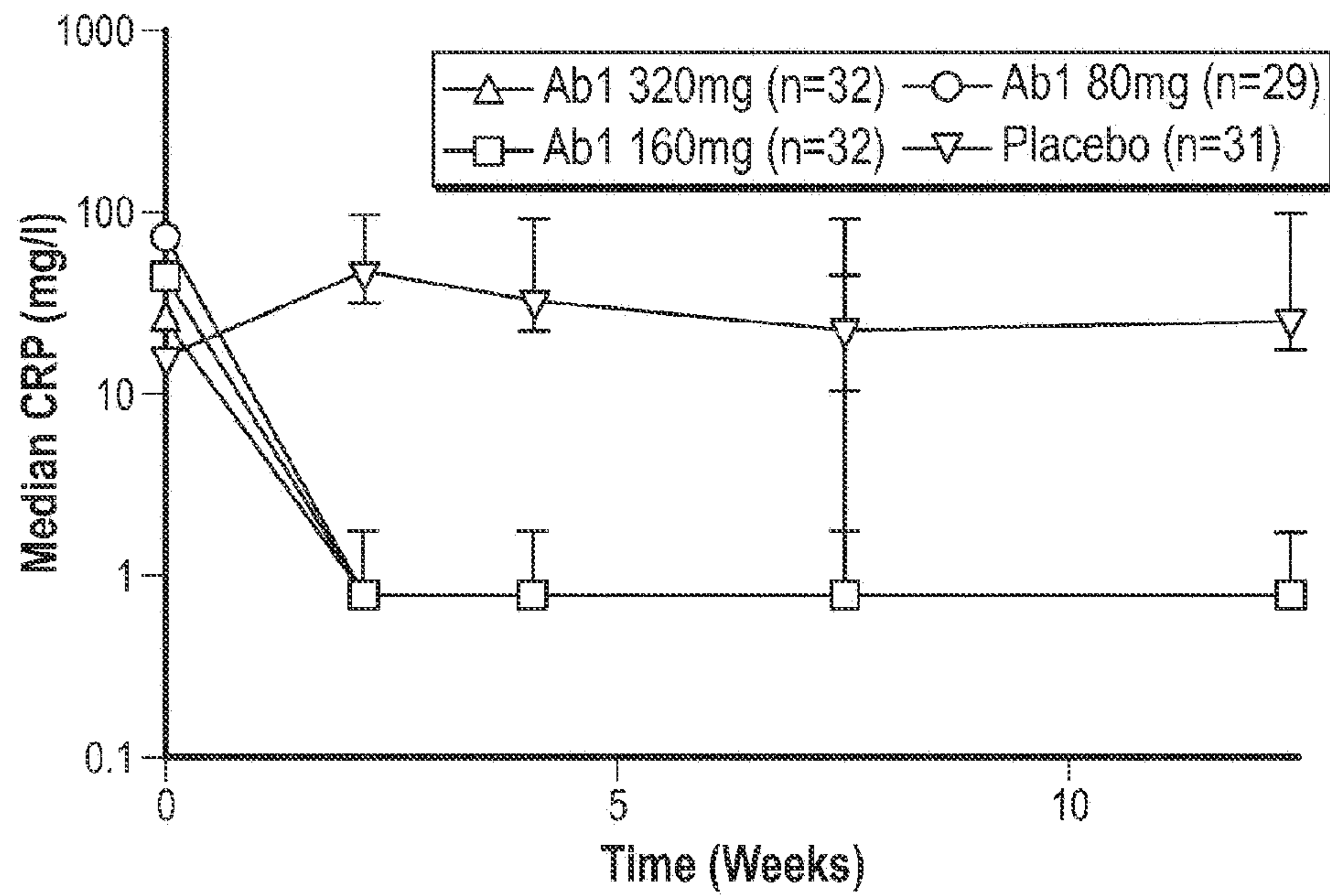


FIG. 15B

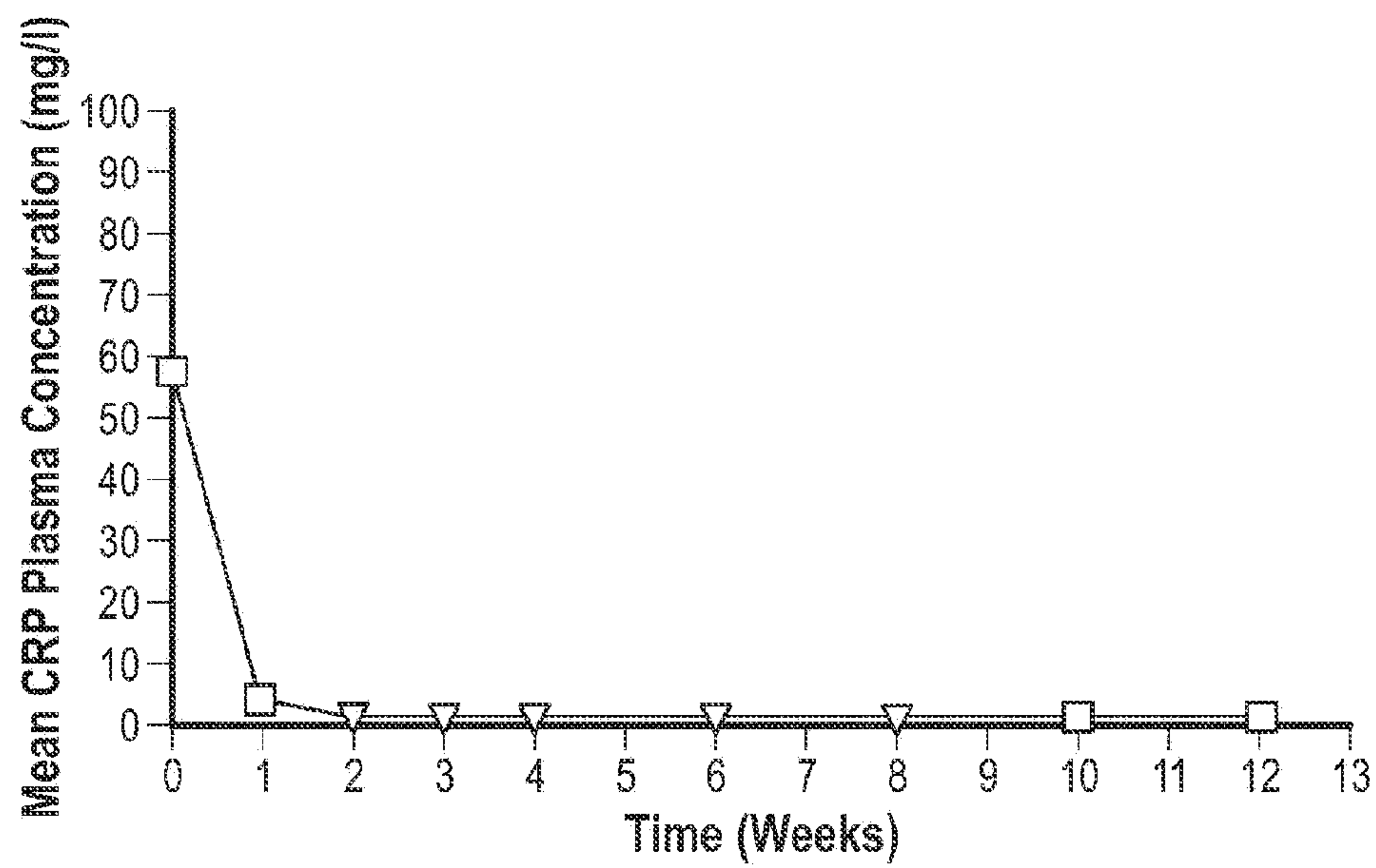


FIG. 16

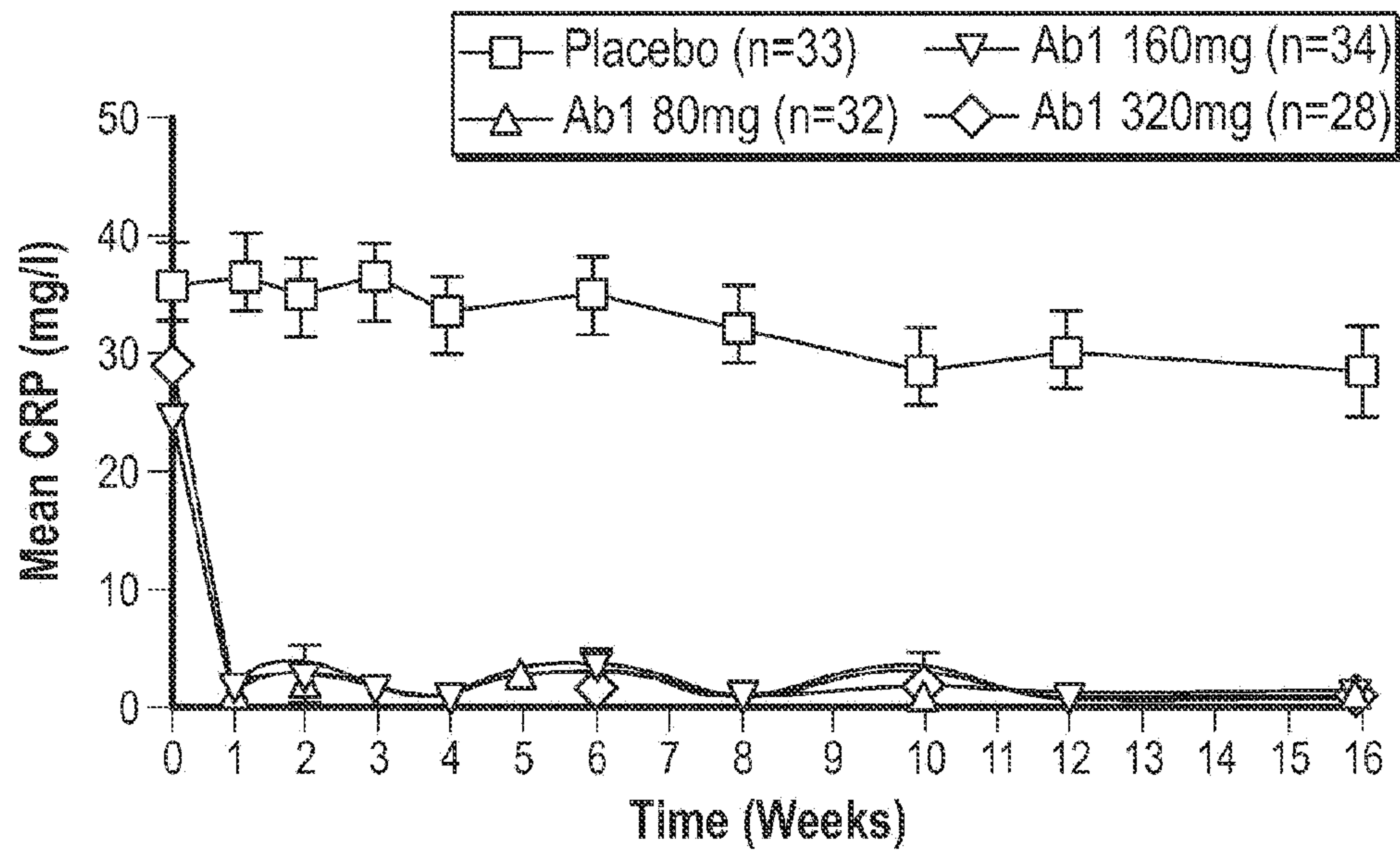


FIG. 17

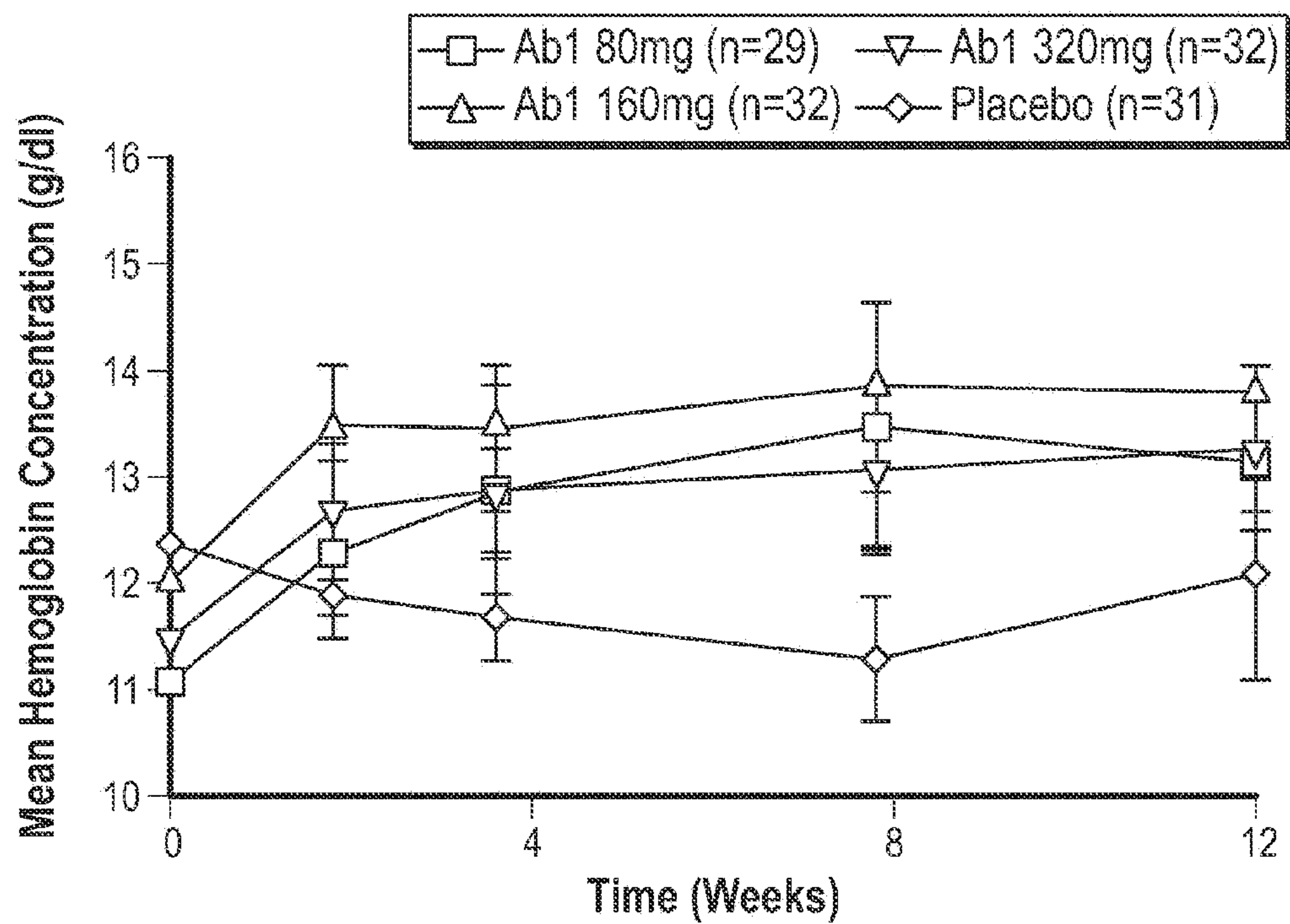


FIG. 18A

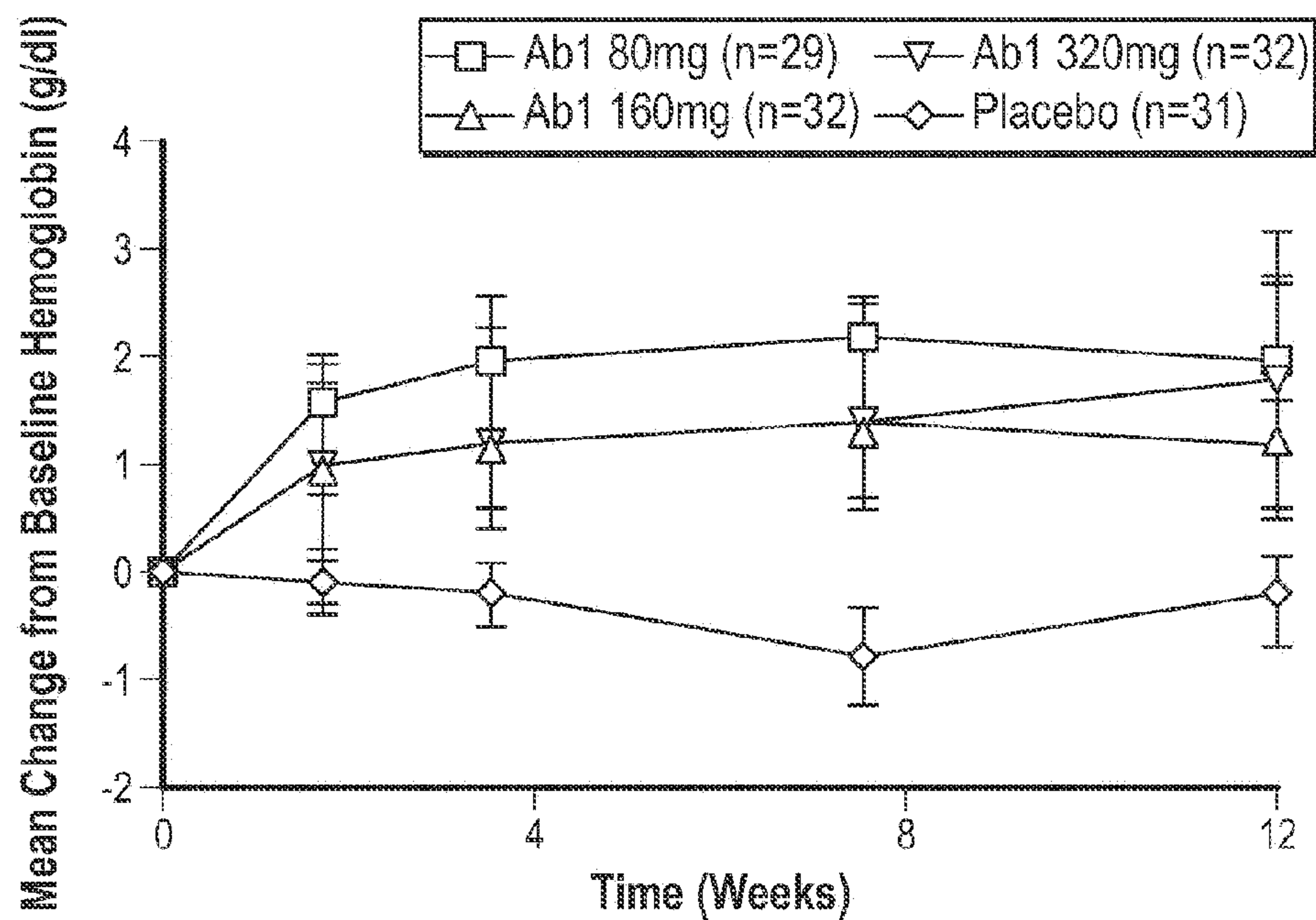


FIG. 18B

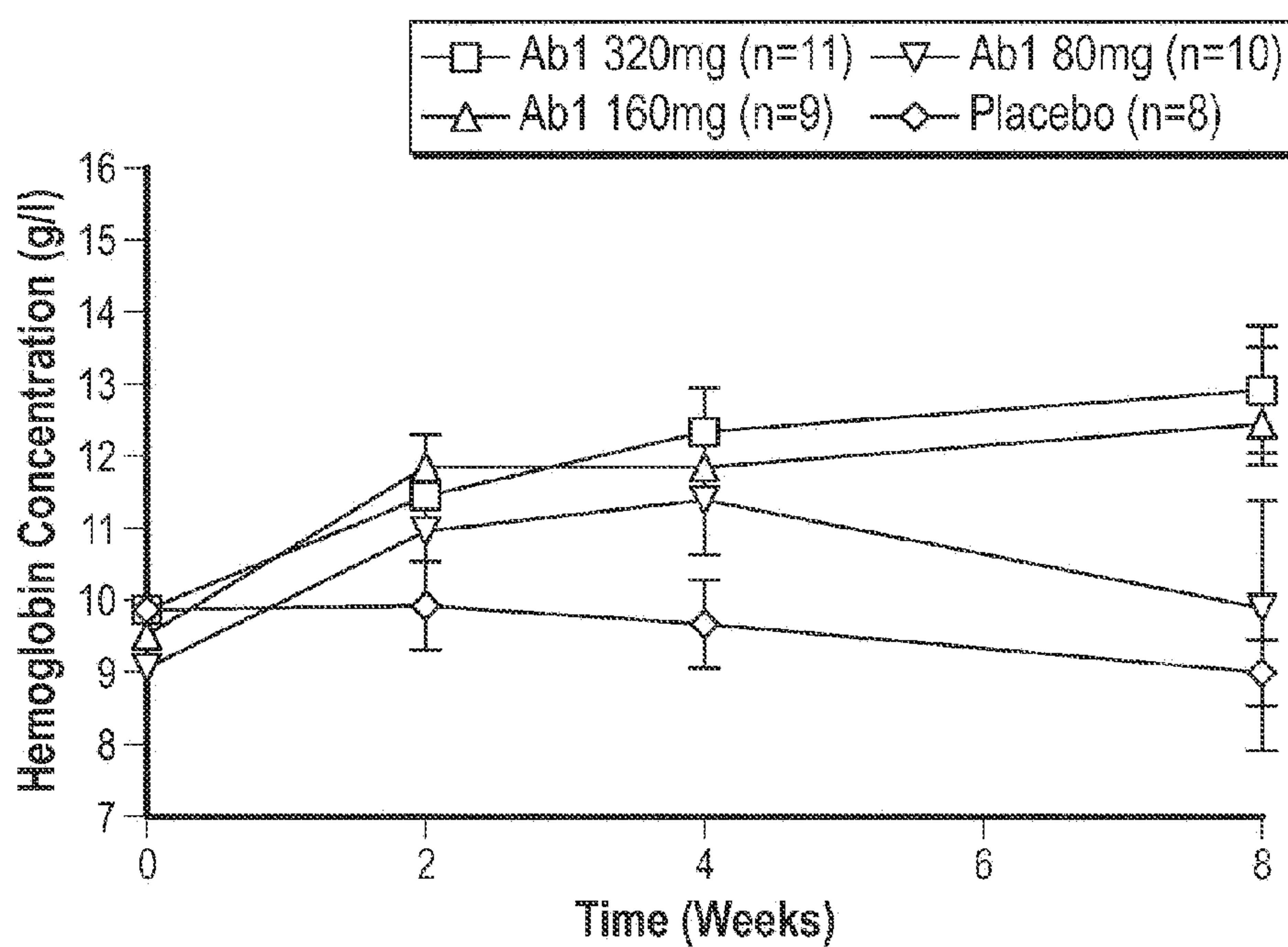


FIG. 18C

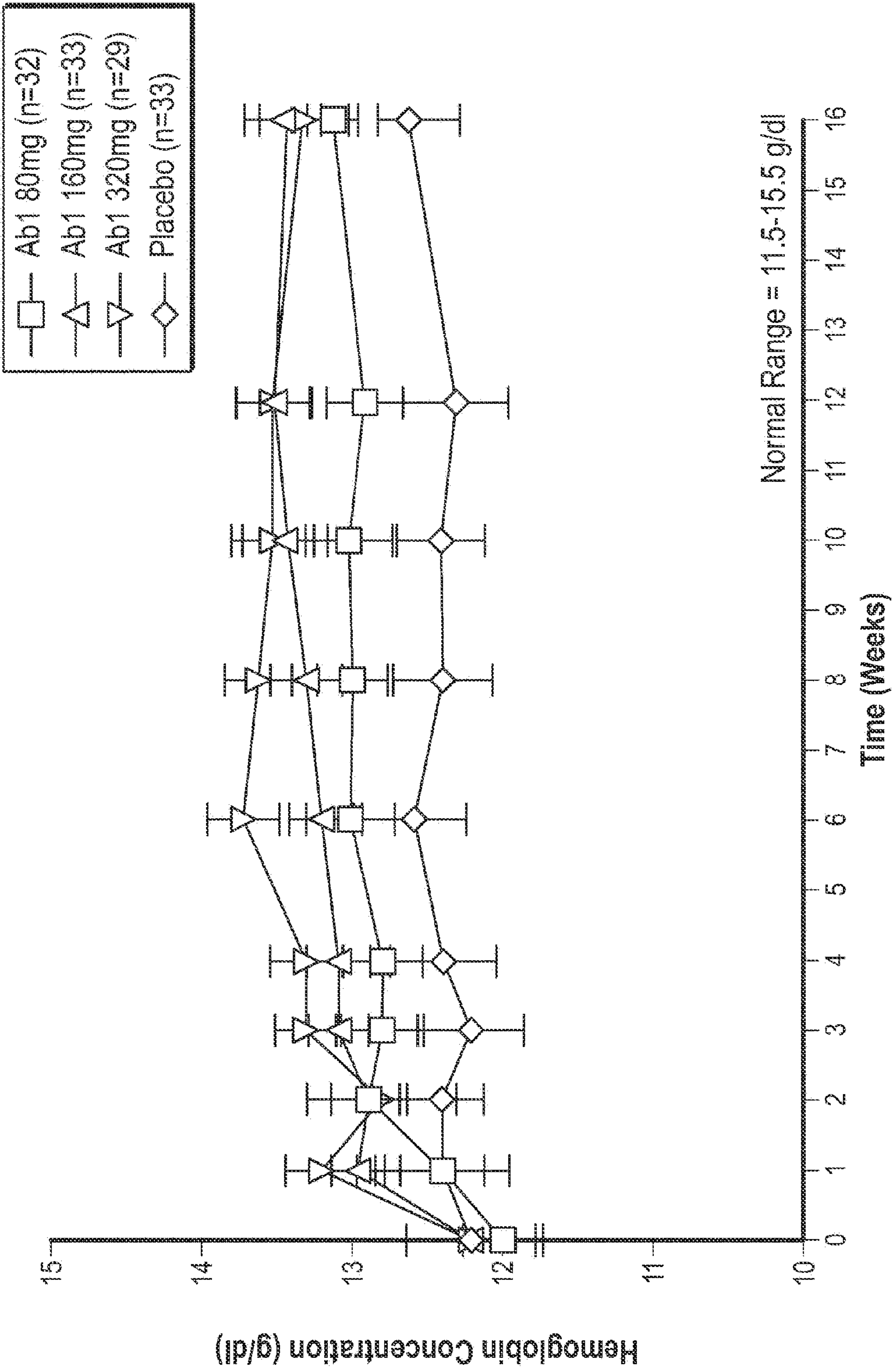


FIG. 19

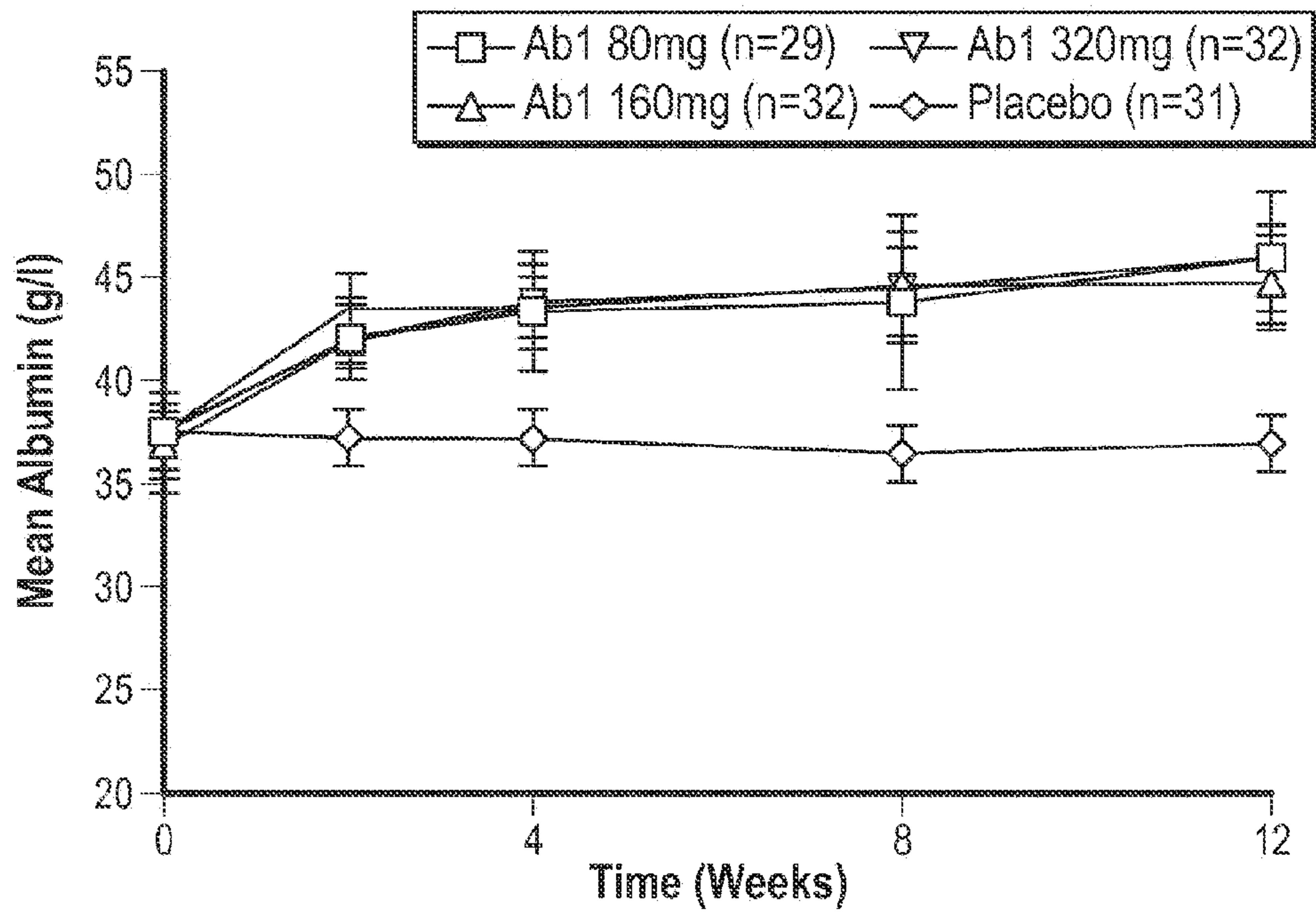


FIG. 20A

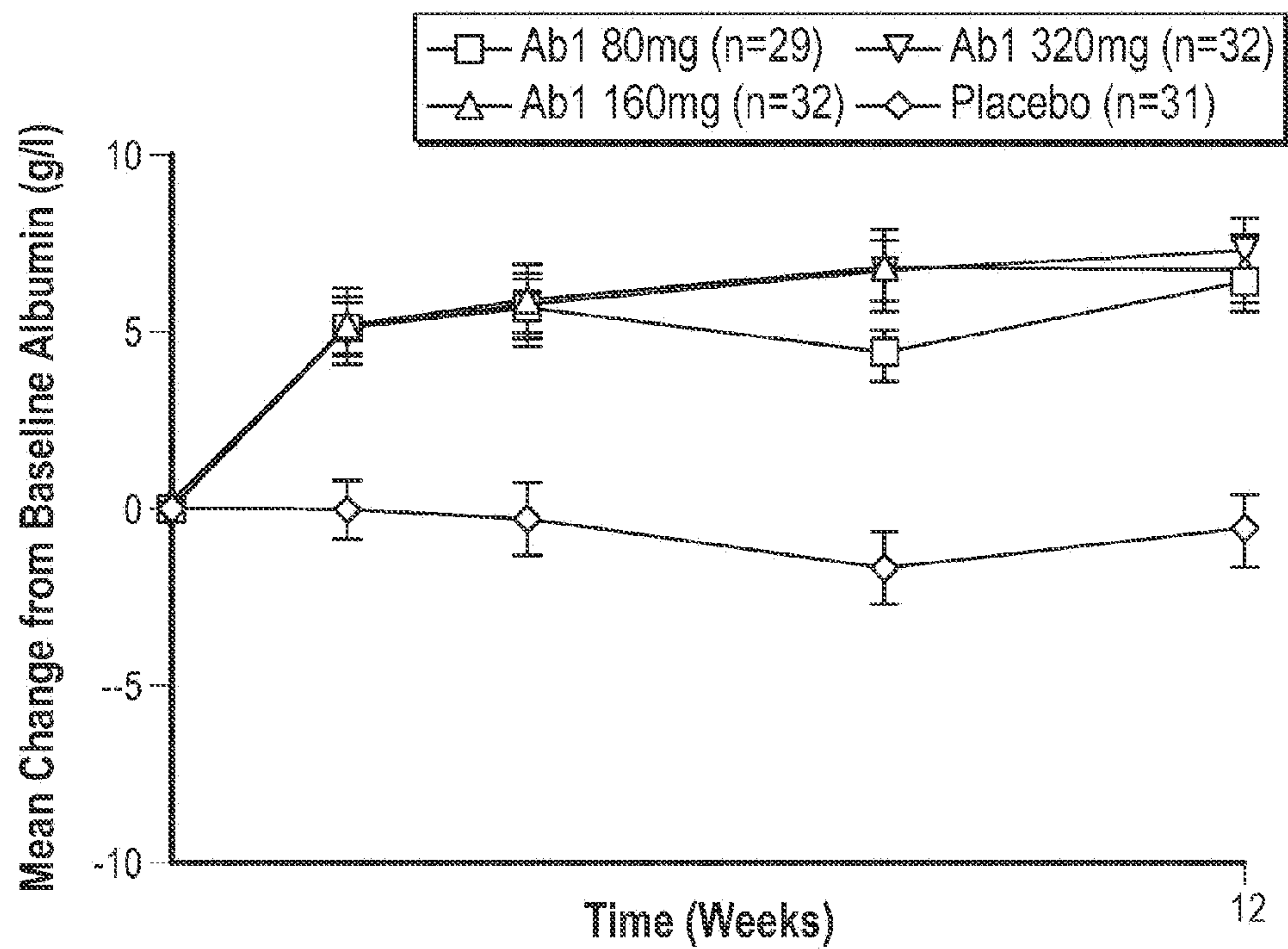


FIG. 20B

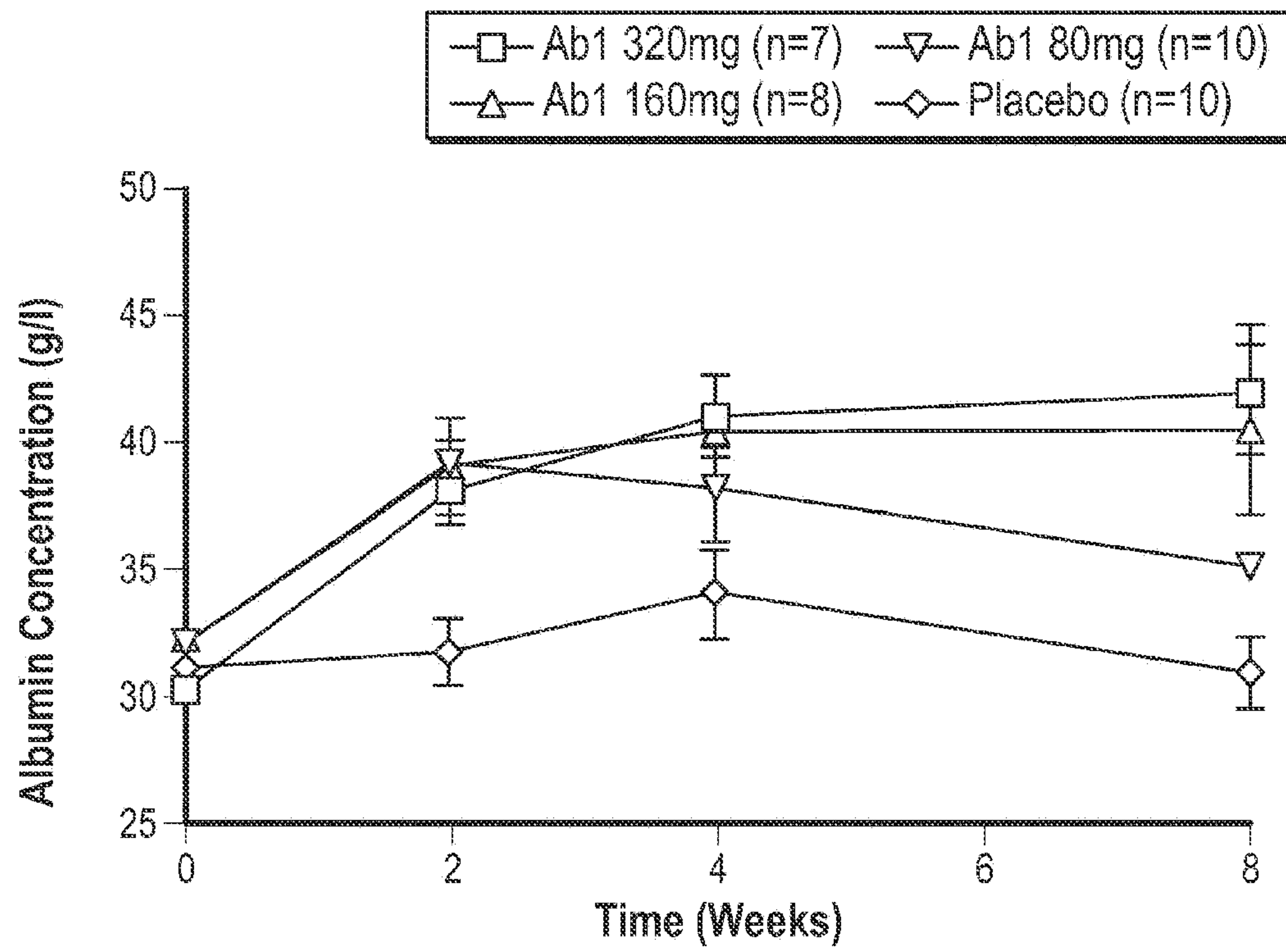
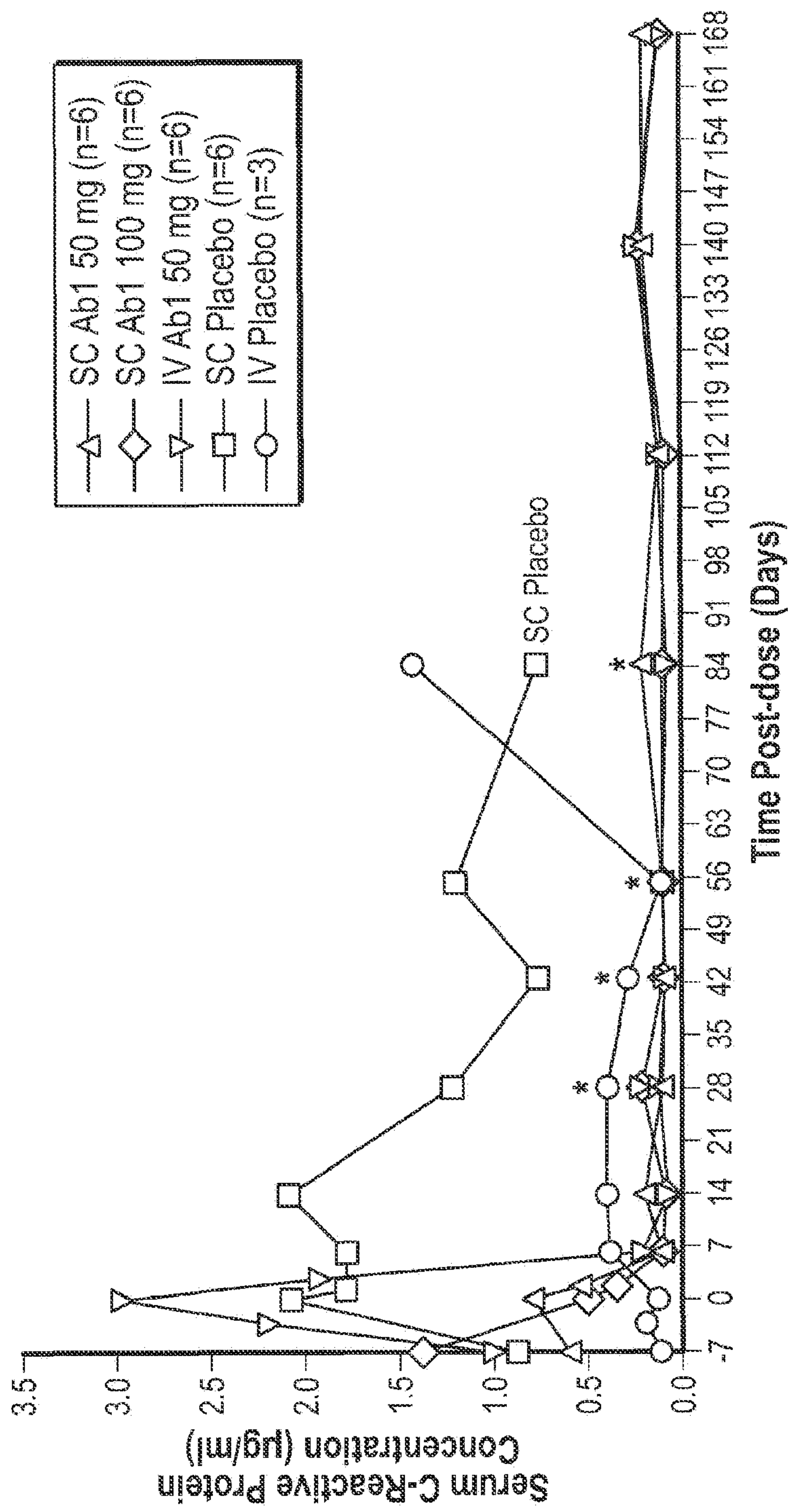
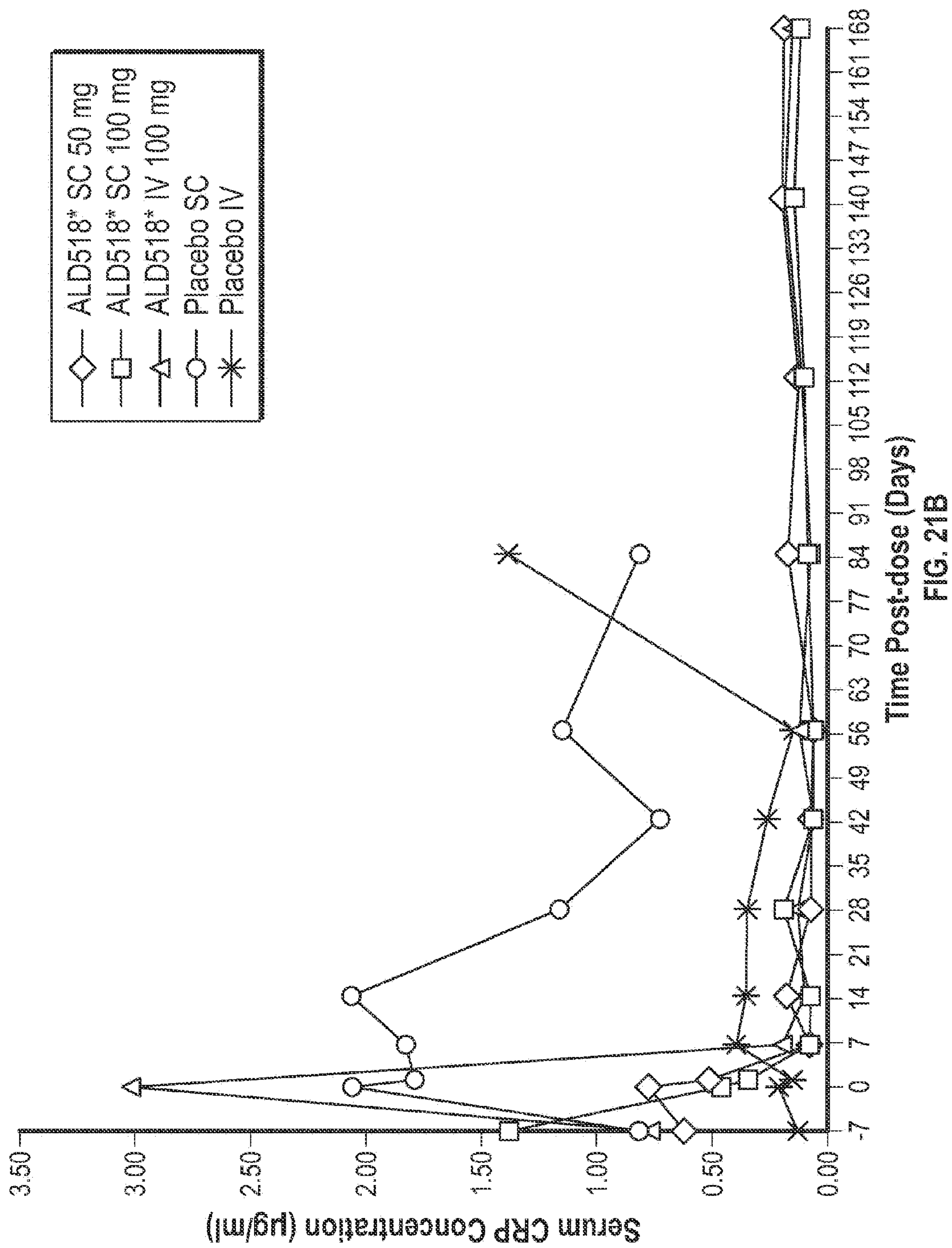


FIG. 20C



*p<0.05 versus placebo using Wilcoxon Rank Sum Test. SC=subcutaneous; IV=intravenous

FIG. 21A



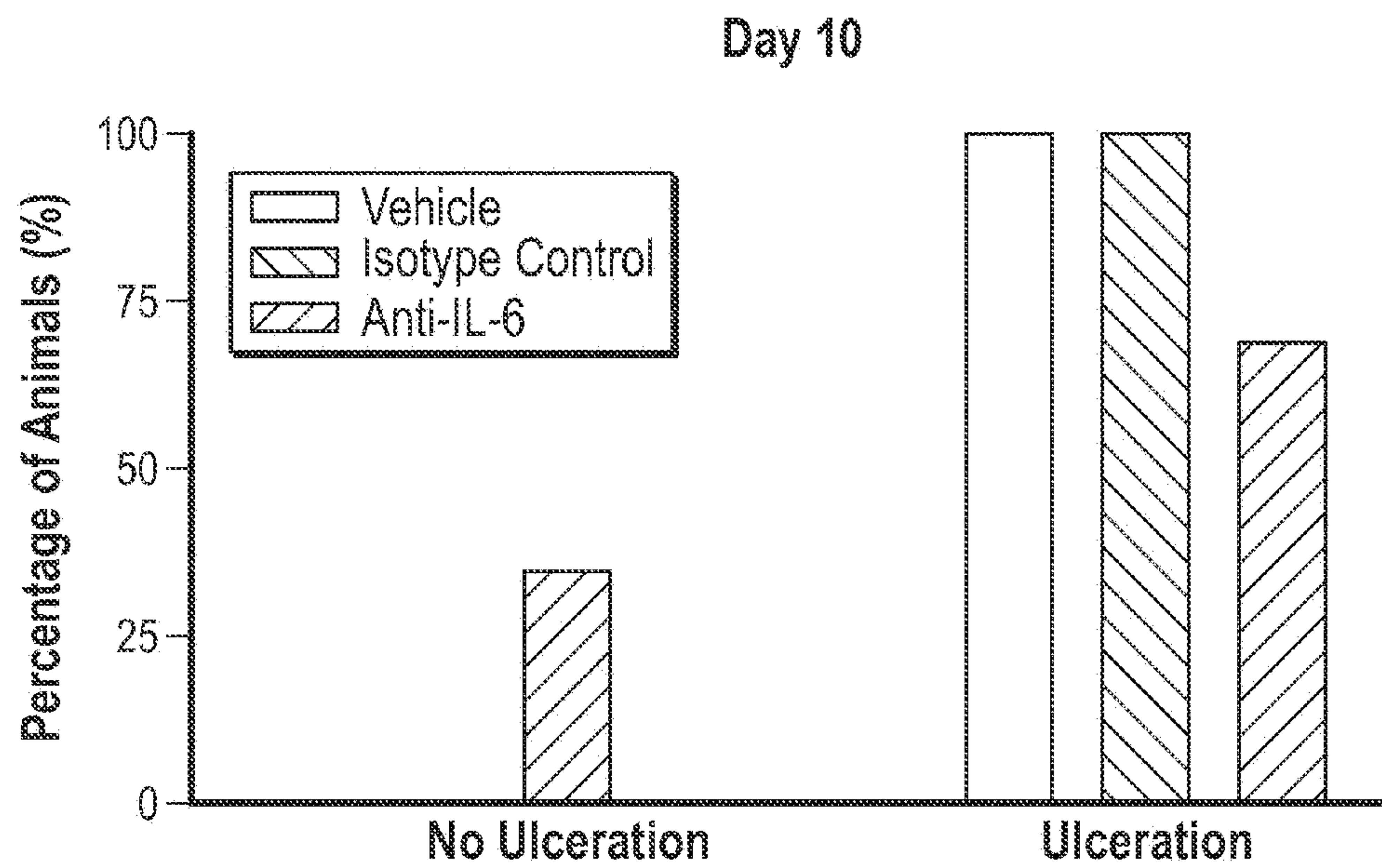


FIG. 22

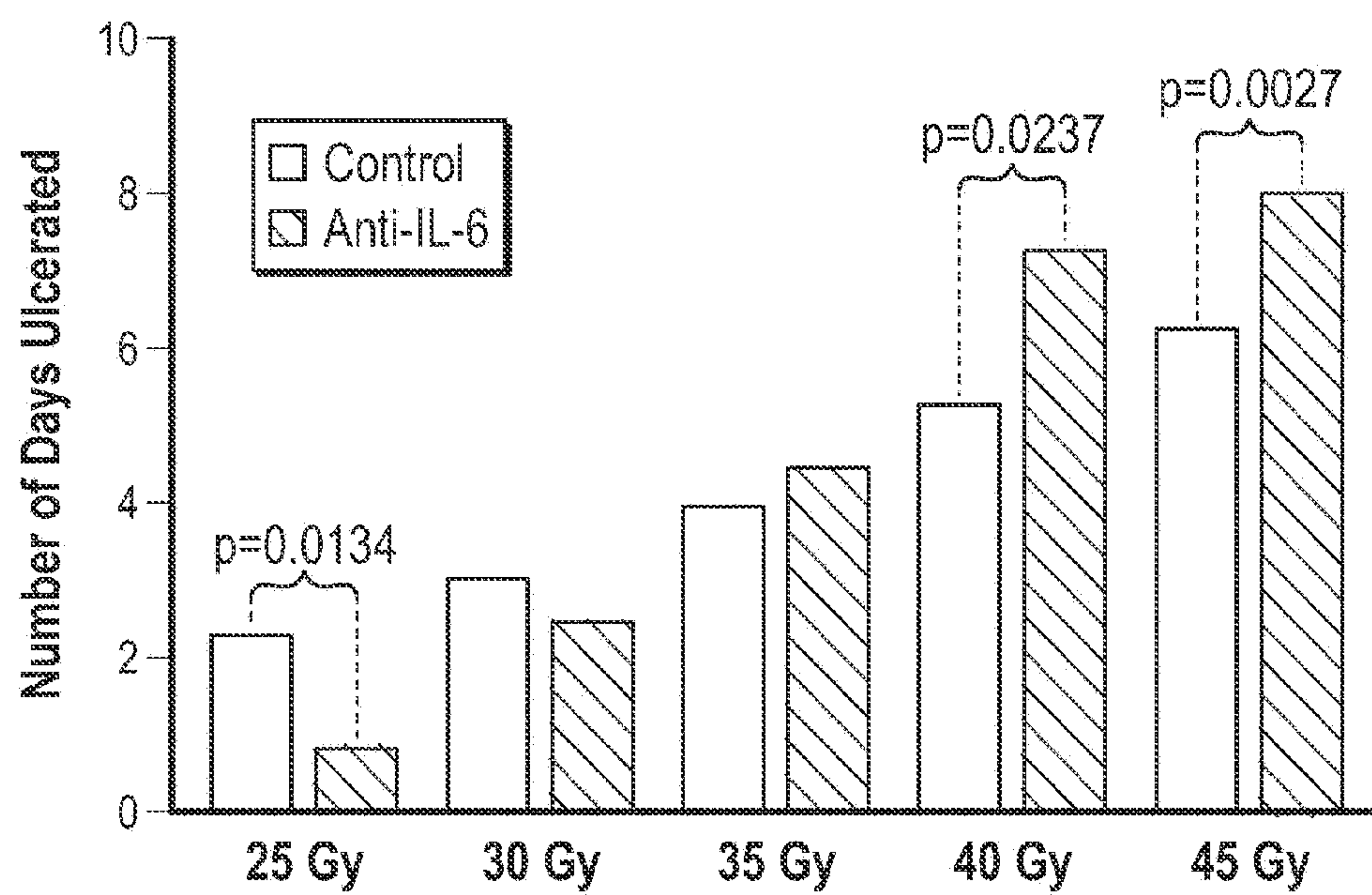


FIG. 23

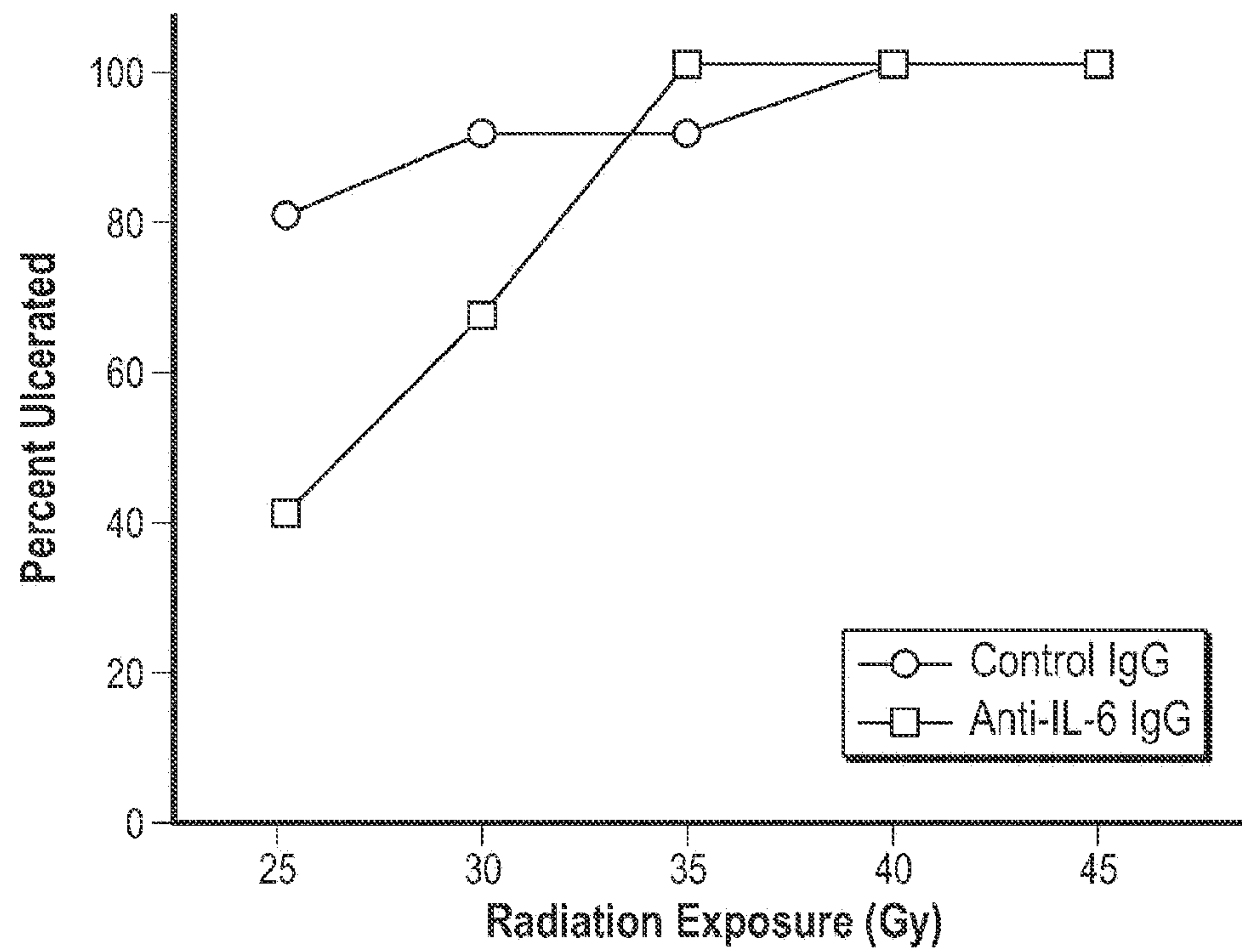


FIG. 24

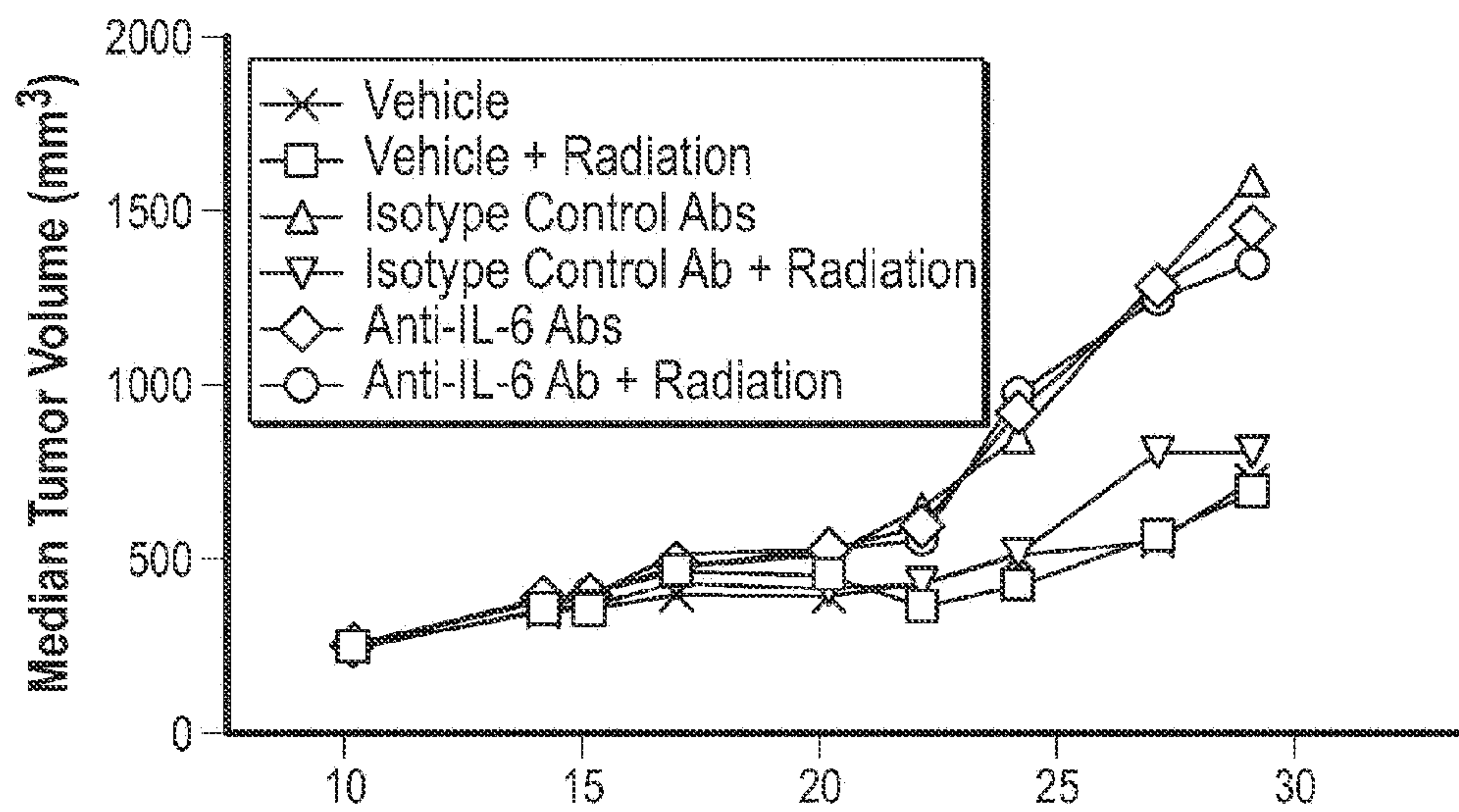


FIG. 25

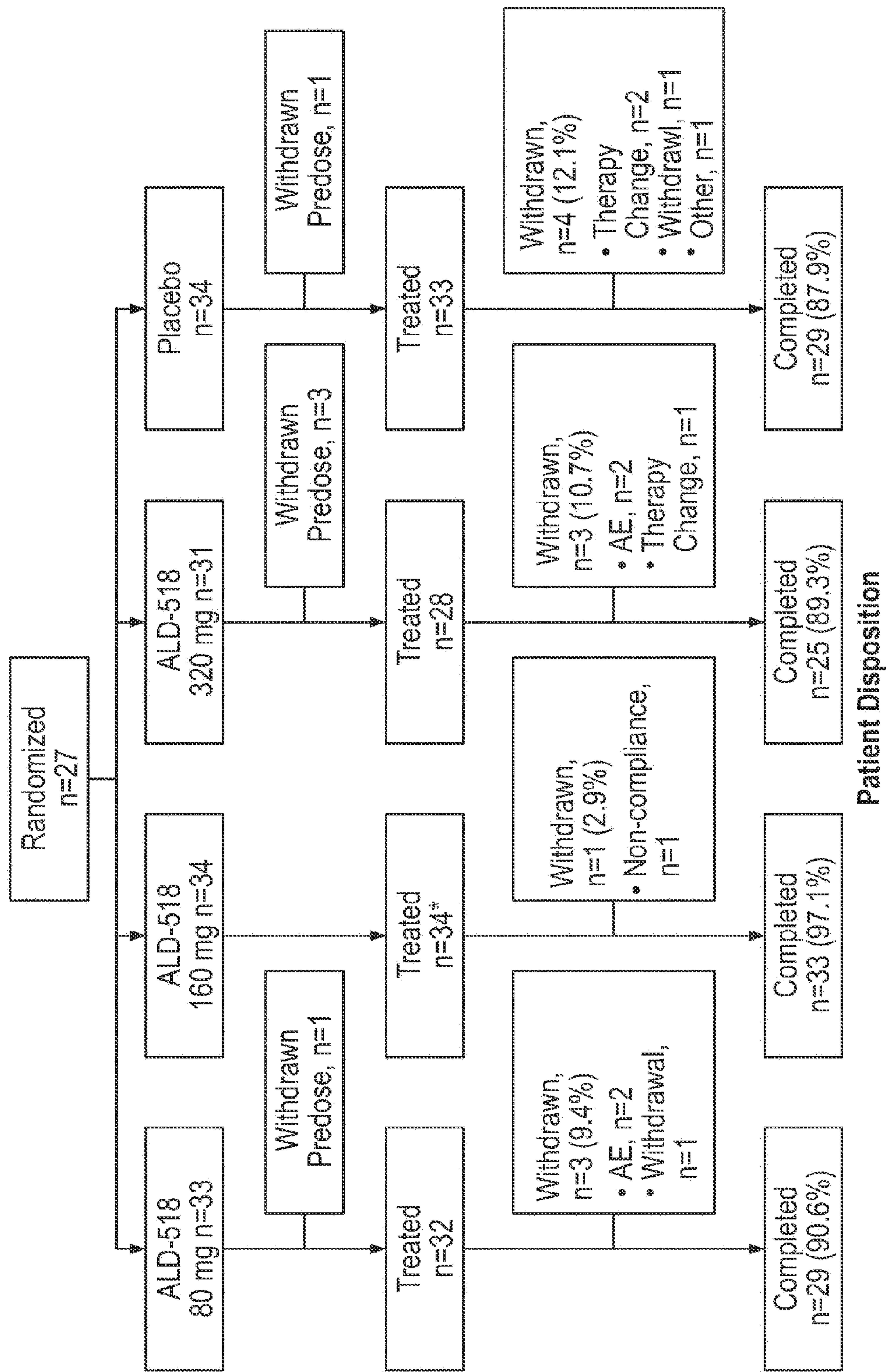
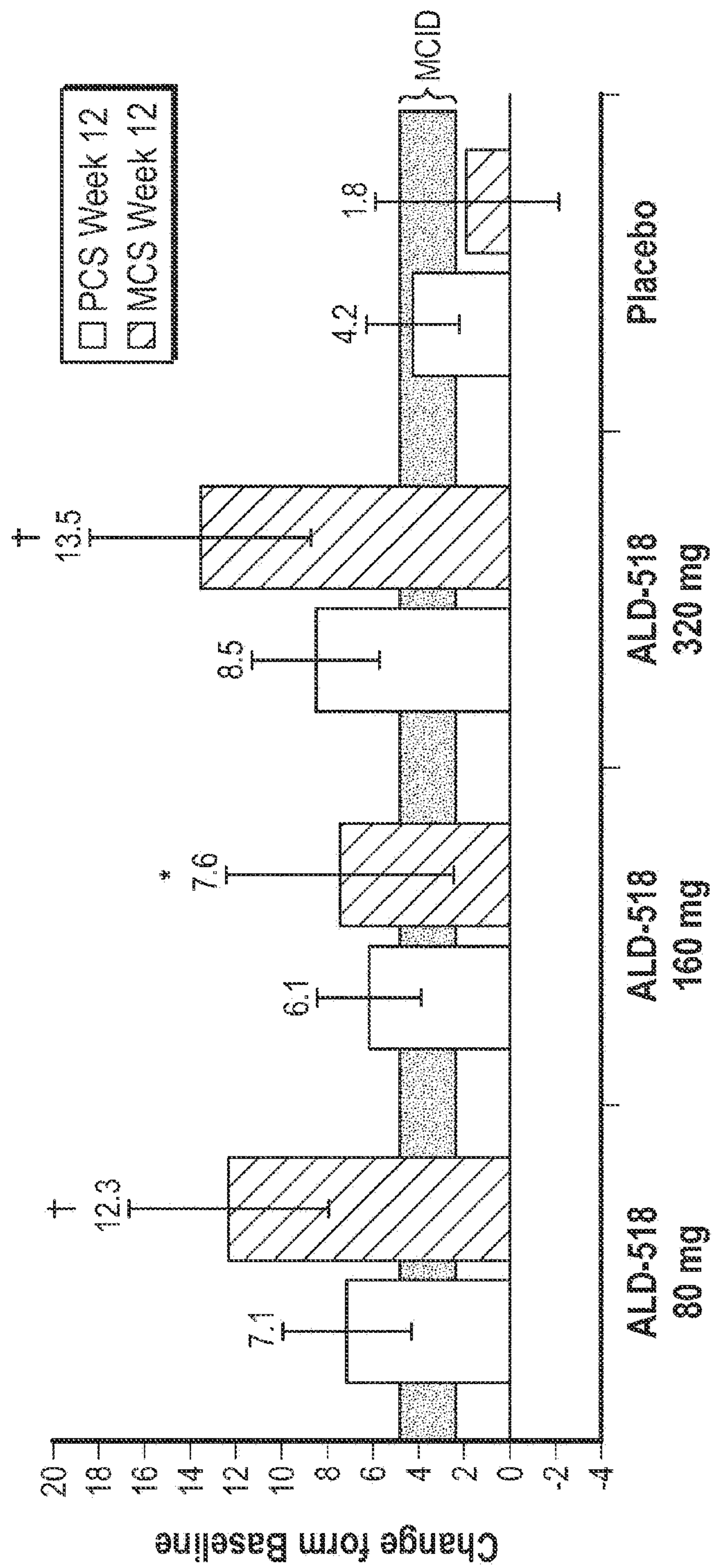


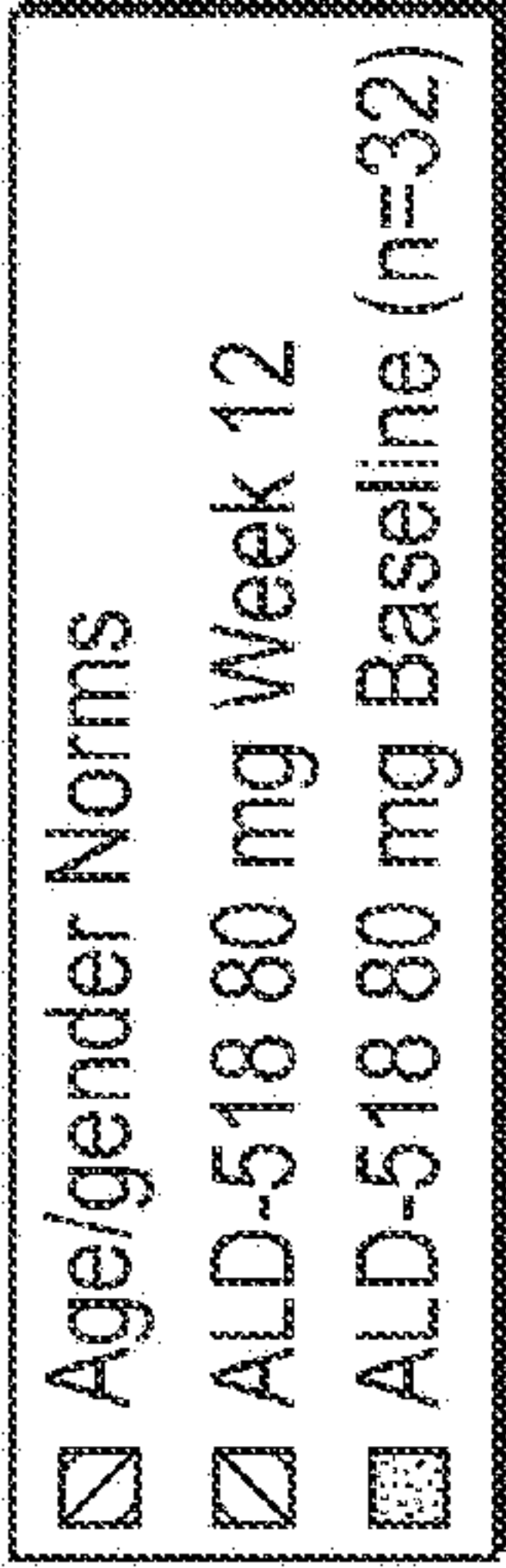
FIG. 26



†p<0.001 versus placebo; *p<0.05 versus placebo

Mean Changes in SF-36 Composite Scores at Week 12

FIG. 27



ALD-518 80 mg

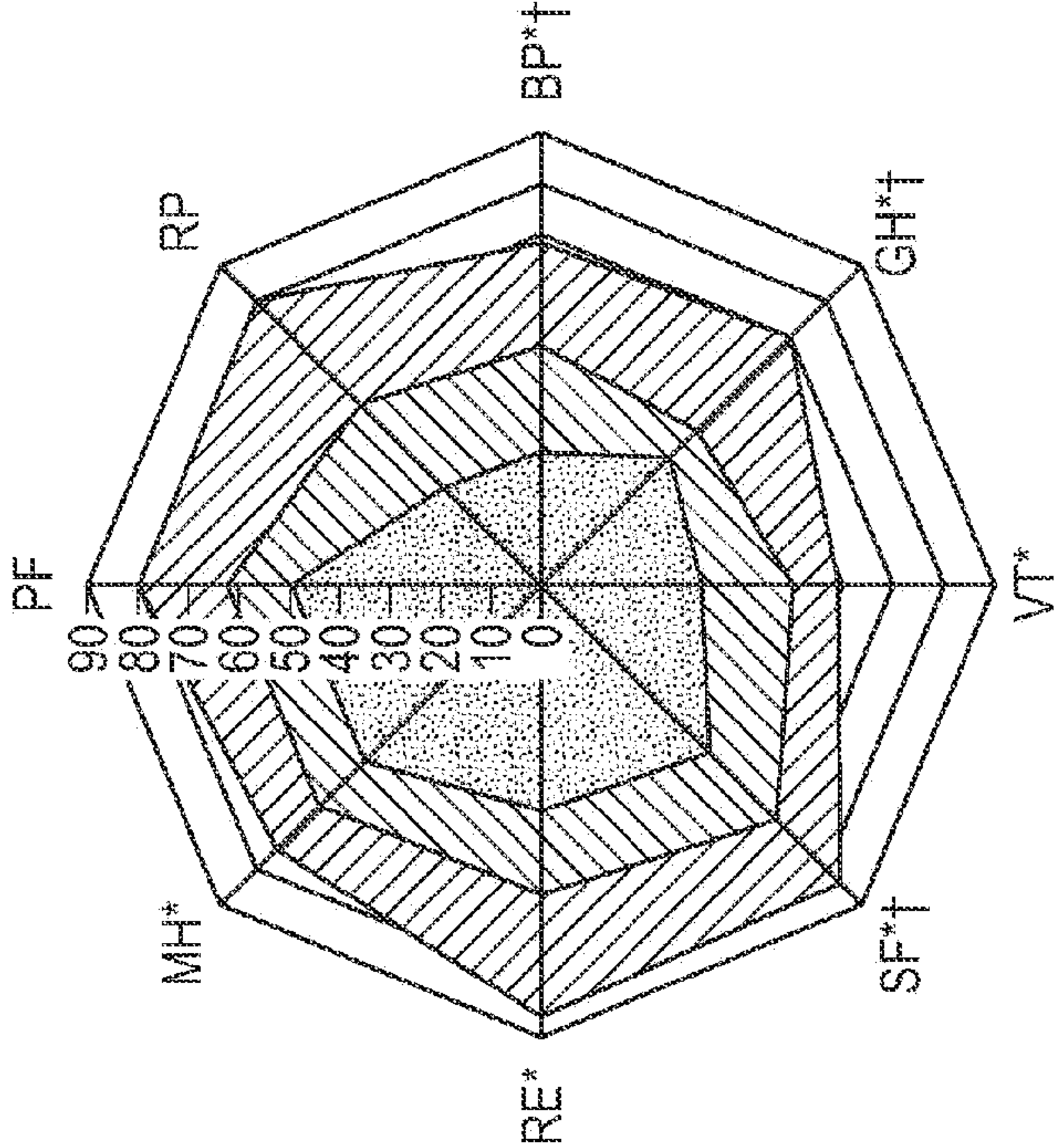
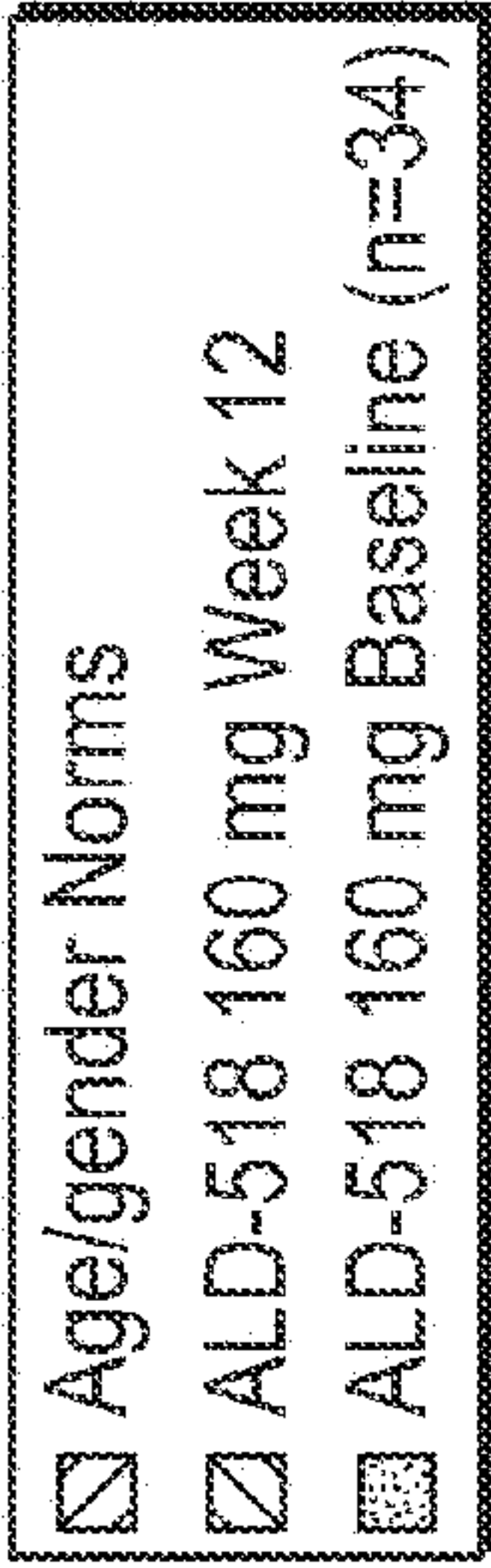


FIG. 28A



ALD-518 160 mg

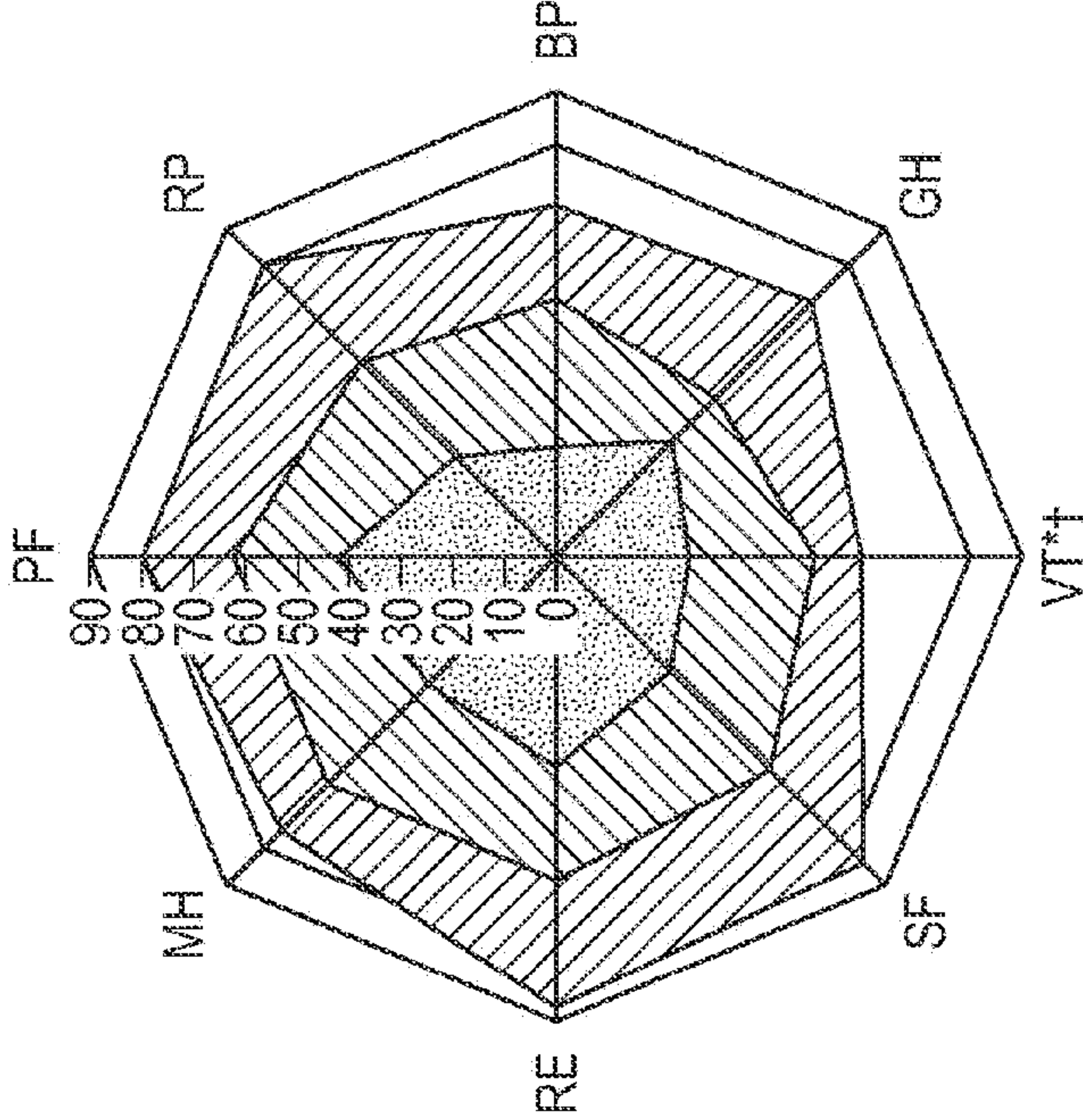
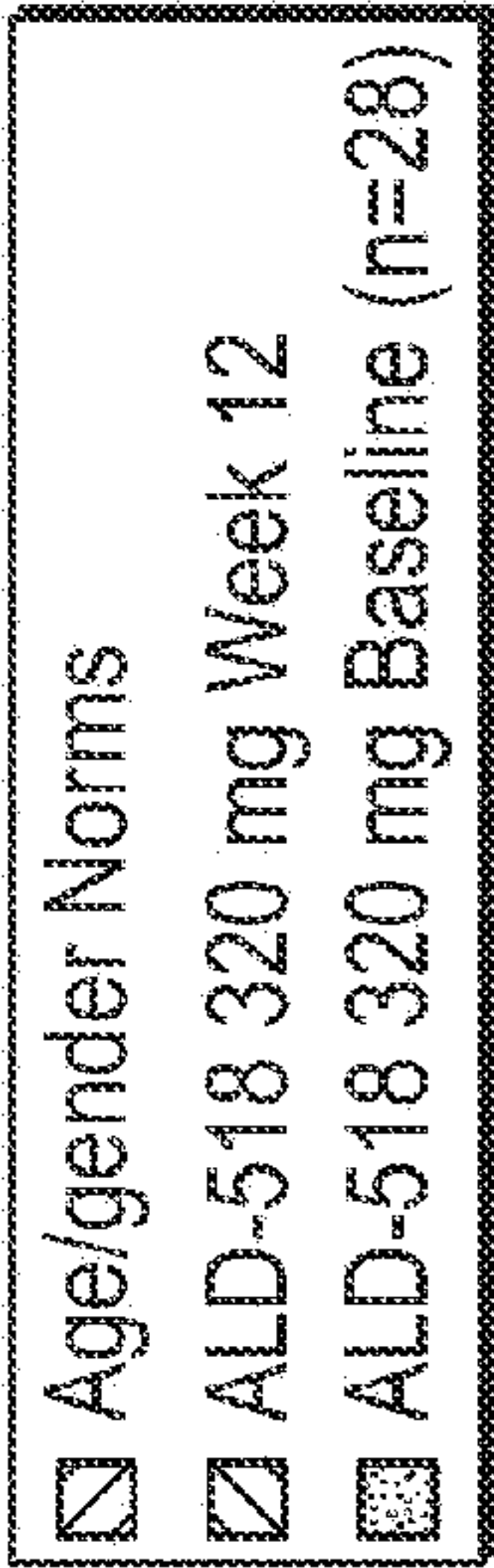


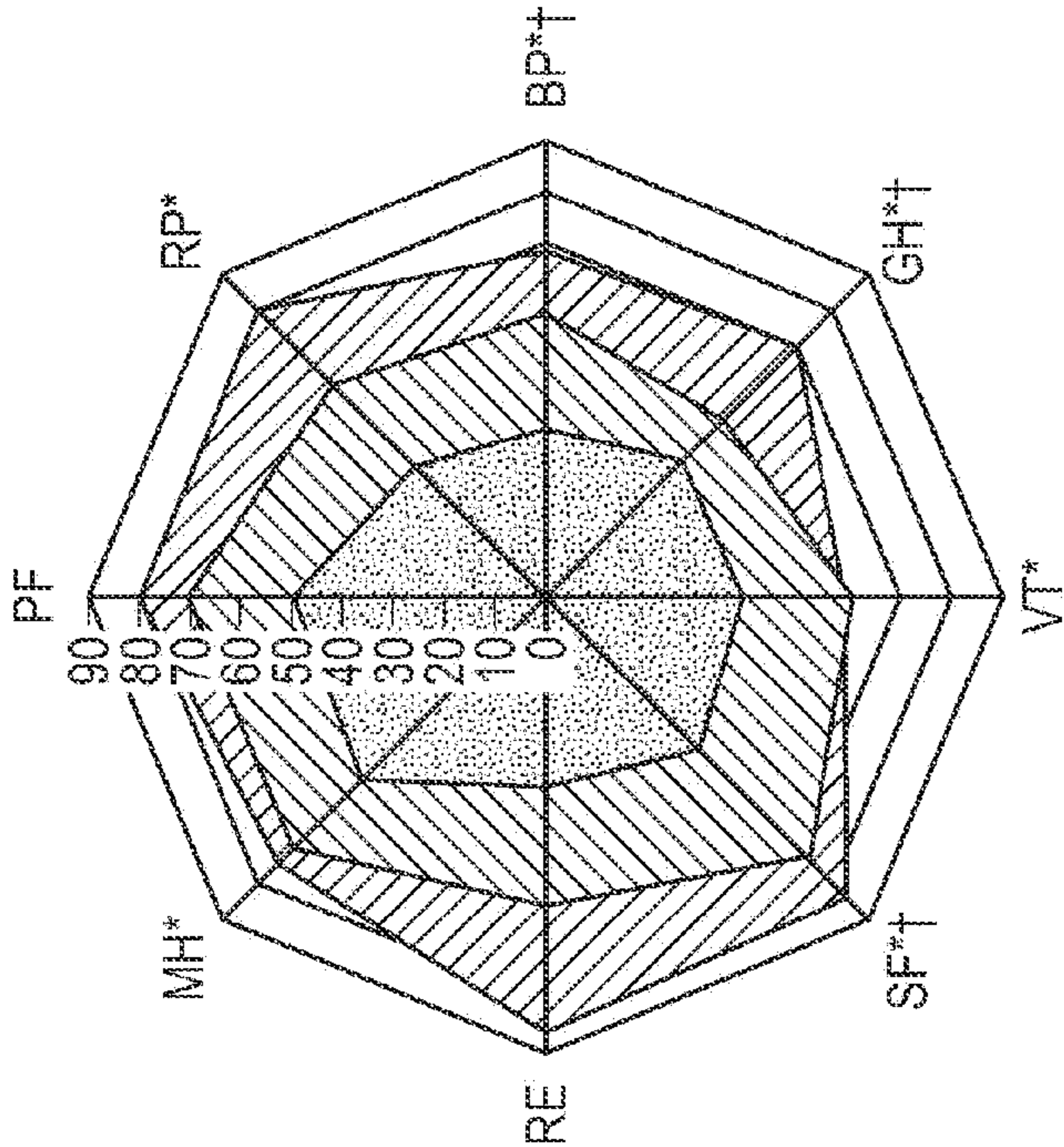
FIG. 28B

*p<0.05 for ALD-518 dose versus placebo at week 12; †p<0.05 for ALD-518 dose versus placebo at week 12 and maintained to week 16;

Changes from Baseline to Week 12 in SF-36 Domain Scores Compared with Age/Gender Matched Norms

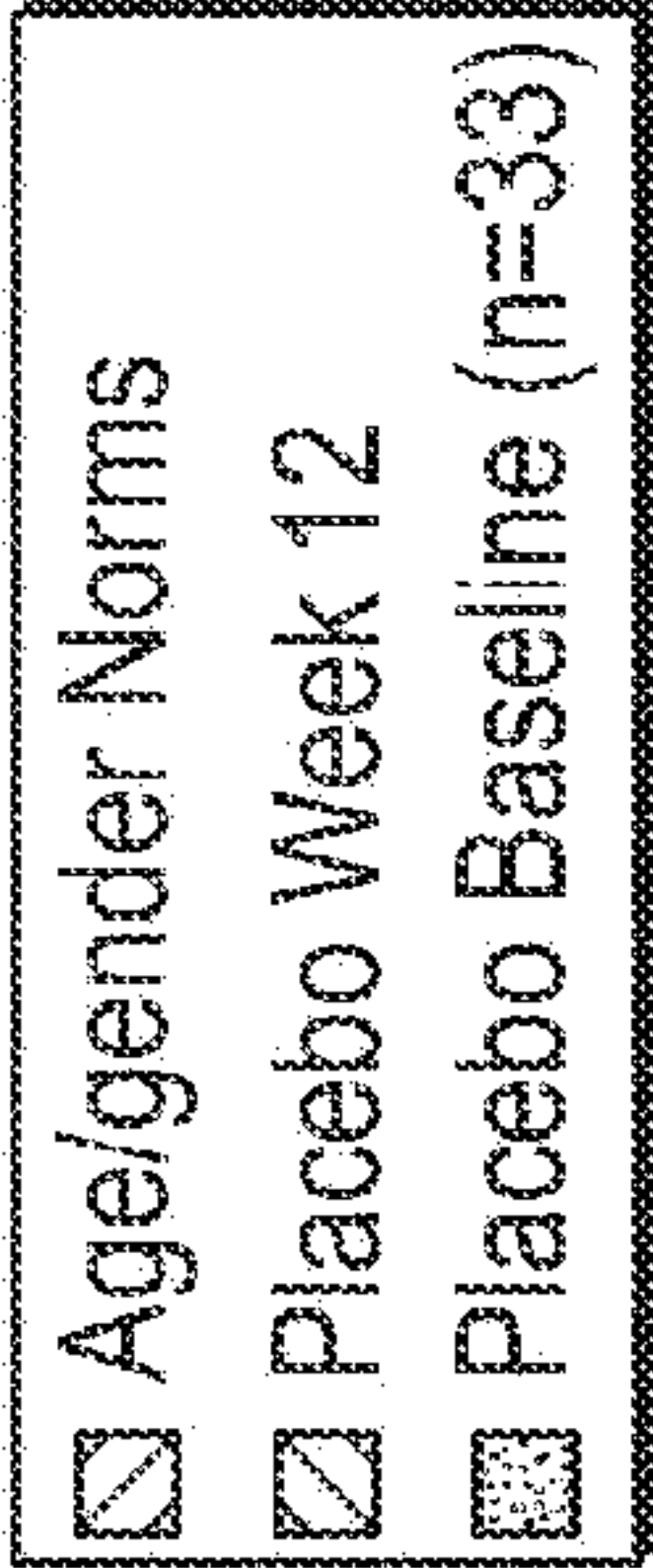


ALD-518 320 mg

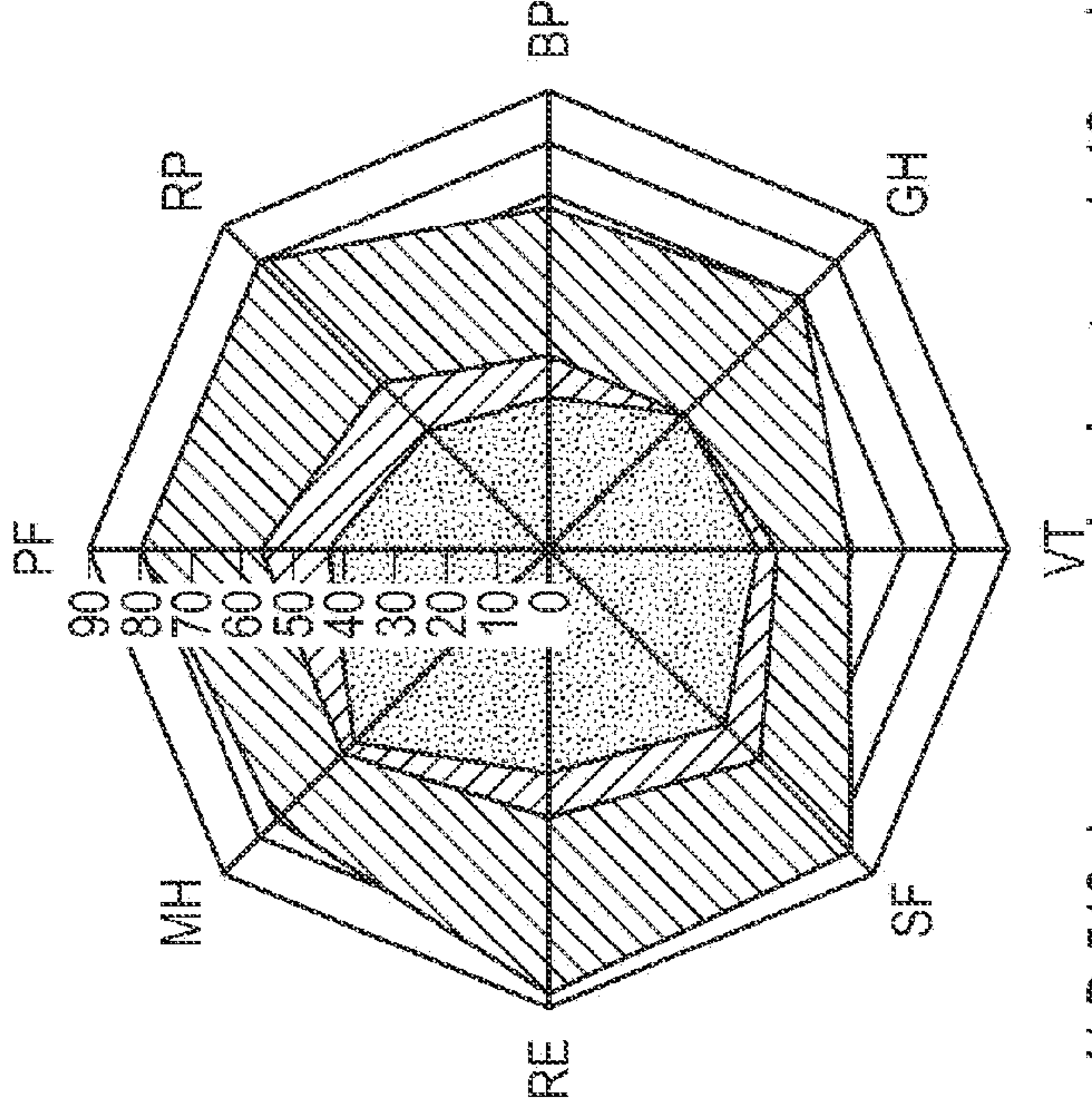


*p<0.05 for ALD-518 dose versus placebo at week 12; †p<0.05 for ALD-518 dose versus placebo at week 12 and maintained to week 16;

FIG. 28C

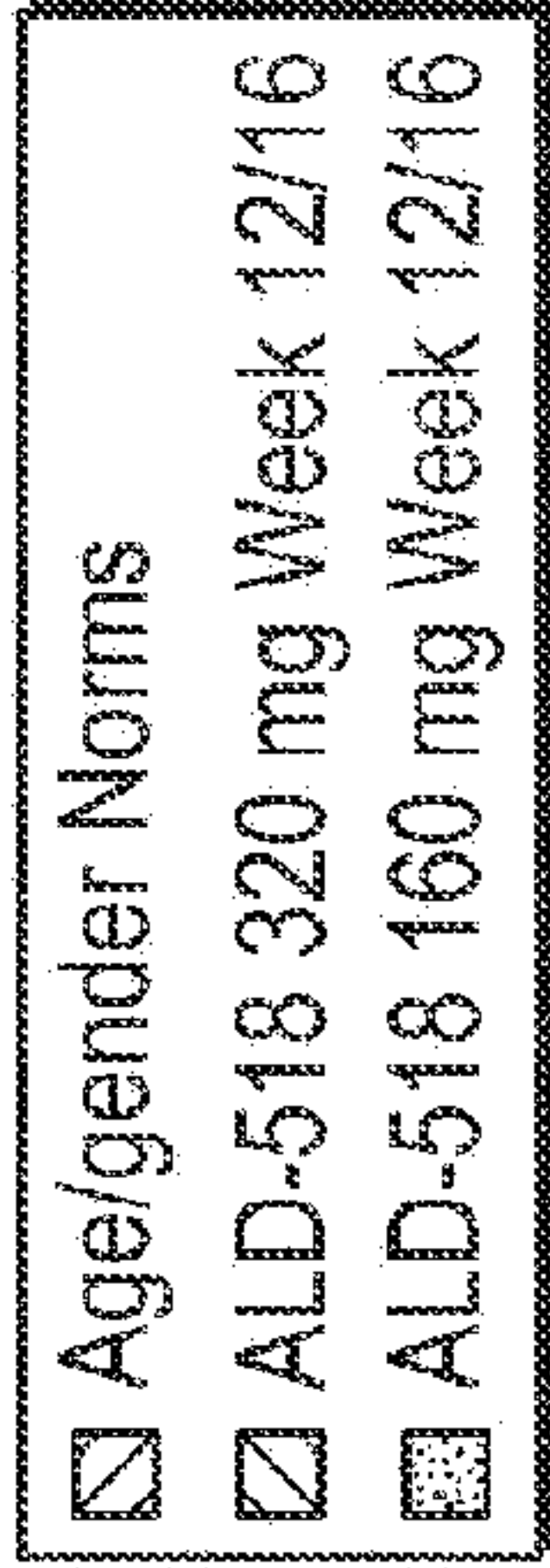


Placebo



Changes from Baseline to Week 12 in SF-36 Domain Scores Compared with Age/Gender Matched Norms

FIG. 28D



All Treatment Groups Week 12

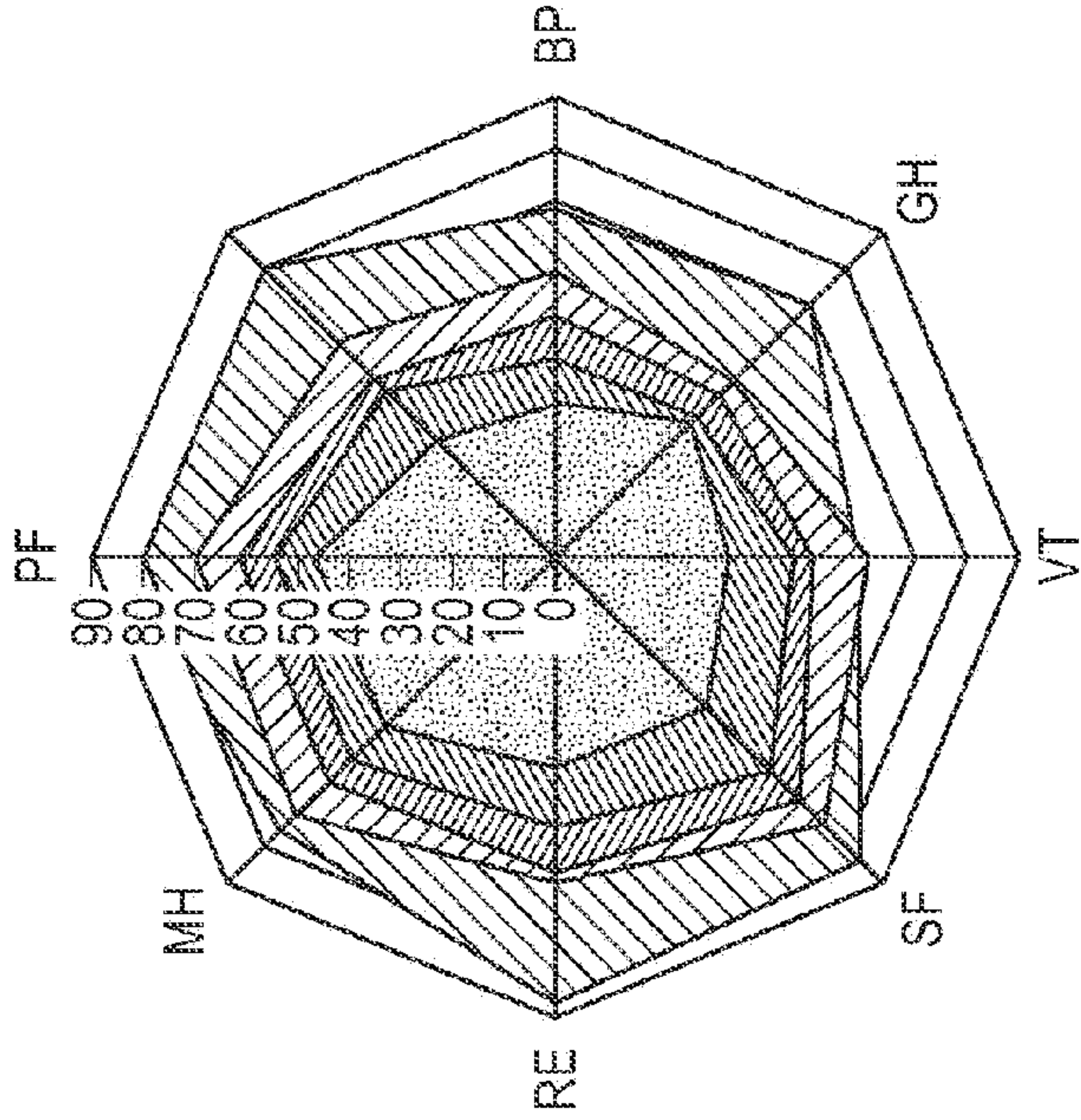
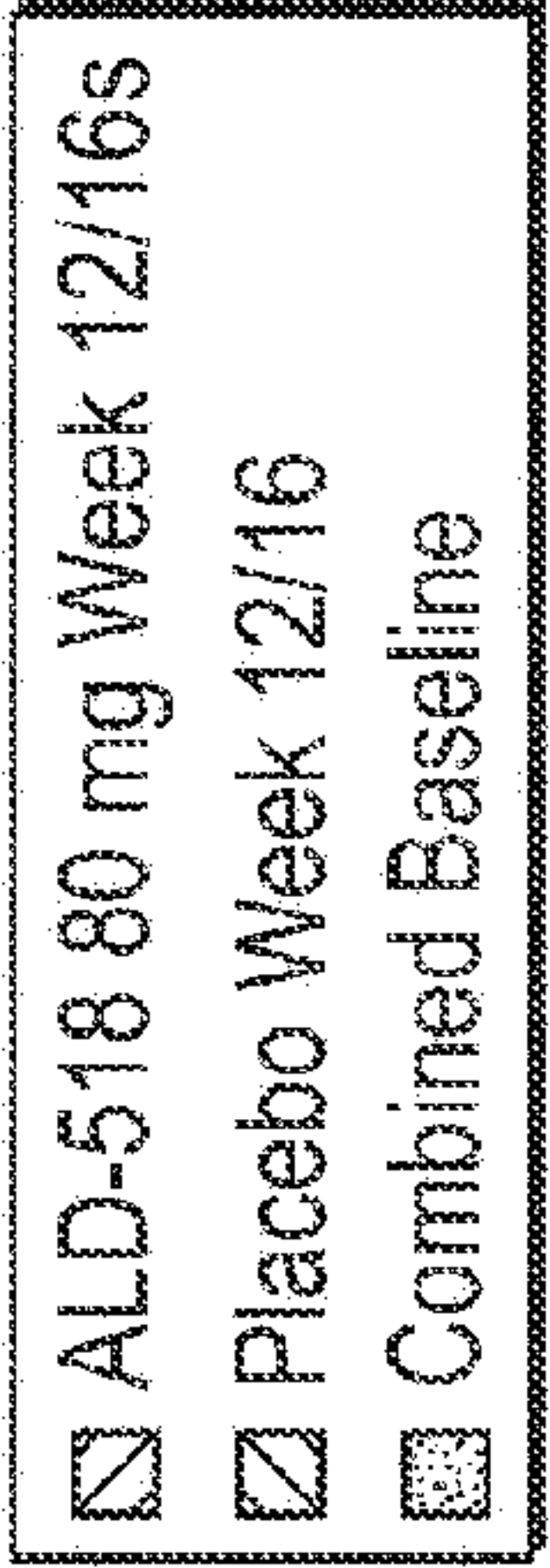


FIG. 29A



All Treatment Groups Week 16

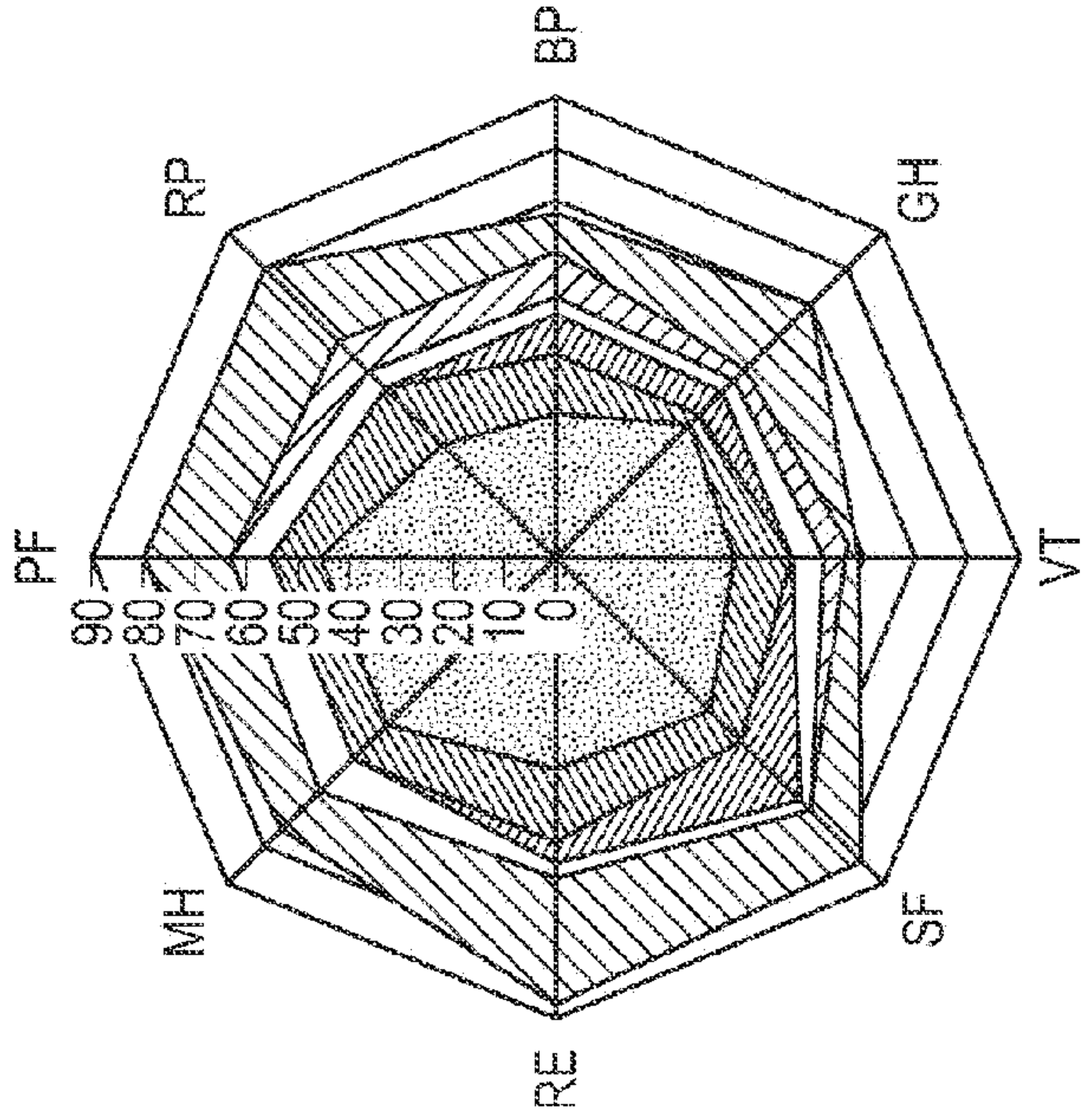
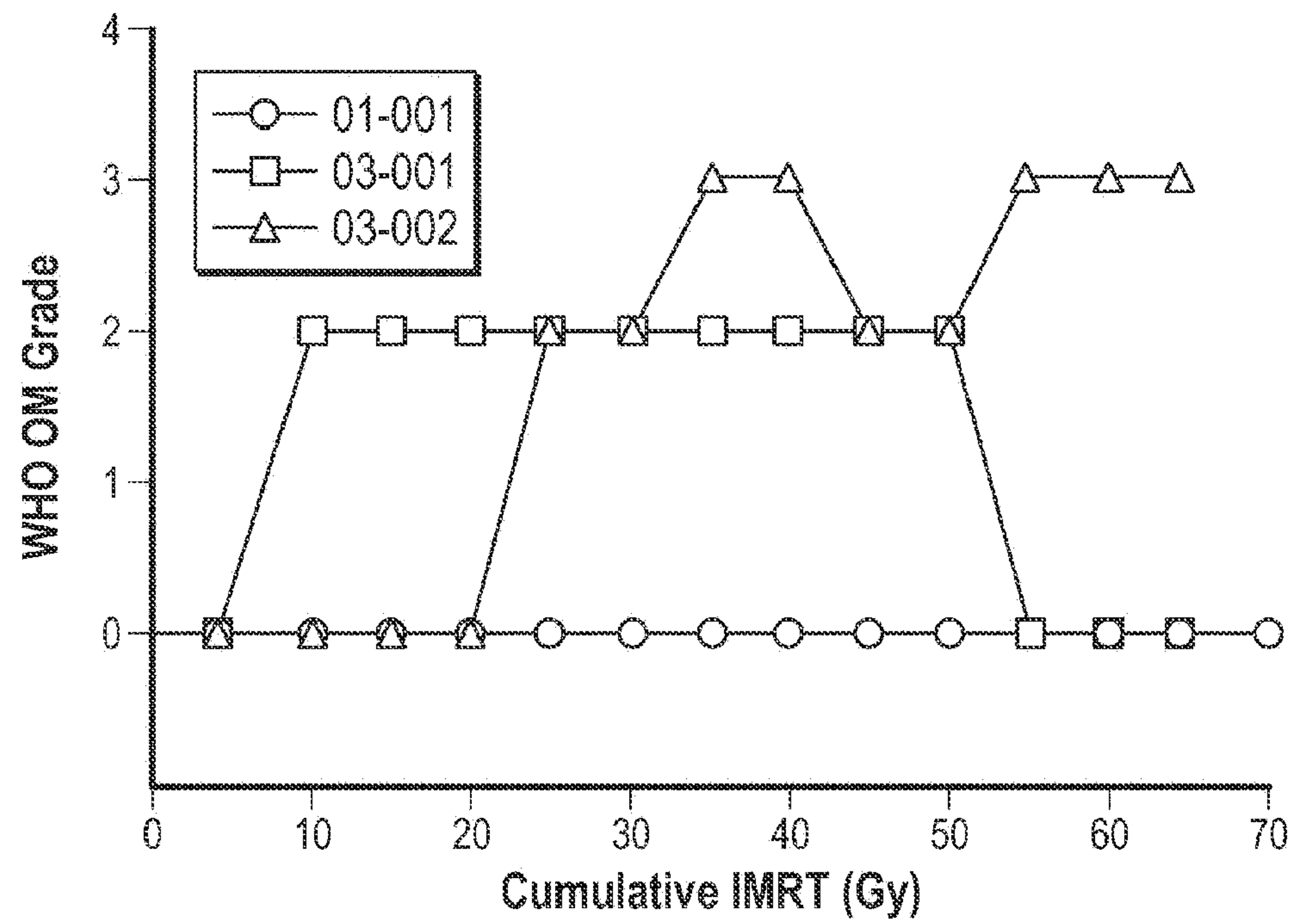


FIG. 29B

Changes from Baseline to Week 12 and 16 in SF-36 Domain Scores Compared with Age/Gender Matched Norms



WHO oral mucositis grade versus cumulative IMRT (Gy): ALD518 160 mg intravenous at week 0 and week 4

FIG. 30