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[Continued on next page]

(54) Title: ANTAGONISTS OF IL-6 TO PREVENT OR TREAT THROMBOSIS

(57) Abstract: The present invention is directed to therapeutic methods using IL-6 antagonists such as antibodies and fragments thereof having binding specificity for IL-6 to prevent or treat thrombosis in diseases associated with abnormal blood coagulation or fibrinolysis. In preferred embodiments these patients will comprise those exhibiting elevated D-dimer or other coagulation cascade related proteins and optionally will further exhibit elevated C reactive protein prior to treatment. The subject therapies also may include the administration of other actives such as chemotherapeutics, anti-coagulants, statins, *et al.*

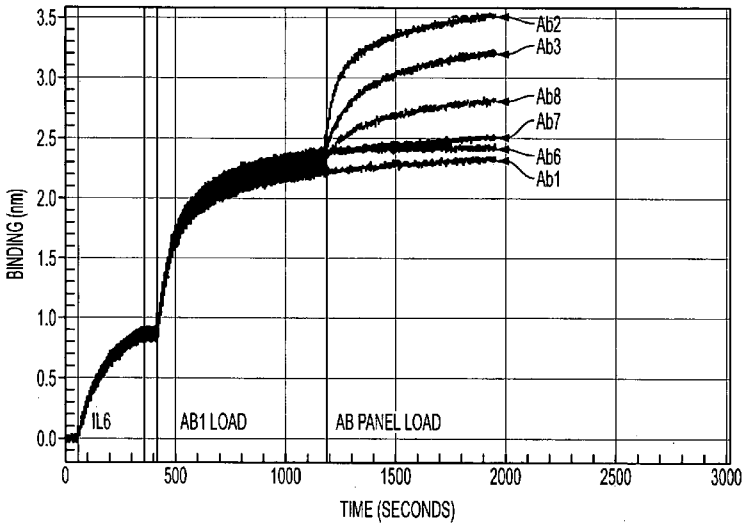


FIG. 1

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ANTAGONISTS OF IL-6 TO PREVENT OR TREAT THROMBOSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. provisional patent application no. 61/117,811, 61/117,861, and 61/117,839 all filed on November 25, 2008; and further is a continuation-in-part of US Application 12/502,581 filed on July 14, 2009, US Serial No. 12/399,156 filed on March 6, 2009, US Serial No. 12/391,717 filed on February 24, 2009, US Serial No. 12/366,567 filed on February 5, 2009, the disclosure of each of which is herein incorporated by reference in its entirety.

[0002] The sequence listing in the file named "67858o708002.txt" having a size of 331,899 bytes that was created November 24, 2009 is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] This invention is an extension of Applicants' prior invention disclosed in the above-referenced patent applications relating to novel anti-IL-6 antibodies and novel therapies and therapeutic protocols using anti-IL-6 antibodies, preferably those described herein. In particular, this invention pertains to methods of preventing or treating thrombosis in a patient in need thereof, comprising administering to the patient an IL-6 antagonist, e.g., an anti-IL-6 antibody as disclosed in applicants' earlier applications referenced herein whereby the patient's coagulation profile is improved.

[0004] In another embodiment the invention provides novel combination therapies wherein thrombosis is prevented or treated by the administration of at least one IL-6 antagonist and at least one other therapeutic compound e.g., a statin compound including but not limited to atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

[0005] In another embodiment, this invention relates to methods of preventing or treating thrombosis in a patient in a state of hypercoagulation, comprising administering to the patient an anti-IL-6 antibody or antibody fragment, whereby the patient's coagulation profile is improved or restored to a normal condition, and monitoring the patient to assess coagulation profile, wherein the anti-IL-6 antibody or antibody fragment 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 Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies. Preferably these antibodies are aglycosylated.

[0006] This invention further pertains to novel methods of preventing or treating thrombosis in a patient in need thereof using anti-IL-6 antibodies, preferably humanized antibodies possessing an elimination half-life which is at least about 25 days.

Description of Related Art

[0007] Thrombosis is a significant cause of mortality in cancer patients. Bick, N Engl J Med 349:109-111 (2003). For example, serious, life-threatening thrombotic events occur in approximately 6% of lung cancer patients. Alguire *et al.*, J Clin Oncol 2004 Vol 22 (July 15th Supplement) No. 14S: 8082. Cancer patients often exhibit hypercoagulation, in which the coagulation system has an increased clotting tendency. Rickles and Edwards, Blood 62:14-31 (1983). Markers of hypercoagulation correlate with poor patient outcome for at least some cancers. Bick, Semin Thromb Hemostat 18:353-372 (1992); Buccheri *et al.*, Cancer 97:3044-3052 (2003); Wojtukiewicz, Blood Coagul Fibrinolysis 3:429-437 (1992). Causes of hypercoagulation include the cancer itself and the cancer treatments (e.g., chemotherapy). Hypercoagulation results in an increased risk of thrombotic events, which can be further exacerbated when patients become bed-ridden. When not contraindicated, anticoagulant therapy has conferred survival benefit in some cancers. Lebeau *et al.*, Cancer 74:38-45 (1994);

Chahinian *et al.*, J Clin Oncol 7:993-1002 (1989). However, therapeutic options are often limited because many cancer patients are at an elevated risk of major bleeding, precluding administration of anticoagulants that could otherwise be given prophylactically to reduce the risk of thrombosis. In summary, the available methods for prevention of thrombosis in cancer patients are unsatisfactory, and thus there is a need for new therapies. Such therapies would enhance cancer patient survival and promote better quality of life.

[0008] Thrombosis can also be a significant cause of adverse events and mortality in other patient groups, including those with chronic illness or chronic inflammation, surgical patients, bed-ridden individuals, and orthopedic patients. When they are not otherwise contraindicated, preventative methods include calf compression and anticoagulants (e.g. low molecular weight heparin). These preventative methods can reduce — but not eliminate — the risk of thrombosis. Because these preventative methods are not always effective and are contraindicated for some patients, and because anticoagulants can cause potentially lethal side-effects such as major bleeding, there is a need for alternative methods to prevent thrombosis in these patients. Such methods should improve patient outcomes.

[0009] Interleukin-6 (hereinafter "IL-6") (also known as interferon-β_2; B-cell differentiation factor; B-cell stimulatory factor-2; hepatocyte stimulatory factor; hybridoma growth factor; and plasmacytoma growth factor) 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* A. Papassotiropoulos *et al*, Neurobiology of Aging, 22:863-871 (2001).

[0010] 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, SA, J. Immunology, 175:3463-3468 (2005).

[0011] 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* A. Papassotiropoulos, *et al*, Neurobiology of Aging, 22:863-871 (2001).

[0012] As set forth in greater detail herein 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. Due to the perceived involvement of IL-6 in a wide range of diseases and disorders, there remains a need in the art for compositions and methods useful for preventing or treating diseases associated with IL-6, as well as methods of screening to identify patients having diseases or disorders associated with IL-6. Particularly preferred anti-IL-6 compositions are those having minimal or minimizing adverse reactions when administered to the patient. Compositions or methods that reduce or inhibit diseases or disorders associated with IL-6 are beneficial to the patient in need thereof.

[0013] 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; Kawano *et al.*, 1988, Nature 332, 6159, 83-85). IL-6 is produced by a wide range of cell types including monocytes/macrophages, fibroblasts, epidermal keratinocytes, vascular endothelial cells, renal messangial cells, glial cells, condrocytes, 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.

[0014] 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 (*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. Gasterenterol. 11:1639-1643; reviewed in Heikkila *et al.*, 2008, Eur J Cancer, 44:937-945). As noted above, IL-6 is known or suspected to play a role in promoting proliferation or survival of at least some types of cancer. Moreover, some

of these studies have demonstrated correlation between IL-6 levels and patient outcome. Together, these results suggest the possibility that inhibition of IL-6 can be therapeutically beneficial. Indeed, 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.

[0015] 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.

[0016] 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].

[0017] 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, 265:621-636; 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).

[0018] Numerous studies have suggested that CRP is a valuable prognostic factor in cancer patients, with elevated CRP levels predicting poor outcome. *See, e.g.*, Hefler et al, Clin Cancer Res, 2008 Feb 1;14(3):710-4; Nagaoka et al, Liver Int, 2007 Oct;27(8):1091-7; Heikkilä et al, J Epidemiol Community Health, 2007

Sep;61(9):824-33, Review; Hara et al, Anticancer Res, 2007 Jul-Aug;27(4C):3001-4; Polterauer et al, Gynecol Oncol, 2007 Oct;107(1):114-7, Epub 2007 Jul 6; Tingstedt et al, Scand J Gastroenterol, 2007 Jun;42(6):754-9; Suh et al, Support Care Cancer, 2007 Jun;15(6):613-20, Epub 2007 Jan 18; Gerhardt et al, World J Gastroenterol, 2006 Sep 14;12(34):5495-500; McArdle et al, Urol Int, 2006;77(2):127-9; Guillem et al, Dis Esophagus, 2005;18(3):146-50; Brown et al, Cancer, 2005 Jan 15;103(2):377-82. Decreased serum albumin (hypoalbuminemia) is also associated with increased morbidity and mortality in many critical illnesses, including cancers (*e.g.*, Vigano *et al.*, Arch Intern Med, 2000 Mar 27;160(6):861-8; Hauser *et al.*, Support Care Cancer, 2006 Oct;14(10):999-1011; Seve *et al.*, Cancer, 2006 Dec 1;107(11):2698-705). The apparent link between hypoalbuminemia and poor patient outcome suggests that restoring albumin levels through direct albumin infusion could promote patient survival, however, albumin infusion has not improved survival of patients with advanced cancer (Demirkazik *et al.*, Proc Am Soc Clin Oncol 21: 2002 (abstr 2892)) or other critically ill patients groups (reviewed in Wilkes *et al.*, Ann Intern Med, 2001 Aug 7;135(3):149-64).

[0019] The Glasgow Prognostic Score (GPS) is an inflammation-based prognostic score that combines levels of albumin (< 35 mg/L = 1 point) and CRP (> 10 mg/L = 1 point) (Forrest *et al.*, Br J Cancer, 2004 May 4;90(9):1704-6). Since its introduction in 2004, the Glasgow Prognostic Score has already been shown to have prognostic value as a predictor of mortality in numerous cancers, including gastro-oesophageal cancer, non-small-cell lung cancer, colorectal cancer, breast cancer, ovarian cancer, bronchogenic cancer, and metastatic renal cancer (Forrest *et al.*, Br J Cancer, 2004 May 4;90(9):1704-6; Sharma *et al.*, Clin Colorectal Cancer, 2008 Sep;7(5):331-7; Sharma *et al.*, Eur J Cancer, 2008 Jan;44(2):251-6; McMillan *et al.*, Nutr Cancer, 2001;41(1-2):64-9; McMillan, Proc Nutr Soc, 2008 Aug;67(3):257-62; Ramsey *et al.*, Cancer, 2007 Jan 15;109(2):205-12). Because the combination of elevated CRP and reduced albumin predicts cancer patient mortality, a treatment that both lowers CRP and raises albumin would suggest a strong possibility of also promoting patient survival.

[0020] U.S. patent application publication no. 20080081041 (relating to treatment of cancer using an anti-IL-6 antibody) discloses that since IL-6 is associated with disease activity and since CRP is a surrogate marker of IL-6 activity, sustained suppression of CRP by neutralization of IL-6 by their anti-IL-6 antibody (CNTO 328,

Zaki *et al.*, Int J Cancer, 2004 Sep 10;111(4):592-5) may be assumed necessary to achieve biological activity.

[0021] The same patent application indicates that the relationship between IL-6 and CRP in patients with benign and malignant prostate disease was previously examined by McArdle (McArdle *et al.* 2004 Br J Cancer 91(10):1755-1757). McArdle reportedly found no significant differences between the concentrations of IL-6 and CRP in the patients with benign disease compared with prostate cancer patients, in the cancer patients there was a significant increase in both IL-6 and CRP concentration with increasing tumor grade. The median serum CRP value for the 86 subjects with prostate cancer was 1.8 mg/L. Based thereon the inventors in this patent application postulate a proposed dose and schedule wherein 6 mg/kg of an anti-IL-6 antibody (CNTO 328) is administered every 2 weeks and allege that this is likely to achieve sustained suppression of CRP in subjects with metastatic HRPC.

[0022] IL-6 signaling is mediated by the Jak-Tyk family of cytoplasmic tyrosine kinases, including JAK1, JAK2, and JAK3 (reviewed in Murray J Immunol. 2007 Mar 1;178(5):2623-9). Sivash *et al.* report abrogation of IL-6-mediated JAK signaling by the cyclopentenone prostaglandin 15d-PGJ_2 in oral squamous carcinoma cells. British Journal of Cancer (2004) 91, 1074–1080. These results suggest that inhibitors of JAK1, JAK2, or JAK3 could be employed as antagonists of IL-6.

[0023] Ulanova *et al.* report that inhibition of the nonreceptor protein tyrosine kinase Syk (using siRNA) decreased production of IL-6 by epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2005 Mar;288(3):L497-507. These results suggest that an inhibitor of Syk could be employed as an antagonist of IL-6.

[0024] Kedar *et al.* report that treatment with thalidomide significantly reduced serum levels of CRP and IL-6 to normal or near normal levels in a substantial fraction of renal cell carcinoma patients. Int J Cancer. 2004 Jun 10;110(2):260-5. These results suggest that thalidomide, and possibly derivatives thereof, such as lenalidomide, may be useful antagonists of IL-6.

[0025] In addition, another published patent application, US 20070292420 teaches a Phase I dose escalating study using an anti-IL-6 (cCLB-8) antibody for treating refractory patients with advanced stage multiple myeloma (N=12) and indicate that this study demonstrated that some patients had disease stabilization. The application also reports that after discontinuation of treatment there was acceleration in the

increase of M protein levels, suggesting disease re-bound after the withdrawal of therapy. Anti-IL-6 cCLB-8 antibody inhibited free circulating IL-6.

[0026] The application also indicates that this antibody trial resulted in no toxicity (except transient thrombocytopenia in two heavily pretreated patients) or allergic reactions were observed and that C-reactive protein (CRP) decreased below detection level in all patients. Their antibody (cCLB-8 antibody) reportedly possessed a circulating half-life of 17.8 days, and that there was no human anti-chimeric antibody (HACA) immune response observed (van Zaanen *et al.* 1998). They allege that the administration of CNTO 328 did not cause changes in blood pressure, pulse rate, temperature, hemoglobin, liver functions and renal functions. Except for transient thrombocytopenia in two heavily pretreated patients, no toxicity or allergic reactions allegedly were observed, and there was no human anti-chimeric antibody (HACA) immune response observed. Three patients in their study reportedly developed infection-related complications during therapy, however, a possible relation with anti-IL-6 cCLB-8 antibody was concluded by the inventors to be unlikely because infectious complications are reportedly common in end stage multiple myeloma and are a major cause of death. They conclude based on their results that this anti-IL-6 cCLB-8 antibody was safe in multiple myeloma patients.

BRIEF SUMMARY OF THE INVENTION

[0027] The present invention is an extension of Applicants' previous invention which is directed to specific antibodies and fragments thereof having binding specificity for IL-6, in particular antibodies having specific epitopic specificity and/or functional properties and novel therapies using these and other anti-IL-6 antibodies. One embodiment of the prior invention encompasses specific humanized antibodies and fragments thereof 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 one or more 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 and in Applicants' earlier applications incorporated by reference herein. In particular, the present

invention pertains to methods of preventing or treating thrombosis in a patient in need thereof, e.g., a patient showing elevated D-dimer and/or CRP levels prior to treatment, comprising administering to the patient an IL-6 antagonist, such as those identified infra, e.g., an anti-IL-6 antibody or antibody fragment, whereby the patient's coagulation profile is improved or restored to a normal condition. In some embodiments these methods may further include the administration of other actives such as statins that may further help (synergize) with the IL-6 antagonist and thereby more effectively treat or prevent thrombosis.

[0028] In a preferred embodiment this is effected by the administration of the antibodies described herein, comprising the sequences of the V_H, V_L and CDR polypeptides described herein, and the polynucleotides encoding them. In more specific embodiments of the invention these antibodies will block gp130 activation and/or possess binding affinities (Kds) less than 50 picomolar and/or K_{off} values less than or equal to 10^{-4} S^{-1}.

[0029] In another embodiment of the invention these antibodies and humanized versions will 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.

[0030] In another embodiment of the invention the subject antibodies may be selected based on their activity in functional assays such as IL-6 driven T1165 proliferation assays, IL-6 simulated HepG2 haptoglobin production assays, and the like. A further embodiment of the invention is directed to fragments from anti-IL-6 antibodies encompassing V_H, V_L and CDR polypeptides, e.g., derived from rabbit immune cells and the polynucleotides encoding the same, as well as the use of these antibody fragments and the polynucleotides encoding them in the creation of novel antibodies and polypeptide compositions capable of recognizing IL-6 and/or IL-6/IL-6R complexes or IL-6/IL-6R/gp130 complexes and/or multimers thereof.

[0031] The invention also contemplates the administration of conjugates of anti-IL-6 antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates methods of making said humanized anti-IL-6 or anti-IL-6/IL-6R complex antibodies and binding fragments thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv and scFv fragments.

[0032] Embodiments of the invention pertain to the use of anti-IL-6 antibodies for the diagnosis, assessment and treatment of diseases and disorders associated with IL-6 or aberrant expression thereof. The invention also contemplates the use of fragments of anti-IL-6 antibodies for the diagnosis, assessment and treatment of diseases and disorders associated with IL-6 or aberrant expression thereof. Preferred usages of the subject antibodies are the treatment and prevention of cancer associated fatigue, and/or cachexia and rheumatoid arthritis.

[0033] Other embodiments of the invention relate to the production of anti-IL-6 antibodies in recombinant host cells, preferably diploid yeast such as diploid Pichia and other yeast strains.

[0034] Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient diagnosed with cancer, comprising administering to the patient an anti-IL-6 antibody or antibody fragment, whereby the patient's serum C-reactive protein ("CRP") level is reduced, and monitoring the patient to assess the reduction in the patient's serum CRP level, wherein the anti-IL-6 antibody or antibody fragment 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies which preferably are aglycosylated.

[0035] Another embodiment of the invention relates to methods of improving muscular strength in a patient diagnosed with cancer, comprising administering to the patient an anti-IL-6 antibody or antibody fragment, whereby the patient's muscular strength is improved, and monitoring the patient to assess muscular strength, wherein the anti-IL-6 antibody or antibody fragment 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33,

Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies, which preferably are aglycosylated. In such methods preferably the patient's muscular strength is improved by at least about 15% within approximately 4 weeks of administering the anti-IL-6 antibody or antibody fragment, as measured by the Hand Grip Strength test and more preferably the patient's muscular strength is improved by at least about 20% within approximately 4 weeks of administering the anti-IL-6 antibody or antibody fragment, as measured by the Hand Grip Strength test.

[0036] Another embodiment of the invention relates to methods of increasing serum albumin in a patient in need thereof, comprising administering to the patient an anti-IL-6 antibody or antibody fragment, whereby the patient's serum albumin level is improved, and monitoring the patient to assess serum albumin level, wherein the anti-IL-6 antibody or antibody fragment 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies, which preferably are aglycosylated. Preferably, these methods are effected under conditions whereby the patient's survivability is improved, and/or under conditions wherein the serum albumin level is increased by about 5 g/L within approximately 6 weeks of administering the anti-IL-6 antibody or antibody fragment. These patients will include, without limitation thereto, those diagnosed with rheumatoid arthritis, cancer, advanced cancer, liver disease, renal disease, inflammatory bowel disease, celiac's disease, trauma, burns, other diseases associated with reduced serum albumin, or any combination thereof.

[0037] Another embodiment of the invention relates to methods of preventing or treating thrombosis in a patient in a state of hypercoagulation or susceptible to hypercoagulation because of disease or therapeutic regimen (e.g., chemotherapy), comprising administering to the patient an IL-6 antagonist, e.g. an anti-IL-6 antibody or antibody fragment, whereby the patient's coagulation profile is improved or restored to a normal condition, and monitoring the patient to assess coagulation

profile. In such methods if the IL-6 antagonist is an anti-IL-6 antibody or antibody fragment preferably this antibody 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies which preferably are aglycosylated. In the inventive methods of preventing or treating thrombosis, the patient's coagulation profile is assessed by measurement of the patient's serum level of one or more of D-dimer, 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 and preferably by a method including measuring the patient's serum D-dimer level prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment if the patient's serum D-dimer level is elevated. In addition, the levels of C reactive protein may also be assessed in the patient prior to treatment and if elevated this may be used as a further indicator as to an increased risk of thrombosis in the patient.

[0038] An embodiment of the invention relates to methods of treating a patient having a disease or condition associated with hypercoagulation, which may comprise administering to the patient an IL-6 antagonist, whereby the patient's coagulation profile is improved or restored to normal, and monitoring the patient to assess coagulation profile.

[0039] In an embodiment of the invention, the patient may have elevated serum D-dimer levels prior to treatment.

[0040] In an embodiment of the invention, the patient may have elevated C-reactive protein (CRP) levels prior to treatment.

[0041] In an embodiment of the invention, the method may further comprise the administration of at least one statin.

[0042] In an embodiment of the invention, the IL-6 antagonist may target IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

[0043] In an embodiment of the invention, the IL-6 antagonist may comprise an antibody, an antibody fragment, a peptide, a glycoalkoid, an antisense nucleic acid, a ribozyme, a retinoid, an avemir, a small molecule, or any combination thereof.

[0044] In an embodiment of the invention, the IL-6 antagonist may comprise an anti-IL-6R, anti-gp130, anti-p38 MAP kinase, anti-JAK1, anti-JAK2, anti-JAK3, or anti-SYK antibody or antibody fragment.

[0045] In one embodiment of the invention, the IL-6 antagonist may comprise a small molecule comprising thalidomide, lenalidomide, or any combination thereof.

[0046] In an embodiment of the invention, the antagonist may comprise an anti-IL-6 antibody or antibody fragment.

[0047] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies which preferably are aglycosylated.

[0048] In an embodiment of the invention, the anti-IL-6 antibody may 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 a fragment thereof as Ab1.

[0049] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies which preferably are aglycosylated.

[0050] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitope(s) on an

intact human IL-6 polypeptide or a fragment thereof as Ab1 or an antibody comprising the same CDRs as Ab1.

[0051] Another embodiment of the invention relates to Ab1, including rabbit and humanized forms thereof, as well as heavy chains, light chains, fragments, variants, and CDRs thereof. In the human clinical trials presented in the Examples, a humanized form of Ab1 was administered.

[0052] In a preferred embodiment the humanized anti-IL-6 antibody will comprise the variable heavy and variable light chain sequences respectively contained in SEQ ID NO:657 and SEQ ID NO:709, and preferably further comprising the heavy chain and light chain constant regions respectively contained in SEQ ID NO:588 and SEQ ID NO:586, or any of the VH and VL sequences contained in Figures 34-37 and variants thereof comprising one or more 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, one or more 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. This embodiment further contemplates nucleic acids encoding variants comprising one or more amino acid substitutions or deletions to the variable heavy and variable light chain sequences respectively contained in SEQ ID NO:657 and SEQ ID NO:709 and the heavy chain and light chain constant regions respectively contained in SEQ ID NO:588 and SEQ ID NO:586, that do not substantially affect IL-6 binding and/or desired effector function.

[0053] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may specifically bind to the same linear or conformational epitopes on an intact IL-6 polypeptide or antibody fragment thereof that is (are) specifically bound by Ab1 and wherein said epitope(s) when ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide includes one or more 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.

[0054] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies which preferably are aglycosylated.

[0055] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment 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.

[0056] In an embodiment of the invention, all of the CDRs in the anti-IL-6 antibody or antibody fragment may be identical to the CDRs contained in an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, human, humanized antibodies or antibody fragments containing most or all of the CDRs of the afore-identified antibodies which preferably are aglycosylated.

[0057] In an embodiment of the invention, all of the CDRs in the anti-IL-6 antibody or antibody fragment may be identical to the CDRs contained in Ab1.

[0058] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be aglycosylated.

[0059] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation. Preferably the Fc region if present is modified to eliminate glycosylation.

[0060] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be a human, humanized, single chain or chimeric antibody.

[0061] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody.

[0062] 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 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.

[0063] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be administered to the patient with a frequency at most once per period of approximately four weeks, approximately eight weeks, approximately twelve weeks, approximately sixteen weeks, approximately twenty weeks, or approximately twenty-four weeks.

[0064] In an embodiment of the invention, the patient's coagulation profile may remain improved for an entire period intervening two consecutive anti-IL-6 antibody administrations.

[0065] In an embodiment of the invention, the patient may have been diagnosed with cancer selected from 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, Anaplastic 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, Klatskin 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 Müllerian 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, or any combination thereof.

[0066] In an embodiment of the invention, the patient may have been diagnosed with a cancer selected from Colorectal Cancer, Non-Small Cell Lung Cancer, Cholangiocarcinoma, Mesothelioma, Castleman's disease, Renal Cell Carcinoma, or any combination thereof.

[0067] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may comprise a VH 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 or the VH sequences contained in the antibodies depicted in Figures 34-37; and may further comprise a VL 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 any of the variable heavy and light chain sequences in Figures 34-37 or a variant thereof wherein one or more of the framework residues (FR residues) in said VH or VL polypeptide may have been substituted with another amino acid residue resulting in an anti-IL-6 antibody or antibody fragment that specifically binds human IL-6. Preferably the variable heavy and light sequences comprise those in SEQ ID NO:657 and 709.

[0068] In an embodiment of the invention, one or more 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.

[0069] In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment may be humanized.

[0070] In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment may be chimeric.

[0071] In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment further may comprise a human Fc.

[0072] 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.

[0073] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may comprise a polypeptide having at least 90% sequence homology to one or more of the polypeptide sequences of 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, 708,, 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 to any of the VH and VL sequences contained in Figures 34-37.

[0074] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may have an elimination half-life of at least about 22 days, at least about 25 days, or at least about 30 days.

[0075] In an embodiment of the invention, the IL-6 antagonist may be co-administered with a chemotherapy agent or as part of a therapeutic regimen including chemotherapy, including without limitation thereto: VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, 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, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

[0076] In an embodiment of the invention, the another therapeutic compound may be a statin.

[0077] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be directly or indirectly attached to a detectable label or therapeutic agent.

[0078] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be Ab1 or a fragment thereof.

[0079] In an embodiment of the invention, the disease or condition may be selected from acute venous thrombosis, pulmonary embolism, thrombosis during pregnancy, hemorrhagic skin necrosis, acute or chronic disseminated intravascular coagulation (DIC), clot formation from surgery, long bed rest, long periods of immobilization, venous thrombosis, fulminant meningococcemia, acute thrombotic stroke, acute coronary occlusion, acute peripheral arterial occlusion, massive pulmonary embolism, axillary vein thrombosis, massive iliofemoral vein thrombosis, occluded arterial cannulae, occluded venous cannulae, cardiomyopathy, venoocclusive disease of the liver, hypotension, decreased cardiac output, decreased vascular resistance, pulmonary hypertension, diminished lung compliance, leukopenia, thrombocytopenia, heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis (HITT), atrial fibrillation, implantation of a prosthetic heart valve, genetic susceptibility to thrombosis, factor V Leiden, prothrombin gene mutation, methylenetetrahydrofolate reductase (MTHFR) polymorphism, platelet-receptor polymorphism, trauma, fractures, burns, or any combination thereof.

[0080] In an embodiment of the invention, may include administration of one or more anti-coagulants or statins.

[0081] In an embodiment of the invention, the one or more anti-coagulants may be selected from abciximab (ReoPro™), acenocoumarol, antithrombin III, argatroban, 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.

[0082] In an embodiment of the invention, the one or more statins may be selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

[0083] In an embodiment of the invention, the patient's coagulation profile may be assessed by measurement of the patient's serum level of one or more of D-dimer, 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.

[0084] In an embodiment of the invention, the patient's coagulation profile may be assessed by a functional measurement of clotting ability.

[0085] In an embodiment of the invention, the functional measurement of clotting ability may be selected from prothrombin time (PT), prothrombin ratio (PR), international normalized ratio (INR), or any combination thereof.

[0086] In an embodiment of the invention, the method may include measuring the patient's international normalized ratio (INR) prior to administration of the IL-6 antagonist, and administering to the patient an IL-6 antagonist if the patient's INR is less than about 0.9.

[0087] In an embodiment of the invention, the invention may include measuring the patient's international normalized ratio (INR) prior to administration of the IL-6 antagonist, and administering to the patient an IL-6 antagonist if the patient's INR is less than about 0.5 or 0.9.

In an embodiment of the invention, the patient's INR may be raised to more than approximately 0.9 within 4 weeks of administering to the patient an IL-6 antagonist.

[0088] In an embodiment of the invention, the method may include measuring the patient's serum D-dimer level prior to administration of the IL-6 antagonist, and administering the IL-6 antagonist if the patient's serum D-dimer level is above the normal reference range.

[0089] In an embodiment of the invention, the patient's serum D-dimer level may be lowered to less than the upper limit of the normal reference range within 4 weeks of administering to the patient an IL-6 antagonist.

[0090] In an embodiment of the invention, the method may result in a prolonged improvement in the patient's coagulation profile.

[0091] In an embodiment of the invention, the patient's coagulation profile may be measurably improved within about 2 weeks of administration of the IL-6 antagonist.

[0092] In an embodiment of the invention, the patient's coagulation profile may remain measurably improved approximately 12 weeks after administering to the patient an IL-6 antagonist.

[0093] In an embodiment of the invention, the patient's survivability may be improved.

[0094] In an embodiment of the invention, the IL-6 antagonist may be an antisense nucleic acid.

[0095] In an embodiment of the invention, the IL-6 antagonist may be an antisense nucleic acid, for example comprising at least approximately 10 nucleotides of a sequence encoding IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.

[0096] In an embodiment of the invention, the antisense nucleic acid or interfering RNA (iRNA) may comprise DNA, RNA, peptide nucleic acid, locked nucleic acid, morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, threose nucleic acid, or any combination thereof.

[0097] In an embodiment of the invention, the IL-6 antagonist may comprise Actemra™ (Tocilizumab), Remicade®, Zenapax™ (daclizumab), or any combination thereof.

[0098] In an embodiment of the invention, the IL-6 antagonist may comprise a polypeptide having a sequence comprising a fragment of IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof, such as a fragment or full-length polypeptide that is at least 40 amino acids in length.

[0099] In an embodiment of the invention, the IL-6 antagonist may comprise a soluble IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

[00100] In an embodiment of the invention, the IL-6 antagonist may be coupled to a half-life increasing moiety.

[00101] In an embodiment of the invention, the method may further comprise administration of one or more statins to the patient, including without limitation

thereto atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

[0100] Another embodiment of the invention relates to a composition comprising an IL-6 antagonist, and an anti-coagulant. In an embodiment of the invention, the one or more anti-coagulants may be selected from abciximab (ReoPro™), acenocoumarol, antithrombin III, argatroban, 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.

[0101] Another embodiment of the invention relates to a composition comprising an IL-6 antagonist, and a chemotherapy agent. In an embodiment of the invention, the chemotherapy agent may be selected from VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, 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, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0102] Fig. 1 shows that a variety of unique epitopes were recognized by the collection of anti-IL-6 antibodies prepared by the antibody selection protocol. Epitope variability was confirmed by antibody-IL-6 binding competition studies (ForteBio Octet).

[0103] Fig. 2 shows alignments of variable light and variable heavy sequences between a rabbit antibody variable light and variable heavy sequences and homologous human sequences and the final 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 one or more 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.

[0104] Fig. 3 demonstrates the high correlation between the IgG produced and antigen specificity for an exemplary IL-6 protocol. 9 of 11 wells showed specific IgG correlation with antigen recognition.

[0105] Fig. 4 provides the α-2-macroglobulin (A2M) dose response curve for antibody Ab1 administered intravenously at different doses one hour after a 100μg/kg s.c. dose of human IL-6.

[0106] Fig. 5 provides survival data for the antibody Ab1 progression groups versus control groups.

[0107] Fig. 6 provides additional survival data for the antibody Ab1 regression groups versus control groups.

[0108] Fig. 7 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).

[0109] Fig. 8 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).

[0110] Fig. 9 provides a pharmacokinetic profile of antibody Ab1 in cynomolgus monkey. Plasma levels of antibody Ab1 were quantitated through antigen capture ELISA. This protein displays a half life of between 12 and 17 days consistent with other full length humanized antibodies.

[0111] Fig. 10 (A-D) provides binding data for antibodies Ab4, Ab3, Ab8 and Ab2, respectively. Fig. 10 E provides binding data for antibodies Ab1, Ab6 and Ab7.

[0112] Fig. 11 summarizes the binding data of Fig. 10 (A-E) in tabular form.

[0113] Fig. 12 presents the sequences of the 15 amino acid peptides used in the peptide mapping experiment of Example 14.

[0114] Fig. 13 presents the results of the blots prepared in Example 14.

[0115] Fig. 14 presents the results of the blots prepared in Example 14.

[0116] Fig. 15A shows affinity and binding kinetics of Ab1 for IL-6 of various species.

[0117] Fig. 15B demonstrates inhibition of IL-6 by Ab1 in the T1165 cell proliferation assay.

[0118] Fig. 16 shows the mean plasma concentration of Ab1 resulting from a single administration of Ab1 to healthy male subjects in several dosage groups.

[0119] Fig. 17 shows mean area under the plasma Ab1 concentration time curve (AUC) for the dosage groups shown in Fig. 16.

[0120] Fig. 18 shows mean peak plasma Ab1 concentration (C_{max}) for the dosage groups shown in Fig. 16.

[0121] Fig. 19 summarizes Ab1 pharmacokinetic measurements of the dosage groups shown in Fig. 16.

[0122] Fig. 20 shows the mean plasma concentration of Ab1 resulting from a single administration of Ab1 to patients with advanced cancer.

[0123] Fig. 21 illustrates the unprecedented elimination half-life of Ab1 compared with other anti-IL-6 antibodies.

[0124] Fig. 22 shows increased hemoglobin concentration following administration of Ab1 to patients with advanced cancer.

[0125] Fig. 23 shows mean plasma lipid concentrations following administration of Ab1 to patients with advanced cancer.

[0126] Fig. 24 shows mean neutrophil counts following administration of Ab1 to patients with advanced cancer.

[0127] Fig. 25 demonstrates suppression of serum CRP levels in healthy individuals.

[0128] Fig. 26 (A-B) demonstrates suppression of serum CRP levels in advanced cancer patients.

[0129] Fig. 27 shows prevention of weight loss by Ab1 in a mouse cancer cachexia model.

[0130] Fig. 28 shows the physical appearance of representative Ab1-treated and control mice in a cancer cachexia model.

[0131] Fig. 29 demonstrates that Ab1 promotes weight gain in advanced cancer patients.

[0132] Fig. 30 demonstrates that Ab1 reduces fatigue in advanced cancer patients.

[0133] Fig. 31 demonstrates that Ab1 promotes hand grip strength in advanced cancer patients.

[0134] Fig. 32 demonstrates that Ab1 suppresses an acute phase protein (Serum Amyloid A) in mice.

[0135] Fig. 33 demonstrates that Ab1 increase plasma albumin concentration in advanced cancer patients.

[0136] FIGs. 34 and 35 show alignments between a rabbit antibody light and variable heavy sequences and homologous human sequences and the final humanized sequences. Framework regions are identified FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3.

[0137] FIGS. 36 and 37 show alignments between light and variable heavy sequences, respectively, of different forms of Ab1. Framework regions are identified FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Sequence differences within the CDR regions highlighted.

[0138] Fig. 38 demonstrates that Ab1 increases mean hemoglobin at 80, 160 and 320 mg after 12 weeks of dosing.

[0139] Figure 39 demonstrates mean change from baseline hemoglobin for the data presented in Figure 38.

[0140] Figure 40 demonstrates that Ab1 increases mean hemoglobin at 160 and 320 mg after 12 weeks of dosing in patients having baseline hemoglobin below 11 g/l.

[0141] Figure 41 demonstrates that Ab1 increases mean hemoglobin at 80, 160 and 320 mg after 16 weeks of dosing.

[0142] Figure 42 demonstrates that Ab1 drops D-dimer levels over placebo at 80, 160 and 320 mg after 16 weeks of dosing.

[0143] Figure 43 demonstrates the percent change from baseline in D-dimer concentration from each dosage concentration group corresponding to Figure 42.

[0144] Figure 44 demonstrates 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.

[0145] Fig. 45 demonstrates the averaged percent change in body weight from each dosage concentration group corresponding to Fig. 44.

[0146] Figure 46 demonstrates the change in averaged lean body mass data for the dosage concentration groups corresponding to Figure 44.

[0147] Figure 47 demonstrates increases in the mean Facit-F FS subscale score for some of the dosage concentration groups in the patient population after dosing at 80, 160 and 320 mg after 8 weeks.

[0148] Fig. 48 demonstrates the change from baseline Facit-F FS subscale score corresponding to Fig. 47.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

[0149] 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.

[0150] 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.

[0151] *Interleukin-6 (IL-6)*: As used herein, interleukin-6 (IL-6) encompasses not only the following 212 amino acid sequence available as GenBank Protein Accession No. NP_000591:

MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPPGEDSKDVAAPHRQPLTSSERID
KQIRYILDGISALRKETCNKSNMCESSKEALAENNLNLPKMAEKDGCFQSGFN
EETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVLIQFLQKKAKN
LDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKEFLQSSLRALRQM

(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.

[0152] *IL-6 antagonist*: As used herein, the terms "IL-6 antagonist," and grammatical variants thereof include 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, Dev Biol. 2002 Mar 15;243(2):209-14; Hannon and Rossi, Nature. 2004 Sep 16;431(7006):371-8; Paul *et al.*, Nat Biotechnol. 2002 May;20(5):505-8; Zhang *et al.*, J Am Chem Soc. 2005 Mar 30;127(12):4174-5; Wahlestedt *et al.*, Proc Natl Acad Sci U S A. 2000 May 9;97(10):5633-8; Hanvey *et al.*, 1992 Nov 27;258(5087):1481-5; Braasch *et al.*, Biochemistry. 2002 Apr 9;41(14):4503-10; Schoning *et al.*, Science. 2000 Nov 17;290(5495):1347-51. In addition IL-6 antagonists specifically include peptides that block IL-6 signaling such as those described in any of US Patent No. 6,599,875; 6,172, 042; 6,838,433; 6,841,533; 5,210,075 *et al.* Also, IL-6 antagonists according to the invention may include p38 MAP kinase inhibitors such as those reported in US20070010529 *et al.* 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 US20050090453 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, antisense nucleic acid, etc. Other IL-6 antagonists include avemirs, such as C326 (Silverman *et al.*, Nat Biotechnol. 2005 Dec;23(12):1556-61) and small molecules, such as synthetic retinoid AM80 (tamibarotene) (Takeda *et al.*, Arterioscler Thromb Vasc Biol. 2006 May;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.

[0153] *Thrombosis*: As used herein, thrombosis refers to a thrombus (blood clot) inside a blood vessel. The term encompasses, without limitation, arterial and venous thrombosis, including deep vein thrombosis, portal vein thrombosis, jugular vein thrombosis, renal vein thrombosis, stroke, myocardial infarction, Budd-Chiari syndrome, Paget-Schroetter disease, and cerebral venous sinus thrombosis. Diseases and conditions associated with thrombosis include, without limitation, acute venous thrombosis, pulmonary embolism, thrombosis during pregnancy, hemorrhagic skin necrosis, acute or chronic disseminated intravascular coagulation (DIC), clot formation from surgery, long bed rest, long periods of immobilization, venous thrombosis, fulminant meningococcemia, acute thrombotic stroke, acute coronary occlusion, acute peripheral arterial occlusion, massive pulmonary embolism, axillary vein thrombosis, massive iliofemoral vein thrombosis, occluded arterial cannulae, occluded venous cannulae, cardiomyopathy, venoocclusive disease of the liver, hypotension, decreased cardiac output, decreased vascular resistance, pulmonary hypertension, diminished lung compliance, leukopenia, and thrombocytopenia.

[0154] *D-Dimer*: As used herein, D-dimer refers to a fibrin degradation product produced during the break down of blood clots by the enzyme plasmin. Monoclonal antibodies specifically reactive against D-dimer are readily available, e.g. DD-3B6/22 (Elms *et al.*, 1986, Am J Clin Pathol. 85:360-4). Clinical measurements of D-dimer levels are routinely performed, *e.g.*, using a red blood cell agglutination test, ELISA,

etc. (reviewed in Dempfle, Semin Vasc Med, 2005 Nov;5(4):315-20). Measurements of D-dimer may vary depending on the measurement method and testing lab; nonetheless, a normal "reference range" may be readily established for any particular method and testing lab, e.g. by taking measurements from healthy individuals. Accordingly, an elevated D-dimer level is understood by persons skilled in the art to refer to a D-dimer level that is above the reference range for the particular method and testing lab.

[0155] *Coagulation profile*: As used herein, coagulation profile refers generally to the functioning of the coagulation system. Both the tissue factor (extrinsic) and contact activation (intrinsic) pathways of clotting are components of the coagulation profile. A normal coagulation profile refers to coagulation functioning as in a normal, healthy individual, *i.e.*, maintaining balance between ability to control bleeding and tendency towards excessive clotting (thrombotic tendency). An abnormal coagulation profile may be a decrease or an increase in coagulation tendency. One particularly abnormal coagulation profile is *hypercoagulation*, which refers to a greatly increased risk of excessive clot formation, resulting in high risk of thrombosis. Coagulation profile may be assessed by various tests and assays known in the art, such as: the activated partial thromboplastin time (aPTT) test; prothrombin time (PT) test (typical reference range of 12 to 15 second); measurements derived from the PT test, such as prothrombin ratio (PR) and international normalized ratio (INR) (typical reference range 0.8 to 1.2); fibrinogen testing (e.g. the Clauss method (Clauss A, "Rapid Physiological Coagulation Method for the Determination of Fibrinogen [German],"Acta Haematol, 1957, 17:237-46) or the Ellis method (Ellis BC and Stransky A, "A Quick and Accurate Method for the Determination of Fibrinogen in Plasma," J Lab Clin Med, 1961, 58:477-88); assays for activated protein C resistance, protein C, protein S, and antithrombin; assays for antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies); elevated homocysteine; assays for plasminogen, dysfibrinogenemia, heparin cofactor II, or platelet hyperaggregability. Other assays useful to assess coagulation profile include measurement of clotting factors and/or indicators of clotting, such as serum levels of D-dimer, Factor II, Factor V, Factor VIII, Factor IX, Factor XI, Factor XII, F/fibrin degradation products, thrombin-antithrombin III complex, thrombocytosis, fibrinogen, plasminogen, prothrombin, and von Willebrand factor. *Worsening in coagulation profile* refers to a measureable change in an indicator of coagulation, *e.g.*, any of the aforementioned

assays, that reflects a deterioration of the normal coagulation tendency, such that the measured value becomes abnormal or deviates farther from the normal range than previously. *Improvement in coagulation profile* refers to a measureable change in an indicator of coagulation, *e.g.*, any of the aforementioned assays, that reflects a partial or full restoration of the normal coagulation tendency, i.e., after a therapeutic intervention, such as administration of an anti-IL-6 antibody, the measured value is in the normal range or closer to the normal range than prior to the therapeutic intervention.

[0156] *Disease or condition*: As used herein, "disease or condition" refers 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, the side-effects of medications or treatments (such as radiation therapy), as well as idiopathic conditions characterized by symptoms that include elevated IL-6.

[0157] *Cachexia*: As used herein, cachexia, also known as wasting disease, refers to any disease marked especially by progressive emaciation, weakness, general ill health, malnutrition, loss of body mass, loss of muscle mass, or an accelerated loss of skeletal muscle in the context of a chronic inflammatory response (reviewed in Kotler, Ann Intern Med. 2000 Oct 17;133(8):622-34). Diseases and conditions in which cachexia is frequently observed include cancer, rheumatoid arthritis, AIDS, heart disease, dehydration, malnutrition, lead exposure, malaria, respiratory disease, old age, hypothyroidism, tuberculosis, hypopituitarism, neurasthenia, hypernatremia, hyponatremia, renal disease, splenica, ankylosing spondylitis, failure to thrive (faltering growth) and other diseases, particularly chronic diseases. Cachexia may also be idiopathic (arising from an uncertain cause). Weight assessment in a patient is understood to exclude growths or fluid accumulations, e.g. tumor weight, extravascular fluid accumulation, etc. Cachexia may be assessed by measurement of a patient's total body mass (exclusive of growths or fluid accumulations), total lean (fat-free) body mass, lean mass of the arms and legs (appendicular lean mass, e.g. measured using dual-energy x-ray absorptiometry or bioelectric impedance spectroscopy), and/or lean body mass index (lean body mass divided by the square of the patient's height). See Kotler, Ann Intern Med. 2000 Oct 17;133(8):622-34; Marcora *et al.*, Rheumatology (Oxford). 2006 Nov;45(11):1385-8.

[0158] *Weakness*: As used herein, weakness refers physical fatigue, which typically manifests as a loss of muscle strength and/or endurance. Weakness may be central (affecting most or all of the muscles in the body) or peripheral (affecting a subset of muscles). Weakness includes "true weakness," in which a patient's muscles have a decrease in some measure of peak and/or sustained force output, and "perceived weakness," in which a patient perceives that a greater effort is required for performance of a task even though objectively measured strength remains nearly the same, and may be objectively measured or self-reported by the patient. For example, weakness may be objectively measured using the hand grip strength test (a medically recognized test for evaluating muscle strength), typically employing a handgrip dynamometer.

[0159] *Fatigue*: As used herein, fatigue refers to mental fatigue (for physical fatigue see "weakness"). Fatigue includes drowsiness (somnolence) and/or decreased attention. Fatigue may be measured using a variety of tests known in the art, such as the FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue) test. See, e.g., Cella, D., Lai, J.S., Chang, C.H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Eton, D.T., Lai,F J-S., Peterman, A.H & Merkel, D.E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. Journal of Pain & Symptom Management, 24 (6) 547-561.

[0160] *Fever*: As used herein, "fever" refers to a body temperature set-point that is elevated by at least 1 to 2 degrees Celsius. Fever is often associated with a subjective feeling of hypothermia exhibited as a cold sensation, shivering, increased heart rate and respiration rate by which the individual's body reaches the increased set-point. As is well understood in the medical arts, normal body temperature typically varies with activity level and time of day, with highest temperatures observed in the afternoon and early evening hours, and lowest temperatures observed during the second half of the sleep cycle, and temperature measurements may be influenced by external factors such as mouth breathing, consumption of food or beverage, smoking, or ambient temperature (depending on the type of measurement). Moreover, the normal temperature set point for individuals may vary by up to about 0.5 degrees Celsius, thus a medical professional may interpret an individual's temperature in view of these factors to diagnose whether a fever is present. Generally

speaking, a fever is typically diagnosed by a core body temperature above 38.0 degrees Celsius, an oral temperature above 37.5 degrees Celsius, or an axillary temperature above 37.2 degrees Celsius.

[0161] *Improved*: As used herein, "improved," "improvement," and other grammatical variants, includes 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 cachexia encompasses any increase in patient's mass, such as total body mass (excluding weight normally excluded during assessment of cachexia, e.g. tumor weight, extravascular fluid accumulation, etc.), lean body mass, and/or appendicular lean mass, as well as any delay or slowing in the rate of loss of mass, or prevention or slowing of loss of mass associated with a disease or condition with which the patient has been diagnosed. For another example, improvement in weakness encompasses any increase in patient's strength, as well as any delay or slowing in the rate of loss of strength, or prevention or slowing of loss of strength associated with a disease or condition with which the patient has been diagnosed. For yet another example, improvement in fatigue encompasses any decrease in patient's fatigue, as well as any delay or slowing in the rate of increase of fatigue, or prevention or slowing of increase in fatigue associated with a disease or condition with which the patient has been diagnosed. For still another example, improvement in fever encompasses any decrease in patient's fever, as well as any delay or slowing in the rate of increase in fever, or prevention or slowing of increase in fever associated with a disease or condition with which the patient has been diagnosed.

[0162] *C-Reactive Protein (CRP)*: As used herein, C-Reactive Protein (CRP) encompasses not only the following 224 amino acid sequence available as GenBank Protein Accession No. NP_000558:

MEKLLCFLVLTSLSHAFGQTDMSRKAFVFPKESDTSYVSLKAPLTKPLKAFTV
CLHFYTELSSTRGYSIFSYATKRQDNEILIFWSKDIGYSFTVGGSEILFEVPEVT
VAPVHICTSWESASGIVEFWVDGKPRVRKSLKKGYTVGAEASIILGQEQDSFG
GNFEGSQSLVGDIGNVNMWDFVLSPDEINTIYLGGPFSPNVLNWRALKYEVQ
GEVFTKPQLWP (SEQ ID NO: 726), but also 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, tumor, 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, etc. As mentioned above CRP levels may in addition be measured in patients having or at risk of developing thrombosis according to the invention.

[0163] *Interleukin-6 receptor (IL-6R); also called IL-6 receptor alpha (IL-6RA)*: As used herein, "interleukin-6 receptor" ("IL-6R"; also "IL-6 receptor alpha" or "IL-6RA") encompasses not only the following 468 amino acid sequence available as Swiss-Prot Protein Accession No. P08887:
MLAVGCALLAALLAAPGAALAPRRCPAQEVARGVLTSLPGDSVTLTCPGVEP
EDNATVHWVLRKPAAGSHPSRWAGMGRRLLLRSVQLHDSGNYSCYRAGRP
AGTVHLLVDVPPEEPQLSCFRKSPLSNVVCEWGPRSTPSLTTKAVLLVRKFQN
SPAEDFQEPCQYSQESQKFSCQLAVPEGDSSFYIVSMCVASSVGSKFSKTQTF
QGCGILQPDPPANITVTAVARNPRWLSVTWQDPHSWNSSFYRLRFELRYRAE
RSKTFTTWMVKDLQHHCVIHDAWSGLRHVVQLRAQEEFGQGEWSEWSPEA
MGTPWTESRSPPAENEVSTPMQALTTNKDDDNILFRDSANATSLPVQDSSSVP
LPTFLVAGGSLAFGTLLCIAIVLRFKKTWKLRALKEGKTSMHPPYSLGQLVPE
RPRPTPVLVPLISPPVSPSSLGSDNTSSHNRPDARDPRSPYDISNTDYFFPR (SEQ ID NO: 727), but also any pre-pro, pro- and mature forms of this amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0164] *gp130*: As used herein, gp130 (also called Interleukin-6 receptor subunit beta) encompasses not only the following 918 precursor amino acid sequence available as Swiss-Prot Protein Accession No. P40189:
MLTLQTWVVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEK
CMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTF
GQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLK
SEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALGKVTSDHI
NFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDAS
TWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGI
TYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTR
WKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQA
THPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQED

GTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRT KKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLS SLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTT LLGVLFCFNKRDLIKKHIWPNVPDPSKSHIAQWSPHTPPRHNFNSKDQMYSD GNFTDVSVVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRP SISSSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQVFSRSESTQPLLDSEERP EDLQLVDHVDGGDGILPRQQYFKQNCSQHESSPDISHFERSKQVSSVNEEDFV RLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEAATD EGMPKSYLPQTVRQGGYMPQ (SEQ ID NO: 728), but also 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.

[0165] *Glasgow Prognostic Score (GPS)*: As used herein, Glasgow Prognostic Score (GPS) refers 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.

[0166] *Effective amount*: As used herein, "effective amount," "amount effective to," "amount of X effective to" and the like, refer to an amount of an active ingredient that is effective to relieve or reduce to some extent one or more 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) one or more 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. 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 to 100 mg/kg of the patient's body-weight.

[0167] *Prolonged improvement in coagulation profile*: As used herein, "prolonged improvement in coagulation profile" and similar phrases refer to a measurable improvement in the subject's coagulation profile relative to the initial coagulation profile (i.e. the coagulation profile at a time before treatment begins) that is detectable within about a week from when treatment begins (e.g. administration of an IL-6 antagonist) and remains improved for a 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.

[0168] *Prolonged reduction in serum CRP*: As used herein, "prolonged reduction in serum CRP" and similar phrases refer 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.

[0169] *Prolonged increase in serum albumin*: As used herein, "prolonged increase in serum albumin" and similar phrases refer to a measurable decrease in serum albumin level relative to the initial serum albumin level (i.e. the serum albumin 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 above the initial serum albumin 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.

[0170] *Prolonged improvement in cachexia*: As used herein, "prolonged improvement in cachexia" refers to a measureable improvement patient's body mass, lean body mass, appendicular lean body mass, and/or lean body mass index, relative to the initial level (i.e. the level at a time before treatment begins) that is detectable within about 4 weeks and remains improved for a prolonged duration, e.g. 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.

[0171] *Prolonged improvement in weakness*: As used herein, "prolonged improvement in weakness" refers to a measureable improvement in muscular strength, relative to the initial level (i.e. the level at a time before treatment begins) that is detectable within about 2 weeks and remains improved for a prolonged duration, e.g. 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.

[0172] *Prolonged improvement in fatigue*: As used herein, "prolonged improvement in fatigue" refers to a measureable improvement in fatigue, relative to the initial level (i.e. the level at a time before treatment begins) that is detectable within about 1 week and remains improved for a 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.

[0173] *Prolonged improvement in fever*: As used herein, "prolonged improvement in fever" refers to a measureable decrease in fever (e.g. peak temperature or amount of time that temperature is elevated), relative to the initial level (i.e. the level at a time before treatment begins) that is detectable within about 1 week and remains improved for a 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.

[0174] *Mating competent yeast species*: In the present invention this is intended to 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.

[0175] In one embodiment of the invention, the mating competent yeast is 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*, *Rhodosporidium*, *Candida*, *Hansenula*, *Filobasium*, *Filobasidellla*, *Sporidiobolus*, *Bullera*, *Leucosporidium* and *Filobasidella*.

[0176] In a preferred embodiment of the invention, the mating competent yeast is a member of the genus *Pichia*. In a further preferred embodiment of the invention, 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 of the invention, the mating competent yeast of the genus *Pichia* is the species *Pichia pastoris*.

[0177] *Haploid Yeast Cell*: A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[0178] *Polyploid Yeast Cell*: A cell having more than one copy of its normal genomic (chromosomal) complement.

[0179] *Diploid Yeast Cell*: 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.

[0180] *Tetraploid Yeast Cell*: 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.

[0181] *Yeast Mating*: The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[0182] *Meiosis*: The 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.

[0183] *Selectable Marker*: 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: ZEO; G418; LYS3; MET1; MET3a; ADE1; ADE3; URA3; and the like.

[0184] *Expression Vector*: These 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, D., Dawson, D., & Stearns, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[0185] 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.

[0186] 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, one or more 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, and the like. A yeast origin of replication is optional, as expression vectors are often integrated into the yeast genome.

[0187] 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.

[0188] 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^{R} Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0189] 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.

[0190] 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.

[0191] 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.

[0192] 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.

[0193] 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. For example, see Hashimoto *et. al.* Protein Eng 11(2) 75 (1998); and Kobayashi *et. al.* Therapeutic Apheresis 2(4) 257 (1998).

[0194] 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.

[0195] 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.

[0196] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated 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.

[0197] 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, in *Lambda II*, Weisberg, ed.(Cold Spring Harbor, NY:Cold Spring Harbor Press), pp.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.

[0198] *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; and the like.

[0199] *Folding*, as used herein, refers 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, *etc.*

[0200] In some instances, for example where the desired product is of synthetic origin, assays based on biological activity will be less meaningful. The proper folding of such molecules may be determined on the basis of physical properties, energetic considerations, modeling studies, and the like.

[0201] The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, *i.e.* foldases, chaperonins, *etc.* Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, *etc.* as 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.

[0202] 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.

[0203] The terms "*desired protein*" or "*target protein*" are used interchangeably and refer generally to a humanized antibody or a binding portion thereof described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more 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, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies such as scFvs, camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', $F(ab')_2$ and the like. *See* Streltsov VA, *et al.*, Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, Protein Sci. 2005 Nov;14(11):2901-9. Epub 2005 Sep 30; Greenberg AS, *et al.*, A new antigen receptor gene family that

undergoes rearrangement and extensive somatic diversification in sharks, Nature. 1995 Mar 9;374(6518):168-73; Nuttall SD, *et al.*, Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, Mol Immunol. 2001 Aug;38(4):313-26; Hamers-Casterman C, *et al.*, Naturally occurring antibodies devoid of light chains, Nature. 1993 Jun 3;363(6428):446-8; Gill DS, *et al.*, Biopharmaceutical drug discovery using novel protein scaffolds, Curr Opin Biotechnol. 2006 Dec;17(6):653-8. Epub 2006 Oct 19.

[0204] For example, antibodies or antigen binding fragments 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.

[0205] 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 one or more 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, *etc*). 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.

[0206] 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.

[0207] 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, incorporated fully herein by reference.

[0208] 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. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[0209] 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. Examples of additional effector molecules are provided *infra*.

[0210] The term "polyploid yeast that stably expresses or expresses a desired secreted heterologous polypeptide for prolonged time" refers 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 1-6 months, and even more preferably for more than a year at threshold expression levels, typically at least 10-25 mg/liter and preferably substantially greater.

[0211] The term "polyploidal yeast culture that secretes desired amounts of recombinant polypeptide" refers to cultures that stably or for prolonged periods secrete at least 10-25 mg/liter of heterologous polypeptide, more preferably at least 50-500 mg/liter, and most preferably 500-1000 mg/liter or more.

[0212] 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.

[0213] A "heterologous" region or domain of a DNA construct is 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.

[0214] A "coding sequence" is 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.

[0215] 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., Principles of Gene Manipulation: An Introduction to Genetic Engineering, Blackwell Scientific Publications, 4th edition, 1989; Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989; Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd Edition, Cold Spring Harbor Laboratory Press, 2001; Gorman, "High Efficiency Gene Transfer into Mammalian Cells," in DNA Cloning, Volume II, Glover, D. M., Ed., IRL Press, Washington, D.C., pp. 143 190 (1985).

[0216] 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-dioleyloxy-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,-dioleyloxy)propyl]-N,N-dimethyl-N-hydroxy ethylammonium bromide (DORIE); N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA); 3 beta [N-(N',N'-dimethylaminoethane)carbamoly] 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, Angew. Chem. Int. Ed. 37:1768 1785 (1998), and Cooper et al., Chem. Eur. J. 4(1): 137 151 (1998). 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., Nature Medicine, 1998, 4(5):(1998), 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. Pat. No. 7,297,759. Additional exemplary liposomes and other lipid aggregates are described in U.S. Pat. No. 7,166,298.

[0217] "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 described in a review article by 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.

[0218] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., Ann. N.Y. Acad. Sci., 190: 5 (1971)). 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 F_{ab} region; the stem portion of the "Y" configuration is designated the F_C 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.

[0219] 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., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., *et al.*, Clinical Immunobiology, pp 1-18, W. B. Sanders (1980); Kohl, S., *et al.*, Immunology, 48: 187 (1983)); 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.

[0220] The expression "variable region" or "VR" refers 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.

[0221] The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more 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.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat *et al.* ("Sequences of Proteins of Immunological Interest," Kabat E., *et al.*, US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, J Mol. Biol. 196 901-917 (1987)). 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, S., Methods, 36:25-34 (2005)).The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). 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.

Anti-IL-6 Antibodies and Binding Fragments Thereof

[0222] The invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below: MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQASQSIN NELSWYQQKPGQRPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISDLECADA ATYYCQQGYSLRNIDNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNN (SEQ ID NO: 2) or

AIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTL ASGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKV EIKR (SEQ ID NO: 709).

[0223] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYV TWVRQAPGKGLEWIGIIYGSDETAYATWAIGRFTISKTSTTVDLKMTSLTAAD TATYFCARDDSSDWDAKFNLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVK (SEQ ID NO: 3) or EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIY GSDETAYATSAIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWD AKFNLWGQGTLVTVSS (SEQ ID NO: 657).

[0224] The invention further contemplates antibodies comprising one or more of 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 709, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8; 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 SEQ ID NO:657 or those contained in Figures 34-37,, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0225] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of 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 709 or the other humanized VL sequences contained in Figures 34-37,, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8; 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 combinations of these polypeptide sequences.

[0226] In another embodiment of the invention, the antibodies of the invention preferably include combinations of the CDRs and the variable heavy and light chain sequences set forth above. In a preferred embodiment the humanized anti-IL-6 antibody will comprise the variable heavy and variable light chain sequences respectively contained in SEQ ID NO:657 and SEQ ID NO:709, and preferably further comprising the heavy chain and light chain constant regions respectively contained in SEQ ID NO:588 and SEQ ID NO:586 or an anti-IL-6IL-6 antibody comprising one or more of the other variable heavy and light chain sequences in Figures 34-37 derived from Ab1, and variants thereof comprising one or more 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, one or more 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. This embodiment further contemplates nucleic acids encoding variants comprising one or more amino acid substitutions or deletions to the variable heavy and variable light chain sequences respectively contained in SEQ ID NO:657 and SEQ ID NO:709 and the heavy chain and light chain constant regions respectively contained in SEQ ID NO:588 and SEQ ID NO:586, that do not substantially affect IL-6 binding and/or desired effector function.

[0227] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 2 or 709 In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 3 or 657.

[0228] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of 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.

[0229] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the

polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8; 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 SEQ ID NO:657.

[0230] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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 or 709; the variable heavy chain region of SEQ ID NO: 3 or SEQ ID NO:657; 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 or 709; and the complementarity-determining regions (SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9) of the variable heavy chain region of SEQ ID NO: 3 or 657.

[0231] The invention also contemplates 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 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.

[0232] In a preferred embodiment of the invention, the anti-IL-6 antibody is 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. In a preferred embodiment, the anti-IL-6 antibody will comprise at least one humanized sequence as shown in Figures 34-37.

[0233] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTINCQASETIY SWLSWYQQKPGQPPKLLIYQASDLASGVPSRFSGSGAGTEYTLTISGVQCDD AATYYCQQGYSGSNVDNVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFY (SEQ ID NO: 21)

[0234] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQEQLKESGGRLVTPGTPLTLTCTASGFSLNDHA MGWVRQAPGKGLEYIGFINSGGSARYASWAEGRFTISRTSTTVDLKMTSLTT EDTATYFCVRGGAVWSIHSFDPWGPGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVK (SEQ ID NO: 22).

[0235] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21, and/or one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0236] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21, and/or one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0237] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 21. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 22.

[0238] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21.

[0239] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22.

[0240] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 21; the variable heavy chain region of SEQ ID NO: 22; the complementarity-determining regions (SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25) of the variable light chain region of SEQ ID NO: 21; and the complementarity-determining regions (SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28) of the variable heavy chain region of SEQ ID NO: 22.

[0241] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab2, comprising SEQ ID NO: 21 and SEQ ID NO: 22, and having at least one of the biological activities set forth herein.

[0242] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQASQSVY
DNNYLSWFQQKPGQPPKLLIYGASTLASGVPSRFVGSGSGTQFTLTITDVQCD
DAATYYCAGVYDDDSDNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTAS
VVCLLNN (SEQ ID NO: 37)

[0243] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSVYYM

NWVRQAPGKGLEWIGFITMSDNINYASWAKGRFTISKTSTTVDLKMTSPTTE DTATYFCARSRGWGTMGRLDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVK (SEQ ID NO: 38).

[0244] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37, and/or one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0245] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37, and/or one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0246] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 37. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 38.

[0247] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37.

[0248] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38.

[0249] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 37; the variable heavy chain region of SEQ ID NO: 38; the complementarity-determining regions (SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41) of the variable light chain region of SEQ ID NO: 37; and the complementarity-determining regions (SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44) of the variable heavy chain region of SEQ ID NO: 38.

[0250] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab3, comprising SEQ ID NO: 37 and SEQ ID NO: 38, and having at least one of the biological activities set forth herein.

[0251] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0252] MDTRAPTQLLGLLLLWLPGAICDPVLTQTPSPVSAPVGGTVSISCQA SQSVYENNYLSWFQQKPGQPPKLLIYGASTLDSGVPSRFKGSGSGTQFTLTIT DVQCDDAATYYCAGVYDDDSDDAFGGGTEVVVKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNN (SEQ ID NO: 53)

[0253] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQEQLKESGGGLVTPGGTLTLTCTASGFSLNAY YMNWVRQAPGKGLEWIGFITLNNNVAYANWAKGRFTFSKTSTTVDLKMTSP TPEDTATYFCARSRGWGAMGRLDLWGHGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVK (SEQ ID NO: 54).

[0254] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53, and/or one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0255] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53, and/or one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0256] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 53. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 54.

[0257] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53.

[0258] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54.

[0259] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 53; the variable heavy chain region of SEQ ID NO: 54; the complementarity-determining regions (SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57) of the variable light chain region of SEQ ID NO: 53; and the complementarity-determining regions (SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60) of the variable heavy chain region of SEQ ID NO: 54.

[0260] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab4, comprising SEQ ID NO: 53 and SEQ ID NO: 54, and having at least one of the biological activities set forth herein.

[0261] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0262] MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSAAVGGTVTINCQ ASQSVDDNNWLGWYQQKRGQPPKYLIYSASTLASGVPSRFKGSGSGTQFTLT ISDLECDDAATYYCAGGFSGNIFAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNF (SEQ ID NO: 69)

[0263] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAM SWVRQAPGKGLEWIGIIGGFGTTYYATWAKGRFTISKTSTTVDLRITSPTTEDT ATYFCARGGPGNGGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKD (SEQ ID NO: 70).

[0264] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69, and/or one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID

NO: 70, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0265] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69, and/or one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and 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. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 69. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 70.

[0267] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69.

[0268] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70.

[0269] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 69; the variable

heavy chain region of SEQ ID NO: 70; the complementarity-determining regions (SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73) of the variable light chain region of SEQ ID NO: 69; and the complementarity-determining regions (SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76) of the variable heavy chain region of SEQ ID NO: 70.

[0270] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab5, comprising SEQ ID NO: 69 and SEQ ID NO: 70, and having at least one of the biological activities set forth herein.

[0271] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0272] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSVPVGGTVTIKCQ SSQSVYNNFLSWYQQKPGQPPKLLIYQASKLASGVPDRFSGSGSGTQFTLTIS GVQCDDAATYYCLGGYDDDADNAFGGGTEVVVKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNF (SEQ ID NO: 85)

[0273] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGIDLSDYAM SWVRQAPGKGLEWIGIIYAGSGSTWYASWAKGRFTISKTSTTVDLKITSPTTE DTATYFCARDGYDDYGDFDRLDLWGPGTLVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKD (SEQ ID NO: 86).

[0274] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85, and/or one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0275] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide

sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85, and/or one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0276] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 85. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 86.

[0277] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85.

[0278] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86.

[0279] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 85; the variable heavy chain region of SEQ ID NO: 86; the complementarity-determining regions (SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89) of the variable light chain region of SEQ ID NO: 85; and the complementarity-determining regions (SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92) of the variable heavy chain region of SEQ ID NO: 86.

[0280] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab6, comprising SEQ ID NO: 85 and SEQ ID NO: 86, and having at least one of the biological activities set forth herein.

[0281] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0282] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKC QASQSINNELSWYQQKSGQRPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISD LECADAATYYCQQGYSLRNIDNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNF (SEQ ID NO: 101)

[0283] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLSGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYM TWVRQAPGKGLEWIGMIYGSDETAYANWAIGRFTISKTSTTVDLKMTSLTAA DTATYFCARDDSSDWDAKFNLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVK (SEQ ID NO: 102).

[0284] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101, and/or one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0285] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101, and/or one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or

hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0286] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 101. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 102.

[0287] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101.

[0288] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102.

[0289] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 101; the variable heavy chain region of SEQ ID NO: 102; the complementarity-determining regions (SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105) of the variable light chain region of SEQ ID NO: 101; and the complementarity-determining regions (SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108) of the variable heavy chain region of SEQ ID NO: 102.

[0290] The invention also contemplates variants wherein either of the heavy chain polypeptide sequences of SEQ ID NO: 117 or SEQ ID NO: 118 is substituted for the heavy chain polypeptide sequence of SEQ ID NO: 102; the light chain polypeptide sequence of SEQ ID NO: 119 is substituted for the light chain polypeptide sequence

of SEQ ID NO: 101; and the heavy chain CDR sequence of SEQ ID NO: 121 is substituted for the heavy chain CDR sequence of SEQ ID NO: 107.

[0291] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab7, comprising SEQ ID NO: 101 and SEQ ID NO: 102, or the alternative SEQ ID NOs set forth in the preceding paragraph, and having at least one of the biological activities set forth herein.

[0292] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0293] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQ SSQSVGNNQDLSWFQQRPGQPPKLLIYEISKLESGVPSRFSGSGSGTHFTLTISG VQCDDAATYYCLGGYDDDADNA (SEQ ID NO: 122)

[0294] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCHSVEESGGRLVTPGTPLTLTCTVSGFSLSSRTM SWVRQAPGKGLEWIGYIWSGGSTYYATWAKGRFTISKTSTTVDLKITSPTTED TATYFCARLGDTGGHAYATRLNL (SEQ ID NO: 123).

[0295] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0296] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID

NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0297] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 122. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 123.

[0298] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122.

[0299] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123.

[0300] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 122; the variable heavy chain region of SEQ ID NO: 123; the complementarity-determining regions (SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126) of the variable light chain region of SEQ ID NO: 122; and the complementarity-determining regions (SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129) of the variable heavy chain region of SEQ ID NO: 123.

[0301] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab8, comprising SEQ ID NO: 122 and SEQ ID NO: 123, and having at least one of the biological activities set forth herein.

[0302] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0303] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSSVSAAVGGTVSISCQ SSQSVYSNKYLAWYQQKPGQPPKLLIYWTSKLASGAPSRFSGSGSGTQFTLTI SGVQCDDAATYYCLGAYDDDADNA (SEQ ID NO: 138)

[0304] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVKPDETLTLTCTASGFSLEGGY MTWVRQAPGKGLEWIGISYDSGSTYYASWAKGRFTISKTSSTTVDLKMTSLT TEDTATYFCVRSLKYPTVTSDDL (SEQ ID NO: 139).

[0305] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138, and/or one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0306] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138, and/or one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0307] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 138. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 139.

[0308] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138.

[0309] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139.

[0310] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 138; the variable heavy chain region of SEQ ID NO: 139; the complementarity-determining regions (SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142) of the variable light chain region of SEQ ID NO: 138; and the complementarity-determining regions (SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145) of the variable heavy chain region of SEQ ID NO: 139.

[0311] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab9, comprising SEQ ID NO: 138 and SEQ ID NO: 139, and having at least one of the biological activities set forth herein.

[0312] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0313] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQ SSQSVYNNNDLAWYQQKPGQPPKLLIYYASTLASGVPSRFKGSGSGTQFTLTI SGVQCDDAAAYYCLGGYDDDADNA (SEQ ID NO: 154)

[0314] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGLSLSSNTIN WVRQAPGKGLEWIGYIWSGGSTYYASWVNGRFTISKTSTTVDLKITSPTTEDT ATYFCARGGYASGGYPYATRLDL (SEQ ID NO: 155).

[0315] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 154, and/or one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 155, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0316] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 154, and/or one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 155, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0317] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 154. In another embodiment of the invention, antibody fragments of the

invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 155.

[0318] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 154.

[0319] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 155.

[0320] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 154; the variable heavy chain region of SEQ ID NO: 155; the complementarity-determining regions (SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158) of the variable light chain region of SEQ ID NO: 154; and the complementarity-determining regions (SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161) of the variable heavy chain region of SEQ ID NO: 155.

[0321] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab10, comprising SEQ ID NO: 154 and SEQ ID NO: 155, and having at least one of the biological activities set forth herein.

[0322] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0323] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSSVSAAVGGTVTINCQ SSQSVYNNDYLSWYQQRPGQRPKLLIYGASKLASGVPSRFKGSGSGKQFTLTI SGVQCDDAATYYCLGDYDDDADNT (SEQ ID NO: 170)

[0324] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFTLSTNYY LSWVRQAPGKGLEWIGIIYPSGNTYCAKWAKGRFTISKTSSTTVDLKMTSPTT EDTATYFCARNYGGDESL (SEQ ID NO: 171).

[0325] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170, and/or one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0326] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170, and/or one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0327] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 170. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 171.

[0328] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170.

[0329] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171.

[0330] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 170; the variable heavy chain region of SEQ ID NO: 171; the complementarity-determining regions (SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174) of the variable light chain region of SEQ ID NO: 170; and the complementarity-determining regions (SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177) of the variable heavy chain region of SEQ ID NO: 171.

[0331] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab11, comprising SEQ ID NO: 170 and SEQ ID NO: 171, and having at least one of the biological activities set forth herein.

[0332] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0333] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKC QASETIGNALAWYQQKSGQPPKLLIYKASKLASGVPSRFKGSGSGTEYTLTIS DLECADAATYYCQWCYFGDSV (SEQ ID NO: 186)

[0334] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVTVLKGVQCQEQLVESGGGLVQPEGSLTLTCTASGFDFSSGY YMCWVRQAPGKGLEWIACIFTITTNTYYASWAKGRFTISKTSSTTVTLQMTSL TAADTATYLCARGIYSDNNYYAL (SEQ ID NO: 187).

[0335] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO:

190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186, and/or one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0336] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186, and/or one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0337] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 186. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 187.

[0338] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186.

[0339] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187.

[0340] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 186; the variable heavy chain region of SEQ ID NO: 187; the complementarity-determining regions (SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190) of the variable light chain region of SEQ ID NO: 186; and the complementarity-determining regions (SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193) of the variable heavy chain region of SEQ ID NO: 187.

[0341] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab12, comprising SEQ ID NO: 186 and SEQ ID NO: 187, and having at least one of the biological activities set forth herein.

[0342] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0343] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKC QASESIGNALAWYQQKPGQPPKLLIYKASTLASGVPSRFSGSGSGTEFTLTISG VQCADAAAYYCQWCYFGDSV (SEQ ID NO: 202)

[0344] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQQQLVESGGGLVKPGASLTLTCKASGFSFSSG YYMCWVRQAPGKGLESIACIFTITDNTYYANWAKGRFTISKPSSPTVTLQMTS LTAADTATYFCARGIYSTDNYYAL (SEQ ID NO: 203).

[0345] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202, and/or one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of

SEQ ID NO: 203, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0346] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202, and/or one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0347] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 202. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 203.

[0348] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202.

[0349] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203.

[0350] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 202; the variable heavy chain region of SEQ ID NO: 203; the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206) of the variable light chain region of SEQ ID NO: 202; and the complementarity-determining regions (SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209) of the variable heavy chain region of SEQ ID NO: 203.

[0351] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab13, comprising SEQ ID NO: 202 and SEQ ID NO: 203, and having at least one of the biological activities set forth herein.

[0352] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0353] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKC QASQSVSSYLNWYQQKPGQPPKLLIYRASTLESGVPSRFKGSGSGTEFTLTISD LECADAATYYCQCTYGTSSSYGAA (SEQ ID NO: 218)

[0354] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGISLSSNAIS WVRQAPGKGLEWIGIISYSGTTYYASWAKGRFTISKTSSTTVDLKITSPTTEDT ATYFCARDDPTTVMVMLIPFGAGMDL (SEQ ID NO: 219).

[0355] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218, and/or one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0356] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218, and/or one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0357] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 218. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 219.

[0358] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218.

[0359] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219.

[0360] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 218; the variable heavy chain region of SEQ ID NO: 219; the complementarity-determining regions (SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222) of the variable light chain region of SEQ ID NO: 218; and the complementarity-determining regions (SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225) of the variable heavy chain region of SEQ ID NO: 219.

[0361] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab14, comprising SEQ ID NO: 218 and SEQ ID NO: 219, and having at least one of the biological activities set forth herein.

[0362] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0363] MDTRAPTQLLGLLLLWLPGATFAQVLTQTASPVSAAVGGTVTINC QASQSVYKNNYLSWYQQKPGQPPKGLIYSASTLDSGVPLRFSGSGSGTQFTLT ISDVQCDDAATYYCLGSYDCSSGDCYA (SEQ ID NO: 234)

[0364] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCTASGFSFSSYWM CWVRQAPGKGLEWIACIVTGNGNTYYANWAKGRFTISKTSSTTVTLQMTSLT AADTATYFCAKAYDL (SEQ ID NO: 235).

[0365] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234, and/or one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0366] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234, and/or one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235, or combinations of these polypeptide sequences. In another embodiment of the

invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0367] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 234. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 235.

[0368] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234.

[0369] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235.

[0370] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 234; the variable heavy chain region of SEQ ID NO: 235; the complementarity-determining regions (SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238) of the variable light chain region of SEQ ID NO: 234; and the complementarity-determining regions (SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241) of the variable heavy chain region of SEQ ID NO: 235.

[0371] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab15, comprising SEQ ID NO: 234 and SEQ ID NO: 235, and having at least one of the biological activities set forth herein.

[0372] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0373] MDTRAPTQLLGLLLLWLPGSTFAAVLTQTPSPVSAAVGGTVSISCQ ASQSVYDNNYLSWYQQKPGQPPKLLIYGASTLASGVPSRFKGTGSGTQFTLTI TDVQCDDAATYYCAGVFNDDSDDA (SEQ ID NO: 250)

[0374] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVPKGVQCQSLEESGGRLVTPGTPLTLTCTLSGFSLSAYYM SWVRQAPGKGLEWIGFITLSDHISYARWAKGRFTISKTSTTVDLKMTSPTTED TATYFCARSRGWGAMGRLDL (SEQ ID NO: 251).

[0375] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250, and/or one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0376] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250, and/or one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0377] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 250. In another embodiment of the invention, antibody fragments of the

invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 251.

[0378] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250.

[0379] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251.

[0380] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 250; the variable heavy chain region of SEQ ID NO: 251; the complementarity-determining regions (SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254) of the variable light chain region of SEQ ID NO: 250; and the complementarity-determining regions (SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257) of the variable heavy chain region of SEQ ID NO: 251.

[0381] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab16, comprising SEQ ID NO: 250 and SEQ ID NO: 251, and having at least one of the biological activities set forth herein.

[0382] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0383] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQ ASQSVYNNKNLAWYQQKSGQPPKLLIYWASTLASGVSSRFSGSGSGTQFTLT VSGVQCDDAATYYCLGVFDDDADNA (SEQ ID NO: 266)

[0384] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTASGFSLSSYSM TWVRQAPGKGLEYIGVIGTSGSTYYATWAKGRFTISRTSTTVALKITSPTTEDT ATYFCVRSLSSITFL (SEQ ID NO: 267).

[0385] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266, and/or one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0386] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266, and/or one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0387] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 266. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 267.

[0388] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266.

[0389] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267.

[0390] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 266; the variable heavy chain region of SEQ ID NO: 267; the complementarity-determining regions (SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270) of the variable light chain region of SEQ ID NO: 266; and the complementarity-determining regions (SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273) of the variable heavy chain region of SEQ ID NO: 267.

[0391] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab17, comprising SEQ ID NO: 266 and SEQ ID NO: 267, and having at least one of the biological activities set forth herein.

[0392] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0393] MDTRAPTQLLGLLLLWLPGARCAFELTQTPASVEAAVGGTVTINCQ ASQNIYRYLAWYQQKPGQPPKFLIYLASTLASGVPSRFKGSGSGTEFTLTISDL ECADAATYYCQSYYSSNSVA (SEQ ID NO: 282)

[0394] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQEQLVESGGDLVQPEGSLTLTCTASELDFSSGY WICWVRQVPGKGLEWIGCIYTGSSGSTFYASWAKGRFTISKTSSTTVTLQMTS LTAADTATYFCARGYSGFGYFKL (SEQ ID NO: 283).

[0395] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO:

286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282, and/or one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0396] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282, and/or one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0397] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 282. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 283.

[0398] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282.

[0399] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283.

[0400] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 282; the variable heavy chain region of SEQ ID NO: 283; the complementarity-determining regions (SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286) of the variable light chain region of SEQ ID NO: 282; and the complementarity-determining regions (SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289) of the variable heavy chain region of SEQ ID NO: 283.

[0401] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab18, comprising SEQ ID NO: 282 and SEQ ID NO: 283, and having at least one of the biological activities set forth herein.

[0402] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0403] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKC QASEDIYRLLAWYQQKPGQPPKLLIYDSSDLASGVPSRFKGSGSGTEFTLAISG VQCDDAATYYCQQAWSYSDIDNA (SEQ ID NO: 298)

[0404] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTASGFSLSSYYM SWVRQAPGKGLEWIGIITTSGNTFYASWAKGRLTISRTSTTVDLKITSPTTEDT ATYFCARTSDIFYYRNL (SEQ ID NO: 299).

[0405] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298, and/or one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of

SEQ ID NO: 299, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0406] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298, and/or one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0407] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 298. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 299.

[0408] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298.

[0409] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299.

[0410] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 298; the variable heavy chain region of SEQ ID NO: 299; the complementarity-determining regions (SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302) of the variable light chain region of SEQ ID NO: 298; and the complementarity-determining regions (SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305) of the variable heavy chain region of SEQ ID NO: 299.

[0411] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab19, comprising SEQ ID NO: 298 and SEQ ID NO: 299, and having at least one of the biological activities set forth herein.

[0412] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0413] MDTRAPTQLLGLLLLWLPGATFAAVLTQTASPVSAAVGATVTINC QSSQSVYNDMDLAWFQQKPGQPPKLLIYSASTLASGVPSRFSGSGSGTEFTLTI SGVQCDDAATYYCLGAFDDDADNT (SEQ ID NO: 314)

[0414] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLTRHAIT WVRQAPGKGLEWIGCIWSGGSTYYATWAKGRFTISKTSTTVDLRITSPTTEDT ATYFCARVIGDTAGYAYFTGLDL (SEQ ID NO: 315).

[0415] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314, and/or one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0416] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314, and/or one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0417] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 314. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 315.

[0418] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314.

[0419] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315.

[0420] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 314; the variable heavy chain region of SEQ ID NO: 315; the complementarity-determining regions (SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318) of the variable light chain region of SEQ ID NO: 314; and the complementarity-determining regions (SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321) of the variable heavy chain region of SEQ ID NO: 315.

[0421] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab20, comprising SEQ ID NO: 314 and SEQ ID NO: 315, and having at least one of the biological activities set forth herein.

[0422] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0423] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKC QASQSVYNWLSWYQQKPGQPPKLLIYTASSLASGVPSRFSGSGSGTEFTLTIS GVECADAATYYCQQGYTSDVDNV (SEQ ID NO: 330)

[0424] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEEAGGRLVTPGTPLTLTCTVSGIDLSSYAM GWVRQAPGKGLEYIGIISSSGSTYYATWAKGRFTISQASSTTVDLKITSPTTED SATYFCARGGAGSGGVWLLDGFDP (SEQ ID NO: 331).

[0425] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 330, and/or one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 331, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0426] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 330, and/or one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 331, or combinations of these polypeptide sequences. In another embodiment of the

invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0427] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 330. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 331.

[0428] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 330.

[0429] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 331.

[0430] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 330; the variable heavy chain region of SEQ ID NO: 331; the complementarity-determining regions (SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334) of the variable light chain region of SEQ ID NO: 330; and the complementarity-determining regions (SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337) of the variable heavy chain region of SEQ ID NO: 331.

[0431] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab21, comprising SEQ ID NO: 330 and SEQ ID NO: 331, and having at least one of the biological activities set forth herein.

[0432] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0433] MDTRAPTQLLGLLLLWLPGAKCADVVMTQTPASVSAAVGGTVTIN CQASENIYNWLAWYQQKPGQPPKLLIYTVGDLASGVSSRFKGSGSGTEFTLTI SDLECADAATYYCQQGYSSSYVDNV (SEQ ID NO: 346)

[0434] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQEQLKESGGRLVTPGTPLTLTCTVSGFSLNDYA VGWFRQAPGKGLEWIGYIRSSGTTAYATWAKGRFTISATSTTVDLKITSPTTE DTATYFCARGGAGSSGVWILDGFAP (SEQ ID NO: 347).

[0435] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346, and/or one or more of the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0436] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346, and/or one or more of the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0437] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 346. In another embodiment of the invention, antibody fragments of the

invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 347.

[0438] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346.

[0439] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.

[0440] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 346; the variable heavy chain region of SEQ ID NO: 347; the complementarity-determining regions (SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350) of the variable light chain region of SEQ ID NO: 346; and the complementarity-determining regions (SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353) of the variable heavy chain region of SEQ ID NO: 347.

[0441] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab22, comprising SEQ ID NO: 346 and SEQ ID NO: 347, and having at least one of the biological activities set forth herein.

[0442] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0443] MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSSVSAAVGGTVTINCQ ASQSVYQNNYLSWFQQKPGQPPKLLIYGAATLASGVPSRFKGSGSGTQFTLTI SDLECDDAATYYCAGAYRDVDS (SEQ ID NO: 362)

[0444] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPGASLTLTCTASGFSFTSTYYI YWVRQAPGKGLEWIACIDAGSSGSTYYATWVNGRFTISKTSSTTVTLQMTSL TAADTATYFCAKWDYGGNVGWGYDL (SEQ ID NO: 363).

[0445] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362, and/or one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0446] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362, and/or one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0447] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 362. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 363.

[0448] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362.

[0449] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363.

[0450] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 362; the variable heavy chain region of SEQ ID NO: 363; the complementarity-determining regions (SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366) of the variable light chain region of SEQ ID NO: 362; and the complementarity-determining regions (SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369) of the variable heavy chain region of SEQ ID NO: 363.

[0451] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab23, comprising SEQ ID NO: 362 and SEQ ID NO: 363, and having at least one of the biological activities set forth herein.

[0452] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0453] MDTRAPTQLLGLLLLWLPGARCAFELTQTPSSVEAAVGGTVTIKCQ ASQSISSYLAWYQQKPGQPPKFLIYRASTLASGVPSRFKGSGSGTEFTLTISDLE CADAATYYCQSYYDSVSNP (SEQ ID NO: 378)

[0454] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCKASGLDLGTYW FMCWVRQAPGKGLEWIACIYTGSSGSTFYASWVNGRFTISKTSSTTVTLQMT SLTAADTATYFCARGYSGYGYFKL (SEQ ID NO: 379).

[0455] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO:

382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378, and/or one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0456] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378, and/or one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0457] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 378. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 379.

[0458] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378.

[0459] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379.

[0460] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 378; the variable heavy chain region of SEQ ID NO: 379; the complementarity-determining regions (SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382) of the variable light chain region of SEQ ID NO: 378; and the complementarity-determining regions (SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385) of the variable heavy chain region of SEQ ID NO: 379.

[0461] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab24, comprising SEQ ID NO: 378 and SEQ ID NO: 379, and having at least one of the biological activities set forth herein.

[0462] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0463] MDTRAPTQLLGLLLLWLPGVTFAIEMTQSPFSVSAAVGGTVSISCQ ASQSVYKNNQLSWYQQKSGQPPKLLIYGASALASGVPSRFKGSGSGTEFTLTI SDVQCDDAATYYCAGAITGSIDTDG (SEQ ID NO: 394)

[0464] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPGASLTLTCTTSGFSFSSSYFI CWVRQAPGKGLEWIACIYGGDGSTYYASWAKGRFTISKTSSTTVTLQMTSLT AADTATYFCAREWAYSQGYFGAFDL (SEQ ID NO: 395).

[0465] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394, and/or one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of

SEQ ID NO: 395, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0466] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394, and/or one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0467] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 394. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 395.

[0468] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394.

[0469] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395.

[0470] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 394; the variable heavy chain region of SEQ ID NO: 395; the complementarity-determining regions (SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398) of the variable light chain region of SEQ ID NO: 394; and the complementarity-determining regions (SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401) of the variable heavy chain region of SEQ ID NO: 395.

[0471] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab25, comprising SEQ ID NO: 394 and SEQ ID NO: 395, and having at least one of the biological activities set forth herein.

[0472] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0473] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKC QASEDISSYLAWYQQKPGQPPKLLIYAASNLESGVSSRFKGSGSGTEYTLTISD LECADAATYYCQCTYGTISISDGNA (SEQ ID NO: 410)

[0474] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFM TWVRQAPGEGLEYIGFINPGGSAYYASWVKGRFTISKSSTTVDLKITSPTTEDT ATYFCARVLIVSYGAFTI (SEQ ID NO: 411).

[0475] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410, and/or one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0476] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410, and/or one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0477] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 410. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 411.

[0478] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410.

[0479] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411.

[0480] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 410; the variable heavy chain region of SEQ ID NO: 411; the complementarity-determining regions (SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414) of the variable light chain region of SEQ ID NO: 410; and the complementarity-determining regions (SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417) of the variable heavy chain region of SEQ ID NO: 411.

[0481] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab26, comprising SEQ ID NO: 410 and SEQ ID NO: 411, and having at least one of the biological activities set forth herein.

[0482] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0483] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVSAAVGGTVTIKC QASEDIESYLAWYQQKPGQPPKLLIYGASNLESGVSSRFKGSGSGTEFTLTISD LECADAATYYCQCTYGIISISDGNA (SEQ ID NO: 426)

[0484] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFM TWVRQAPGEGLEYIGFMNTGDNAYYASWAKGRFTISKTSTTVDLKITSPTTE DTATYFCARVLVVAYGAFNI (SEQ ID NO: 427).

[0485] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426, and/or one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0486] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426, and/or one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427, or combinations of these polypeptide sequences. In another embodiment of the

invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0487] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 426. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 427.

[0488] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426.

[0489] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427.

[0490] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 426; the variable heavy chain region of SEQ ID NO: 427; the complementarity-determining regions (SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430) of the variable light chain region of SEQ ID NO: 426; and the complementarity-determining regions (SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433) of the variable heavy chain region of SEQ ID NO: 427.

[0491] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab27, comprising SEQ ID NO: 426 and SEQ ID NO: 427, and having at least one of the biological activities set forth herein.

[0492] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0493] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSEPVGGTVSISCQS SKSVMNNNYLAWYQQKPGQPPKLLIYGASNLASGVPSRFSGSGSGTQFTLTIS DVQCDDAATYYCQGGYTGYSDHGT (SEQ ID NO: 442)

[0494] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVKPDETLTLTCTVSGIDLSSYPM NWVRQAPGKGLEWIGFINTGGTIVYASWAKGRFTISKTSTTVDLKMTSPTTE DTATYFCARGSYVSSGYAYYFNV (SEQ ID NO: 443).

[0495] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442, and/or one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0496] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442, and/or one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0497] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 442. In another embodiment of the invention, antibody fragments of the

invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 443.

[0498] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442.

[0499] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443.

[0500] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 442; the variable heavy chain region of SEQ ID NO: 443; the complementarity-determining regions (SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446) of the variable light chain region of SEQ ID NO: 442; and the complementarity-determining regions (SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449) of the variable heavy chain region of SEQ ID NO: 443.

[0501] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab28, comprising SEQ ID NO: 442 and SEQ ID NO: 443, and having at least one of the biological activities set forth herein.

[0502] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0503] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQ SSQSVYNNNWLSWFQQKPGQPPKLLIYKASTLASGVPSRFKGSGSGTQFTLTI SDVQCDDVATYYCAGGYLDSVI (SEQ ID NO: 458)

[0504] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSTYSIN WVRQAPGKGLEWIGIIANSGTTFYANWAKGRFTVSKTSTTVDLKITSPTTEDT ATYFCARESGMYNEYGKFNI (SEQ ID NO: 459).

[0505] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458, and/or one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0506] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458, and/or one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0507] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 458. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 459.

[0508] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458.

[0509] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459.

[0510] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 458; the variable heavy chain region of SEQ ID NO: 459; the complementarity-determining regions (SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462) of the variable light chain region of SEQ ID NO: 458; and the complementarity-determining regions (SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465) of the variable heavy chain region of SEQ ID NO: 459.

[0511] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab29, comprising SEQ ID NO: 458 and SEQ ID NO: 459, and having at least one of the biological activities set forth herein.

[0512] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0513] MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINC QASENIYSFLAWYQQKPGQPPKLLIFKASTLASGVSSRFKGSGSGTQFTLTISD LECDDAATYYCQQGATVYDIDNN (SEQ ID NO: 474)

[0514] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGIDLSAYAM IWVRQAPGEGLEWITIIYPNGITYYANWAKGRFTVSKTSTAMDLKITSPTTED TATYFCARDAESSKNAYWGYFNV (SEQ ID NO: 475).

[0515] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO:

478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474, and/or one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0516] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474, and/or one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0517] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 474. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 475.

[0518] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474.

[0519] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475.

[0520] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 474; the variable heavy chain region of SEQ ID NO: 475; the complementarity-determining regions (SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478) of the variable light chain region of SEQ ID NO: 474; and the complementarity-determining regions (SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481) of the variable heavy chain region of SEQ ID NO: 475.

[0521] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab30, comprising SEQ ID NO: 474 and SEQ ID NO: 475, and having at least one of the biological activities set forth herein.

[0522] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0523] MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINC QASENIYSFLAWYQQKPGQPPKLLIFRASTLASGVSSRFKGSGSGTQFTLTISD LECDDAATYYCQQGATVYDIDNN (SEQ ID NO: 490)

[0524] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGIDLSAYAM IWVRQAPGEGLEWITIIYPNGITYYANWAKGRFTVSKTSTAMDLKITSPTTED TATYFCARDAESSKNAYWGYFNV (SEQ ID NO: 491).

[0525] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490, and/or one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of

SEQ ID NO: 491, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0526] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490, and/or one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0527] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 490. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 491.

[0528] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490.

[0529] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491.

[0530] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 490; the variable heavy chain region of SEQ ID NO: 491; the complementarity-determining regions (SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494) of the variable light chain region of SEQ ID NO: 490; and the complementarity-determining regions (SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497) of the variable heavy chain region of SEQ ID NO: 491.

[0531] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab31, comprising SEQ ID NO: 490 and SEQ ID NO: 491, and having at least one of the biological activities set forth herein.

[0532] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0533] MDTRAPTQLLGLLLLWLPGATFAIEMTQTPSPVSAAVGGTVTINCQ ASESVFNNMLSWYQQKPGHSPKLLIYDASDLASGVPSRFKGSGSGTQFTLTIS GVECDDAATYYCAGYKSDSNDGDNV (SEQ ID NO: 506)

[0534] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLNRNSIT WVRQAPGEGLEWIGIITGSGRTYYANWAKGRFTISKTSTTVDLKMTSPTTEDT ATYFCARGHPGLGSGNI (SEQ ID NO: 507).

[0535] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506, and/or one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0536] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506, and/or one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0537] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 506. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 507.

[0538] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506.

[0539] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507.

[0540] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 506; the variable heavy chain region of SEQ ID NO: 507; the complementarity-determining regions (SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510) of the variable light chain region of SEQ ID NO: 506; and the complementarity-determining regions (SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513) of the variable heavy chain region of SEQ ID NO: 507.

[0541] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab32, comprising SEQ ID NO: 506 and SEQ ID NO: 507, and having at least one of the biological activities set forth herein.

[0542] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0543] MDTRAPTQLLGLLLLWLPGATFAQVLTQTASSVSAAVGGTVTINC QSSQSVYNNYLSWYQQKPGQPPKLLIYTASSLASGVPSRFKGSGSGTQFTLTIS EVQCDDAATYYCQGYYSGPIIT (SEQ ID NO: 522)

[0544] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLNNYYI QWVRQAPGEGLEWIGIIYAGGSAYYATWANGRFTIAKTSSTTVDLKMTSLTT EDTATYFCARGTFDGYEL (SEQ ID NO: 523).

[0545] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522, and/or one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0546] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522, and/or one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523, or combinations of these polypeptide sequences. In another embodiment of the

invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0547] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 522. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 523.

[0548] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522.

[0549] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523.

[0550] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 522; the variable heavy chain region of SEQ ID NO: 523; the complementarity-determining regions (SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526) of the variable light chain region of SEQ ID NO: 522; and the complementarity-determining regions (SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529) of the variable heavy chain region of SEQ ID NO: 523.

[0551] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab33, comprising SEQ ID NO: 522 and SEQ ID NO: 523, and having at least one of the biological activities set forth herein.

[0552] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0553] MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSVPVGDTVTISCQ SSESVYSNNLLSWYQQKPGQPPKLLIYRASNLASGVPSRFKGSGSGTQFTLTIS GAQCDDAATYYCQGYYSGVINS (SEQ ID NO: 538)

[0554] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFM SWVRQAPGEGLEYIGFINPGGSAYYASWASGRLTISKTSTTVDLKITSPTTEDT ATYFCARILIVSYGAFTI (SEQ ID NO: 539).

[0555] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538, and/or one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0556] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538, and/or one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0557] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 538. In another embodiment of the invention, antibody fragments of the

invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 539.

[0558] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538.

[0559] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539.

[0560] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 538; the variable heavy chain region of SEQ ID NO: 539; the complementarity-determining regions (SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542) of the variable light chain region of SEQ ID NO: 538; and the complementarity-determining regions (SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545) of the variable heavy chain region of SEQ ID NO: 539.

[0561] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab34, comprising SEQ ID NO: 538 and SEQ ID NO: 539, and having at least one of the biological activities set forth herein.

[0562] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0563] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKC QATESIGNELSWYQQKPGQAPKLLIYSASTLASGVPSRFKGSGSGTQFTLTITG VECDDAATYYCQQGYSSANIDNA (SEQ ID NO: 554)

[0564] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLSKYYM SWVRQAPEKGLKYIGYIDSTTVNTYYATWARGRFTISKTSTTVDLKITSPTSE DTATYFCARGSTYFTDGGHRLDL (SEQ ID NO: 555).

[0565] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554, and/or one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0566] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554, and/or one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0567] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 554. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 555.

[0568] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554.

[0569] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555.

[0570] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 554; the variable heavy chain region of SEQ ID NO: 555; the complementarity-determining regions (SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558) of the variable light chain region of SEQ ID NO: 554; and the complementarity-determining regions (SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561) of the variable heavy chain region of SEQ ID NO: 555.

[0571] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab35, comprising SEQ ID NO: 554 and SEQ ID NO: 555, and having at least one of the biological activities set forth herein.

[0572] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0573] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKC QATESIGNELSWYQQKPGQAPKLLIYSASTLASGVPSRFKGSGSGTQFTLTITG VECDDAATYYCQQGYSSANIDNA (SEQ ID NO: 570)

[0574] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLSTYNM GWVRQAPGKGLEWIGSITIDGRTYYASWAKGRFTVSKSSTTVDLKMTSLTTG DTATYFCARILIVSYGAFTI (SEQ ID NO: 571).

[0575] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO:

574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570, and/or one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0576] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570, and/or one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0577] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 570. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 571.

[0578] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570.

[0579] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577

which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571.

[0580] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 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: 570; the variable heavy chain region of SEQ ID NO: 571; the complementarity-determining regions (SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574) of the variable light chain region of SEQ ID NO: 570; and the complementarity-determining regions (SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577) of the variable heavy chain region of SEQ ID NO: 571.

[0581] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab36, comprising SEQ ID NO: 570 and SEQ ID NO: 571, and having at least one of the biological activities set forth herein.

[0582] Sequences of anti-IL-6 antibodies of the present invention are shown in Table 1. Exemplary sequence variants other alternative forms of the heavy and light chains of Ab1 through Ab7 are shown. The antibodies of the present invention encompass additional sequence variants, including conservative substitutions, substitution of one or more CDR sequences and/or FR sequences, etc.

[0583] Exemplary Ab1 embodiments 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 one or more 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 one or more 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 one or more 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).

[0584] 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 one or more 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 one or more 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 1 (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 one or more 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).

[0585] In another embodiment, the invention contemplates other antibodies, such as for example chimeric or humanized antibodies, comprising one or more of 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/or one or more of 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, or combinations of these polypeptide sequences. In another embodiment of the invention, the

antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above including those set forth in FIGS. 2 and 34-37, and those identified in Table 1.

[0586] In another embodiment the anti-IL-6 antibody of the invention 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 invention embraces such nucleic acid sequences and variants thereof.

[0587] In another embodiment the invention 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.

[0588] In another embodiment the anti-IL-6 antibody of the invention comprises 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. In addition the invention is directed to the corresponding polypeptides encoded by any of the foregoing nucleic acid sequences and combinations thereof.

[0589] In a specific embodiment of the invention the anti-IL-6 antibodies or a portion thereof will be 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.

[0590] In another specific embodiment of the invention the variable light chain will be encoded by SEQ ID NO: 10, 662, 698, 701, 705, 720, 721, 722, or 723 and

the variable heavy chain of the anti-IL-6 antibodies will be encoded by SEQ ID NO: 11, 663, 700, 703, 707, 724, or 725.

[0591] In a more specific embodiment variable light and heavy chains of the anti-IL-6 antibody respectively will 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.

[0592] In another specific embodiment the invention covers 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

[0593] In another specific embodiment the invention covers 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. These polypeptides optionally may be attached directly or indirectly to other immunoglobulin polypeptides or effector moieties such as therapeutic or detectable entities.

[0594] In another embodiment the anti-IL-6 antibody is one 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.

[0595] In another embodiment the anti-IL-6 antibody is a variant of the foregoing sequences that includes one or more substitution in the framework and/or CDR sequences and which has one or more of the properties of Ab1 *in vitro* and/or upon *in vivo* administration.

[0596] 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 (Kd) 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 hypoalbunemia; 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."

[0597] In another embodiment the anti-IL-6 antibody includes one or more of the Ab1 light-chain and/or heavy chain CDR sequences (see Table 1) or variant(s) thereof which has one or more 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 one or more scaffold which may comprise human or other mammalian framework sequences, or their functional orthologs derived from a SMIP, camelbody, nanobody, IgNAR or other immunoglobulin or other engineered antibody. For example, embodiments 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:

[0598] a polypeptide having at least 72.7% (i.e., 8 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0599] 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;

[0600] 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;

[0601] a polypeptide having 100% (i.e., 11 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0602] a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;

[0603] a polypeptide having 100% (i.e., 7 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;

[0604] a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0605] a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0606] 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;

[0607] 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;

[0608] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0609] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0610] a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0611] a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;

[0612] a polypeptide having 100% (i.e., 5 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;

[0613] a polypeptide having at least 50% (i.e., 8 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0614] a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0615] a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0616] a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0617] a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0618] a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0619] a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0620] a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0621] a polypeptide having 100% (i.e., 16 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0622] a polypeptide having at least 33.3% (i.e., 4 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0623] a polypeptide having at least 41.6% (i.e., 5 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0624] a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0625] a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0626] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0627] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0628] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0629] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0630] a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0631] a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;

[0632] a polypeptide having 100% (i.e., 11 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;

[0633] a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;

[0634] a polypeptide having 100% (i.e., 7 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;

[0635] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0636] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0637] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0638] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0639] a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0640] a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0641] a polypeptide having 100% (i.e., 5 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0642] a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0643] a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0644] a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0645] a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0646] a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0647] a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0648] a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0649] a polypeptide having 100% (i.e., 16 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0650] a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0651] a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0652] a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0653] a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0654] a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0655] a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0656] a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9.

[0657] Other exemplary embodiments include one or more polynucleotides encoding any of the foregoing, e.g., a polynucleotide encoding a polypeptide that

specifically binds to human IL-6 and includes one, two, three, four, five, six, or more of the following CDRs or variants thereof:

[0658] a polynucleotide encoding a polypeptide having at least 72.7% (i.e., 8 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0659] a polynucleotide encoding 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;

[0660] a polynucleotide encoding 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;

[0661] a polynucleotide encoding a polypeptide having 100% (i.e., 11 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

[0662] a polynucleotide encoding a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;

[0663] a polynucleotide encoding a polypeptide having 100% (i.e., 7 out of 7 amino acids) identity to the light chain CDR2 of SEQ ID NO: 5;

[0664] a polynucleotide encoding a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0665] a polynucleotide encoding a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0666] a polynucleotide encoding 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;

[0667] a polynucleotide encoding 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;

[0668] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0669] a polynucleotide encoding a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0670] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the light chain CDR3 of SEQ ID NO: 6;

[0671] a polynucleotide encoding a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;

[0672] a polynucleotide encoding a polypeptide having 100% (i.e., 5 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;

[0673] a polynucleotide encoding a polypeptide having at least 50% (i.e., 8 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0674] a polynucleotide encoding a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0675] a polynucleotide encoding a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0676] a polynucleotide encoding a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0677] a polynucleotide encoding a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0678] a polynucleotide encoding a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0679] a polynucleotide encoding a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0680] a polynucleotide encoding a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0681] a polynucleotide encoding a polypeptide having 100% (i.e., 16 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;

[0682] a polynucleotide encoding a polypeptide having at least 33.3% (i.e., 4 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0683] a polynucleotide encoding a polypeptide having at least 41.6% (i.e., 5 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0684] a polynucleotide encoding a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0685] a polynucleotide encoding a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0686] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0687] a polynucleotide encoding a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0688] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0689] a polynucleotide encoding a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0690] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) identity to the heavy chain CDR3 of SEQ ID NO: 9;

[0691] a polynucleotide encoding a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;

[0692] a polynucleotide encoding a polypeptide having 100% (i.e., 11 out of 11 amino acids) similarity to the light chain CDR1 of SEQ ID NO: 4;

[0693] a polynucleotide encoding a polypeptide having at least 85.7% (i.e., 6 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;

[0694] a polynucleotide encoding a polypeptide having 100% (i.e., 7 out of 7 amino acids) similarity to the light chain CDR2 of SEQ ID NO: 5;

[0695] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0696] a polynucleotide encoding a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0697] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0698] a polynucleotide encoding a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0699] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the light chain CDR3 of SEQ ID NO: 6;

[0700] a polynucleotide encoding a polypeptide having at least 80% (i.e., 4 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0701] a polynucleotide encoding a polypeptide having 100% (i.e., 5 out of 5 amino acids) similarity to the heavy chain CDR1 of SEQ ID NO: 7;

[0702] a polynucleotide encoding a polypeptide having at least 56.2% (i.e., 9 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0703] a polynucleotide encoding a polypeptide having at least 62.5% (i.e., 10 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0704] a polynucleotide encoding a polypeptide having at least 68.7% (i.e., 11 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0705] a polynucleotide encoding a polypeptide having at least 75% (i.e., 12 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0706] a polynucleotide encoding a polypeptide having at least 81.2% (i.e., 13 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0707] a polynucleotide encoding a polypeptide having at least 87.5% (i.e., 14 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0708] a polynucleotide encoding a polypeptide having at least 93.7% (i.e., 15 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0709] a polynucleotide encoding a polypeptide having 100% (i.e., 16 out of 16 amino acids) similarity to the heavy chain CDR2 of SEQ ID NO: 120;

[0710] a polynucleotide encoding a polypeptide having at least 50% (i.e., 6 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0711] a polynucleotide encoding a polypeptide having at least 58.3% (i.e., 7 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0712] a polynucleotide encoding a polypeptide having at least 66.6% (i.e., 8 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0713] a polynucleotide encoding a polypeptide having at least 75% (i.e., 9 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0714] a polynucleotide encoding a polypeptide having at least 83.3% (i.e., 10 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0715] a polynucleotide encoding a polypeptide having at least 91.6% (i.e., 11 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9;

[0716] a polynucleotide encoding a polypeptide having 100% (i.e., 12 out of 12 amino acids) similarity to the heavy chain CDR3 of SEQ ID NO: 9.

[0717] **Table 1.** Sequences of exemplary anti-IL-6 antibodies.

Antibody	Antibody chains		CDR1		CDR2		CDR3	
	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.	PRT.	Nuc.
Ab1 light chains *	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
	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			
Ab1 heavy chains	3	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
	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
	708	707	7	15	120	696	9	697
Human heavy chains used in Ab1 humanization	653		716		717			
	654		716		717			
	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
	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
	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
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
	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
	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
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
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
	691		106	114	107	115	108	116
	692		106	114	121		108	116
Ab8 light chain	122	130	124	132	125	133	126	134
Ab8 heavy chain	123	131	127	135	128	136	129	137
Ab9 light chain	138	146	140	148	141	149	142	150
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
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

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
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
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
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
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
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
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
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
Ab27 light chain	426	434	428	436	429	437	430	438
Ab27 heavy chain	427	435	431	439	432	440	433	441

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
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
Ab31 light chain	490	498	492	500	493	501	494	502
Ab31 heavy chain	491	499	495	503	496	504	497	505
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
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
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

[0718] * Exemplary sequence variant forms of heavy and light chains are shown on separate lines.

[0719] PRT.: Polypeptide sequence.

[0720] Nuc.: Exemplary coding sequence.

[0721] For reference, sequence identifiers other than those included in Table 1 are summarized in Table 2.

[0722] **Table 2.** Summary of sequence identifiers in this application.

SEQ ID	Description
1	Human IL-6
586	kappa constant light chain polypeptide sequence
587	kappa constant light chain polynucleotide sequence
588	gamma-1 constant heavy chain polypeptide sequence
589	gamma-1 constant heavy chain polynucleotide sequence
590 - 646	Human IL-6 peptides (see FIG. 12 and 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
727	IL-6 receptor alpha
728	IL-6 receptor beta / gp130

[0723] Such antibody fragments may be present in one or more 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 below:

[0724] VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC (SEQ ID NO: 586).

[0725] 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 below:

[0726] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 588)

[0727] and

[0728] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 719).

[0729] 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. 36A and 37A as follows:

rabbit Ig leader sequences in SEQ ID NOs: 2 and 660 (MD. . .) and SEQ ID NOs: 3 and 661 (ME. . .); 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, etc. 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.

[0730] In another embodiment, the invention contemplates 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 or any of the VH sequences depicted in Figures 34-37; 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 any of the other VL sequences depicted in Figures 34-37 or a variant thereof wherein one or more of the framework residues (FR 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. 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 contained in SEQ ID NO:588 and SEQ ID NO:586..

[0731] In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0732] In another embodiment of the invention, the anti-IL-6 antibodies and fragments 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* (also known as the cynomolgus monkey) and the Rhesus monkey. In another embodiment of the invention, the anti-IL-6 antibodies and fragments 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 one or more of the foregoing.

[0733] As stated above, antibodies and fragments 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.

[0734] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, *beta*-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, and phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties 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, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^{3}H) and Phosphorus 32 (^{32}P).

[0735] Regarding functional moieties, exemplary cytotoxic agents include, 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, cyclothosphamide, 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 antimytotic 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, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0736] 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, gemcytabine, 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, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, 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.*, Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, *et al.*, Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, *et al.*, Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

[0737] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include 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) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

[0738] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those

methods described by Hunter *et al*, Nature 144:945 (1962); David *et al*, Biochemistry 13:1014 (1974); Pain *et al*, J. Immunol. Meth. 40:219 (1981); and Nygren, J., Histochem. and Cytochem. 30:407 (1982).

[0739] Embodiments described herein further include 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 one or more 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. What is intended by a conservative amino acid substitution is well known in the art.

[0740] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more 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.

[0741] In another embodiment, the invention further contemplates 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*.

[0742] In another embodiment, the invention further contemplates the generation and use of anti-idiotypic antibodies that bind any of the foregoing sequences. In an exemplary embodiment, 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. Such anti-idiotypic antibodies could also be useful for treatment of an autoimmune disease characterized by the presence of anti-IL-6

antibodies. A further exemplary use of such anti-idiotypic antibodies is for detection of the anti-IL-6 antibodies of the present invention, for example to monitor the levels of the anti-IL-6 antibodies present in a subject's blood or other bodily fluids.

[0743] The present invention also contemplates anti-IL-6 antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

Additional Exemplary Embodiments of the Invention

[0744] In another embodiment, the invention contemplates one or more anti-IL-6 antibodies or antibody fragment 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36. In a preferred embodiment, the anti-IL-6 antibody or fragment 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 a fragment thereof as Ab1.

[0745] In another embodiment of the invention, the anti-IL-6 antibody which specifically binds to the same linear or conformational epitopes on an intact IL-6 polypeptide or fragment thereof that is (are) specifically bound by Ab1 binds to a 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. In one embodiment of the invention, the IL-6 epitope comprises, or alternatively consists of, one or more 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.

[0746] The invention is also directed to 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36 and chimeric, humanized, human or fragments containing all or most of the CDRs of the afore-identified antibodies which specifically bind IL-6, preferably aglycosylated antibodies.

[0747] In another embodiment, the invention is also directed to an isolated anti-IL-6 antibody or antibody fragment comprising one or more 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 one or more 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 or the VH and VL sequences depicted in the antibody alignments comprised in Figures 34-37 of this application..

[0748] In one embodiment of the invention, the anti-IL-6 antibody discussed in the two prior paragraphs comprises 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, human or fragments containing all or most of the CDRs of the afore-identified antibodies which specifically bind IL-6, preferably aglycosylated antibodies. 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, or antibodies comprising any combination of the humanized sequence contained in Figures 34-37.

[0749] In a preferred embodiment, the anti-IL-6 antibody discussed above comprises 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 and chimeric, humanized, human or fragments containing all or most of the CDRs of the afore-identified antibodies which specifically bind IL-6, preferably aglycosylated antibodies.

[0750] . 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 and more preferably will be comprised in one of the variable heavy and light antibody sequences depicted in Figures 34-37.

[0751] The invention further contemplates that the one or more anti-IL-6 antibodies discussed above are aglycosylated; 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 encode by the nucleic acid sequences in SEQ ID NO:589 and SEQ ID NO:587.

[0752] The invention further contemplates one or more 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.

[0753] In one embodiment of the invention, the anti-IL-6 antibody or fragment 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.

[0754] In another embodiment, the disease is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, stress-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, fibromyalgia, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosis (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). In a preferred embodiment, the disease is selected from a cancer, inflammatory disorder, viral disorder, or autoimmune disorder. In a particularly preferred embodiment, the disease is arthritis, cachexia, and wasting syndrome.

[0755] The invention further contemplates anti-IL-6 antibodies or fragments directly or indirectly attached to a detectable label or therapeutic agent.

[0756] The invention also contemplates one or more nucleic acid sequences which result in the expression of an anti-IL-6 antibody or antibody fragment as set forth above, including those comprising, or alternatively consisting of, yeast or human

preferred codons. The invention also contemplates vectors (including plasmids or recombinant viral vectors) comprising said nucleic acid sequence(s). The invention also contemplates host cells or recombinant host cells expressing at least one of the antibodies set forth above, including a mammalian, yeast, bacterial, and insect cells. In a preferred embodiment, the host cell is a yeast cell. In a further preferred embodiment, the yeast cell is a diploidal yeast cell. In a more preferred embodiment, the yeast cell is a Pichia yeast.

[0757] The invention also contemplates a method of treatment comprising administering to a patient with a disease or condition associated with IL-6 expressing cells a therapeutically effective amount of at least one anti-IL-6 antibody or fragment. The diseases that may be treated are presented in the non-limiting list set forth above. In a preferred embodiment, the disease is selected from a cancer, autoimmune disease, or inflammatory condition. In a particularly preferred embodiment, the disease is cancer or viral infection. In another embodiment the treatment further includes the administration of another therapeutic agent or regimen selected from chemotherapy, radiotherapy, cytokine administration or gene therapy.

[0758] The invention further contemplates a method of in vivo imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of at least one anti-IL-6 antibody. In one embodiment, said administration further includes the administration of a radionuclide or fluorophore that facilitates detection of the antibody at IL-6 expressing disease sites. In another embodiment of the invention, the method of in vivo imaging is used to detect IL-6 expressing tumors or metastases or is used to detect the presence of sites of autoimmune disorders associated with IL-6 expressing cells. In a further embodiment, the results of said in vivo imaging method are used to facilitate design of an appropriate therapeutic regimen, including therapeutic regimens including radiotherapy, chemotherapy or a combination thereof.

Polynucleotides Encoding Anti-IL-6 Antibody Polypeptides

[0759] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 2:

[0760] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC GGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTC AGAGCATTAACAATGAATTATCCTGGTATCAGCAGAAACCAGGGCAGCGT CCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCTCATCG CGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA CCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCT GAGGAATATTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAAC GTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGT TGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTT (SEQ ID NO: 10)

[0761] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 3:

[0762] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTA ACTACTACGTGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGG ATCGGAATCATTTATGGTAGTGATGAAACGGCCTACGCGACCTGGGCGAT AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGA CCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGAT AGTAGTGACTGGGATGCAAAATTTAACTTGTGGGGCCAAGGCACCCTGGT CACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACC CTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCA AGG (SEQ ID NO: 11).

[0763] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 700:

[0764] GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGG GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTCCCTCAGTAACTA CTACGTGACCTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCG GCATCATCTATGGTAGTGATGAAACCGCCTACGCTACCTCCGCTATAGGCC GATTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTTCAAATG AACAGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGA

TAGTAGTGACTGGGATGCAAAGTTCAACTTGTGGGGCCAAGGGACCCTCG TCACCGTCTCGAGC (SEQ ID NO: 700).

[0765] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 723:

[0766] GCTATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTA GGAGACAGAGTCACCATCACTTGCCAGGCCAGTCAGAGCATTAACAATGA GTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCT ATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGT GGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA TTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAA TGCTTTCGGCGGAGGGACCAAGGTGGAAATCAAACGT (SEQ ID NO: 723).

[0767] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 12; SEQ ID NO: 13; and SEQ ID NO: 14 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 2 or 709 or any of those contained in Figures 34-37.

[0768] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17 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 657 or any of those contained in Figures 34-37.

[0769] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 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 NO:700 encoding the VH polypeptide in SEQ ID NO:657, the polynucleotide 723 encoding the VL polypeptide contained in SEQ ID NO:709 or any of the other VL or VH polypeptides contained in Figures 34-37, polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 12; SEQ ID NO: 13; and SEQ ID NO: 14) of the light chain variable region of SEQ ID NO: 10; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17) of the heavy chain variable region of SEQ ID NO: 11.

[0770] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 21:

[0771] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC
TGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTG
AGACCATTTACAGTTGGTTATCCTGGTATCAGCAGAAGCCAGGGCAGCCT
CCCAAGCTCCTGATCTACCAGGCATCCGATCTGGCATCTGGGGTCCCATCG
CGATTCAGCGGCAGTGGGGCTGGGACAGAGTACACTCTCACCATCAGCGG
CGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTG
GTAGTAATGTTGATAATGTTTTCGGCGGAGGGACCGAGGTGGTGGTCAAA
CGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG
TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAG (SEQ ID NO: 29)

[0772] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 22:

[0773] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCA
CGCCTGGGACACCCCTGACACTTACCTGCACAGCCTCTGGATTCTCCCTCA
ATGACCATGCAATGGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA
ATACATCGGATTCATTAATAGTGGTGGTAGCGCACGCTACGCGAGCTGGG
CAGAAGGCCGATTCACCATCTCCAGAACCTCGACCACGGTGGATCTGAAA
ATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGTCAGAGG

GGGTGCTGTTTGGAGTATTCATAGTTTTGATCCCTGGGGCCCAGGGACCCT GGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGC ACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGG TCAAG (SEQ ID NO: 30).

[0774] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 21.

[0775] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 22.

[0776] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 29 encoding the light chain variable region of SEQ ID NO: 21; the polynucleotide SEQ ID NO: 30 encoding the heavy chain variable region of SEQ ID NO: 22; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33) of the light chain variable region of SEQ ID NO: 29; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36) of the heavy chain variable region of SEQ ID NO: 30.

[0777] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 37:

[0778] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCC CGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTC AGAGTGTTTATGACAACAACTACTTATCCTGGTTTCAGCAGAAACCAGGG CAGCCTCCCAAGCTCCTGATCTATGGTGCATCCACTCTGGCATCTGGGGTC CCATCGCGGTTCGTGGGCAGTGGATCTGGGACACAGTTCACTCTCACCATC ACAGACGTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGGCGTTTAT GATGATGATAGTGATAATGCCTTCGGCGGAGGGACCGAGGTGGTGGTCAA ACGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT (SEQ ID NO: 45)

[0779] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 38:

[0780] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTGGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACCC CTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTG TCTACTACATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGG ATCGGATTCATTACAATGAGTGATAATATAAATTACGCGAGCTGGGCGAA AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGAGTCGT GGCTGGGGTACAATGGGTCGGTTGGATCTCTGGGGCCCAGGCACCCTCGT CACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACC CTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCA AGG (SEQ ID NO: 46).

[0781] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 47; SEQ ID NO: 48; and SEQ ID NO: 49 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 37.

[0782] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 50; SEQ ID

NO: 51; and SEQ ID NO: 52 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 38.

[0783] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 45 encoding the light chain variable region of SEQ ID NO: 37; the polynucleotide SEQ ID NO: 46 encoding the heavy chain variable region of SEQ ID NO: 38; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 47; SEQ ID NO: 48; and SEQ ID NO: 49) of the light chain variable region of SEQ ID NO: 37; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 50; SEQ ID NO: 51; and SEQ ID NO: 52) of the heavy chain variable region of SEQ ID NO: 38.

[0784] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 53:

[0785] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCATATGTGACCCTGTGCTGACCCAGACTCCATCTCC
CGTATCTGCACCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTC
AGAGTGTTTATGAGAACAACTATTTATCCTGGTTTCAGCAGAAACCAGGG
CAGCCTCCCAAGCTCCTGATCTATGGTGCATCCACTCTGGATTCTGGGGTC
CCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCAT
TACAGACGTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGGCGTTTA
TGATGATGATAGTGATGATGCCTTCGGCGGAGGGACCGAGGTGGTGGTCA
AACGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGC
AGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTT (SEQ ID NO: 61)

[0786] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 54:

[0787] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTGGCTGTGCTCAA AGGTGTCCAGTGTCAGGAGCAGCTGAAGGAGTCCGGAGGAGGCCTGGTA ACGCCTGGAGGAACCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTC AATGCCTACTACATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA ATGGATCGGATTCATTACTCTGAATAATAATGTAGCTTACGCGAACTGGG CGAAAGGCCGATTCACCTTCTCCAAAACCTCGACCACGGTGGATCTGAAA ATGACCAGTCCGACACCCGAGGACACGGCCACCTATTTCTGTGCCAGGAG TCGTGGCTGGGGTGCAATGGGTCGGTTGGATCTCTGGGGCCATGGCACCC TGGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGG CACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG GTCAAGG (SEQ ID NO: 62).

[0788] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 63; SEQ ID NO: 64; and SEQ ID NO: 65 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 53.

[0789] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 66; SEQ ID NO: 67; and SEQ ID NO: 68 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 54.

[0790] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 61 encoding the light chain variable region of SEQ ID NO: 53; the polynucleotide SEQ ID NO: 62 encoding the heavy chain variable region of SEQ ID NO: 54; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 63; SEQ ID NO: 64; and SEQ ID NO: 65) of the light chain variable region of SEQ ID NO: 53; and polynucleotides

encoding the complementarity-determining regions (SEQ ID NO: 66; SEQ ID NO: 67; and SEQ ID NO: 68) of the heavy chain variable region of SEQ ID NO: 54.

[0791] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 69:

[0792] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTCCATCGCC TGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAACTGCCAGGCCAGTC AGAGTGTTGATGATAACAACTGGTTAGGCTGGTATCAGCAGAAACGAGGG CAGCCTCCCAAGTACCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTC CCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCAT CAGCGACCTGGAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGGTT TTAGTGGTAATATCTTTGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAA CGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT (SEQ ID NO: 77)

[0793] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 70:

[0794] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGCTTCTCCCTCAGTA GCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGG ATCGGAATCATTGGTGGTTTTGGTACCACATACTACGCGACCTGGGCGAA AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAGAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGTGGT CCTGGTAATGGTGGTGACATCTGGGGCCAAGGGACCCTGGTCACCGTCTC GAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAA GAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT (SEQ ID NO: 78).

[0795] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively

consist of, one or more of the polynucleotide sequences of SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 69.

[0796] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 70.

[0797] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 77 encoding the light chain variable region of SEQ ID NO: 69; the polynucleotide SEQ ID NO: 78 encoding the heavy chain variable region of SEQ ID NO: 70; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81) of the light chain variable region of SEQ ID NO: 69; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84) of the heavy chain variable region of SEQ ID NO: 70.

[0798] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 85:

[0799] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCGC
CCGTGTCTGTACCTGTGGGAGGCACAGTCACCATCAAGTGCCAGTCCAGT
CAGAGTGTTTATAATAATTTCTTATCGTGGTATCAGCAGAAACCAGGGCA
GCCTCCCAAGCTCCTGATCTACCAGGCATCCAAACTGGCATCTGGGGTCCC
AGATAGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCA
GCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGGTTATG

ATGATGATGCTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAA CGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTC (SEQ ID NO: 93)

[0800] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 86:

[0801] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACGCTCACCTGCACAGTCTCTGGAATCGACCTCAGT GACTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATG GATCGGAATCATTTATGCTGGTAGTGGTAGCACATGGTACGCGAGCTGGG CGAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAA ATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGA TGGATACGATGACTATGGTGATTTCGATCGATTGGATCTCTGGGGCCCAG GCACCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCC CCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGC TGCCTGGTCAAGGACT (SEQ ID NO: 94).

[0802] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 85.

[0803] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 86.

[0804] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one,

two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 93 encoding the light chain variable region of SEQ ID NO: 85; the polynucleotide SEQ ID NO: 94 encoding the heavy chain variable region of SEQ ID NO: 86; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97) of the light chain variable region of SEQ ID NO: 85; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100) of the heavy chain variable region of SEQ ID NO: 86.

[0805] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 101:

[0806] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC GGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAATGCCAGGCCAGTC AGAGCATTAACAATGAATTATCCTGGTATCAGCAGAAATCAGGGCAGCGT CCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCTCATCG CGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA CCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCT GAGGAATATTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAAC GTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGT TGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTC (SEQ ID NO: 109)

[0807] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 102:

[0808] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCTCA GGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCC TGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAA CTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGA TCGGAATGATTTATGGTAGTGATGAAACAGCCTACGCGAACTGGGCGATA GGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGAC CAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATA

GTAGTGACTGGGATGCAAAATTTAACTTGTGGGGCCAAGGGACCCTCGTC ACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCC TCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAA GG (SEQ ID NO: 110).

[0809] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 111; SEQ ID NO: 112; and SEQ ID NO: 113 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 101.

[0810] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 114; SEQ ID NO: 115; and SEQ ID NO: 116 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 102.

[0811] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 109 encoding the light chain variable region of SEQ ID NO: 101; the polynucleotide SEQ ID NO: 110 encoding the heavy chain variable region of SEQ ID NO: 102; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 111; SEQ ID NO: 112; and SEQ ID NO: 113) of the light chain variable region of SEQ ID NO: 101; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 114; SEQ ID NO: 115; and SEQ ID NO: 116) of the heavy chain variable region of SEQ ID NO: 102.

[0812] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 122:

[0813] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCAC CCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCCAGT CAGAGTGTTGGTAATAACCAGGACTTATCCTGGTTTCAGCAGAGACCAGG GCAGCCTCCCAAGCTCCTGATCTACGAAATATCCAAACTGGAATCTGGGG TCCCATCGCGGTTCAGCGGCAGTGGATCTGGGACACACTTCACTCTCACCA TCAGCGGCGTACAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGGTT ATGATGATGATGCTGATAATGCT (SEQ ID NO: 130)

[0814] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 123:

[0815] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCACTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTA GTCGTACAATGTCCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG ATCGGATACATTTGGAGTGGTGGTAGCACATACTACGCGACCTGGGCGAA AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATTGGGC GATACTGGTGGTCACGCTTATGCTACTCGCTTAAATCTC (SEQ ID NO: 131).

[0816] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 132; SEQ ID NO: 133; and SEQ ID NO: 134 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 122.

[0817] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 123.

[0818] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the

antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 130 encoding the light chain variable region of SEQ ID NO: 122; the polynucleotide SEQ ID NO: 131 encoding the heavy chain variable region of SEQ ID NO: 123; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 132; SEQ ID NO: 133; and SEQ ID NO: 134) of the light chain variable region of SEQ ID NO: 122; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137) of the heavy chain variable region of SEQ ID NO: 123.

[0819] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide, sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 138:

[0820] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCGTC
CGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTC
AGAGTGTTTATAGTAATAAGTACCTAGCCTGGTATCAGCAGAAACCAGGG
CAGCCTCCCAAGCTCCTGATCTACTGGACATCCAAACTGGCATCTGGGGC
CCCATCACGGTTCAGCGGCAGTGGATCTGGGACACAATTCACTCTCACCA
TCAGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGCTT
ATGATGATGATGCTGATAATGCT (SEQ ID NO: 146)

[0821] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 139:

[0822] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGGTGGAAGAGTCCGGGGGTCGCCTGGTCAAGC
CTGACGAAACCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTGGAG
GGCGGCTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATG
GATCGGAATCAGTTATGATAGTGGTAGCACATACTACGCGAGCTGGGCGA
AAGGCCGATTCACCATCTCCAAGACCTCGTCGACCACGGTGGATCTGAAA
ATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGCGTCAGATC
ACTAAAATATCCTACTGTTACTTCTGATGACTTG (SEQ ID NO: 147).

[0823] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 138.

[0824] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 151; SEQ ID NO: 152; and SEQ ID NO: 153 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 139.

[0825] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 146 encoding the light chain variable region of SEQ ID NO: 138; the polynucleotide SEQ ID NO: 147 encoding the heavy chain variable region of SEQ ID NO: 139; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150) of the light chain variable region of SEQ ID NO: 138; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 151; SEQ ID NO: 152; and SEQ ID NO: 153) of the heavy chain variable region of SEQ ID NO: 139.

[0826] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 154:

[0827] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCAC
CCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCCAGT
CAGAGTGTTTATAATAATAACGACTTAGCCTGGTATCAGCAGAAACCAGG

GCAGCCTCCTAAACTCCTGATCTATTATGCATCCACTCTGGCATCTGGGGT
CCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCA
TCAGCGGCGTGCAGTGTGACGATGCTGCCGCTTACTACTGTCTAGGCGGTT
ATGATGATGATGCTGATAATGCT (SEQ ID NO: 162)

[0828] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 155:

[0829] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC
CTGGGACACCCCTGACACTCACCTGCACAGTATCTGGATTATCCCTCAGTA
GCAATACAATAAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTG
GATCGGATACATTTGGAGTGGTGGTAGTACATACTACGCGAGCTGGGTGA
ATGGTCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATC
ACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGGG
TTACGCTAGTGGTGGTTATCCTTATGCCACTCGGTTGGATCTC (SEQ ID NO: 163).

[0830] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 164; SEQ ID NO: 165; and SEQ ID NO: 166 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 154.

[0831] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 167; SEQ ID NO: 168; and SEQ ID NO: 169 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 155.

[0832] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 162 encoding the light chain variable

region of SEQ ID NO: 154; the polynucleotide SEQ ID NO: 163 encoding the heavy chain variable region of SEQ ID NO: 155; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 164; SEQ ID NO: 165; and SEQ ID NO: 166) of the light chain variable region of SEQ ID NO: 154; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 167; SEQ ID NO: 168; and SEQ ID NO: 169) of the heavy chain variable region of SEQ ID NO: 155.

[0833] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 170:

[0834] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCCTC
CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGTCCAGTC
AGAGTGTTTATAATAACGACTACTTATCCTGGTATCAACAGAGGCCAGGG
CAACGTCCCAAGCTCCTAATCTATGGTGCTTCCAAACTGGCATCTGGGGTC
CCGTCACGGTTCAAAGGCAGTGGATCTGGGAAACAGTTTACTCTCACCAT
CAGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTGGGCGATT
ATGATGATGATGCTGATAATACT (SEQ ID NO: 178)

[0835] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 171:

[0836] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC
CTGGGACACCCCTGACACTCACTTGCACAGTCTCTGGATTCACCCTCAGTA
CCAACTACTACCTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTAGAA
TGGATCGGAATCATTTATCCTAGTGGTAACACATATTGCGCGAAGTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGA
AAATGACCAGTCCGACAACCGAGGACACAGCCACGTATTTCTGTGCCAGA
AATTATGGTGGTGATGAAAGTTTG (SEQ ID NO: 179).

[0837] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 180; SEQ ID

NO: 181; and SEQ ID NO: 182 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 170.

[0838] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 183; SEQ ID NO: 184; and SEQ ID NO: 185 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 171.

[0839] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 178 encoding the light chain variable region of SEQ ID NO: 170; the polynucleotide SEQ ID NO: 179 encoding the heavy chain variable region of SEQ ID NO: 171; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 180; SEQ ID NO: 181; and SEQ ID NO: 182) of the light chain variable region of SEQ ID NO: 170; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 183; SEQ ID NO: 184; and SEQ ID NO: 185) of the heavy chain variable region of SEQ ID NO: 171.

[0840] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 186:

[0841] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTC
CGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTG
AGACCATTGGCAATGCATTAGCCTGGTATCAGCAGAAATCAGGGCAGCCT
CCCAAGCTCCTGATCTACAAGGCATCCAAACTGGCATCTGGGGTCCCATC
GCGGTTCAAAGGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAGCG

ACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGGTGTTATTTTG GTGATAGTGTT (SEQ ID NO: 194)

[0842] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 187:

[0843] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCACTGTGCTCAA AGGTGTCCAGTGTCAGGAGCAGCTGGTGGAGTCCGGGGGAGGCCTGGTCC AGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCA GTAGCGGCTACTACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTG GAGTGGATCGCGTGTATTTTCACTATTACTACTAACACTTACTACGCGAGC TGGGCGAAAGGCCGATTCACCATCTCCAAGACCTCGTCGACCACGGTGAC TCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATCTCTGTG CGAGAGGGATTTATTCTGATAATAATTATTATGCCTTG (SEQ ID NO: 195).

[0844] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 196; SEQ ID NO: 197; and SEQ ID NO: 198 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 186.

[0845] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 199; SEQ ID NO: 200; and SEQ ID NO: 201 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 187.

[0846] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 194 encoding the light chain variable region of SEQ ID NO: 186; the polynucleotide SEQ ID NO: 195 encoding the heavy chain variable region of SEQ ID NO: 187; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 196; SEQ ID NO: 197; and SEQ

ID NO: 198) of the light chain variable region of SEQ ID NO: 186; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 199; SEQ ID NO: 200; and SEQ ID NO: 201) of the heavy chain variable region of SEQ ID NO: 187.

[0847] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 202:

[0848] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTC CGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTG AGAGCATTGGCAATGCATTAGCCTGGTATCAGCAGAAACCAGGGCAGCCT CCCAAGCTCCTGATCTACAAGGCATCCACTCTGGCATCTGGGGTCCCATCG CGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGG CGTGCAGTGTGCCGATGCTGCCGCTTACTACTGTCAATGGTGTTATTTTGG TGATAGTGTT (SEQ ID NO: 210)

[0849] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 203:

[0850] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGCAGCAGCTGGTGGAGTCCGGGGGAGGCCTGGTCA AGCCGGGGGCATCCCTGACACTCACCTGCAAAGCCTCTGGATTCTCCTTCA GTAGCGGCTACTACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTG GAGTCGATCGCATGCATTTTTACTATTACTGATAACACTTACTACGCGAAC TGGGCGAAAGGCCGATTCACCATCTCCAAGCCCTCGTCGCCCACGGTGAC TCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTG CGAGGGGGATTTATTCTACTGATAATTATTATGCCTTG (SEQ ID NO: 211).

[0851] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 212; SEQ ID NO: 213; and SEQ ID NO: 214 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 202.

[0852] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 203.

[0853] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 210 encoding the light chain variable region of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain variable region of SEQ ID NO: 203; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 212; SEQ ID NO: 213; and SEQ ID NO: 214) of the light chain variable region of SEQ ID NO: 202; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217) of the heavy chain variable region of SEQ ID NO: 203.

[0854] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 218:

[0855] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTC
CGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTC
AGAGCGTTAGTAGCTACTTAAACTGGTATCAGCAGAAACCAGGGCAGCCT
CCCAAGCTCCTGATCTACAGGGCATCCACTCTGGAATCTGGGGTCCCATCG
CGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA
CCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGTACTTATGGTAC
TAGTAGTAGTTATGGTGCTGCT (SEQ ID NO: 226)

[0856] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 219:

[0857] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGTATCTCCCTCAGTA GCAATGCAATAAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATG GATCGGAATCATTAGTTATAGTGGTACCACATACTACGCGAGCTGGGCGA AAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAA ATCACTAGTCCGACAACCGAGGACACGGCCACCTACTTCTGTGCCAGAGA TGACCCTACGACAGTTATGGTTATGTTGATACCTTTTGGAGCCGGCATGGA CCTC (SEQ ID NO: 227).

[0858] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 218.

[0859] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 231; SEQ ID NO: 232; and SEQ ID NO: 233 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 219.

[0860] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 226 encoding the light chain variable region of SEQ ID NO: 218; the polynucleotide SEQ ID NO: 227 encoding the heavy chain variable region of SEQ ID NO: 219; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230) of the light chain variable region of SEQ ID NO: 218; and

polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 231; SEQ ID NO: 232; and SEQ ID NO: 233) of the heavy chain variable region of SEQ ID NO: 219.

[0861] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 234:

[0862] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTGCATCGCC CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAACTGCCAGGCCAGTC AGAGTGTTTATAAGAACAACTACTTATCCTGGTATCAGCAGAAACCAGGG CAGCCTCCCAAAGGCCTGATCTATTCTGCATCGACTCTAGATTCTGGGGTC CCATTGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATC AGCGACGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCAGTTAT GATTGTAGTAGTGGTGATTGTTATGCT (SEQ ID NO: 242)

[0863] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 235:

[0864] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGC CTGAGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCTTCAGTA GCTACTGGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG ATCGCATGCATTGTTACTGGTAATGGTAACACTTACTACGCGAACTGGGC GAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGC AAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTTTGTGCGAAA GCCTATGACTTG (SEQ ID NO: 243).

[0865] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 244; SEQ ID NO: 245; and SEQ ID NO: 246 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 234.

[0866] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 247; SEQ ID NO: 248; and SEQ ID NO: 249 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 235.

[0867] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 242 encoding the light chain variable region of SEQ ID NO: 234; the polynucleotide SEQ ID NO: 243 encoding the heavy chain variable region of SEQ ID NO: 235; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 244; SEQ ID NO: 245; and SEQ ID NO: 246) of the light chain variable region of SEQ ID NO: 234; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 247; SEQ ID NO: 248; and SEQ ID NO: 249) of the heavy chain variable region of SEQ ID NO: 235.

[0868] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 250:

[0869] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTTCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCC
CGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTC
AGAGTGTTTATGACAACAACTATTTATCCTGGTATCAGCAGAAACCAGGA
CAGCCTCCCAAGCTCCTGATCTATGGTGCATCCACTCTGGCATCTGGGGTC
CCATCGCGGTTCAAAGGCACGGGATCTGGGACACAGTTCACTCTCACCAT
CACAGACGTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGGCGTTTT
TAATGATGATAGTGATGATGCC (SEQ ID NO: 258)

[0870] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 251:

[0871] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCCCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACACTCTCTGGATTCTCCCTCAGTG CATACTATATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGG ATCGGATTCATTACTCTGAGTGATCATATATCTTACGCGAGGTGGGCGAA AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGAGTCGT GGCTGGGGTGCAATGGGTCGGTTGGATCTC (SEQ ID NO: 259).

[0872] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 260; SEQ ID NO: 261; and SEQ ID NO: 262 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 250.

[0873] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 263; SEQ ID NO: 264; and SEQ ID NO: 265 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 251.

[0874] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 258 encoding the light chain variable region of SEQ ID NO: 250; the polynucleotide SEQ ID NO: 259 encoding the heavy chain variable region of SEQ ID NO: 251; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 260; SEQ ID NO: 261; and SEQ ID NO: 262) of the light chain variable region of SEQ ID NO: 250; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO:

263; SEQ ID NO: 264; and SEQ ID NO: 265) of the heavy chain variable region of SEQ ID NO: 251.

[0875] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 266:

[0876] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTCGCAGCCGTGCTGACCCAGACACCATCGC
CCGTGTCTGCGGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGGCCAGT
CAGAGTGTTTATAACAACAAAAATTTAGCCTGGTATCAGCAGAAATCAGG
GCAGCCTCCCAAGCTCCTGATCTACTGGGCATCCACTCTGGCATCTGGGGT
CTCATCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCGT
CAGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGTTTT
TGATGATGATGCTGATAATGCT (SEQ ID NO: 274)

[0877] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 267:

[0878] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAATGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC
CTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTA
GCTACTCCATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATAT
ATCGGAGTCATTGGTACTAGTGGTAGCACATACTACGCGACCTGGGCGAA
AGGCCGATTCACCATCTCCAGAACCTCGACCACGGTGGCTCTGAAAATCA
CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGTCAGGAGTCTTT
CTTCTATTACTTTCTTG (SEQ ID NO: 275).

[0879] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 276; SEQ ID NO: 277; and SEQ ID NO: 278 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 266.

[0880] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively

consist of, one or more of the polynucleotide sequences of SEQ ID NO: 279; SEQ ID NO: 280; and SEQ ID NO: 281 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 267.

[0881] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 274 encoding the light chain variable region of SEQ ID NO: 266; the polynucleotide SEQ ID NO: 275 encoding the heavy chain variable region of SEQ ID NO: 267; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 276; SEQ ID NO: 277; and SEQ ID NO: 278) of the light chain variable region of SEQ ID NO: 266; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 279; SEQ ID NO: 280; and SEQ ID NO: 281) of the heavy chain variable region of SEQ ID NO: 267.

[0882] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 282:

[0883] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGCATTCGAATTGACCCAGACTCCAGCCTC
CGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTC
AGAACATTTATAGATACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCT
CCCAAGTTCCTGATCTATCTGGCATCTACTCTGGCATCTGGGGTCCCATCG
CGGTTTAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA
CCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAAAGTTATTATAGTAG
TAATAGTGTCGCT (SEQ ID NO: 290)

[0884] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 283:

[0885] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGGAGCAGCTGGTGGAGTCCGGGGGAGACCTGGTCC AGCCTGAGGGATCCCTGACACTCACCTGCACAGCTTCTGAGTTAGACTTCA GTAGCGGCTACTGGATATGCTGGGTCCGCCAGGTTCCAGGGAAGGGGCTG GAGTGGATCGGATGCATTTATACTGGTAGTAGTGGTAGCACTTTTTACGCG AGTTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGT GACTCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCT GTGCGAGAGGTTATAGTGGCTTTGGTTACTTTAAGTTG (SEQ ID NO: 291).

[0886] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 292; SEQ ID NO: 293; and SEQ ID NO: 294 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 282.

[0887] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 295; SEQ ID NO: 296; and SEQ ID NO: 297 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 283.

[0888] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 290 encoding the light chain variable region of SEQ ID NO: 282; the polynucleotide SEQ ID NO: 291 encoding the heavy chain variable region of SEQ ID NO: 283; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 292; SEQ ID NO: 293; and SEQ ID NO: 294) of the light chain variable region of SEQ ID NO: 282; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 295; SEQ ID NO: 296; and SEQ ID NO: 297) of the heavy chain variable region of SEQ ID NO: 283.

[0889] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 298:

[0890] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC TGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTG AGGACATTTATAGGTTATTGGCCTGGTATCAACAGAAACCAGGGCAGCCT CCCAAGCTCCTGATCTATGATTCATCCGATCTGGCATCTGGGGTCCCATCG CGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCGCCATCAGCGG TGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAACAGGCTTGGAGTTA TAGTGATATTGATAATGCT (SEQ ID NO: 306)

[0891] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 299:

[0892] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CGGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTA GCTACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGG ATCGGAATCATTACTACTAGTGGTAATACATTTTACGCGAGCTGGGCGAA AGGCCGGCTCACCATCTCCAGAACCTCGACCACGGTGGATCTGAAAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAACTTCT GATATTTTTTATTATCGTAACTTG (SEQ ID NO: 307).

[0893] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 308; SEQ ID NO: 309; and SEQ ID NO: 310 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 298.

[0894] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 311; SEQ ID NO: 312; and SEQ ID NO: 313 which correspond to polynucleotides encoding the

complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 299.

[0895] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 306 encoding the light chain variable region of SEQ ID NO: 298; the polynucleotide SEQ ID NO: 307 encoding the heavy chain variable region of SEQ ID NO: 299; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 308; SEQ ID NO: 309; and SEQ ID NO: 310) of the light chain variable region of SEQ ID NO: 298; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 311; SEQ ID NO: 312; and SEQ ID NO: 313) of the heavy chain variable region of SEQ ID NO: 299.

[0896] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 314:

[0897] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACGTTTGCAGCCGTGCTGACCCAGACTGCATCACC
CGTGTCTGCCGCTGTGGGAGCCACAGTCACCATCAACTGCCAGTCCAGTC
AGAGTGTTTATAATGACATGGACTTAGCCTGGTTTCAGCAGAAACCAGGG
CAGCCTCCCAAGCTCCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTC
CCATCGCGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCAT
CAGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGCTTT
TGATGATGATGCTGATAATACT (SEQ ID NO: 322)

[0898] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 315:

[0899] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC
CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCACTA

GGCATGCAATAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATG GATCGGATGCATTTGGAGTGGTGGTAGCACATACTACGCGACCTGGGCGA AAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTCAGAATC ACCAGTCCGACAACCGAGGACACGGCCACCTACTTCTGTGCCAGAGTCAT TGGCGATACTGCTGGTTATGCTTATTTTACGGGGCTTGACTTG (SEQ ID NO: 323).

[0900] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 324; SEQ ID NO: 325; and SEQ ID NO: 326 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 314.

[0901] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 327; SEQ ID NO: 328; and SEQ ID NO: 329 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 315.

[0902] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 322 encoding the light chain variable region of SEQ ID NO: 314; the polynucleotide SEQ ID NO: 323 encoding the heavy chain variable region of SEQ ID NO: 315; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 324; SEQ ID NO: 325; and SEQ ID NO: 326) of the light chain variable region of SEQ ID NO: 314; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 327; SEQ ID NO: 328; and SEQ ID NO: 329) of the heavy chain variable region of SEQ ID NO: 315.

[0903] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the

following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 330:

[0904] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC TGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTC AGAGTGTTTATAATTGGTTATCCTGGTATCAGCAGAAACCAGGGCAGCCT CCCAAGCTCCTGATCTATACTGCATCCAGTCTGGCATCTGGGGTCCCATCG CGGTTCAGTGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGG CGTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATACTAG TGATGTTGATAATGTT (SEQ ID NO: 338)

[0905] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 331:

[0906] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGGCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGAATCGACCTCAGT AGCTATGCAATGGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATA CATCGGAATCATTAGTAGTAGTGGTAGCACATACTACGCGACCTGGGCGA AAGGCCGATTCACCATCTCACAAGCCTCGTCGACCACGGTGGATCTGAAA ATTACCAGTCCGACAACCGAGGACTCGGCCACATATTTCTGTGCCAGAGG GGGTGCTGGTAGTGGTGGTGTTTGGCTGCTTGATGGTTTTGATCCC (SEQ ID NO: 339).

[0907] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 340; SEQ ID NO: 341; and SEQ ID NO: 342 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 330.

[0908] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 343; SEQ ID NO: 344; and SEQ ID NO: 345 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 331.

[0909] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 338 encoding the light chain variable region of SEQ ID NO: 330; the polynucleotide SEQ ID NO: 339 encoding the heavy chain variable region of SEQ ID NO: 331; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 340; SEQ ID NO: 341; and SEQ ID NO: 342) of the light chain variable region of SEQ ID NO: 330; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 343; SEQ ID NO: 344; and SEQ ID NO: 345) of the heavy chain variable region of SEQ ID NO: 331.

[0910] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 346:

[0911] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAAATGTGCCGATGTTGTGATGACCCAGACTCCAG
CCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCC
AGTGAGAACATTTATAATTGGTTAGCCTGGTATCAGCAGAAACCAGGGCA
GCCTCCCAAGCTCCTGATCTATACTGTAGGCGATCTGGCATCTGGGGTCTC
ATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCA
GCGACCTGGAGTGTGCCGATGCTGCCACTTACTATTGTCAACAGGGTTATA
GTAGTAGTTATGTTGATAATGTT (SEQ ID NO: 354)

[0912] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 347:

[0913] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCA
CGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCA
ATGACTATGCAGTGGGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAA
TGGATCGGATACATTCGTAGTAGTGGTACCACAGCCTACGCGACCTGGGC

GAAAGGCCGATTCACCATCTCCGCTACCTCGACCACGGTGGATCTGAAAA TCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGG GGTGCTGGTAGTAGTGGTGTGTGGATCCTTGATGGTTTTGCTCCC (SEQ ID NO: 355).

[0914] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 356; SEQ ID NO: 357; and SEQ ID NO: 358 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 346.

[0915] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 359; SEQ ID NO: 360; and SEQ ID NO: 361 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 347.

[0916] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 354 encoding the light chain variable region of SEQ ID NO: 346; the polynucleotide SEQ ID NO: 355 encoding the heavy chain variable region of SEQ ID NO: 347; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 356; SEQ ID NO: 357; and SEQ ID NO: 358) of the light chain variable region of SEQ ID NO: 346; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 359; SEQ ID NO: 360; and SEQ ID NO: 361) of the heavy chain variable region of SEQ ID NO: 347.

[0917] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 362:

[0918] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCTCAAGTGCTGACCCAGACTCCATCCTC CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTC AGAGTGTTTATCAGAACAACTACTTATCCTGGTTTCAGCAGAAACCAGGG CAGCCTCCCAAGCTCCTGATCTATGGTGCGGCCACTCTGGCATCTGGGGTC CCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCAT CAGCGACCTGGAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGCTT ATAGGGATGTGGATTCT (SEQ ID NO: 370)

[0919] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 363:

[0920] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGC CTGGGGCATCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCTTTACTA GTACCTACTACATCTACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGATCGCATGTATTGATGCTGGTAGTAGTGGTAGCACTTACTACGCGACC TGGGTGAATGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGAC TCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTG CGAAATGGGATTATGGTGGTAATGTTGGTTGGGGTTATGACTTG (SEQ ID NO: 371).

[0921] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 372; SEQ ID NO: 373; and SEQ ID NO: 374 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 362.

[0922] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 375; SEQ ID NO: 376; and SEQ ID NO: 377 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 363.

[0923] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein.

In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 370 encoding the light chain variable region of SEQ ID NO: 362; the polynucleotide SEQ ID NO: 371 encoding the heavy chain variable region of SEQ ID NO: 363; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 372; SEQ ID NO: 373; and SEQ ID NO: 374) of the light chain variable region of SEQ ID NO: 362; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 375; SEQ ID NO: 376; and SEQ ID NO: 377) of the heavy chain variable region of SEQ ID NO: 363.

[0924] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 378:

[0925] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGCATTCGAATTGACCCAGACTCCATCCTC
CGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTC
AGAGCATTAGTAGTTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCT
CCCAAGTTCCTGATCTACAGGGCGTCCACTCTGGCATCTGGGGTCCCATCG
CGATTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA
CCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAAAGCTATTATGATAG
TGTTTCAAATCCT (SEQ ID NO: 386)

[0926] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 379:

[0927] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGC
CTGAGGGATCCCTGACACTCACCTGCAAAGCCTCTGGACTCGACCTCGGT
ACCTACTGGTTCATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA
GTGGATCGCTTGTATTTATACTGGTAGTAGTGGTTCCACTTTCTACGCGAG
CTGGGTGAATGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGA

CTCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACTTATTTTTGTG CGAGAGGTTATAGTGGTTATGGTTATTTTAAGTTG (SEQ ID NO: 387).

[0928] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 388; SEQ ID NO: 389; and SEQ ID NO: 390 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 378.

[0929] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 391; SEQ ID NO: 392; and SEQ ID NO: 393 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 379.

[0930] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 386 encoding the light chain variable region of SEQ ID NO: 378; the polynucleotide SEQ ID NO: 387 encoding the heavy chain variable region of SEQ ID NO: 379; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 388; SEQ ID NO: 389; and SEQ ID NO: 390) of the light chain variable region of SEQ ID NO: 378; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 391; SEQ ID NO: 392; and SEQ ID NO: 393) of the heavy chain variable region of SEQ ID NO: 379.

[0931] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 394:

[0932] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGTCACATTTGCCATCGAAATGACCCAGAGTCCATTCTC

CGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTC
AGAGTGTTTATAAGAACAACCAATTATCCTGGTATCAGCAGAAATCAGGG
CAGCCTCCCAAGCTCCTGATCTATGGTGCATCGGCTCTGGCATCTGGGGTC
CCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCAT
CAGCGACGTGCAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGCTA
TTACTGGTAGTATTGATACGGATGGT (SEQ ID NO: 402)

[0933] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 395:

[0934] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGC
CTGGGGCATCCCTGACACTCACCTGCACAACTTCTGGATTCTCCTTCAGTA
GCAGCTACTTCATTTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG
TGGATCGCATGCATTTATGGTGGTGATGGCAGCACATACTACGCGAGCTG
GGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACGC
TGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCG
AGAGAATGGGCATATAGTCAAGGTTATTTTGGTGCTTTTGATCTC (SEQ ID NO: 403).

[0935] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 404; SEQ ID NO: 405; and SEQ ID NO: 406 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 394.

[0936] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 407; SEQ ID NO: 408; and SEQ ID NO: 409 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 395.

[0937] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one,

two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 402 encoding the light chain variable region of SEQ ID NO: 394; the polynucleotide SEQ ID NO: 403 encoding the heavy chain variable region of SEQ ID NO: 395; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 404; SEQ ID NO: 405; and SEQ ID NO: 406) of the light chain variable region of SEQ ID NO: 394; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 407; SEQ ID NO: 408; and SEQ ID NO: 409) of the heavy chain variable region of SEQ ID NO: 395.

[0938] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 410:

[0939] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTC
CGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTG
AGGATATTAGTAGCTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCT
CCCAAGCTCCTGATCTATGCTGCATCCAATCTGGAATCTGGGGTCTCATCG
CGATTCAAAGGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAGCGA
CCTGGAGTGTGCCGATGCTGCCACCTATTACTGTCAATGTACTTATGGTAC
TATTTCTATTAGTGATGGTAATGCT (SEQ ID NO: 418)

[0940] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 411:

[0941] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAATGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC
CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTA
GCTACTTCATGACCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATAC
ATCGGATTCATTAATCCTGGTGGTAGCGCTTACTACGCGAGCTGGGTGAA
AGGCCGATTCACCATCTCCAAGTCCTCGACCACGGTAGATCTGAAAATCA
CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGGTTCTG
ATTGTTTCTTATGGAGCCTTTACCATC (SEQ ID NO: 419).

[0942] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 420; SEQ ID NO: 421; and SEQ ID NO: 422 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 410.

[0943] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 423; SEQ ID NO: 424; and SEQ ID NO: 425 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 411.

[0944] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 418 encoding the light chain variable region of SEQ ID NO: 410; the polynucleotide SEQ ID NO: 419 encoding the heavy chain variable region of SEQ ID NO: 411; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 420; SEQ ID NO: 421; and SEQ ID NO: 422) of the light chain variable region of SEQ ID NO: 410; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 423; SEQ ID NO: 424; and SEQ ID NO: 425) of the heavy chain variable region of SEQ ID NO: 411.

[0945] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 426:

[0946] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTC
CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTG
AGGACATTGAAAGCTATCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCT

CCCAAGCTCCTGATCTATGGTGCATCCAATCTGGAATCTGGGGTCTCATCG
CGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA
CCTGGAGTGTGCCGATGCTGCCACTTACTATTGTCAATGCACTTATGGTAT
TATTAGTATTAGTGATGGTAATGCT (SEQ ID NO: 434)

[0947] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 427:

[0948] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA
AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC
CTGGGACACCCCTGACACTCACCTGCACAGTGTCTGGATTCTCCCTCAGTA
GCTACTTCATGACCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATAC
ATCGGATTCATGAATACTGGTGATAACGCATACTACGCGAGCTGGGCGAA
AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCA
CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGGTTCTT
GTTGTTGCTTATGGAGCCTTTAACATC (SEQ ID NO: 435).

[0949] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 436; SEQ ID NO: 437; and SEQ ID NO: 438 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 426.

[0950] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 439; SEQ ID NO: 440; and SEQ ID NO: 441 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 427.

[0951] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 434 encoding the light chain variable region of SEQ ID NO: 426; the polynucleotide SEQ ID NO: 435 encoding the heavy

chain variable region of SEQ ID NO: 427; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 436; SEQ ID NO: 437; and SEQ ID NO: 438) of the light chain variable region of SEQ ID NO: 426; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 439; SEQ ID NO: 440; and SEQ ID NO: 441) of the heavy chain variable region of SEQ ID NO: 427.

[0952] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 442:

[0953] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCC CGTGTCTGAACCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGGG CAGCCTCCCAAGCTCCTGATCTATGGTGCATCCAATCTGGCATCTGGGGTC CCATCACGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCAT CAGCGACGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCGGTT ATACTGGTTATAGTGATCATGGGACT (SEQ ID NO: 450)

[0954] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 443:

[0955] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCAAGC CTGACGAAACCCTGACACTCACCTGCACAGTCTCTGGAATCGACCTCAGT AGCTATCCAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATG GATCGGATTCATTAATACTGGTGGTACCATAGTCTACGCGAGCTGGGCAA AAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATG ACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGCAG TTATGTTTCATCTGGTTATGCCTACTATTTTAATGTC (SEQ ID NO: 451).

[0956] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 452; SEQ ID NO: 453; and SEQ ID NO: 454 which correspond to polynucleotides encoding the

complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 442.

[0957] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 455; SEQ ID NO: 456; and SEQ ID NO: 457 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 443.

[0958] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 450 encoding the light chain variable region of SEQ ID NO: 442; the polynucleotide SEQ ID NO: 451 encoding the heavy chain variable region of SEQ ID NO: 443; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 452; SEQ ID NO: 453; and SEQ ID NO: 454) of the light chain variable region of SEQ ID NO: 442; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 455; SEQ ID NO: 456; and SEQ ID NO: 457) of the heavy chain variable region of SEQ ID NO: 443.

[0959] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 458:

[0960] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCC
CGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTC
AGAGTGTTTATAATAACAACTGGTTATCCTGGTTTCAGCAGAAACCAGGG
CAGCCTCCCAAGCTCCTGATCTACAAGGCATCCACTCTGGCATCTGGGGTC
CCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCAT
CAGCGACGTGCAGTGTGACGATGTTGCCACTTACTACTGTGCGGGCGGTT
ATCTTGATAGTGTTATT (SEQ ID NO: 466)

[0961] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 459:

[0962] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTA CCTATTCAATAAACTGGGTCCGCCAGGCTCCAGGGAAGGGCCTGGAATGG ATCGGAATCATTGCTAATAGTGGTACCACATTCTACGCGAACTGGGCGAA AGGCCGATTCACCGTCTCCAAAACCTCGACCACGGTGGATCTGAAAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGAGAGT GGAATGTACAATGAATATGGTAAATTTAACATC (SEQ ID NO: 467).

[0963] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 468; SEQ ID NO: 469; and SEQ ID NO: 470 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 458.

[0964] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 471; SEQ ID NO: 472; and SEQ ID NO: 473 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 459.

[0965] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 466 encoding the light chain variable region of SEQ ID NO: 458; the polynucleotide SEQ ID NO: 467 encoding the heavy chain variable region of SEQ ID NO: 459; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 468; SEQ ID NO: 469; and SEQ ID NO: 470) of the light chain variable region of SEQ ID NO: 458; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO:

471; SEQ ID NO: 472; and SEQ ID NO: 473) of the heavy chain variable region of SEQ ID NO: 459.

[0966] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 474:

[0967] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGCCTCTGATATGACCCAGACTCCATCCTC CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTG AGAACATTTATAGCTTTTTGGCCTGGTATCAGCAGAAACCAGGGCAGCCT CCCAAGCTCCTGATCTTCAAGGCTTCCACTCTGGCATCTGGGGTCTCATCG CGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGA CCTGGAGTGTGACGATGCTGCCACTTACTACTGTCAACAGGGTGCTACTGT GTATGATATTGATAATAAT (SEQ ID NO: 482)

[0968] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 475:

[0969] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTTTCTGGAATCGACCTCAGTG CCTATGCAATGATCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGG ATCACAATCATTTATCCTAATGGTATCACATACTACGCGAACTGGGCGAA AGGCCGATTCACCGTCTCCAAAACCTCGACCGCGATGGATCTGAAAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGCA GAAAGTAGTAAGAATGCTTATTGGGGCTACTTTAACGTC (SEQ ID NO: 483).

[0970] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 474.

[0971] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 487; SEQ ID NO: 488; and SEQ ID NO: 489 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 475.

[0972] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 482 encoding the light chain variable region of SEQ ID NO: 474; the polynucleotide SEQ ID NO: 483 encoding the heavy chain variable region of SEQ ID NO: 475; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486) of the light chain variable region of SEQ ID NO: 474; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 487; SEQ ID NO: 488; and SEQ ID NO: 489) of the heavy chain variable region of SEQ ID NO: 475.

[0973] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 490:

[0974] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGCCTCTGATATGACCCAGACTCCATCCTC
CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTG
AGAACATTTATAGCTTTTTGGCCTGGTATCAGCAGAAACCAGGGCAGCCT
CCCAAGCTCCTGATCTTCAGGGCTTCCACTCTGGCATCTGGGGTCTCATCG
CGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGA
CCTGGAGTGTGACGATGCTGCCACTTACTACTGTCAACAGGGTGCTACTGT
GTATGATATTGATAATAAT (SEQ ID NO: 498)

[0975] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 491:

[0976] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTTTCTGGAATCGACCTCAGTG CCTATGCAATGATCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGG ATCACAATCATTTATCCTAATGGTATCACATACTACGCGAACTGGGCGAA AGGCCGATTCACCGTCTCCAAAACCTCGACCGCGATGGATCTGAAAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGCA GAAAGTAGTAAGAATGCTTATTGGGGCTACTTTAACGTC (SEQ ID NO: 499).

[0977] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 500; SEQ ID NO: 501; and SEQ ID NO: 502 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 490.

[0978] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 503; SEQ ID NO: 504; and SEQ ID NO: 505 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 491.

[0979] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 498 encoding the light chain variable region of SEQ ID NO: 490; the polynucleotide SEQ ID NO: 499 encoding the heavy chain variable region of SEQ ID NO: 491; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 500; SEQ ID NO: 501; and SEQ ID NO: 502) of the light chain variable region of SEQ ID NO: 490; and

polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 503; SEQ ID NO: 504; and SEQ ID NO: 505) of the heavy chain variable region of SEQ ID NO: 491.

[0980] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 506:

[0981] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCCATTGAAATGACCCAGACTCCATCCCC CGTGTCTGCCGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTG AGAGTGTTTTTAATAATATGTTATCCTGGTATCAGCAGAAACCAGGGCACT CTCCTAAGCTCCTGATCTATGATGCATCCGATCTGGCATCTGGGGTCCCAT CGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGT GGCGTGGAGTGTGACGATGCTGCCACTTACTATTGTGCAGGGTATAAAAG TGATAGTAATGATGGCGATAATGTT (SEQ ID NO: 514)

[0982] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 507:

[0983] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAACA GGAATTCAATAACCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGG ATCGGAATCATTACTGGTAGTGGTAGAACGTACTACGCGAACTGGGCAAA AGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGCCAT CCTGGTCTTGGTAGTGGTAACATC (SEQ ID NO: 515).

[0984] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 506.

[0985] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID NO: 521 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 507.

[0986] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 514 encoding the light chain variable region of SEQ ID NO: 506; the polynucleotide SEQ ID NO: 515 encoding the heavy chain variable region of SEQ ID NO: 507; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518) of the light chain variable region of SEQ ID NO: 506; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID NO: 521) of the heavy chain variable region of SEQ ID NO: 507.

[0987] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 522:

[0988] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCACATTTGCGCAAGTGCTGACCCAGACTGCATCGTC
CGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGTCCAGTC
AGAGTGTTTATAATAACTACTTATCCTGGTATCAGCAGAAACCAGGGCAG
CCTCCCAAGCTCCTGATCTATACTGCATCCAGCCTGGCATCTGGGGTCCCA
TCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAG
CGAAGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCTATTATA
GTGGTCCTATAATTACT (SEQ ID NO: 530)

[0989] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 523:

[0990] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAATA ACTACTACATACAATGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGG ATCGGGATCATTTATGCTGGTGGTAGCGCATACTACGCGACCTGGGCAAA CGGCCGATTCACCATCGCCAAAACCTCGTCGACCACGGTGGATCTGAAGA TGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGG ACATTTGATGGTTATGAGTTG (SEQ ID NO: 531).

[0991] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 532; SEQ ID NO: 533; and SEQ ID NO: 534 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 522.

[0992] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 535; SEQ ID NO: 536; and SEQ ID NO: 537 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 523.

[0993] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 530 encoding the light chain variable region of SEQ ID NO: 522; the polynucleotide SEQ ID NO: 531 encoding the heavy chain variable region of SEQ ID NO: 523; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 532; SEQ ID NO: 533; and SEQ ID NO: 534) of the light chain variable region of SEQ ID NO: 522; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO:

535; SEQ ID NO: 536; and SEQ ID NO: 537) of the heavy chain variable region of SEQ ID NO: 523.

[0994] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 538:

[0995] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTCCATCCCC TGTGTCTGTCCCTGTGGGAGACACAGTCACCATCAGTTGCCAGTCCAGTGA GAGCGTTTATAGTAATAACCTCTTATCCTGGTATCAGCAGAAACCAGGGC AGCCTCCCAAGCTCCTGATCTACAGGGCATCCAATCTGGCATCTGGTGTCC CATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATC AGCGGCGCACAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCTATTA TAGTGGTGTCATTAATAGT (SEQ ID NO: 546)

[0996] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 539:

[0997] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACAGTGTCTGGATTCTCCCTCAGTA GCTACTTCATGAGCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATAC ATCGGATTCATTAATCCTGGTGGTAGCGCATACTACGCGAGCTGGGCGAG TGGCCGACTCACCATCTCCAAAACCTCGACCACGGTAGATCTGAAAATCA CCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGATTCTT ATTGTTTCTTATGGAGCCTTTACCATC (SEQ ID NO: 547).

[0998] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 548; SEQ ID NO: 549; and SEQ ID NO: 550 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 538.

[0999] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively

consist of, one or more of the polynucleotide sequences of SEQ ID NO: 551; SEQ ID NO: 552; and SEQ ID NO: 553 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 539.

[01000] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 546 encoding the light chain variable region of SEQ ID NO: 538; the polynucleotide SEQ ID NO: 547 encoding the heavy chain variable region of SEQ ID NO: 539; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 548; SEQ ID NO: 549; and SEQ ID NO: 550) of the light chain variable region of SEQ ID NO: 538; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 551; SEQ ID NO: 552; and SEQ ID NO: 553) of the heavy chain variable region of SEQ ID NO: 539.

[01001] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 554:

[01002] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT
CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC
TGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCACTG
AGAGCATTGGCAATGAGTTATCCTGGTATCAGCAGAAACCAGGGCAGGCT
CCCAAGCTCCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCG
CGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCACCGG
CGTGGAGTGTGATGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTA
GTGCTAATATTGATAATGCT (SEQ ID NO: 562)

[01003] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 555:

[01004] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGC CTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGATTCTCCCTCAGTA AGTACTACATGAGCTGGGTCCGCCAGGCTCCAGAGAAGGGGCTGAAATAC ATCGGATACATTGATAGTACTACTGTTAATACATACTACGCGACCTGGGC GAGAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAGA TCACCAGTCCGACAAGTGAGGACACGGCCACCTATTTCTGTGCCAGAGGA AGTACTTATTTTACTGATGGAGGCCATCGGTTGGATCTC (SEQ ID NO: 563).

[01005] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 564; SEQ ID NO: 565; and SEQ ID NO: 566 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 554.

[01006] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 567; SEQ ID NO: 568; and SEQ ID NO: 569 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 555.

[01007] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 562 encoding the light chain variable region of SEQ ID NO: 554; the polynucleotide SEQ ID NO: 563 encoding the heavy chain variable region of SEQ ID NO: 555; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 564; SEQ ID NO: 565; and SEQ ID NO: 566) of the light chain variable region of SEQ ID NO: 554; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 567; SEQ ID NO: 568; and SEQ ID NO: 569) of the heavy chain variable region of SEQ ID NO: 555.

[01008] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 570:

[01009] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCT CTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTC TGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCACTG AGAGCATTGGCAATGAGTTATCCTGGTATCAGCAGAAACCAGGGCAGGCT CCCAAGCTCCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCG CGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCACCGG CGTGGAGTGTGATGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTA GTGCTAATATTGATAATGCT (SEQ ID NO: 578)

[01010] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 571:

[01011] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAA AGGTGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTAACGC CTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTA CCTACAACATGGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGG ATCGGAAGTATTACTATTGATGGTCGCACATACTACGCGAGCTGGGCGAA AGGCCGATTCACCGTCTCCAAAAGCTCGACCACGGTGGATCTGAAAATGA CCAGTCTGACAACCGGGGACACGGCCACCTATTTCTGTGCCAGGATTCTTA TTGTTTCTTATGGGGCCTTTACCATC (SEQ ID NO: 579).

[01012] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 580; SEQ ID NO: 581; and SEQ ID NO: 582 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 570.

[01013] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 583; SEQ ID NO: 584; and SEQ ID NO: 585 which correspond to polynucleotides encoding the

complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 571.

[01014] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 578 encoding the light chain variable region of SEQ ID NO: 570; the polynucleotide SEQ ID NO: 579 encoding the heavy chain variable region of SEQ ID NO: 571; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 580; SEQ ID NO: 581; and SEQ ID NO: 582) of the light chain variable region of SEQ ID NO: 570; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 583; SEQ ID NO: 584; and SEQ ID NO: 585) of the heavy chain variable region of SEQ ID NO: 571.

[01015] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the kappa constant light chain sequence of SEQ ID NO: 586:

[01016] GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTA ACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAG CCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAA GTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAA GAGCTTCAACAGGGGAGAGTGT (SEQ ID NO: 587).

[01017] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the gamma-1 constant heavy chain polypeptide sequence of SEQ ID NO: 588:

[01018] GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA CTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCG GCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATC TGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTG

AGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCT
GAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA
CACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACG
TGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAAT
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTG
TACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT
GACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCT
GGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGA
GCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
(SEQ ID NO: 589).

[01019] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 700:

[01020] GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGG
GGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTCCCTCAGTAACTA
CTACGTGACCTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCG
GCATCATCTATGGTAGTGATGAAACCGCCTACGCTACCTCCGCTATAGGCC
GATTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTTCAAATG
AACAGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGA
TAGTAGTGACTGGGATGCAAAGTTCAACTTGTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 700).

[01021] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 723:

[01022] GCTATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTA
GGAGACAGAGTCACCATCACTTGCCAGGCCAGTCAGAGCATTAACAATGA
GTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCT
ATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGT
GGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA

TTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAA TGCTTTCGGCGGAGGGACCAAGGTGGAAATCAAACGT (SEQ ID NO: 723).

[01023] In one embodiment, the invention is directed to 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, 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 or another shown in Figures 34-37 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.

[01024] In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-IL-6 V_L antibody amino acid sequence of 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 another depicted in Figures 34-37 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.

[01025] In yet another embodiment, the invention is directed to one or more heterologous polynucleotides comprising a sequence encoding the polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:657 and SEQ ID NO:709, 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; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO:101 and SEQ ID NO:118; SEQ ID NO:119 and SEQ ID NO:102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO:122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID

NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 and the other combinations of variable heavy and light chain sequences contained in the antibodies derived from Ab1 depicted in Figures 34-37. In preferred embodiments the anti-IL-6 antibody will comprises the CDRs in an anti-IL-6 antibody comprising the VH and VL in SEQ ID NO:657 and SEQ ID NO:709 respectively.

[01026] In another embodiment, the invention is directed to 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 contained in 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, 708, 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. Exemplary nucleic acid sequence encoding the VH and VL polypeptides SEQ ID NO:657 and SEQ ID NO:709 are comprised in SEQ ID NO:700 and SEQ ID NO:723 respectively, and the variable heavy and light chain sequences contained in Figures 34-37.

[01027] Host cells and vectors comprising said polynucleotides are also contemplated.

[01028] In another specific embodiment the invention covers 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.

[01029] The invention further contemplates 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. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus *Pichia*. In particular the invention includes nucleic acid sequences and vectors containing that encode the variable heavy and light chain polypeptides in SEQ ID NO:657 and 709 and also those other variable heavy and light chain polypeptides contained in Figures 34-37 and especially the nucleic acid sequences contained in SEQ ID encoding SEQ ID NO:657 and 709 contained in SEQ ID NO: 700 and 723 or those encoding the other VH and VL polypeptide sequences contained in Figures 34-37.

[01030] In some instances, more than one exemplary polynucleotide encoding a given polypeptide sequence is provided, as summarized in Table 3.

[01031] **Table 3.** 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
476	484, 500
477	213, 469, 485
478	486, 502
479	487, 503
480	488, 504
481	489, 505
491	483, 499
492	484, 500
493	13, 112, 389, 501
494	486, 502
495	487, 503
496	488, 504
497	489, 505
525	341, 533
545	553, 585
554	562, 578
556	564, 580
557	80, 325, 565, 581
558	566, 582
570	562, 578
572	564, 580
573	80, 325, 565, 581
574	566, 582
577	553, 585

[01032] In some instances, multiple sequence identifiers refer to the same polypeptide or polynucleotide sequence, as summarized in Table 4. References to these sequence identifiers are understood to be interchangeable, except where context indicates otherwise.

[01033] Table 4. Repeated sequences. Each cell lists a group of repeated sequences included in the sequence listing.

SEQ ID NOs of repeated sequences
4, 103
5, 104, 381, 493
6, 105
9, 108
12, 111
13, 112
14, 113
17, 116
39, 252
40, 253
48, 261
60, 257
68, 265
72, 317, 557, 573
80, 325, 565, 581
89, 126, 158
97, 134, 166
120, 659
190, 206
191, 207
198, 214
199, 215
205, 461, 477
213, 469
333, 525
415, 431
423, 439
475, 491
476, 492
478, 494
479, 495
480, 496
481, 497
483, 499
484, 500
486, 502
487, 503
488, 504
489, 505
545, 577
554, 570
556, 572
558, 574

562, 578
564, 580
566, 582

[01034] Certain exemplary embodiments include polynucleotides that hybridize under moderately or highly stringent hybridization conditions to a polynucleotide having one of the exemplary coding sequences recited in Table 1, 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 1, or polypeptide encoded by any of the foregoing polynucleotides.

[01035] 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 (Tm) for the specific sequence at a defined ionic strength pH. The Tm 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 Tm, 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, 5×SSC, and 1% SDS, incubating at 42 °C, or, 5×SSC, 1% SDS, incubating at 65 °C, with wash in 0.2×SSC,

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.

[01036] 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.

[01037] ***Exemplary Embodiments of Heavy and Light Chain Polypeptides and Polynucleotides***

[01038] 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.

[01039] In certain embodiments, the present invention encompasses polynucleotides having at least 70%, such as at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity 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, etc.) that have at least one of the biological activities set forth herein, including without limitation thereto specific binding to an IL-6 polypeptide. In another aspect, the invention encompasses a composition comprising such a polynucleotide and/or a polypeptide encoded by such a polynucleotide. In yet another aspect, the invention encompasses 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. cachexia, cancer fatigue, arthritis, etc.) comprising administration of a composition comprising such a polynucleotide and/or polypeptide.

[01040] In certain preferred embodiments, a heavy chain polypeptide will comprise one or more 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 one or more of the framework region polypeptides recited herein, including those depicted in Figs. 2 and 34-37 or Table 1, and contained in the heavy and light chain polypeptide sequences recited herein. In certain preferred embodiments, a heavy chain polypeptide will comprise one or more Framework 4 region sequences as depicted in Figs. 2 and 34-37 or Table 1, or as contained in a heavy or light chain polypeptide recited herein.

[01041] In certain preferred embodiments, a light chain polypeptide will comprise one or more 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 one or more of the Framework region polypeptides recited herein, including those depicted in Figs. 2 and 34-37 or Table 1, and contained in the heavy and light chain polypeptide sequences recited herein. In certain preferred embodiments, a light chain polypeptide will comprise one or more Framework 4 region sequences as depicted in Figs. 2 and 34-37 or Table 1, or as contained in a heavy or light chain polypeptide recited herein.

[01042] In any of the embodiments recited herein, certain of the 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 one or more 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. 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).

Anti-IL-6 Activity

[01043] 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.

[01044] It is believed that the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, are useful by exhibiting anti-IL-6 activity. In one non-limiting embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments 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 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.

[01045] The anti-IL-6 activity of the anti-IL-6 antibody of the present invention, and fragments 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 of the present invention, 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 $5x10^{-7}$, 10^{-7}, $5x10^{-8}$, 10^{-8}, $5x10^{-9}$, 10^{-9}, $5x10^{-10}$, 10^{-10}, $5x10^{-11}$, 10^{-11}, $5x10^{-12}$, 10^{-12}, $5x10^{-13}$, 10^{-13}, $5x10^{-14}$, 10^{-14}, $5x10^{-15}$ or 10^{-15}. Preferably, the anti-IL-6 antibodies and fragments thereof bind IL-6 with a dissociation constant of less than or equal to $5x10^{-10}$.

[01046] In another embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments 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}, $5x10^{-5}$ S^{-1}, 10^{-5} S^{-1}, $5x10^{-6}$ S^{-1}, 10^{-6} S^{-1}, $5x10^{-7}$ S^{-1}, or 10^{-7} S^{-1}. In one embodiment of the invention, the anti-IL-6 antibodies of the invention, and fragments thereof having binding specificity to IL-6, bind to a linear or conformational IL-6 epitope.

[01047] In a further embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments 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*. As noted cancer-related fatigue, cachexia and rheumatoid arthritis are preferred indications for the subject anti-IL-6 antibodies.

[01048] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, do not have binding specificity for IL-6R or the gp-130 signal-transducing glycoprotein.

B-cell Screening and Isolation

[01049] In one embodiment, the present invention provides 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.

[01050] In one embodiment, the present invention provides a method comprising the steps of:

[01051] a. preparing a cell population comprising at least one antigen-specific B cell;

[01052] b. enriching the cell population, e.g., by chromatography, to form an enriched cell population comprising at least one antigen-specific B cell;

[01053] c. isolating a single B cell from the enriched B cell population; and

[01054] d. determining whether the single B cell produces an antibody specific to the antigen.

[01055] In another embodiment, the present invention provides 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.

[01056] 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.

[01057] 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.

[01058] 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, in one embodiment, the present invention provides a method:

[01059] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[01060] b. creating at least one single cell suspension from the harvested cell population;

[01061] c. enriching at least one single cell suspension to form a first enriched cell population;

[01062] d. enriching the first enriched cell population to form a second enriched cell population;

[01063] e. enriching the second enriched cell population to form a third enriched cell population; and

[01064] f. selecting an antibody produced by an antigen-specific cell of the third enriched cell population.

[01065] 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, one or more 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.

[01066] In one embodiment, the present invention provides 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 greater than or equal to about 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or 100%.

[01067] In another embodiment, the present invention provides 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.

[01068] 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, etc. 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.

[01069] 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.

[01070] 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.

[01071] 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.

[01072] 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.

[01073] The cell populations of the present invention 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.

[01074] In such embodiment, 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, the present invention also provides methods for obtaining an enriched

cell population containing at least one antigen-specific, antibody-secreting cell. In one embodiment, the present invention provides an enriched cell population containing about 50% to about 100%, or increments therein, or greater than or equal to about 60%, 70%, 80%, 90%, or 100% of antigen-specific, antibody-secreting cells.

[01075] In one embodiment, the present invention provides 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. In one embodiment, 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.

[01076] In one embodiment, a method of enriching a cell population is used in a method for antibody production and/or selection. Thus, the present invention provides 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. In a preferred embodiment, the enriched cell population contains more than one antigen-specific cell. In one embodiment, 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.

[01077] In the antibody selection methods of the present invention, 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 one or more 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).

[01078] In addition to the enrichment step, the method for antibody selection can also include one or more 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. In one embodiment, the antibody functionality screen is 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). In one embodiment, the method for antibody selection includes a step of screening the cell population for antibody functionality by measuring the inhibitory concentration (IC50). In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody having an IC50 of less than about 100, 50, 30, 25, 10 μg/mL, or increments therein.

[01079] In addition to the enrichment step, the method for antibody selection can also include one or more 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™). In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody having a high antigen affinity, e.g., a dissociation constant (Kd) of less than about $5x10^{-10}$ M-1, preferably about $1x10^{-13}$ to $5x10^{-10}$, $1x10^{-12}$ to $1x10^{-10}$, $1x10^{-12}$ to $7.5x10^{-11}$, $1x10^{-11}$ to $2x10^{-11}$, about $1.5x10^{-11}$ or less, or increments therein. In this embodiment, the antibodies are said to be affinity mature. In a preferred embodiment, the affinity of the antibodies is comparable to or higher than the affinity of any one of Panorex® (edrecolomab), Rituxan® (rituximab), Herceptin® (traztuzumab), Mylotarg® (gentuzumab), Campath® (alemtuzumab), Zevalin™ (ibritumomab), Erbitux™ (cetuximab), Avastin™ (bevicizumab), Raptiva™ (efalizumab), Remicade® (infliximab), Humira™ (adalimumab), and 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. In one embodiment, at least one

cell population is screened for at least one of, preferably both, antibody functionality and antibody binding strength.

[01080] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antibody sequence homology, especially human homology. In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody that has a homology to a human antibody of about 50% to about 100%, or increments therein, or greater than 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).

[01081] In another embodiment, the present invention also provides the antibodies themselves according to any of the embodiments described above in terms of IC50, Kd, and/or homology.

[01082] The B cell selection protocol disclosed herein has a number of intrinsic advantages versus other methods for obtaining antibody-secreting B cells and monoclonal antibodies specific to desired target antigens. These advantages include, but are not restricted to, the following:

[01083] First, it has been found that when these selection procedures are utilized with a desired antigen such as IL-6 or TNF-α, the methods reproducibly result in antigen-specific B cells capable of generating what appears to be a substantially comprehensive complement of antibodies, i.e., antibodies that bind to the various different epitopes of the antigen. Without being bound by theory, it is hypothesized that the comprehensive complement is attributable to the antigen enrichment step that is performed prior to initial B cell recovery. Moreover, this advantage allows for the isolation and selection of antibodies with different properties as these properties may vary depending on the epitopic specificity of the particular antibody.

[01084] Second, it has been found that the B cell selection protocol reproducibly yields a clonal B cell culture containing a single B cell, or its progeny, secreting a single monoclonal antibody that generally binds to the desired antigen with a relatively high binding affinity, i.e. picomolar or better antigen binding affinities. By contrast, prior antibody selection methods tend to yield relatively few high affinity antibodies and therefore require extensive screening procedures to isolate an antibody with therapeutic potential. Without being bound by theory, it is hypothesized that the protocol results in both in vivo B cell immunization of the host (primary

immunization) followed by a second in vitro B cell stimulation (secondary antigen priming step) that may enhance the ability and propensity of the recovered clonal B cells to secrete a single high affinity monoclonal antibody specific to the antigen target.

[01085] Third, it has been observed (as shown herein with IL-6 specific B cells) that the B cell selection protocol reproducibly yields enriched B cells producing IgG's that are, on average, highly selective (antigen specific) to the desired target. Antigen-enriched B cells recovered by these methods are believed to contain B cells capable of yielding the desired full complement of epitopic specificities as discussed above.

[01086] Fourth, it has been observed that the B cell selection protocols, even when used with small antigens, i.e., peptides of 100 amino acids or less, e.g., 5-50 amino acids long, reproducibly give rise to a clonal B cell culture that secretes a single high affinity antibody to the small antigen, e.g., a peptide. This is highly surprising as it is generally quite difficult, labor intensive, and sometimes not even feasible to produce high affinity antibodies to small peptides. Accordingly, the invention can be used to produce therapeutic antibodies to desired peptide targets, e.g., viral, bacterial or autoantigen peptides, thereby allowing for the production of monoclonal antibodies with very discrete binding properties or even the production of a cocktail of monoclonal antibodies to different peptide targets, e.g., different viral strains. This advantage may especially be useful in the context of the production of a therapeutic or prophylactic vaccine having a desired valency, such as an HPV vaccine that induces protective immunity to different HPV strains.

[01087] Fifth, the B cell selection protocol, particularly when used with B cells derived from rabbits, tends to reproducibly yield antigen-specific antibody sequences that are very similar to endogenous human immunoglobulins (around 90% similar at the amino acid level) and that contain CDRs that possess a length very analogous to human immunoglobulins and therefore require little or no sequence modification (typically at most only a few CDR residues may be modified in the parent antibody sequence and no framework exogenous residues introduced) in order to eliminate potential immunogenicity concerns. In particular, preferably the recombinant antibody will contain only the host (rabbit) CDR1 and CDR2 residues required for antigen recognition and the entire CDR3. Thereby, the high antigen binding affinity of the recovered antibody sequences produced according to the B cell and antibody selection protocol remains intact or substantially intact even with humanization.

[01088] In sum, these methods can be used to produce antibodies exhibiting higher binding affinities to more distinct epitopes by the use of a more efficient protocol than was previously known.

[01089] In a specific embodiment, the present invention provides a method for identifying a single B cell that secretes an antibody specific to a desired antigen and that optionally possesses at least one desired functional property such as affinity, avidity, cytolytic activity, and the like by a process including the following steps:

[01090] a. immunizing a host against an antigen;

[01091] b. harvesting B cells from the host;

[01092] c. enriching the harvested B cells to increase the frequency of antigen-specific cells;

[01093] d. creating at least one single cell suspension;

[01094] e. culturing a sub-population from the single cell suspension under conditions that favor the survival of a single antigen-specific B cell per culture well;

[01095] f. isolating B cells from the sub-population; and

[01096] g. determining whether the single B cell produces an antibody specific to the antigen.

[01097] Typically, these methods will further comprise an additional step of isolating and sequencing, in whole or in part, the polypeptide and nucleic acid sequences encoding the desired antibody. These sequences or modified versions or portions thereof can be expressed in desired host cells in order to produce recombinant antibodies to a desired antigen.

[01098] As noted previously, it is believed that the clonal population of B cells predominantly comprises antibody-secreting B cells producing antibody against the desired antigen. It is also believed based on experimental results obtained with several antigens and with different B cell populations that the clonally produced B cells and the isolated antigen-specific B cells derived therefrom produced according to the invention secrete a monoclonal antibody that is typically of relatively high affinity and moreover is capable of efficiently and reproducibly producing a selection of monoclonal antibodies of greater epitopic variability as compared to other methods of deriving monoclonal antibodies from cultured antigen-specific B cells. In an exemplary embodiment the population of immune cells used in such B cell selection methods will be derived from a rabbit. However, other hosts that produce antibodies, including non-human and human hosts, can alternatively be used as a source of

immune B cells. It is believed that the use of rabbits as a source of B cells may enhance the diversity of monoclonal antibodies that may be derived by the methods. Also, the antibody sequences derived from rabbits according to the invention typically possess sequences having a high degree of sequence identity to human antibody sequences making them favored for use in humans since they should possess little antigenicity. In the course of humanization, the final humanized antibody contains a much lower foreign/host residue content, usually restricted to a subset of the host CDR residues that differ dramatically due to their nature versus the human target sequence used in the grafting. This enhances the probability of complete activity recovery in the humanized antibody protein.

[01099] The methods of antibody selection using an enrichment step disclosed herein include a step of obtaining an immune cell-containing cell population from an immunized host. Methods of obtaining an immune cell-containing cell population from an immunized host are known in the art and generally include inducing an immune response in a host and harvesting cells from the host to obtain one or more cell populations. The response can be elicited by immunizing the host against a desired antigen. Alternatively, the host used as a source of such immune cells can be naturally exposed to the desired antigen such as an individual who has been infected with a particular pathogen such as a bacterium or virus or alternatively has mounted a specific antibody response to a cancer that the individual is afflicted with.

[01100] Host animals are well-known in the art and include, but are not limited to, guinea pig, rabbit, mouse, rat, non-human primate, human, as well as other mammals and rodents, chicken, cow, pig, goat, and sheep. Preferably the host is a mammal, more preferably, rabbit, mouse, rat, or human. When exposed to an antigen, the host produces antibodies as part of the native immune response to the antigen. As mentioned, the immune response can occur naturally, as a result of disease, or it can be induced by immunization with the antigen. Immunization can be performed by any method known in the art, such as, by one or more injections of the antigen with or without an agent to enhance immune response, such as complete or incomplete Freund's adjuvant. In another embodiment, the invention also contemplates intrasplenic immunization. As an alternative to immunizing a host animal in vivo, the method can comprise immunizing a host cell culture in vitro.

[01101] After allowing time for the immune response (e.g., as measured by serum antibody detection), host animal cells are harvested to obtain one or more cell

populations. In a preferred embodiment, a harvested cell population is screened for antibody binding strength and/or antibody functionality. A harvested cell population is preferably from at least one of the spleen, lymph nodes, bone marrow, and/or peripheral blood mononuclear cells (PBMCs). The cells can be harvested from more than one source and pooled. Certain sources may be preferred for certain antigens. For example, the spleen, lymph nodes, and PBMCs are preferred for IL-6; and the lymph nodes are preferred for TNF. The cell population is harvested about 20 to about 90 days or increments therein after immunization, preferably about 50 to about 60 days. A harvested cell population and/or a single cell suspension therefrom can be enriched, screened, and/or cultured for antibody selection. The frequency of antigen-specific cells within a harvested cell population is usually about 1% to about 5%, or increments therein.

[01102] In one embodiment, a single cell suspension from a harvested cell population is enriched, preferably by using Miltenyi beads. From the harvested cell population having a frequency of antigen-specific cells of about 1% to about 5%, an enriched cell population is thus derived having a frequency of antigen-specific cells approaching 100%.

[01103] The method of antibody selection using an enrichment step includes a step of producing antibodies from at least one antigen-specific cell from an enriched cell population. Methods of producing antibodies in vitro are well known in the art, and any suitable method can be employed. In one embodiment, an enriched cell population, such as an antigen-specific single cell suspension from a harvested cell population, is plated at various cell densities, such as 50, 100, 250, 500, or other increments between 1 and 1000 cells per well. Preferably, the sub-population comprises no more than about 10,000 antigen-specific, antibody-secreting cells, more preferably about 50-10,000, about 50-5,000, about 50-1,000, about 50-500, about 50-250 antigen-specific, antibody-secreting cells, or increments therein. Then, these sub-populations are cultured with suitable medium (e.g., an activated T cell conditioned medium, particularly 1-5% activated rabbit T cell conditioned medium) on a feeder layer, preferably under conditions that favor the survival of a single proliferating antibody-secreting cell per culture well. The feeder layer, generally comprised of irradiated cell matter, e.g., EL4B cells, does not constitute part of the cell population. The cells are cultured in a suitable media for a time sufficient for antibody production, for example about 1 day to about 2 weeks, about 1 day to about 10 days, at least about

3 days, about 3 to about 5 days, about 5 days to about 7 days, at least about 7 days, or other increments therein. In one embodiment, more than one sub-population is cultured simultaneously. Preferably, a single antibody-producing cell and progeny thereof survives in each well, thereby providing a clonal population of antigen-specific B cells in each well. At this stage, the immunoglobulin G (IgG) produced by the clonal population is highly correlative with antigen specificity. In a preferred embodiment, the IgGs exhibit a correlation with antigen specificity that is greater than about 50%, more preferably greater than 70%, 85%, 90%, 95%, 99%, or increments therein. See Fig. 3, which demonstrates an exemplary correlation for IL-6. The correlations were demonstrated by setting up B cell cultures under limiting conditions to establish single antigen-specific antibody products per well. Antigen-specific versus general IgG synthesis was compared. Three populations were observed: IgG that recognized a single format of antigen (biotinylated and direct coating), detectable IgG and antigen recognition irrespective of immobilization, and IgG production alone. IgG production was highly correlated with antigen-specificity.

[01104] A supernatant containing the antibodies is optionally collected, which can be enriched, screened, and/or cultured for antibody selection according to the steps described above. In one embodiment, the supernatant is enriched (preferably by an antigen-specificity assay, especially an ELISA assay) and/or screened for antibody functionality.

[01105] In another embodiment, the enriched, preferably clonal, antigen-specific B cell population from which a supernatant described above is optionally screened in order to detect the presence of the desired secreted monoclonal antibody is used for the isolation of a few B cells, preferably a single B cell, which is then tested in an appropriate assay in order to confirm the presence of a single antibody-producing B cell in the clonal B cell population. In one embodiment about 1 to about 20 cells are isolated from the clonal B cell population, preferably less than about 15, 12, 10, 5, or 3 cells, or increments therein, most preferably a single cell. The screen is preferably effected by an antigen-specificity assay, especially a halo assay. The halo assay can be performed with the full length protein, or a fragment thereof. The antibody-containing supernatant can also be screened for at least one of: antigen binding affinity; agonism or antagonism of antigen-ligand binding, induction or inhibition of the proliferation of a specific target cell type; induction or inhibition of lysis of a target cell, and induction or inhibition of a biological pathway involving the antigen.

[01106] The identified antigen-specific cell can be used to derive the corresponding nucleic acid sequences encoding the desired monoclonal antibody. (An AluI digest can confirm that only a single monoclonal antibody type is produced per well.) As mentioned above, these sequences can be mutated, such as by humanization, in order to render them suitable for use in human medicaments.

[01107] As mentioned, the enriched B cell population used in the process can also be further enriched, screened, and/or cultured for antibody selection according to the steps described above which can be repeated or performed in a different order. In a preferred embodiment, at least one cell of an enriched, preferably clonal, antigen-specific cell population is isolated, cultured, and used for antibody selection.

[01108] Thus, in one embodiment, the present invention provides a method comprising:

[01109] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[01110] b. creating at least one single cell suspension from a harvested cell population;

[01111] c. enriching at least one single cell suspension, preferably by chromatography, to form a first enriched cell population;

[01112] d. enriching the first enriched cell population, preferably by ELISA assay, to form a second enriched cell population which preferably is clonal, i.e., it contains only a single type of antigen-specific B cell;

[01113] e. enriching the second enriched cell population, preferably by halo assay, to form a third enriched cell population containing a single or a few number of B cells that produce an antibody specific to a desired antigen; and

[01114] f. selecting an antibody produced by an antigen-specific cell isolated from the third enriched cell population.

[01115] The method can further include one or more steps of screening the harvested cell population for antibody binding strength (affinity, avidity) and/or antibody functionality. Suitable screening steps include, but are not limited to, assay methods that detect: whether the antibody produced by the identified antigen-specific B cell produces an antibody possessing a minimal antigen binding affinity, whether the antibody agonizes or antagonizes the binding of a desired antigen to a ligand; whether the antibody induces or inhibits the proliferation of a specific cell type; whether the antibody induces or elicits a cytolytic reaction against target cells;

whether the antibody binds to a specific epitope; and whether the antibody modulates (inhibits or agonizes) a specific biological pathway or pathways involving the antigen.

[01116] Similarly, the method can include one or more steps of screening the second enriched cell population for antibody binding strength and/or antibody functionality.

[01117] The method can further include a step of sequencing the polypeptide sequence or the corresponding nucleic acid sequence of the selected antibody. The method can also include a step of producing a recombinant antibody using the sequence, a fragment thereof, or a genetically modified version of the selected antibody. Methods for mutating antibody sequences in order to retain desired properties are well known to those skilled in the art and include humanization, chimerisation, production of single chain antibodies; these mutation methods can yield recombinant antibodies possessing desired effector function, immunogenicity, stability, removal or addition of glycosylation, and the like. The recombinant antibody can be produced by any suitable recombinant cell, including, but not limited to mammalian cells such as CHO, COS, BHK, HEK-293, bacterial cells, yeast cells, plant cells, insect cells, and amphibian cells. In one embodiment, the antibodies are expressed in polyploidal yeast cells, i.e., diploid yeast cells, particularly Pichia.

[01118] In one embodiment, the method comprises:

[01119] a. immunizing a host against an antigen to yield host antibodies;

[01120] b. screening the host antibodies for antigen specificity and neutralization;

[01121] c. harvesting B cells from the host;

[01122] d. enriching the harvested B cells to create an enriched cell population having an increased frequency of antigen-specific cells;

[01123] e. culturing one or more sub-populations from the enriched cell population under conditions that favor the survival of a single B cell to produce a clonal population in at least one culture well;

[01124] f. determining whether the clonal population produces an antibody specific to the antigen;

[01125] g. isolating a single B cell; and

[01126] h. sequencing the nucleic acid sequence of the antibody produced by the single B cell.

Methods of Humanizing Antibodies

[01127] In another embodiment of the invention, there is provided a method for humanizing antibody heavy and light chains. In this embodiment, the following method is followed for the humanization of the heavy and light chains:

[01128] Light Chain

[01129] 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.

[01130] Example: RbtVL Amino acid residue 1 in Fig. 2, starting 'AYDM...'

[01131] 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.

[01132] Example: RbtVL amino acid residue 88 in Fig. 2, ending as 'TYYC'

[01133] 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).

[01134] Example: RbtVL amino acid sequence from residues numbered 1 through 88 in Fig. 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Fig. 2 as L12A, V1 and Vx02.

[01135] 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.

[01136] Example: In Fig. 2, L12A was the most homologous human germline variable light chain sequence and is used as the basis for the humanization of RbtVL.

[01137] 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.

[01138] Example: In Fig. 2, the RbtVL sequence is aligned with the human homologous sequence L12A, and the framework and CDR domains are indicated.

[01139] 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.

[01140] Example: In Fig. 2, 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.

[01141] 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...', however some variation may exist in these residues.

[01142] Example: In Fig. 2, 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.

[01143] 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' 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'. 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.

[01144] Example: In Fig. 2, 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.

[01145] Heavy Chain

[01146] 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.

[01147] Example: RbtVH Amino acid residue 1 in Fig. 2, starting 'QEQL...'

[01148] 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.

[01149] Example: RbtVH amino acid residue 98 in Fig. 2, ending as '...FCVR'.

[01150] 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).

[01151] Example: RbtVH amino acid sequence from residues numbered 1 through 98 in Fig. 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Fig. 2 as 3-64-04, 3-66-04, and 3-53-02.

[01152] 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.

[01153] Example: 3-64-04 in Fig. 2 was the most homologous human germline variable heavy chain sequence and is used as the basis for the humanization of RbtVH.

[01154] 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.

[01155] Example: In Fig. 2, the RbtVH sequence is aligned with the human homologous sequence 3-64-04, and the framework and CDR domains are indicated.

[01156] 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.

[01157] Example: In Fig. 2, 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.

[01158] 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

WGXG...(where X is usually Q or P), however some variation may exist in these residues.

[01159] 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.

[01160] 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' 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 'WGQGTLVTVSS'. 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.

[01161] Example: In Fig. 2, 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.

Methods of Producing Antibodies and Fragments thereof

[01162] The invention is also directed to the production of the antibodies described herein or fragments thereof. Recombinant polypeptides corresponding to the antibodies described herein or fragments thereof are secreted from polyploidal, preferably diploid or tetraploid strains of mating competent yeast. In an exemplary embodiment, the invention is directed to 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).

[01163] In one embodiment of the invention 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. In another embodiment diploid yeast cells will be transformed with one or more expression vectors that provide for the expression and secretion of one or more of the recombinant polypeptides. In still another embodiment a single haploid cell may be transformed with one or more vectors and used to produce a polyploidal yeast by fusion or mating strategies. In yet another embodiment a diploid yeast culture may be transformed with one or more 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; *etc.* 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.

[01164] 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.

[01165] 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.

[01166] 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) P.N.A.S. 98:12866-12868.

[01167] In one embodiment of the invention, 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).

[01168] In a preferred embodiment 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, etc.*), nucleosides (*e.g. ura3, ade1, etc.*); 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.

[01169] 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.

[01170] As noted above, in some embodiments 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 one or more vectors that provide for the expression and secretion of a desired heterologous polypeptide by the diploid yeast cell.

[01171] In one embodiment of the invention, 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.

[01172] In another embodiment of the invention, 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 LC, J Immunol Methods. 2002 May 1;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, *etc.* 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; *etc.* 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.

[01173] 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.

[01174] 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, etc., using methods known in the art.

[01175] 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, *etc.* 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.

[01176] In one embodiment of the invention, 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.

[01177] The methods of the invention provide for expression of secreted, active protein, preferably a mammalian protein. In one embodiment, 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.

[01178] The methods of the invention 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.

[01179] 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.

[01180] 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*, for example, U.S. Patent No. 4,816,567 to Cabilly *et al.*; Morrison *et al.*, P.N.A.S. USA, 81:8651-55 (1984); Neuberger, M.S. *et al.*, Nature, 314:268-270 (1985); Boulianne, G.L. *et al.*, Nature, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

[1000] Likewise, other methods of producing humanized antibodies are now well known in the art (*See*, for example, U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen *et al*; U.S. Patent Nos. 5,225,539 and 6,548,640 to Winter; U.S. Patent Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter *et al*; U.S. Patent No. 6,632,927 to Adair; Jones, P.T. *et al*, Nature, 321:522-525 (1986); Reichmann, L., *et al*, Nature, 332:323-327 (1988); Verhoeyen, M, *et al*, Science, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[1001] Antibody polypeptides of the invention 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.

[1002] 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.

[1003] 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.

[1004] 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.

[1005] 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.

[1006] 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.

[1007] 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.

[1008] 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*, for example, Saragobi *et al*, Science, 253:792-795 (1991), the contents of which are herein incorporated by reference in its entirety.

Screening Assays

[1009] The invention also includes 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.

[1010] In one embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments 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.

[1011] Another embodiment of the invention provides 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 thereof. The anti-IL-6 antibody or binding fragment thereof may be post-translationally modified to include a detectable moiety such as set forth previously in the disclosure.

[1012] The IL-6 level in the biological sample is determined using a modified anti-IL-6 antibody or binding fragment 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.

[1013] 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.

[1014] The invention is also directed to a method of *in vivo* imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of a diagnostic composition. Said in vivo imaging is useful for the detection and imaging of IL-6 expressing tumors or metastases and IL-6 expressing inflammatory sites, for example, and can be used as part of a planning regimen for design of an effective cancer or arthritis treatment protocol. The treatment protocol may include, for example, one or more of radiation, chemotherapy, cytokine therapy, gene therapy, and antibody therapy, as well as an anti-IL-6 antibody or fragment thereof.

[1015] 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.

Methods of Ameliorating or Reducing Symptoms of, or Treating, or Preventing, Diseases and Disorders Associated with, IL-6

[1016] In an embodiment of the invention, IL-6 antagonists described herein are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with IL-6. IL-6 antagonists described herein can also be administered in a therapeutically effective amount to patients in need of treatment of diseases and disorders associated with IL-6 in the form of a pharmaceutical composition as described in greater detail below.

[1017] In one embodiment of the invention, IL-6 antagonists described herein are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with elevated C-reactive protein (CRP). Such diseases include any disease that exhibits chronic inflammation, e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, systemic lupus erythematosis, Crohn's disease, ulcerative colitis, pemphigus, dermatomyositis, polymyositis, polymyalgia rheumatica, giant cell arteritis, vasculitis, polyarteritis nodosa, Wegener's granulomatosis, Kawasaki disease, isolated CNS vasculitis, Churg-Strauss arteritis, microscopic polyarteritis, microscopic polyangiitis, Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis, rheumatoid vasculitis, cryoglobulinemia, relapsing polychondritis, Behcet's disease, Takayasu's arteritis, ischemic heart disease, stroke, multiple sclerosis, sepsis, vasculitis secondary to viral infection (e.g., hepatitis B, hepatitis C, HIV, cytomegalovirus, Epstein-Barr virus, Parvo B19 virus, etc.), Buerger's Disease, cancer, advanced cancer, Osteoarthritis, systemic sclerosis, CREST syndrome, Reiter's disease, Paget's disease of bone, Sjogran's syndrome, diabetes type 1, diabetes type 2, familial Mediterranean fever, autoimmune thrombocytopenia, autoimmune hemolytic anemia, autoimmune thyroid diseases, pernicious anemia, vitiligo, alopecia areata, primary biliary cirrhosis, autoimmune chronic active hepatitis, alcoholic cirrhosis, viral hepatitis including hepatitis B and C, other organ specific autoimmune diseases, burns, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, allergic asthma, other allergic conditions or any combination thereof.

[1018] In one embodiment of the invention, IL-6 antagonists described herein are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with reduced serum albumin, e.g. rheumatoid arthritis, cancer, advanced cancer, liver disease, renal disease, inflammatory bowel

disease, celiac's disease, trauma, burns, other diseases associated with reduced serum albumin, or any combination thereof.

[1019] In another embodiment of the invention, IL-6 antagonists described herein are administered to a patient in combination with another active agent. For example, IL-6 antagonist may be co-administered with one or more chemotherapy agents, such as VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, 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, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

[1020] In one embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with fatigue. Diseases and disorders associated with fatigue include, but are not limited to, general fatigue, exercise-induced fatigue, cancer-related fatigue, fibromyalgia, inflammatory disease-related fatigue and chronic fatigue syndrome. *See*, for example, Esper DH, *et al*, The cancer cachexia syndrome: a review of metabolic and clinical manifestations, Nutr Clin Pract., 2005 Aug;20 (4):369-76; Vgontzas AN, *et al*, IL-6 and its circadian secretion in humans, Neuroimmunomodulation, 2005;12(3):131-40; Robson-Ansley, PJ, *et al*, Acute interleukin-6 administration impairs athletic performance in healthy, trained male runners, Can J Appl Physiol., 2004 Aug;29(4):411-8; Shephard RJ., Cytokine responses to physical activity, with particular reference to IL-6: sources, actions, and clinical implications, Crit Rev Immunol., 2002;22(3):165-82; Arnold, MC, *et al*, Using an interleukin-6 challenge to evaluate neuropsychological performance in chronic fatigue syndrome, Psychol Med., 2002 Aug;32(6):1075-89; Kurzrock R., The role of cytokines in cancer-related fatigue, Cancer, 2001 Sep 15;92(6 Suppl):1684-8; Nishimoto N, *et al*, Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy, Blood, 2000 Jan 1; 95 (1):56-61; Vgontzas AN, *et al*, Circadian interleukin-6 secretion and quantity and depth of sleep, J Clin Endocrinol Metab., 1999 Aug;84(8):2603-7; and Spath-Schwalbe E, *et*

al, Acute effects of recombinant human interleukin 6 on endocrine and central nervous sleep functions in healthy men, J Clin Endocrinol Metab., 1998 May;83(5):1573-9; the disclosures of each of which are herein incorporated by reference in their entireties.

[1021] In a preferred embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, cachexia. Diseases and disorders associated with cachexia include, but are not limited to, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia and age-related cachexia. *See*, for example, Barton, BE., Interleukin-6 and new strategies for the treatment of cancer, hyperproliferative diseases and paraneoplastic syndromes, Expert Opin Ther Targets, 2005 Aug;9(4):737-52; Zaki MH, *et al*, CNTO 328, a monoclonal antibody to IL-6, inhibits human tumor-induced cachexia in nude mice, Int J Cancer, 2004 Sep 10;111(4):592-5; Trikha M, *et al*, Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence, Clin Cancer Res., 2003 Oct 15;9(13):4653-65; Lelli G, *et al*, Treatment of the cancer anorexia-cachexia syndrome: a critical reappraisal, J Chemother., 2003 Jun;15(3):220-5; Argiles JM, *et al*, Cytokines in the pathogenesis of cancer cachexia, Curr Opin Clin Nutr Metab Care, 2003 Jul;6(4):401-6; Barton BE., IL-6-like cytokines and cancer cachexia: consequences of chronic inflammation, Immunol Res., 2001;23(1):41-58; Yamashita JI, *et al*, Medroxyprogesterone acetate and cancer cachexia: interleukin-6 involvement, Breast Cancer, 2000;7(2):130-5; Yeh SS, *et al*, Geriatric cachexia: the role of cytokines, Am J Clin Nutr., 1999 Aug;70(2):183-97; Strassmann G, *et al*, Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine-receptor therapy, Cytokines Mol Ther., 1995 Jun;1(2):107-13; Fujita J, *et al*, Anti-interleukin-6 receptor antibody prevents muscle atrophy in colon-26 adenocarcinoma-bearing mice with modulation of lysosomal and ATP-ubiquitin-dependent proteolytic pathways, Int J Cancer, 1996 Nov 27;68(5):637-43; Tsujinaka T, *et al*, Interleukin 6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice, J Clin Invest., 1996 Jan l;97(l):244-9; Emilie D, *et al*, Administration of an anti-interleukin-6 monoclonal antibody to patients with acquired immunodeficiency syndrome and lymphoma: effect on lymphoma growth and on B clinical Symptoms, Blood, 1994 Oct 15;84 (8):2472-9; and Strassmann G, *et al*, Evidence for the involvement of interleukin 6 in experimental cancer cachexia, J Clin

Invest., 1992 May;89(5):1681-4; the disclosures of each of which are herein incorporated by reference in their entireties.

[1022] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, autoimmune diseases and disorders. Diseases and disorders associated with autoimmunity include, but are not limited to, rheumatoid arthritis, systemic lupus erythematosis (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. In a preferred embodiment of the invention, humanized anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, rheumatoid arthritis and systemic juvenile idiopathic arthritis. *See*, for example, Nishimoto N., Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan, Clin Rev Allergy Immunol., 2005 Jun;28(3):221-30; Nishimoto N, *et al*, Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial, Arthritis Rheum., 2004 Jun;50(6):1761-9; Choy E., Interleukin 6 receptor as a target for the treatment of rheumatoid arthritis, Ann Rheum Dis., 2003 Nov;62 Suppl 2:ii68-9; Nishimoto N, *et al*, Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study, J Rheumatol., 2003 Jul;30(7):1426-35; Mihara M, *et al*, Humanized antibody to human interleukin-6 receptor inhibits the development of collagen arthritis in cynomolgus monkeys, Clin Immunol., 2001 Mar;98(3):319-26; Nishimoto N, *et al*, Anti-interleukin 6 receptor antibody treatment in rheumatic disease, Ann Rheum Dis., 2000 Nov;59 Suppl 1:i21-7; Tackey E, *et al*, Rationale for interleukin-6 blockade in systemic lupus erythematosus, Lupus, 2004;13(5):339-43; Finck BK, *et al*, Interleukin 6 promotes murine lupus in NZB/NZW Fl mice, J Clin Invest., 1994 Aug;94 (2):585-91; Kitani A, *et al*, Autostimulatory effects of IL-6 on excessive B cell differentiation in patients with systemic lupus erythematosus: analysis of IL-6 production and IL-6R expression, Clin Exp Immunol., 1992 Apr;88(1):75-83; Stuart RA, *et al*, Elevated serum interleukin-6 levels associated with active disease in systemic connective tissue disorders, Clin Exp Rheumatol., 1995 Jan-Feb;l3 (1):17-22; Mihara M, *et al*, IL-6

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2002 Nov;37 Suppl 14:56-61; Ito H., Anti-interleukin-6 therapy for Crohn's disease, Curr Pharm Des., 2003;9(4):295-305; Salvarani C, *et al*, Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: a prospective follow-up study, Arthritis Rheum., 2005 Feb 15;53(1):33-8; Roche NE, *et al*, Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis, Arthritis Rheum., 1993 Sep;36(9):1286-94; Gupta M, *et al*, Cytokine modulation with immune gamma-globulin in peripheral blood of normal children and its implications in Kawasaki disease treatment, J Clin Immunol., 2001 May;21(3):193-9; Noris M, *et al*, Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions?, Circulation, 1999 Jul 6;100(1):55-60; Besbas N, *et al*, The role of cytokines in Henoch Schonlein purpura, Scand J Rheumatol., 1997;26(6):456-60; Hirohata S, *et al*, Cerebrospinal fluid interleukin-6 in progressive Neuro-Behcet's syndrome, Clin Immunol Immunopathol., 1997 Jan;82(1):12-7; Yamakawa Y, *et al*, Interleukin-6 (IL-6) in patients with Behcet's disease, J Dermatol Sci., 1996 Mar;11(3):189-95; Kim DS., Serum interleukin-6 in Kawasaki disease, Yonsei Med J., 1992 Jun;33(2):183-8; Lange, A., *et al*, Cytokines, adhesion molecules (E-selectin and VCAM-l) and graft-versus-host disease, Arch. Immunol Ther Exp., 1995, 43(2):99-105; Tanaka, J., *et al*, Cytokine gene expression after allogeneic bone marrow transplantation, Leuk. Lymphoma, 1995 16(5-6):413-418; Dickenson, AM, *et al*, Predicting outcome in hematological stem cell transplantation, Arch Immunol Ther Exp., 2002 50(6):371-8; Zeiser, R, *et al*, Immunopathogenesis of acute graft-versus-host disease: implications for novel preventive and therapeutic strategies, Ann Hematol., 2004 83(9):551-65; Dickinson, AM, *et al*, Genetic polymorphisms predicting the outcome of bone marrow transplants, Br. J Haematol., 2004 127(5):479-90; and Scheinberg MA, *et al*, Interleukin 6: a possible marker of disease activity in adult onset Still's disease, Clin Exp Rheumatol., 1996 Nov-Dec;14 (6):653-5, the disclosures of each of which are herein incorporated by reference in their entireties.

[1023] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with the skeletal system. Diseases and disorders associated with the skeletal system include, but are not limited to, osteoarthritis, osteoporosis and Paget's disease of bone. In a preferred embodiment of the invention, humanized anti-IL-6 antibodies described herein, or

fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, osteoarthritis. *See*, for example, Malemud CJ., Cytokines as therapeutic targets for osteoarthritis, BioDrugs, 2004;18(1):23-35; Westacott CI, *et al*, Cytokines in osteoarthritis: mediators or markers of joint destruction?, Semin Arthritis Rheum., 1996 Feb;25(4):254-72; Sugiyama T., Involvement of interleukin-6 and prostaglandin E2 in particular osteoporosis of postmenopausal women with rheumatoid arthritis, J Bone Miner Metab., 2001;19(2):89-96; Abrahamsen B, *et al*, Cytokines and bone loss in a 5-year longitudinal study - hormone replacement therapy suppresses serum soluble interleukin-6 receptor and increases interleukin-1-receptor antagonist: the Danish Osteoporosis Prevention Study, J Bone Miner Res., 2000 Aug;15(8):1545-54; Straub RH, *et al*, Hormone replacement therapy and interrelation between serum interleukin-6 and body mass index in postmenopausal women: a population-based study, J Clin Endocrinol Metab., 2000 Mar;85(3):1340-4; Manolagas SC, The role of IL-6 type cytokines and their receptors in bone, Ann N Y Acad Sci., 1998 May 1;840:194-204; Ershler WB, *et al*, Immunologic aspects of osteoporosis, Dev Comp Immunol., 1997 Nov-Dec;21(6):487-99; Jilka RL, *et al*, Increased osteoclast development after estrogen loss: mediation by interleukin-6, Science, 1992 Jul 3;257(5066):88-91; Kallen KJ, *et al*, New developments in IL-6 dependent biology and therapy: where do we stand and what are the options?, Expert Opin Investig Drugs, 1999 Sep;8(9):1327-49; Neale SD, *et al*, The influence of serum cytokines and growth factors on osteoclast formation in Paget's disease, QJM, 2002 Apr;95 (4):233 - 40; Roodman GD, Osteoclast function In Paget's disease and multiple myeloma, Bone, 1995 Aug;17(2 Suppl):57S-61S; Hoyland JA, *et al*, Interleukin-6, IL-6 receptor, and IL-6 nuclear factor gene expression in Paget's disease, J Bone Miner Res., 1994 Jan;9(1):75-80; and Roodman GD, *et al*, Interleukin 6. A potential autocrine/paracrine factor in Paget's disease of bone, J Clin Invest., 1992 Jan;89(1):46-52; the disclosures of each of which are herein incorporated by reference in their entireties.

[1024] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with cancer. Diseases and disorders associated with cancer include, but are not limited to, 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, Anaplastic 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, Klatskin 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 Müllerian 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, or any combination thereof, as well as drug resistance in cancer chemotherapy and cancer chemotherapy toxicity. *See*, for example, Hirata T, *et al*, Humanized anti-interleukin-6 receptor monoclonal antibody induced apoptosis of fresh and cloned human myeloma cells in vitro, Leuk Res., 2003 Apr;27(4):343-9, Bataille R, *et al*, Biologic effects of anti-interleukin-6 murine monoclonal antibody in advanced multiple myeloma, Blood, 1995 Jul 15;86 (2):685-91; Goto H, *et al*, Mouse anti-human interleukin-6 receptor monoclonal antibody inhibits proliferation of fresh human myeloma cells in vitro, Jpn J Cancer Res., 1994 Sep;85(9):958-65; Klein B, *et al*,

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Agents, 2002 Apr-Jun;16 (2):105-9; the disclosures of each of which are herein incorporated by reference in their entireties.

[1025] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, 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, and transplant rejection. *See*, for example, Tzoulaki I, *et al*, C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study, Circulation, 2005 Aug 16;l12(7):976-83, Epub 2005 Aug 8; Rattazzi M, *et al*, C-reactive protein and interleukin-6 in vascular disease: culprits or passive bystanders?, J Hypertens., 2003 Oct;21(10):1787-803; Ito T, *et al*, HMG-CoA reductase inhibitors reduce interleukin-6 synthesis in human vascular smooth muscle cells, Cardiovasc Drugs Ther., 2002 Mar;16(2):121-6; Stenvinkel P, *et al*, Mortality, malnutrition, and atherosclerosis in ESRD: what is the role of interleukin-6?, Kidney Int Suppl., 2002 May;(80):103-8; Yudkin JS, *et al*, Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?, Atherosclerosis, 2000 Feb;148(2):209-14; Huber SA, *et al*, Interleukin-6 exacerbates early atherosclerosis in mice, Arterioscler Thromb Vasc Biol., 1999 Oct;19(10):2364-7; Kado S, *et al*, Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus, Acta Diabetol.,1999 Jun;36(1-2):67-72; Sukovich DA, *et al*, Expression of interleukin-6 in atherosclerotic lesions of male ApoE-knockout mice: inhibition by 17beta-estradiol, Arterioscler Thromb Vasc Biol.,1998 Sept;8(9):1498-505; Klover PJ, *et al*, Interleukin-6 depletion selectively improves hepatic insulin action in obesity, Endocrinology, 2005 Aug;146(8):3417-27, Epub 2005 Apr 21; Lee YH, *et al*, The evolving role of inflammation in obesity and the metabolic syndrome, Curr Diab Rep., 2005 Feb;5(1):70-5; Diamant M, *et al*, The association between abdominal visceral fat and carotid stiffness is mediated by circulating inflammatory markers in uncomplicated type 2 diabetes, J Clin Endocrinol Metab., 2005 Mar;90(3):1495-501, Epub 2004 Dec

21; Bray GA, Medical consequences of obesity, J Clin Endocrinol Metab., 2004 Jun;89(6):2583 9; Klover PJ, *et al*, Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice, Diabetes, 2003 Nov;52 (11):2784-9; Yudkin JS, *et al*, Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?, Atherosclerosis, 2000 Feb;148(2):209-14; Doganci A, *et al*, Pathological role of IL-6 in the experimental allergic bronchial asthma in mice, Clin Rev Allergy Immunol., 2005 Jun;28(3):257-70; Doganci A, *et al*, The IL-6R alpha chain controls lung CD4+CD25+ Treg development and function during allergic airway inflammation *in vivo*, J Clin Invest., 2005 Feb;l15(2):313 25, (Erratum in: J Clin Invest., 2005 May;l15(5):1388, Lehr, Hans A [added]); Stelmasiak Z, *et al*, IL 6 and sIL-6R concentration in the cerebrospinal fluid and serum of MS patients, Med Sci Monit., 2001 Sep-Oct;7(5):914-8; Tilgner J, *et al*, Continuous interleukin-6 application *in vivo* via macroencapsulation of interleukin-6-expressing COS-7 cells induces massive gliosis, Glia, 2001 Sep;35(3):234-45, Brunello AG, *et al*, Astrocytic alterations in interleukin-6 Soluble interleukin-6 receptor alpha double-transgenic mice, Am J Pathol., 2000 Nov;157(5):1485-93; Hampel H, *et al*, Pattern of interleukin-6 receptor complex immunoreactivity between cortical regions of rapid autopsy normal and Alzheimer's disease brain, Eur Arch Psychiatry Clin Neurosci., 2005 Aug;255(4):269-78, Epub 2004 Nov 26; Cacquevel M, *et al*, Cytokines in neuroinflammation and Alzheimer's disease, Curr Drug Targets, 2004 Aug;5(6):529-34; Quintanilla RA, *et al*, Interleukin 6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway, Exp Cell Res., 2004 Apr 15; 295 (1):245-57; Gadient RA, *et al*, Interleukin-6 (IL-6)--a molecule with both beneficial and destructive potentials, Prog Neurobiol., 1997 Aug;52(5):379-90; Hull M, *et al*, Occurrence of interleukin-6 in cortical plaques of Alzheimer's disease patients may precede transformation of diffuse into neuritic plaques, Ann N Y Acad Sci., 1996 Jan 17;777:205-12; Rallidis LS, *et al*, Inflammatory markers and in-hospital mortality in acute ischaemic stroke, Atherosclerosis, 2005 Dec 30; Emsley HC, *et al*, Interleukin-6 and acute ischaemic stroke, Acta Neurol Scand., 2005 Oct;112(4):273-4; Smith CJ, *et al*, Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome, BMC Neurol., 2004 Jan 15;4:2; Vila N, *et al*, Proinflammatory cytokines and early neurological worsening in ischemic stroke, Stroke, 2000 Oct;31(10):2325-9; and Tarkowski E, *et al*, Early intrathecal production of

interleukin-6 predicts the size of brain lesion in stroke, Stroke, 1995 Aug;26(8):1393-8; the disclosures of each of which are herein incorporated by reference in their entireties.

[1026] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with cytokine storm. Diseases and disorders associated with cytokine storm include, but are not limited to, 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). *See*, for example, Cecil, R. L., Goldman, L., & Bennett, J. C. (2000). Cecil textbook of medicine. Philadelphia: W.B. Saunders; Ferrara JL, *et al.*, Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1, Transplant Proc. 1993 Feb;25(1 Pt 2):1216-7; Osterholm MT, Preparing for the Next Pandemic, N Engl J Med. 2005 May 5;352(18):1839-42; Huang KJ, *et al.*, An interferon-gamma-related cytokine storm in SARS patients, J Med Virol. 2005 Feb;75(2):185-94; and Cheung CY, *et al.*, Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? Lancet. 2002 Dec 7;360(9348):1831-7.

[1027] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful as a wakefulness aid.

Administration

[1028] In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are 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. In a preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are 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. In another preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations thereof, are 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.

[1029] It is understood that the effective dosage may depend on recipient subject attributes, such as, for example, age, gender, pregnancy status, body mass index, lean body mass, condition or conditions for which the composition is given, other health conditions of the recipient subject that may affect metabolism or tolerance of the composition, levels of IL-6 in the recipient subject, and resistance to the composition (for example, arising from the patient developing antibodies against the composition). 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, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

[1030] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject in a pharmaceutical formulation.

[1031] 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* one or more 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.

[1032] In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, may be optionally administered in combination with one or more 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-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), 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, Dexketoprofen, Diclofenac, Diflunisal, Droxicam, Ethenzamide, Etodolac, Etoricoxib, Faislamine, fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, 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, Oxicams, Oxyphenbutazone, Parecoxib, Phenazone, Phenylbutazone, Phenylbutazone, Piroxicam, Pirprofen, profens, Proglumetacin, Pyrazolidine derivatives, Rofecoxib, Salicyl salicylate, Salicylamide, Salicylates, Sulfinpyrazone, 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, 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, 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. Antiviral agents include 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, podophyllotoxin, 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 or a regimen that includes administration thereof in association with an anti-IL-6 antibody according to the invention.

[1033] 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 one or more fragments 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 Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[1034] 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.

[1035] In one embodiment of the invention that may be used to intravenously administer antibodies of the invention, including Ab1, for cancer 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.

[1036] In another embodiment of the invention that may be used to intravenously administer antibodies of the invention, including Ab1, for cancer 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.

[1037] In one embodiment of the invention that may be used to subcutaneously administer antibodies of the invention, 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.

[1038] In another embodiment of the invention that may be used to subcutaneously administer antibodies of the invention, including Ab1, for rheumatoid arthritis 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.

[1039] 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.

[1040] 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.

[1041] 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.

[1042] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[1043] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[1044] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[1045] Certain teachings related to methods for obtaining a clonal population of antigen-specific B cells were disclosed in U.S. Provisional patent application no. 60/801,412, filed May 19, 2006, the disclosure of which is herein incorporated by reference in its entirety.

[1046] Certain teachings related to humanization of rabbit-derived monoclonal antibodies and preferred sequence modifications to maintain antigen binding affinity were disclosed in International Application No. 12/124,723, corresponding to Attorney Docket No. 67858.704001, entitled "Novel Rabbit Antibody Humanization Method and Humanized Rabbit Antibodies", filed May 21, 2008, the disclosure of which is herein incorporated by reference in its entirety.

[1047] Certain teachings related to producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S.

Patent application no. 11/429,053, filed May 8, 2006, (U.S. Patent Application Publication No. US2006/0270045), the disclosure of which is herein incorporated by reference in its entirety.

[1048] 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. provisional patent application no. 60/924,550, filed May 21, 2007, the disclosure of which is herein incorporated by reference in its entirety.

[1049] Certain teachings related to anti-IL-6 antibodies and methods of using those antibodies or fragments thereof to treat thrombosis or hypercoagulation disorders were disclosed in U.S. provisional patent application no. 61/117,861, filed November 25, 2008, the disclosure of which is herein incorporated by reference in its entirety.

[1050] 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.

[1051] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

[1052] 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, *etc.*) 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

Example 1 Production of Enriched Antigen-Specific B Cell Antibody Culture

[1053] 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.

[1054] 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.

[1055] 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.

Example 2 Production of Clonal, Antigen-Specific B Cell-Containing Culture

[1056] 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 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 **Screening of Antibody Supernatants for Monoclonal Antibody of Desired Specificity and/or Functional Properties**

[1057] 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 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.

Example 4 **Recovery of Single, Antibody-Producing B Cell of Desired Antigen Specificity**

[1058] 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, antibody-secreting cell. Dynal 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, etc.) 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 sequence recovery is initiated.

Example 5 **Isolation of Antibody Sequences From Antigen-Specific B Cell**

[1059] 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**

[1060] 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**

[1061] 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.

[1062] Immunization Strategy

[1063] 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.

[1064] Antibody Selection Titer Assessment

[1065] 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 Prizm software, and titers were determined.

[1066] Functional Titer Assessment

[1067] 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.

[1068] 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 huIL-6). Column 11 was medium only for IL-6 control. 30 µl/well of huIL-6 at 4x concentration of the final EC50 (concentration previously determined) were added to all wells (huIL-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 h at 37 °C in 4% CO_2. At 72 h, 20 µl/well of CellTiter96 (Promega) reagents was added to all test wells per

manufacturer protocol, and plates were incubated for 2 h at 37 °C. At 2 h, 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 μg/ml (final concentration) followed by 1:3 dilutions across the plate.

[1069] Tissue Harvesting

[1070] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[1071] 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 huIL-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.

[1072] 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 above.

[1073] B cell culture

[1074] 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 huIL-6 (B huIL-6) was added to the cell suspension at the final concentration of 3 μg/mL and incubated for 30 minutes at 4 °C. Unbound B huIL-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 (Milteni)/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 (Milteni) was pre-rinsed with 500 ml of PBF on a magnetic stand (Milteni). 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.

[1075] 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 μL/well. Cultures were incubated for 5 to 7 days at 37 °C in 4% CO_2 .

[1076] Identification of Selective Antibody Secreting B Cells

[1077] Cultures were tested for antigen recognition and functional activity between days 5 and 7.

[1078] Antigen Recognition Screening

[1079] The ELISA format used is as described above except 50 μL 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 μL/well and adding 60 μL/well of 16% DMSO in FBS. Plates were wrapped in paper towels to slow freezing and placed at –70 °C.

[1080] Functional Activity Screening

[1081] 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 μL/well, single points). 40 μL 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 h incubation, the Ab/Ag complex was transferred to a tissue culture (TC) treated, 96-well, flat-bottom plate. 20 μL of cell suspension in modified RPMI medium without huIL-6 (T1165 at 20,000 cells/well) was added to all wells (100 μL final volume per well). Background was subtracted, and observed OD values were transformed into % of inhibition.

[1082] B cell recovery

[1083] Plates containing wells of interest were removed from –70 °C, and the cells from each well were recovered with 5-200 μL 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.

[1084] The tube was inverted, the spin repeated, and the supernatant carefully removed. Cells were resuspended in 100 μL/tube of medium. 100 μL biotinylated IL-6 coated streptavidin M280 dynabeads (Invitrogen) and 16 μL of goat anti-rabbit H&L IgG-FITC diluted 1:100 in medium was added to the cell suspension.

[1085] 20 μL of cell/beads/FITC suspension was removed, and 5 μL 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% CO_2 in the dark.

[1086] 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 μL 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**

[1087] *Antibody genes:* Genes were cloned and constructed that directed the synthesis of a chimeric humanized rabbit monoclonal antibody.

[1088] *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).

[1089] *P. pastoris* strains: *P. 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.

[1090] 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-fluoro-orotic 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).

[1091] Methods

[1092] *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 AGCGCTTATTCCGCTATCCAGATGACCCAGTC-the AfeI site is single underlined. The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable light chain (not underlined); the reverse CGTACGTTTGATTTCCACCTTG.

[1093] 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 AfeI and BsiWI this enable insertion in-frame with the pGAPZ vector using the human HAS leader sequence in frame with the human kapp light chain constant region for export. (2) A similar strategy is performed for the heavy chain. The forward primer employed is AGCGCTTATTCCGAGGTGCAGCTGGTGGAGTC. The AfeI 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. 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.

[1094] *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.

[1095] 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.* Biotechniques 21 808-812 (1996). 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.

[1096] 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.

[1097] 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.

[1098] 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/$CaCl_2$. 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.

[1099] 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.

[1100] 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 Coomasie blue strained SDS-PAGE and immunoblotting for antibody protein. Antibody is characterized using the ELISA described above for IL-6 recognition.

[1101] *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.

[1102] 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 α-2 macroglobulin (A2M). A study was designed to assess the dose of antibody Ab1 required to ablate the A2M response to a single s.c. 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). The results are presented in Fig. 4.

[1103] The IC50 for antibody Ab1 was 0.1 mg/kg with complete suppression of the A2M response at the 0.3 mg/kg. This firmly establishes *in vivo* neutralization of human IL-6 can be accomplished by antibody Ab1.

Example 10 RXF393 Cachexia Model Study 1.

[1104] Introduction

[1105] 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.

[1106] Methods

[1107] 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.

[1108] Animals were euthanized at either day 28, when the tumor reached 4,000 mm^3 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.

[1109] Results - Survival

[1110] 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.

[1111] The survival curves for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) groups are presented in Fig. 5.

[1112] The survival curves for the two control groups and the antibody Ab1 regression (dosed from day 8 of the study) groups are presented in Fig. 6.

[1113] 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 ($p=0.97$).

[1114] Results – Tumor Size

[1115] 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.

[1116] 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.

[1117] Results – Weight Loss

[1118] Mean Percent Body Weight (MPBW) (± SEM) versus time is shown in Fig. 27. 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.

[1119] Representative photographs of control and Ab1-treated mice (Fig. 28) illustrate the emaciated condition of the control mice, compared to the normal appearance of the Ab1-treated mouse, at the end of the study (note externally visible tumor sites in right flank).

[1120] These results suggest that Ab1 may be useful to prevent or treat cachexia caused by elevated IL-6 in humans.

[1121] Results – Plasma Serum Amyloid A

[1122] The mean (± 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 5 and graphically in Fig. 32.

Table 5: Mean Plasma SAA - antibody Ab1, all groups versus control groups

	Mean Plasma SAA±SEM Day 5 (μg/ml)	Mean Plasma SAA±SEM Day 13 (μg/ml)	Mean Plasma SAA±SEM Terminal Bleed (μg/ml)
Polyclonal IgG iv weekly from day 1	675 ± 240 (n=5)	3198 ± 628 (n=4)	13371 ± 2413 (n=4)
PBS iv weekly from day 1	355 ± 207 (n=5)	4844 ± 1126 (n=5)	15826 ± 802 (n=3)
Ab1 30 mg/kg iv weekly from day 1	246 ± 100 (n=5)	2979 ± 170 (n=5)	841 ± 469 (n=10)
Ab1 10 mg/kg iv weekly from day 1	3629 ± 624 (n=5)	3096 ± 690 (n=5)	996 ± 348 (n=10)
Ab1 3 mg/kg iv weekly from day 1	106 ± 9 (n=5)	1623 ± 595 (n=4)	435 ± 70 (n=9)
Ab1 30 mg/kg iv weekly from day 8	375 ± 177 (n=5)	1492 ± 418 (n=4)	498 ± 83 (n=9)
Ab1 10 mg/kg iv weekly from day 8	487 ± 170 (n=5)	1403 ± 187 (n=5)	396 ± 58 (n=10)
Ab1 3 mg/kg iv weekly from day 8	1255 ± 516 (n=5)	466 ± 157 (n=5)	685 ± 350 (n=5)

[1123] 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.

[1124] Introduction

[1125] 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.

[1126] Methods

[1127] 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 mm^3 or if they became very debilitated (>30% loss of body weight).

[1128] 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.

[1129] Results -survival

[1130] 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 Fig. 7.

[1131] 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).

[1132] 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 Fig. 8. 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.

[1133] Antibody Ab1 was dosed in a single bolus infusion to a single male and single female cynomologus monkey in phosphate buffered saline. Plasma samples were removed at fixed time intervals and the level of antibody Ab1 was quantitated through of 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.

[1134] 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 cynomologus monkeys and the experiment replicated using an identical sampling plan. The resulting concentrations are then plot vs. time as show in Fig. 9.

[1135] 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.

[1136] 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.

[1137] 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.

[1138] 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 30C and 1000 rpm. For these studies, all proteins were diluted using ForteBio's sample diluent buffer (part number 18-5028).

[1139] Results are presented in Fig. 10 (A-E) and Fig. 11.

Example 14 Peptide Mapping.

[1140] 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 (shown below). 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 are shown in Fig. 12. Blots were prepared and probed according to the manufacturer's recommendations.

[1141] 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 results of the blots are shown in Fig. 13 and Fig. 14.

[1142] The sequence of the form of human IL-6 utilized to generate peptide library is set forth:

VPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMCESSKE ALAENNLNLPKMAEKDGCFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESS EEQARAVQMSTKVLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQD MTTHLILRSFKEFLQSSLRALRQM (SEQ ID NO: 1).

Example 15 Ab1 has high affinity for IL-6.

[1143] 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 (Fig. 15A). 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.

[1144] 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 (IC50) was measured. Inhibition was consistent with the measured dissociation constants (Fig. 15B). 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.

Example 16 **Multi-dose Pharmacokinetic Evaluation of Antibody Ab1 in Healthy Human Volunteers.**

[1145] 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.

[1146] Average plasma concentration of Ab1 for each dosage group versus time is shown in Fig. 16. Mean AUC and C_{max} increased linearly with dosage (Fig. 17 and Fig. 18, respectively). For dosages of 30 mg and above, the average Ab1 half-life in each dosage group was between approximately 25 and 30 days (Fig. 19).

Example 17 **Pharmacokinetics of Ab1 in patients with advanced cancer.**

[1147] 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.

[1148] Average plasma concentration of Ab1 in these individuals as a function of time is shown in Fig. 20. The average Ab1 half-life was approximately 31 days.

Example 18 **Unprecedented half-life of Ab1.**

[1149] 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 is unprecedented when compared with the half-lives of other anti-IL-6 antibodies (Fig. 21). 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 unprecedented half-life of Ab1 is at least partially attributable to the humanization and lack of glycosylation. The particular sequence and/or structure of the antigen binding surfaces may also contribute to Ab1's half-life.

Example 19 **Ab1 Effect on Hemoglobin Concentration, Plasma Lipid Concentration, and Neutrophil Counts in Patients with Advanced Cancer.**

[1150] 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 (Fig. 22), as did total cholesterol and triglycerides (Fig. 23), while mean neutrophil counts fell slightly (Fig. 24).

[1151] 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 effectively 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.**

[1152] Introduction

[1153] 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, K., *et al.*, Cancer, 103(9):1856-1864 (2005)). 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.

[1154] 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, P.I., *et al.*, Cancer, 110(6):1241-1247 (2007)). 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.

[1155] Methods

[1156] 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.

[1157] 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.

[1158] Results

[1159] Healthy Volunteers

[1160] 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 (Fig. 25). 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).

[1161] Cancer Patients

[1162] 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 (Fig. 26A). 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). The CRP levels of two representative individuals are shown in Fig. 26B. In those 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 advanced cancer 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

[1163] Introduction

[1164] 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.

[1165] Methods

[1166] 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.

[1167] 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, D., Lai, J.S., Chang, C.H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Eton, D.T., Lai,F J-S., Peterman, A.H & Merkel, D.E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. 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).

[1168] Results

[1169] Weight Change

[1170] 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 (Fig. 29).

[1171] Fatigue

[1172] 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 (Fig. 30).

[1173] Hand-Grip Strength

[1174] 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 (Fig. 31).

Example 22 Ab1 For Prevention of Thrombosis

[1175] Prior studies have shown that administration of an anti-IL-6 antibody can cause decreased platelet counts. Emilie, D. *et al.*, Blood, 84(8):2472-9 (1994); Blay *et al.*, Int J Cancer, 72(3):424-30 (1997). 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.

[1176] 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 A (see Fig. 32 and 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.

[1177] 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, etc. either individually or in combinations.

Example 23 Ab1 Increases Plasma Albumin Concentration in Patients with Advanced Cancer

[1178] Introduction

[1179] 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, M., *et al.*, Hepatogastroenterology, 47(36):1744-46 (2000)). 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.*

[1180] 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." (J.R. Senior and B.J. Maroni, Am. Soc. Nutr. Sci., 129:313S-314S (1999)).

[1181] 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, A., *et al.*, Proc. Am. Soc. Clin. Oncol., 21:Abstr 2892 (2002)).

[1182] 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.

[1183] Methods

[1184] 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.

[1185] 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.

[1186] Results

[1187] 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 (Fig. 33).

Example 24 Ab1 Increases Hemoglobin in Patients with Advanced Cancer

[1188] 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 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. 38 and 39).

[1189] 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. 40).

[1190] 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 25 Ab1 Increases Hemoglobin in Patients with Rheumatoid Arthritis.

[1191] 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. 41).

[1192] 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 26 Ab1 Decreases D-dimer Levels in Patients with Advanced Cancer

[1193] Introduction

[1194] D-dimer concentrations are recognized as useful diagnostic tools in predicting risks of thrombotic events in patients. (Adam *et al.*, 113 Blood 2878-87 (2009)) 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.*, 349 N. Engl. J. Med. 1227-35 (2003)) Clinical evaluation in combination with negative D-dimer test can effectively lower the instance of pulmonary embolism to 0.5%. (Van Belle *et al.*, 295 JAMA 172-79 (2006); Kruip *et al.*, 162 Arch. Intern. Med. 1631-35 (2002); Wells *et al.*, 135 Ann. Intern. Med. 98-107 (2001))

[1195] 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.*, 113 Blood 2878-87 (2009); Schutgens *et al.*, 144 J. Lab. Clin. Med. 100-07 (2004)) This discovery led to the conclusion that D-dimer levels monitoring could be used to assess treatment responsiveness. (Adam *et al.*, 113 Blood at 2883)

[1196] For patients with cancer, D-dimer analysis may have additional significance, as cancer increases the prevalence of thrombosis. (Adam *et al.*, 113 Blood 2878-87 (2009)) 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.*, 247 Radiology 854-61 (2008)) 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.*, 123 Thromb. Res. 177-83 (2008)) A higher threshold for a negative D-dimer result may be necessary in cancer patients. (Righini *et al.*, 95 Haemost. 715-19 (2006))

[1197] 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.

[1198] Methods

[1199] 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 microparticle 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.

[1200] Results

[1201] The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Ab1 monoclonal antibody are plotted in Figure 42. Error bars were omitted from the graph for clarity purposes. The percent change from baseline in D-dimer concentration is plotted in Figure 43. All dosage levels of Ab1 antibody demonstrated a drop in D-dimer levels over placebo over the period of 8 weeks.

Example 27 Ab1 Improved Weight and Reduced Fatigue in Patients with Advanced Cancer

[1202] Introduction

[1203] 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.

[1204] Methods

[1205] 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.

[1206] 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: a.) any change in weight; and b.) fatigue as measured using the Facit-F Fatigue Subscale questionnaire a medically recognized test for evaluating fatigue (See, e.g., Cella, D., Lai, J.S., Chang, C.H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general population. Cancer, 94(2), 528-538; Cella, D., Eton, D.T., Lai,F J-S., Peterman, A.H & Merkel,

D.E. (2002). Combining anchor and distribution based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy anemia and fatigue scales. Journal of Pain & Symptom Management, 24 (6) 547-561.).

[1207] Results

[1208] Weight Change

[1209] 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 is plotted in Figure 44. The average percent change in body weight from each dosage concentration is plotted in Fig. 45. The averaged lean body mass data for the dosage concentration groups is plotted in Figure 46.

[1210] Fatigue

[1211] 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 (Fig. 47). The change from baseline Facit-F subscale score is plotted in Figure 48.

SEQUENCE LISTING

The biological sequences referenced herein are provided below:

SEQ ID NO: 1

VPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMCESSKEALAENNLNLP
KMAEKDGCFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVLIQFLQK
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SEQ ID NO: 2

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQASQSINNELSWYQQKP
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SEQ ID NO: 3

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WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

SEQ ID NO: 4

QASQSINNELS

SEQ ID NO: 5

RASTLAS

SEQ ID NO: 6

QQGYSLRNIDNA

SEQ ID NO: 7

NYYVT

SEQ ID NO: 8

IIYGSDETAYATWAIG

SEQ ID NO: 9

DDSSDWDAKFNL

SEQ ID NO: 10

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GAATAACTT

SEQ ID NO: 11

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GACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGC
AAAATTTAACTTGTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGCGCCTCCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG
GGCTGCCTGGTCAAGG

SEQ ID NO: 12

CAGGCCAGTCAGAGCATTAACAATGAATTATCC

SEQ ID NO: 13

AGGGCATCCACTCTGGCATCT

SEQ ID NO: 14

CAACAGGGTTATAGTCTGAGGAATATTGATAATGCT

SEQ ID NO: 15

AACTACTACGTGACC

SEQ ID NO: 16

ATCATTTATGGTAGTGATGAAACGGCCTACGCGACCTGGGCGATAGGC

SEQ ID NO: 17

GATGATAGTAGTGACTGGGATGCAAAATTTAACTTG

SEQ ID NO: 18

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYATW
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SEQ ID NO: 19

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PWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

SEQ ID NO: 23

QASETIYSWLS

SEQ ID NO: 24

QASDLAS

SEQ ID NO: 25

QQGYSGSNVDNV

SEQ ID NO: 26

DHAMG

SEQ ID NO: 27

FINSGGSARYASWAEG

SEQ ID NO: 28

GGAVWSIHSFDP

SEQ ID NO: 29

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GGGCAGAAGGCCGATTCACCATCTCCAGAACCTCGACCACGGTGGATCTGAAAATGACCA
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SEQ ID NO: 31

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SEQ ID NO: 32

CAGGCATCCGATCTGGCATCT

SEQ ID NO: 33

CAACAGGGTTATAGTGGTAGTAATGTTGATAATGTT

SEQ ID NO: 34

GACCATGCAATGGGC

SEQ ID NO: 35

TTCATTAATAGTGGTGGTAGCGCACGCTACGCGAGCTGGGCAGAAGGC

SEQ ID NO: 36

GGGGGTGCTGTTTGGAGTATTCATAGTTTTGATCCC

SEQ ID NO: 37

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQASQSVYDNNYLSWFQQ
KPGQPPKLLIYGASTLASGVPSRFVGSGSGTQFTLTITDVQCDDAATYYCAGVYDDDSDNAFG
GGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF

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SEQ ID NO: 39

QASQSVYDNNYLS

SEQ ID NO: 40

GASTLAS

SEQ ID NO: 41

AGVYDDDSDNA

SEQ ID NO: 42

VYYMN

SEQ ID NO: 43

FITMSDNINYASWAKG

SEQ ID NO: 44

SRGWGTMGRLDL

SEQ ID NO: 45

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SEQ ID NO: 47

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SEQ ID NO: 48

GGTGCATCCACTCTGGCATCT

SEQ ID NO: 49

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SEQ ID NO: 50

GTCTACTACATGAAC

SEQ ID NO: 51

TTCATTACAATGAGTGATAATATAAATTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 52

AGTCGTGGCTGGGGTACAATGGGTCGGTTGGATCTC

SEQ ID NO: 53

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GTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN

SEQ ID NO: 54

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LDLWGHGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

SEQ ID NO: 55

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SEQ ID NO: 56

GASTLDS

SEQ ID NO: 57

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SEQ ID NO: 58

AYYMN

SEQ ID NO: 59

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SEQ ID NO: 60

SRGWGAMGRLDL

SEQ ID NO: 61

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SEQ ID NO: 63

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SEQ ID NO: 64

GGTGCATCCACTCTGGATTCT

SEQ ID NO: 65

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SEQ ID NO: 66

GCCTACTACATGAAC

SEQ ID NO: 67

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SEQ ID NO: 68

AGTCGTGGCTGGGGTGCAATGGGTCGGTTGGATCTC

SEQ ID NO: 69

MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSAAVGGTVTINCQASQSVDDNNWLGWYQ
QKRGQPPKYLIYSASTLASGVPSRFKGSGSGTQFTLTISDLECDDAATYYCAGGFSGNIFAFGG
GTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF

SEQ ID NO: 70

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TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

SEQ ID NO: 71

QASQSVDDNNWLG

SEQ ID NO: 72

SASTLAS

SEQ ID NO: 73

AGGFSGNIFA

SEQ ID NO: 74

SYAMS

SEQ ID NO: 75

IIGGFGTTYYATWAKG

SEQ ID NO: 76

GGPGNGGDI

SEQ ID NO: 77

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SEQ ID NO: 78

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SEQ ID NO: 79

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SEQ ID NO: 80

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SEQ ID NO: 81

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SEQ ID NO: 82

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SEQ ID NO: 85

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SEQ ID NO: 87

QSSQSVYNNFLS

SEQ ID NO: 88

QASKLAS

SEQ ID NO: 89

LGGYDDDADNA

SEQ ID NO: 90

DYAMS

SEQ ID NO: 91

IIYAGSGSTWYASWAKG

SEQ ID NO: 92

DGYDDYGDFDRLDL

SEQ ID NO: 93

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AGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACCAGGCATCCAAACTGGCATCTGGGG
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SEQ ID NO: 96

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SEQ ID NO: 97

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SEQ ID NO: 98

GACTATGCAATGAGC

SEQ ID NO: 99

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SEQ ID NO: 100

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SEQ ID NO: 101

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SEQ ID NO: 102

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LWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

SEQ ID NO: 103

QASQSINNELS

SEQ ID NO: 104

RASTLAS

SEQ ID NO: 105

QQGYSLRNIDNA

SEQ ID NO: 106

NYYMT

SEQ ID NO: 107

MIYGSDETAYANWAIG

SEQ ID NO: 108

DDSSDWDAKFNL

SEQ ID NO: 109

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GTCACCATCAAATGCCAGGCCAGTCAGAGCATTAACAATGAATTATCCTGGTATCAGCAG
AAATCAGGGCAGCGTCCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCT
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TGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTGTCTT
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AATAACTTC

SEQ ID NO: 110

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GACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGC
AAAATTTAACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGG
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SEQ ID NO: 111

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SEQ ID NO: 112

AGGGCATCCACTCTGGCATCT

SEQ ID NO: 113

CAACAGGGTTATAGTCTGAGGAATATTGATAATGCT

SEQ ID NO: 114

AACTACTACATGACC

SEQ ID NO: 115

ATGATTTATGGTAGTGATGAAACAGCCTACGCGAACTGGGCGATAGGC

SEQ ID NO: 116

GATGATAGTAGTGACTGGGATGCAAAATTTAACTTG

SEQ ID NO: 117

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYMTWVRQAPGKGLEWVGMIYGSDETAYAN
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SEQ ID NO: 118

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYMTWVRQAPGKGLEWVGMIYGSDETAYAN
SAIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNL

SEQ ID NO: 119

DIQMTQSPSTLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGS
GSGTEFTLTISSLQPDDFATYYCQQGYSLRNIDNA

SEQ ID NO: 120

IIYGSDETAYATSAIG

SEQ ID NO: 121

MIYGSDETAYANSAIG

SEQ ID NO: 122

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQSSQSVGNNQDLSWFQQ
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SEQ ID NO: 123

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LEWIGYIWSGGSTYYATWAKGRFTISKTSTTVDLKITSPTTEDTATYFCARLGDTGGHAYATR
LNL

SEQ ID NO: 124

QSSQSVGNNQDLS

SEQ ID NO: 125

EISKLES

SEQ ID NO: 126

LGGYDDDADNA

SEQ ID NO: 127

SRTMS

SEQ ID NO: 128

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SEQ ID NO: 129

LGDTGGHAYATRLNL

SEQ ID NO: 130

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCAGCCGTGCTGACCCAGACACCATCACCCGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAGTTGCCAGTCCAGTCAGAGTGTTGGTAATAACCAGGACTTATCCTGGTTTC
AGCAGAGACCAGGGCAGCCTCCCAAGCTCCTGATCTACGAAATATCCAAACTGGAATCTG

GGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGGACACACTTCACTCTCACCATCAGCG
GCGTACAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGGTTATGATGATGATGCTGA
TAATGCT

SEQ ID NO: 131

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCACT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGATTCTCCCTCAGTAGTCGTACAATGTCCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGATCGGATACATTTGGAGTGGTGGTAGCACATACTACGCGACCTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATTGGGCGATACTGGTGGTCACGC
TTATGCTACTCGCTTAAATCTC

SEQ ID NO: 132

CAGTCCAGTCAGAGTGTTGGTAATAACCAGGACTTATCC

SEQ ID NO: 133

GAAATATCCAAACTGGAATCT

SEQ ID NO: 134

CTAGGCGGTTATGATGATGATGCTGATAATGCT

SEQ ID NO: 135

AGTCGTACAATGTCC

SEQ ID NO: 136

TACATTTGGAGTGGTGGTAGCACATACTACGCGACCTGGGCGAAAGGC

SEQ ID NO: 137

TTGGGCGATACTGGTGGTCACGCTTATGCTACTCGCTTAAATCTC

SEQ ID NO: 138

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSSVSAAVGGTVSISCQSSQSVYSNKYLAWYQQ
KPGQPPKLLIYWTSKLASGAPSRFSGSGSGTQFTLTISGVQCDDAATYYCLGAYDDDADNA

SEQ ID NO: 139

METGLRWLLLVAVLKGVQCQSVEESGGRLVKPDETLTLTCTASGFSLEGGYMTWVRQAPGK
GLEWIGISYDSGSTYYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCVRSLKYPTVTSDD
L

SEQ ID NO: 140

QSSQSVYSNKYLA

SEQ ID NO: 141

WTSKLAS

SEQ ID NO: 142

LGAYDDDADNA

SEQ ID NO: 143

GGYMT

SEQ ID NO: 144

ISYDSGSTYYASWAKG

SEQ ID NO: 145

SLKYPTVTSDDL

SEQ ID NO: 146

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCAGCCGTGCTGACCCAGACACCATCGTCCGTGTCTGCAGCTGTGGGAGGCACA
GTCAGCATCAGTTGCCAGTCCAGTCAGAGTGTTTATAGTAATAAGTACCTAGCCTGGTATC
AGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACTGGACATCCAAACTGGCATCTG
GGGCCCCATCACGGTTCAGCGGCAGTGGATCTGGGACACAATTCACTCTCACCATCAGCG
GCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGCTTATGATGATGATGCTGA
TAATGCT

SEQ ID NO: 147

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAAGAGTCCGGGGGTCGCCTGGTCAAGCCTGACGAAACCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTGGAGGGCGGCTACATGACCTGGGTCCGCCAGGCTCCAGGGA
AGGGGCTGGAATGGATCGGAATCAGTTATGATAGTGGTAGCACATACTACGCGAGCTGGG
CGAAAGGCCGATTCACCATCTCCAAGACCTCGTCGACCACGGTGGATCTGAAAATGACCA
GTCTGACAACCGAGGACACGGCCACCTATTTCTGCGTCAGATCACTAAAATATCCTACTGT
TACTTCTGATGACTTG

SEQ ID NO: 148

CAGTCCAGTCAGAGTGTTTATAGTAATAAGTACCTAGCC

SEQ ID NO: 149

TGGACATCCAAACTGGCATCT

SEQ ID NO: 150

CTAGGCGCTTATGATGATGATGCTGATAATGCT

SEQ ID NO: 151

GGCGGCTACATGACC

SEQ ID NO: 152

ATCAGTTATGATAGTGGTAGCACATACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 153

TCACTAAAATATCCTACTGTTACTTCTGATGACTTG

SEQ ID NO: 154

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQSSQSVYNNNDLAWYQQ
KPGQPPKLLIYYASTLASGVPSRFKGSGSGTQFTLTISGVQCDDAAAYYCLGGYDDDADNA

SEQ ID NO: 155

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGLSLSSNTINWVRQAPGKG
LEWIGYIWSGGSTYYASWVNGRFTISKTSTTVDLKITSPTTEDTATYFCARGGYASGGYPYAT
RLDL

SEQ ID NO: 156

QSSQSVYNNNDLA

SEQ ID NO: 157

YASTLAS

SEQ ID NO: 158

LGGYDDDADNA

SEQ ID NO: 159

SNTIN

SEQ ID NO: 160

YIWSGGSTYYASWVNG

SEQ ID NO: 161

GGYASGGYPYATRLDL

SEQ ID NO: 162

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCAGCCGTGCTGACCCAGACACCATCACCCGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAGTTGCCAGTCCAGTCAGAGTGTTTATAATAATAACGACTTAGCCTGGTATC
AGCAGAAACCAGGGCAGCCTCCTAAACTCCTGATCTATTATGCATCCACTCTGGCATCTGG
GGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGG
CGTGCAGTGTGACGATGCTGCCGCTTACTACTGTCTAGGCGGTTATGATGATGATGCTGAT
AATGCT

SEQ ID NO: 163

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTATCTGGATTATCCCTCAGTAGCAATACAATAAACTGGGTCCGCCAGGCTCCAGGGA
AGGGGCTGGAGTGGATCGGATACATTTGGAGTGGTGGTAGTACATACTACGCGAGCTGGG
TGAATGGTCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTC
CGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGGGTTACGCTAGTGGTGGTT
ATCCTTATGCCACTCGGTTGGATCTC

SEQ ID NO: 164

CAGTCCAGTCAGAGTGTTTATAATAATAACGACTTAGCC

SEQ ID NO: 165

TATGCATCCACTCTGGCATCT

SEQ ID NO: 166

CTAGGCGGTTATGATGATGATGCTGATAATGCT

SEQ ID NO: 167

AGCAATACAATAAAC

SEQ ID NO: 168

TACATTTGGAGTGGTGGTAGTACATACTACGCGAGCTGGGTGAATGGT

SEQ ID NO: 169

GGGGGTTACGCTAGTGGTGGTTATCCTTATGCCACTCGGTTGGATCTC

SEQ ID NO: 170

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSSVSAAVGGTVTINCQSSQSVYNNDYLSWYQQ
RPGQRPKLLIYGASKLASGVPSRFKGSGSGKQFTLTISGVQCDDAATYYCLGDYDDDADNT

SEQ ID NO: 171

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFTLSTNYYLSWVRQAPGK
GLEWIGIIYPSGNTYCAKWAKGRFTISKTSSTTVDLKMTSPTTEDTATYFCARNYGGDESL

SEQ ID NO: 172

QSSQSVYNNDYLS

SEQ ID NO: 173

GASKLAS

SEQ ID NO: 174

LGDYDDDADNT

SEQ ID NO: 175

TNYYLS

SEQ ID NO: 176

IIYPSGNTYCAKWAKG

SEQ ID NO: 177

NYGGDESL

SEQ ID NO: 178

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCAGCCGTGCTGACCCAGACACCATCCTCCGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAATTGCCAGTCCAGTCAGAGTGTTTATAATAACGACTACTTATCCTGGTATC
AACAGAGGCCAGGGCAACGTCCCAAGCTCCTAATCTATGGTGCTTCCAAACTGGCATCTG
GGGTCCCGTCACGGTTCAAAGGCAGTGGATCTGGGAAACAGTTTACTCTCACCATCAGCG
GCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTGGGCGATTATGATGATGATGCTGA
TAATACT

SEQ ID NO: 179

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACTTGCA
CAGTCTCTGGATTCACCCTCAGTACCAACTACTACCTGAGCTGGGTCCGCCAGGCTCCAGG
GAAGGGGCTAGAATGGATCGGAATCATTTATCCTAGTGGTAACACATATTGCGCGAAGTG
GGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATGAC
CAGTCCGACAACCGAGGACACAGCCACGTATTTCTGTGCCAGAAATTATGGTGGTGATGA
AAGTTTG

SEQ ID NO: 180

CAGTCCAGTCAGAGTGTTTATAATAACGACTACTTATCC

SEQ ID NO: 181

GGTGCTTCCAAACTGGCATCT

SEQ ID NO: 182

CTGGGCGATTATGATGATGATGCTGATAATACT

SEQ ID NO: 183

ACCAACTACTACCTGAGC

SEQ ID NO: 184

ATCATTTATCCTAGTGGTAACACATATTGCGCGAAGTGGGCGAAAGGC

SEQ ID NO: 185

AATTATGGTGGTGATGAAAGTTTG

SEQ ID NO: 186

MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQASETIGNALAWYQQK
SGQPPKLLIYKASKLASGVPSRFKGSGSGTEYTLTISDLECADAATYYCQWCYFGDSV

SEQ ID NO: 187

METGLRWLLLVTVLKGVQCQEQLVESGGGLVQPEGSLTLTCTASGFDFSSGYYMCWVRQAP
GKGLEWIACIFTITTNTYYASWAKGRFTISKTSSTTVTLQMTSLTAADTATYLCARGIYSDNNY
YAL

SEQ ID NO: 188

QASETIGNALA

SEQ ID NO: 189

KASKLAS

SEQ ID NO: 190

QWCYFGDSV

SEQ ID NO: 191

SGYYMC

SEQ ID NO: 192

CIFTITTNTYYASWAKG

SEQ ID NO: 193

GIYSDNNYYAL

SEQ ID NO: 194

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTGAGACCATTGGCAATGCATTAGCCTGGTATCAGCAG
AAATCAGGGCAGCCTCCCAAGCTCCTGATCTACAAGGCATCCAAACTGGCATCTGGGGTC
CCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAGCGACCTG
GAGTGTGCCGATGCTGCCACTTACTACTGTCAATGGTGTTATTTTGGTGATAGTGTT

SEQ ID NO: 195

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCACTGTGCTCAAAGGTGTCCAGTGTCAGG
AGCAGCTGGTGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCT
GCACAGCCTCTGGATTCGACTTCAGTAGCGGCTACTACATGTGCTGGGTCCGCCAGGCTCC
AGGGAAGGGGCTGGAGTGGATCGCGTGTATTTTCACTATTACTACTAACACTTACTACGCG
AGCTGGGCGAAAGGCCGATTCACCATCTCCAAGACCTCGTCGACCACGGTGACTCTGCAA
ATGACCAGTCTGACAGCCGCGGACACGGCCACCTATCTCTGTGCGAGAGGGATTTATTCT
GATAATAATTATTATGCCTTG

SEQ ID NO: 196

CAGGCCAGTGAGACCATTGGCAATGCATTAGCC

SEQ ID NO: 197

AAGGCATCCAAACTGGCATCT

SEQ ID NO: 198

CAATGGTGTTATTTTGGTGATAGTGTT

SEQ ID NO: 199

AGCGGCTACTACATGTGC

SEQ ID NO: 200

TGTATTTTCACTATTACTACTAACACTTACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 201

GGGATTTATTCTGATAATAATTATTATGCCTTG

SEQ ID NO: 202

MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQASESIGNALAWYQQK
PGQPPKLLIYKASTLASGVPSRFSGSGSGTEFTLTISGVQCADAAAYYCQWCYFGDSV

SEQ ID NO: 203

METGLRWLLLVAVLKGVQCQQQLVESGGGLVKPGASLTLTCKASGFSFSSGYYMCWVRQAP
GKGLESIACIFTITDNTYYANWAKGRFTISKPSSPTVTLQMTSLTAADTATYFCARGIYSTDNY
YAL

SEQ ID NO: 204

QASESIGNALA

SEQ ID NO: 205

KASTLAS

SEQ ID NO: 206

QWCYFGDSV

SEQ ID NO: 207

SGYYMC

SEQ ID NO: 208

CIFTITDNTYYANWAKG

SEQ ID NO: 209

GIYSTDNYYAL

SEQ ID NO: 210

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTGAGAGCATTGGCAATGCATTAGCCTGGTATCAGCAG
AAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAAGGCATCCACTCTGGCATCTGGGGTC
CCATCGCGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGGCGTG
CAGTGTGCCGATGCTGCCGCTTACTACTGTCAATGGTGTTATTTTGGTGATAGTGTT

SEQ ID NO: 211

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGC
AGCAGCTGGTGGAGTCCGGGGGAGGCCTGGTCAAGCCGGGGGCATCCCTGACACTCACCT
GCAAAGCCTCTGGATTCTCCTTCAGTAGCGGCTACTACATGTGCTGGGTCCGCCAGGCTCC
AGGGAAGGGGCTGGAGTCGATCGCATGCATTTTTACTATTACTGATAACACTTACTACGCG

AACTGGGCGAAAGGCCGATTCACCATCTCCAAGCCCTCGTCGCCCACGGTGACTCTGCAA
ATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGGGGGATTTATTCTA
CTGATAATTATTATGCCTTG

SEQ ID NO: 212

CAGGCCAGTGAGAGCATTGGCAATGCATTAGCC

SEQ ID NO: 213

AAGGCATCCACTCTGGCATCT

SEQ ID NO: 214

CAATGGTGTTATTTTGGTGATAGTGTT

SEQ ID NO: 215

AGCGGCTACTACATGTGC

SEQ ID NO: 216

TGCATTTTTACTATTACTGATAACACTTACTACGCGAACTGGGCGAAAGGC

SEQ ID NO: 217

GGGATTTATTCTACTGATAATTATTATGCCTTG

SEQ ID NO: 218

MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQASQSVSSYLNWYQQK
PGQPPKLLIYRASTLESGVPSRFKGSGSGTEFTLTISDLECADAATYYCQCTYGTSSSYGAA

SEQ ID NO: 219

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGISLSSNAISWVRQAPGKGL
EWIGIISYSGTTYYASWAKGRFTISKTSSTTVDLKITSPTTEDTATYFCARDDPTTVMVMLIPFG
AGMDL

SEQ ID NO: 220

QASQSVSSYLN

SEQ ID NO: 221

RASTLES

SEQ ID NO: 222

QCTYGTSSSYGAA

SEQ ID NO: 223

SNAIS

SEQ ID NO: 224

IISYSGTTYYASWAKG

SEQ ID NO: 225

DDPTTVMVMLIPFGAGMDL

SEQ ID NO: 226

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTCAGAGCGTTAGTAGCTACTTAAACTGGTATCAGCAG
AAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAGGGCATCCACTCTGGAATCTGGGGTC
CCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTG

GAGTGTGCCGATGCTGCCACTTACTACTGTCAATGTACTTATGGTACTAGTAGTAGTTATG
GTGCTGCT

SEQ ID NO: 227

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CCGTCTCTGGTATCTCCCTCAGTAGCAATGCAATAAGCTGGGTCCGCCAGGCTCCAGGGA
AGGGGCTGGAATGGATCGGAATCATTAGTTATAGTGGTACCACATACTACGCGAGCTGGG
CGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATCACTA
GTCCGACAACCGAGGACACGGCCACCTACTTCTGTGCCAGAGATGACCCTACGACAGTTA
TGGTTATGTTGATACCTTTTGGAGCCGGCATGGACCTC

SEQ ID NO: 228

CAGGCCAGTCAGAGCGTTAGTAGCTACTTAAAC

SEQ ID NO: 229

AGGGCATCCACTCTGGAATCT

SEQ ID NO: 230

CAATGTACTTATGGTACTAGTAGTAGTTATGGTGCTGCT

SEQ ID NO: 231

AGCAATGCAATAAGC

SEQ ID NO: 232

ATCATTAGTTATAGTGGTACCACATACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 233

GATGACCCTACGACAGTTATGGTTATGTTGATACCTTTTGGAGCCGGCATGGACCTC

SEQ ID NO: 234

MDTRAPTQLLGLLLLWLPGATFAQVLTQTASPVSAAVGGTVTINCQASQSVYKNNYLSWYQ
QKPGQPPKGLIYSASTLDSGVPLRFSGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSSGDCYA

SEQ ID NO: 235

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCTASGFSFSSYWMCWVRQAPGK
GLEWIACIVTGNGNTYYANWAKGRFTISKTSSTTVTLQMTSLTAADTATYFCAKAYDL

SEQ ID NO: 236

QASQSVYKNNYLS

SEQ ID NO: 237

SASTLDS

SEQ ID NO: 238

LGSYDCSSGDCYA

SEQ ID NO: 239

SYWMC

SEQ ID NO: 240

CIVTGNGNTYYANWAKG

SEQ ID NO: 241

AYDL

SEQ ID NO: 242

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCCAAGTGCTGACCCAGACTGCATCGCCCGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAACTGCCAGGCCAGTCAGAGTGTTTATAAGAACAACTACTTATCCTGGTATC
AGCAGAAACCAGGGCAGCCTCCCAAAGGCCTGATCTATTCTGCATCGACTCTAGATTCTG
GGGTCCCATTGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCG
ACGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCAGTTATGATTGTAGTAGTGG
TGATTGTTATGCT

SEQ ID NO: 243

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGGGATCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCTTCAGTAGCTACTGGATGTGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAGTGGATCGCATGCATTGTTACTGGTAATGGTAACACTTACTACGCGAACTG
GGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAAATGAC
CAGTCTGACAGCCGCGGACACGGCCACCTATTTTTGTGCGAAAGCCTATGACTTG

SEQ ID NO: 244

CAGGCCAGTCAGAGTGTTTATAAGAACAACTACTTATCC

SEQ ID NO: 245

TCTGCATCGACTCTAGATTCT

SEQ ID NO: 246

CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTATGCT

SEQ ID NO: 247

AGCTACTGGATGTGC

SEQ ID NO: 248

TGCATTGTTACTGGTAATGGTAACACTTACTACGCGAACTGGGCGAAAGGC

SEQ ID NO: 249

GCCTATGACTTG

SEQ ID NO: 250

MDTRAPTQLLGLLLLWLPGSTFAAVLTQTPSPVSAAVGGTVSISCQASQSVYDNNYLSWYQQ
KPGQPPKLLIYGASTLASGVPSRFKGTGSGTQFTLTITDVQCDDAATYYCAGVFNDDSDDA

SEQ ID NO: 251

METGLRWLLLVAVPKGVQCQSLEESGGRLVTPGTPLTLTCTLSGFSLSAYYMSWVRQAPGKG
LEWIGFITLSDHISYARWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCARSRGWGAMGRLDL

SEQ ID NO: 252

QASQSVYDNNYLS

SEQ ID NO: 253

GASTLAS

SEQ ID NO: 254

AGVFNDDSDDA

SEQ ID NO: 255

AYYMS

SEQ ID NO: 256

FITLSDHISYARWAKG

SEQ ID NO: 257

SRGWGAMGRLDL

SEQ ID NO: 258

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTTCCA
CATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTCTGCAGCTGTGGGAGGCACAGT
CAGCATCAGTTGCCAGGCCAGTCAGAGTGTTTATGACAACAACTATTTATCCTGGTATCAG
CAGAAACCAGGACAGCCTCCCAAGCTCCTGATCTATGGTGCATCCACTCTGGCATCTGGG
GTCCCATCGCGGTTCAAAGGCACGGGATCTGGGACACAGTTCACTCTCACCATCACAGAC
GTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGGCGTTTTTAATGATGATAGTGATG
ATGCC

SEQ ID NO: 259

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCCCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CACTCTCTGGATTCTCCCTCAGTGCATACTATATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGATTCATTACTCTGAGTGATCATATATCTTACGCGAGGTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGAGTCGTGGCTGGGGTGCAATGGG
TCGGTTGGATCTC

SEQ ID NO: 260

CAGGCCAGTCAGAGTGTTTATGACAACAACTATTTATCC

SEQ ID NO: 261

GGTGCATCCACTCTGGCATCT

SEQ ID NO: 262

GCAGGCGTTTTTAATGATGATAGTGATGATGCC

SEQ ID NO: 263

GCATACTATATGAGC

SEQ ID NO: 264

TTCATTACTCTGAGTGATCATATATCTTACGCGAGGTGGGCGAAAGGC

SEQ ID NO: 265

AGTCGTGGCTGGGGTGCAATGGGTCGGTTGGATCTC

SEQ ID NO: 266

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQASQSVYNNKNLAWYQQ
KSGQPPKLLIYWASTLASGVSSRFSGSGSGTQFTLTVSGVQCDDAATYYCLGVFDDDADNA

SEQ ID NO: 267

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTASGFSLSSYSMTWVRQAPGKG
LEYIGVIGTSGSTYYATWAKGRFTISRTSTTVALKITSPTTEDTATYFCVRSLSSITFL

SEQ ID NO: 268

QASQSVYNNKNLA

SEQ ID NO: 269

WASTLAS

SEQ ID NO: 270

LGVFDDDADNA

SEQ ID NO: 271

SYSMT

SEQ ID NO: 272

VIGTSGSTYYATWAKG

SEQ ID NO: 273

SLSSITFL

SEQ ID NO: 274

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTCGCAGCCGTGCTGACCCAGACACCATCGCCCGTGTCTGCGGCTGTGGGAGGCACA
GTCACCATCAGTTGCCAGGCCAGTCAGAGTGTTTATAACAACAAAAATTTAGCCTGGTATC
AGCAGAAATCAGGGCAGCCTCCCAAGCTCCTGATCTACTGGGCATCCACTCTGGCATCTG
GGGTCTCATCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCGTCAGCG
GCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGTTTTTGATGATGATGCTGA
TAATGCT

SEQ ID NO: 275

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAATGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTCAGTAGCTACTCCATGACCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATATATCGGAGTCATTGGTACTAGTGGTAGCACATACTACGCGACCTGGGC
GAAAGGCCGATTCACCATCTCCAGAACCTCGACCACGGTGGCTCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGTCAGGAGTCTTTCTTCTATTACTTTCTTG

SEQ ID NO: 276

CAGGCCAGTCAGAGTGTTTATAACAACAAAAATTTAGCC

SEQ ID NO: 277

TGGGCATCCACTCTGGCATCT

SEQ ID NO: 278

CTAGGCGTTTTTGATGATGATGCTGATAATGCT

SEQ ID NO: 279

AGCTACTCCATGACC

SEQ ID NO: 280

GTCATTGGTACTAGTGGTAGCACATACTACGCGACCTGGGCGAAAGGC

SEQ ID NO: 281

AGTCTTTCTTCTATTACTTTCTTG

SEQ ID NO: 282

MDTRAPTQLLGLLLLWLPGARCAFELTQTPASVEAAVGGTVTINCQASQNIYRYLAWYQQKP
GQPPKFLIYLASTLASGVPSRFKGSGSGTEFTLTISDLECADAATYYCQSYYSSNSVA

SEQ ID NO: 283

METGLRWLLLVAVLKGVQCQEQLVESGGDLVQPEGSLTLTCTASELDFSSGYWICWVRQVPG
KGLEWIGCIYTGSSGSTFYASWAKGRFTISKTSSTTVTLQMTSLTAADTATYFCARGYSGFGYF
KL

SEQ ID NO: 284

QASQNIYRYLA

SEQ ID NO: 285

LASTLAS

SEQ ID NO: 286

QSYYSSNSVA

SEQ ID NO: 287

SGYWIC

SEQ ID NO: 288

CIYTGSSGSTFYASWAKG

SEQ ID NO: 289

GYSGFGYFKL

SEQ ID NO: 290

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCATTCGAATTGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACA
GTCACCATCAATTGCCAGGCCAGTCAGAACATTTATAGATACTTAGCCTGGTATCAGCAG
AAACCAGGGCAGCCTCCCAAGTTCCTGATCTATCTGGCATCTACTCTGGCATCTGGGGTCC
CATCGCGGTTTAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGG
AGTGTGCCGATGCTGCCACTTACTACTGTCAAAGTTATTATAGTAGTAATAGTGTCGCT

SEQ ID NO: 291

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGG
AGCAGCTGGTGGAGTCCGGGGGAGACCTGGTCCAGCCTGAGGGATCCCTGACACTCACCT
GCACAGCTTCTGAGTTAGACTTCAGTAGCGGCTACTGGATATGCTGGGTCCGCCAGGTTCC
AGGGAAGGGGCTGGAGTGGATCGGATGCATTTATACTGGTAGTAGTGGTAGCACTTTTTA
CGCGAGTTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCT
GCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGAGGTTATAG
TGGCTTTGGTTACTTTAAGTTG

SEQ ID NO: 292

CAGGCCAGTCAGAACATTTATAGATACTTAGCC

SEQ ID NO: 293

CTGGCATCTACTCTGGCATCT

SEQ ID NO: 294

CAAAGTTATTATAGTAGTAATAGTGTCGCT

SEQ ID NO: 295

AGCGGCTACTGGATATGC

SEQ ID NO: 296

TGCATTTATACTGGTAGTAGTGGTAGCACTTTTTACGCGAGTTGGGCGAAAGGC

SEQ ID NO: 297

GGTTATAGTGGCTTTGGTTACTTTAAGTTG

SEQ ID NO: 298

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQASEDIYRLLAWYQQK
PGQPPKLLIYDSSDLASGVPSRFKGSGSGTEFTLAISGVQCDDAATYYCQQAWSYSDIDNA

SEQ ID NO: 299

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTASGFSLSSYYMSWVRQAPGKG
LEWIGIITTSGNTFYASWAKGRLTISRTSTTVDLKITSPTTEDTATYFCARTSDIFYYRNL

SEQ ID NO: 300

QASEDIYRLLA

SEQ ID NO: 301

DSSDLAS

SEQ ID NO: 302

QQAWSYSDIDNA

SEQ ID NO: 303

SYYMS

SEQ ID NO: 304

IITTSGNTFYASWAKG

SEQ ID NO: 305

TSDIFYYRNL

SEQ ID NO: 306

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTGAGGACATTTATAGGTTATTGGCCTGGTATCAACAG
AAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGATTCATCCGATCTGGCATCTGGGGTCC
CATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCGCCATCAGCGGTGTGC
AGTGTGACGATGCTGCCACTTACTACTGTCAACAGGCTTGGAGTTATAGTGATATTGATAA
TGCT

SEQ ID NO: 307

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCGGGGACACCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTCAGTAGCTACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGAATCATTACTACTAGTGGTAATACATTTTACGCGAGCTGGGC
GAAAGGCCGGCTCACCATCTCCAGAACCTCGACCACGGTGGATCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAACTTCTGATATTTTTTATTATCGT
AACTTG

SEQ ID NO: 308

CAGGCCAGTGAGGACATTTATAGGTTATTGGCC

SEQ ID NO: 309

GATTCATCCGATCTGGCATCT

SEQ ID NO: 310

CAACAGGCTTGGAGTTATAGTGATATTGATAATGCT

SEQ ID NO: 311

AGCTACTACATGAGC

SEQ ID NO: 312

ATCATTACTACTAGTGGTAATACATTTTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 313

ACTTCTGATATTTTTTATTATCGTAACTTG

SEQ ID NO: 314

MDTRAPTQLLGLLLLWLPGATFAAVLTQTASPVSAAVGATVTINCQSSQSVYNDMDLAWFQ
QKPGQPPKLLIYSASTLASGVPSRFSGSGSGTEFTLTISGVQCDDAATYYCLGAFDDDADNT

SEQ ID NO: 315

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLTRHAITWVRQAPGKG
LEWIGCIWSGGSTYYATWAKGRFTISKTSTTVDLRITSPTTEDTATYFCARVIGDTAGYAYFTG
LDL

SEQ ID NO: 316

QSSQSVYNDMDLA

SEQ ID NO: 317

SASTLAS

SEQ ID NO: 318

LGAFDDDADNT

SEQ ID NO: 319

RHAIT

SEQ ID NO: 320

CIWSGGSTYYATWAKG

SEQ ID NO: 321

VIGDTAGYAYFTGLDL

SEQ ID NO: 322

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACGTTTGCAGCCGTGCTGACCCAGACTGCATCACCCGTGTCTGCCGCTGTGGGAGCCACA
GTCACCATCAACTGCCAGTCCAGTCAGAGTGTTTATAATGACATGGACTTAGCCTGGTTTC
AGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATTCTGCATCCACTCTGGCATCTGG
GGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGG
CGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGCTTTTGATGATGATGCTGAT
AATACT

SEQ ID NO: 323

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGATTCTCCCTCACTAGGCATGCAATAACCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGATGCATTTGGAGTGGTGGTAGCACATACTACGCGACCTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTCAGAATCACCAGTCC
GACAACCGAGGACACGGCCACCTACTTCTGTGCCAGAGTCATTGGCGATACTGCTGGTTA
TGCTTATTTTACGGGGCTTGACTTG

SEQ ID NO: 324

CAGTCCAGTCAGAGTGTTTATAATGACATGGACTTAGCC

SEQ ID NO: 325

TCTGCATCCACTCTGGCATCT

SEQ ID NO: 326

CTAGGCGCTTTTGATGATGATGCTGATAATACT

SEQ ID NO: 327

AGGCATGCAATAACC

SEQ ID NO: 328

TGCATTTGGAGTGGTGGTAGCACATACTACGCGACCTGGGCGAAAGGC

SEQ ID NO: 329

GTCATTGGCGATACTGCTGGTTATGCTTATTTTACGGGGCTTGACTTG

SEQ ID NO: 330

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQASQSVYNWLSWYQQ
KPGQPPKLLIYTASSLASGVPSRFSGSGSGTEFTLTISGVECADAATYYCQQGYTSDVDNV

SEQ ID NO: 331

METGLRWLLLVAVLKGVQCQSLEEAGGRLVTPGTPLTLTCTVSGIDLSSYAMGWVRQAPGK
GLEYIGIISSSGSTYYATWAKGRFTISQASSTTVDLKITSPTTEDSATYFCARGGAGSGGVWLLD
GFDP

SEQ ID NO: 332

QASQSVYNWLS

SEQ ID NO: 333

TASSLAS

SEQ ID NO: 334

QQGYTSDVDNV

SEQ ID NO: 335

SYAMG

SEQ ID NO: 336

IISSSGSTYYATWAKG

SEQ ID NO: 337

GGAGSGGVWLLDGFDP

SEQ ID NO: 338

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTCAGAGTGTTTATAATTGGTTATCCTGGTATCAGCAGA
AACCAGGGCAGCCTCCCAAGCTCCTGATCTATACTGCATCCAGTCTGGCATCTGGGGTCCC
ATCGCGGTTCAGTGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGGCGTGGA
GTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATACTAGTGATGTTGATAATGTT

SEQ ID NO: 339

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGGCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGAATCGACCTCAGTAGCTATGCAATGGGCTGGGTCCGCCAGGCTCCAGGGA
AGGGGCTGGAATACATCGGAATCATTAGTAGTAGTGGTAGCACATACTACGCGACCTGGG
CGAAAGGCCGATTCACCATCTCACAAGCCTCGTCGACCACGGTGGATCTGAAAATTACCA
GTCCGACAACCGAGGACTCGGCCACATATTTCTGTGCCAGAGGGGGTGCTGGTAGTGGTG
GTGTTTGGCTGCTTGATGGTTTTGATCCC

SEQ ID NO: 340

CAGGCCAGTCAGAGTGTTTATAATTGGTTATCC

SEQ ID NO: 341

ACTGCATCCAGTCTGGCATCT

SEQ ID NO: 342

CAACAGGGTTATACTAGTGATGTTGATAATGTT

SEQ ID NO: 343

AGCTATGCAATGGGC

SEQ ID NO: 344

ATCATTAGTAGTAGTGGTAGCACATACTACGCGACCTGGGCGAAAGGC

SEQ ID NO: 345

GGGGGTGCTGGTAGTGGTGGTGTTTGGCTGCTTGATGGTTTTGATCCC

SEQ ID NO: 346

MDTRAPTQLLGLLLLWLPGAKCADVVMTQTPASVSAAVGGTVTINCQASENIYNWLAWYQQ
KPGQPPKLLIYTVGDLASGVSSRFKGSGSGTEFTLTISDLECADAATYYCQQGYSSSYVDNV

SEQ ID NO: 347

METGLRWLLLVAVLKGVQCQEQLKESGGRLVTPGTPLTLTCTVSGFSLNDYAVGWFRQAPG
KGLEWIGYIRSSGTTAYATWAKGRFTISATSTTVDLKITSPTTEDTATYFCARGGAGSSGVWIL
DGFAP

SEQ ID NO: 348

QASENIYNWLA

SEQ ID NO: 349

TVGDLAS

SEQ ID NO: 350

QQGYSSSYVDNV

SEQ ID NO: 351

DYAVG

SEQ ID NO: 352

YIRSSGTTAYATWAKG

SEQ ID NO: 353

GGAGSSGVWILDGFAP

SEQ ID NO: 354

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AAATGTGCCGATGTTGTGATGACCCAGACTCCAGCCTCCGTGTCTGCAGCTGTGGGAGGC
ACAGTCACCATCAATTGCCAGGCCAGTGAGAACATTTATAATTGGTTAGCCTGGTATCAGC
AGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATACTGTAGGCGATCTGGCATCTGGGG
TCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCT
GGAGTGTGCCGATGCTGCCACTTACTATTGTCAACAGGGTTATAGTAGTAGTTATGTTGAT
AATGTT

SEQ ID NO: 355

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGG
AGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCT
GCACAGTCTCTGGATTCTCCCTCAATGACTATGCAGTGGGCTGGTTCCGCCAGGCTCCAGG
GAAGGGGCTGGAATGGATCGGATACATTCGTAGTAGTGGTACCACAGCCTACGCGACCTG
GGCGAAAGGCCGATTCACCATCTCCGCTACCTCGACCACGGTGGATCTGAAAATCACCAG
TCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGGGTGCTGGTAGTAGTGG
TGTGTGGATCCTTGATGGTTTTGCTCCC

SEQ ID NO: 356

CAGGCCAGTGAGAACATTTATAATTGGTTAGCC

SEQ ID NO: 357

ACTGTAGGCGATCTGGCATCT

SEQ ID NO: 358

CAACAGGGTTATAGTAGTAGTTATGTTGATAATGTT

SEQ ID NO: 359

GACTATGCAGTGGGC

SEQ ID NO: 360

TACATTCGTAGTAGTGGTACCACAGCCTACGCGACCTGGGCGAAAGGC

SEQ ID NO: 361

GGGGGTGCTGGTAGTAGTGGTGTGTGGATCCTTGATGGTTTTGCTCCC

SEQ ID NO: 362

MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSSVSAAVGGTVTINCQASQSVYQNNYLSWFQQ
KPGQPPKLLIYGAATLASGVPSRFKGSGSGTQFTLTISDLECDDAATYYCAGAYRDVDS

SEQ ID NO: 363

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPGASLTLTCTASGFSFTSTYYIYWVRQAPGK
GLEWIACIDAGSSGSTYYATWVNGRFTISKTSSTTVTLQMTSLTAADTATYFCAKWDYGGNV
GWGYDL

SEQ ID NO: 364

QASQSVYQNNYLS

SEQ ID NO: 365

GAATLAS

SEQ ID NO: 366

AGAYRDVDS

SEQ ID NO: 367

STYYIY

SEQ ID NO: 368

CIDAGSSGSTYYATWVNG

SEQ ID NO: 369

WDYGGNVGWGYDL

SEQ ID NO: 370

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCTCAAGTGCTGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAG
TCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCAGAACAACTACTTATCCTGGTTTCA
GCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGCGGCCACTCTGGCATCTGG
GGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGA
CCTGGAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGCTTATAGGGATGTGGATTCT

SEQ ID NO: 371

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGGGGCATCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCTTTACTAGTACCTACTACATCTACTGGGTCCGCCAGGCTCCAGG
GAAGGGGCTGGAGTGGATCGCATGTATTGATGCTGGTAGTAGTGGTAGCACTTACTACGC
GACCTGGGTGAATGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCA
AATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAAATGGGATTATGG
TGGTAATGTTGGTTGGGGTTATGACTTG

SEQ ID NO: 372

CAGGCCAGTCAGAGTGTTTATCAGAACAACTACTTATCC

SEQ ID NO: 373

GGTGCGGCCACTCTGGCATCT

SEQ ID NO: 374

GCAGGCGCTTATAGGGATGTGGATTCT

SEQ ID NO: 375

AGTACCTACTACATCTAC

SEQ ID NO: 376

TGTATTGATGCTGGTAGTAGTGGTAGCACTTACTACGCGACCTGGGTGAATGGC

SEQ ID NO: 377

TGGGATTATGGTGGTAATGTTGGTTGGGGTTATGACTTG

SEQ ID NO: 378

MDTRAPTQLLGLLLLWLPGARCAFELTQTPSSVEAAVGGTVTIKCQASQSISSYLAWYQQKPG
QPPKFLIYRASTLASGVPSRFKGSGSGTEFTLTISDLECADAATYYCQSYYDSVSNP

SEQ ID NO: 379

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCKASGLDLGTYWFMCWVRQAPG
KGLEWIACIYTGSSGSTFYASWVNGRFTISKTSSTTVTLQMTSLTAADTATYFCARGYSGYGY
FKL

SEQ ID NO: 380

QASQSISSYLA

SEQ ID NO: 381

RASTLAS

SEQ ID NO: 382

QSYYDSVSNP

SEQ ID NO: 383

TYWFMC

SEQ ID NO: 384

CIYTGSSGSTFYASWVNG

SEQ ID NO: 385

GYSGYGYFKL

SEQ ID NO: 386

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCATTCGAATTGACCCAGACTCCATCCTCCGTGGAGGCAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTCAGAGCATTAGTAGTTACTTAGCCTGGTATCAGCAG
AAACCAGGGCAGCCTCCCAAGTTCCTGATCTACAGGGCGTCCACTCTGGCATCTGGGGTC
CCATCGCGATTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTG
GAGTGTGCCGATGCTGCCACTTACTACTGTCAAAGCTATTATGATAGTGTTTCAAATCCT

SEQ ID NO: 387

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGGGATCCCTGACACTCACCTGCA
AAGCCTCTGGACTCGACCTCGGTACCTACTGGTTCATGTGCTGGGTCCGCCAGGCTCCAGG
GAAGGGGCTGGAGTGGATCGCTTGTATTTATACTGGTAGTAGTGGTTCCACTTTCTACGCG
AGCTGGGTGAATGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAA
ATGACCAGTCTGACAGCCGCGGACACGGCCACTTATTTTTGTGCGAGAGGTTATAGTGGTT
ATGGTTATTTTAAGTTG

SEQ ID NO: 388

CAGGCCAGTCAGAGCATTAGTAGTTACTTAGCC

SEQ ID NO: 389

AGGGCGTCCACTCTGGCATCT

SEQ ID NO: 390

CAAAGCTATTATGATAGTGTTTCAAATCCT

SEQ ID NO: 391

ACCTACTGGTTCATGTGC

SEQ ID NO: 392

TGTATTTATACTGGTAGTAGTGGTTCCACTTTCTACGCGAGCTGGGTGAATGGC

SEQ ID NO: 393

GGTTATAGTGGTTATGGTTATTTTAAGTTG

SEQ ID NO: 394

MDTRAPTQLLGLLLLWLPGVTFAIEMTQSPFSVSAAVGGTVSISCQASQSVYKNNQLSWYQQ
KSGQPPKLLIYGASALASGVPSRFKGSGSGTEFTLTISDVQCDDAATYYCAGAITGSIDTDG

SEQ ID NO: 395

METGLRWLLLVAVLKGVQCQSLEESGGDLVKPGASLTLTCTTSGFSFSSSYFICWVRQAPGKG
LEWIACIYGGDGSTYYASWAKGRFTISKTSSTTVTLQMTSLTAADTATYFCAREWAYSQGYF
GAFDL

SEQ ID NO: 396

QASQSVYKNNQLS

SEQ ID NO: 397

GASALAS

SEQ ID NO: 398

AGAITGSIDTDG

SEQ ID NO: 399

SSYFIC

SEQ ID NO: 400

CIYGGDGSTYYASWAKG

SEQ ID NO: 401

EWAYSQGYFGAFDL

SEQ ID NO: 402

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGTCA
CATTTGCCATCGAAATGACCCAGAGTCCATTCTCCGTGTCTGCAGCTGTGGGAGGCACAGT
CAGCATCAGTTGCCAGGCCAGTCAGAGTGTTTATAAGAACAACCAATTATCCTGGTATCA
GCAGAAATCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGCATCGGCTCTGGCATCTGG
GGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGA
CGTGCAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGCTATTACTGGTAGTATTGAT
ACGGATGGT

SEQ ID NO: 403

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGGGGCATCCCTGACACTCACCTGCA
CAACTTCTGGATTCTCCTTCAGTAGCAGCTACTTCATTTGCTGGGTCCGCCAGGCTCCAGG
GAAGGGGCTGGAGTGGATCGCATGCATTTATGGTGGTGATGGCAGCACATACTACGCGAG
CTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACGCTGCAAAT
GACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGAGAATGGGCATATAG
TCAAGGTTATTTTGGTGCTTTTGATCTC

SEQ ID NO: 404

CAGGCCAGTCAGAGTGTTTATAAGAACAACCAATTATCC

SEQ ID NO: 405

GGTGCATCGGCTCTGGCATCT

SEQ ID NO: 406

GCAGGCGCTATTACTGGTAGTATTGATACGGATGGT

SEQ ID NO: 407

AGCAGCTACTTCATTTGC

SEQ ID NO: 408

TGCATTTATGGTGGTGATGGCAGCACATACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 409

GAATGGGCATATAGTCAAGGTTATTTTGGTGCTTTTGATCTC

SEQ ID NO: 410

MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQASEDISSYLAWYQQKP
GQPPKLLIYAASNLESGVSSRFKGSGSGTEYTLTISDLECADAATYYCQCTYGTISISDGNA

SEQ ID NO: 411

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFMTWVRQAPGEG
LEYIGFINPGGSAYYASWVKGRFTISKSSTTVDLKITSPTTEDTATYFCARVLIVSYGAFTI

SEQ ID NO: 412

QASEDISSYLA

SEQ ID NO: 413

AASNLES

SEQ ID NO: 414

QCTYGTISISDGNA

SEQ ID NO: 415

SYFMT

SEQ ID NO: 416

FINPGGSAYYASWVKG

SEQ ID NO: 417

VLIVSYGAFTI

SEQ ID NO: 418

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTGAGGATATTAGTAGCTACTTAGCCTGGTATCAGCAG
AAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGCTGCATCCAATCTGGAATCTGGGGTCT
CATCGCGATTCAAAGGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAGCGACCTGG
AGTGTGCCGATGCTGCCACCTATTACTGTCAATGTACTTATGGTACTATTTCTATTAGTGAT
GGTAATGCT

SEQ ID NO: 419

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAATGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGATTCTCCCTCAGTAGCTACTTCATGACCTGGGTCCGCCAGGCTCCAGGGGA
GGGGCTGGAATACATCGGATTCATTAATCCTGGTGGTAGCGCTTACTACGCGAGCTGGGT
GAAAGGCCGATTCACCATCTCCAAGTCCTCGACCACGGTAGATCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGGTTCTGATTGTTTCTTATGGAGCC
TTTACCATC

SEQ ID NO: 420

CAGGCCAGTGAGGATATTAGTAGCTACTTAGCC

SEQ ID NO: 421

GCTGCATCCAATCTGGAATCT

SEQ ID NO: 422

CAATGTACTTATGGTACTATTTCTATTAGTGATGGTAATGCT

SEQ ID NO: 423

AGCTACTTCATGACC

SEQ ID NO: 424

TTCATTAATCCTGGTGGTAGCGCTTACTACGCGAGCTGGGTGAAAGGC

SEQ ID NO: 425

GTTCTGATTGTTTCTTATGGAGCCTTTACCATC

SEQ ID NO: 426

MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVSAAVGGTVTIKCQASEDIESYLAWYQQKP
GQPPKLLIYGASNLESGVSSRFKGSGSGTEFTLTISDLECADAATYYCQCTYGIISISDGNA

SEQ ID NO: 427

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFMTWVRQAPGEG
LEYIGFMNTGDNAYYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFCARVLVVAYGAFNI

SEQ ID NO: 428

QASEDIESYLA

SEQ ID NO: 429

GASNLES

SEQ ID NO: 430

QCTYGIISISDGNA

SEQ ID NO: 431

SYFMT

SEQ ID NO: 432

FMNTGDNAYYASWAKG

SEQ ID NO: 433

VLVVAYGAFNI

SEQ ID NO: 434

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGTCTGCAGCTGTGGGAGGCACA

GTCACCATCAAGTGCCAGGCCAGTGAGGACATTGAAAGCTATCTAGCCTGGTATCAGCAG
AAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGCATCCAATCTGGAATCTGGGGTCT
CATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGG
AGTGTGCCGATGCTGCCACTTACTATTGTCAATGCACTTATGGTATTATTAGTATTAGTGA
TGGTAATGCT

SEQ ID NO: 435

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTGTCTGGATTCTCCCTCAGTAGCTACTTCATGACCTGGGTCCGCCAGGCTCCAGGGGA
GGGGCTGGAATACATCGGATTCATGAATACTGGTGATAACGCATACTACGCGAGCTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGGTTCTTGTTGTTGCTTATGGAGCC
TTTAACATC

SEQ ID NO: 436

CAGGCCAGTGAGGACATTGAAAGCTATCTAGCC

SEQ ID NO: 437

GGTGCATCCAATCTGGAATCT

SEQ ID NO: 438

CAATGCACTTATGGTATTATTAGTATTAGTGATGGTAATGCT

SEQ ID NO: 439

AGCTACTTCATGACC

SEQ ID NO: 440

TTCATGAATACTGGTGATAACGCATACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 441

GTTCTTGTTGTTGCTTATGGAGCCTTTAACATC

SEQ ID NO: 442

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSEPVGGTVSISCQSSKSVMNNNYLAWYQQ
KPGQPPKLLIYGASNLASGVPSRFSGSGSGTQFTLTISDVQCDDAATYYCQGGYTGYSDHGT

SEQ ID NO: 443

METGLRWLLLVAVLKGVQCQSVEESGGRLVKPDETLTLTCTVSGIDLSSYPMNWVRQAPGK
GLEWIGFINTGGTIVYASWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCARGSYVSSGYAYYF
NV

SEQ ID NO: 444

QSSKSVMNNNYLA

SEQ ID NO: 445

GASNLAS

SEQ ID NO: 446

QGGYTGYSDHGT

SEQ ID NO: 447

SYPMN

SEQ ID NO: 448

FINTGGTIVYASWAKG

SEQ ID NO: 449

GSYVSSGYAYYFNV

SEQ ID NO: 450

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTCTGAACCTGTGGGAGGCACAG
TCAGCATCAGTTGCCAGTCCAGTAAGAGTGTTATGAATAACAACTACTTAGCCTGGTATCA
GCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGCATCCAATCTGGCATCTGG
GGTCCCATCACGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGA
CGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCGGTTATACTGGTTATAGTGAT
CATGGGACT

SEQ ID NO: 451

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCAAGCCTGACGAAACCCTGACACTCACCTGCA
CAGTCTCTGGAATCGACCTCAGTAGCTATCCAATGAACTGGGTCCGCCAGGCTCCAGGGA
AGGGGCTGGAATGGATCGGATTCATTAATACTGGTGGTACCATAGTCTACGCGAGCTGGG
CAAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTC
CGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGCAGTTATGTTTCATCTGGTTA
TGCCTACTATTTTAATGTC

SEQ ID NO: 452

CAGTCCAGTAAGAGTGTTATGAATAACAACTACTTAGCC

SEQ ID NO: 453

GGTGCATCCAATCTGGCATCT

SEQ ID NO: 454

CAAGGCGGTTATACTGGTTATAGTGATCATGGGACT

SEQ ID NO: 455

AGCTATCCAATGAAC

SEQ ID NO: 456

TTCATTAATACTGGTGGTACCATAGTCTACGCGAGCTGGGCAAAAGGC

SEQ ID NO: 457

GGCAGTTATGTTTCATCTGGTTATGCCTACTATTTTAATGTC

SEQ ID NO: 458

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQSSQSVYNNNWLSWFQQ
KPGQPPKLLIYKASTLASGVPSRFKGSGSGTQFTLTISDVQCDDVATYYCAGGYLDSVI

SEQ ID NO: 459

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSTYSINWVRQAPGKG
LEWIGIIANSGTTFYANWAKGRFTVSKTSTTVDLKITSPTTEDTATYFCARESGMYNEYGKFNI

SEQ ID NO: 460

QSSQSVYNNNWLS

SEQ ID NO: 461

KASTLAS

SEQ ID NO: 462

AGGYLDSVI

SEQ ID NO: 463

TYSIN

SEQ ID NO: 464

IIANSGTTFYANWAKG

SEQ ID NO: 465

ESGMYNEYGKFNI

SEQ ID NO: 466

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTCTGCAGCTGTGGGAGGCACAG
TCAGCATCAGTTGCCAGTCCAGTCAGAGTGTTTATAATAACAACTGGTTATCCTGGTTTCA
GCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAAGGCATCCACTCTGGCATCTGG
GGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGA
CGTGCAGTGTGACGATGTTGCCACTTACTACTGTGCGGGCGGTTATCTTGATAGTGTTATT

SEQ ID NO: 467

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGATTCTCCCTCAGTACCTATTCAATAAACTGGGTCCGCCAGGCTCCAGGGAA
GGGCCTGGAATGGATCGGAATCATTGCTAATAGTGGTACCACATTCTACGCGAACTGGGC
GAAAGGCCGATTCACCGTCTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGAGAGTGGAATGTACAATGAATA
TGGTAAATTTAACATC

SEQ ID NO: 468

CAGTCCAGTCAGAGTGTTTATAATAACAACTGGTTATCC

SEQ ID NO: 469

AAGGCATCCACTCTGGCATCT

SEQ ID NO: 470

GCGGGCGGTTATCTTGATAGTGTTATT

SEQ ID NO: 471

ACCTATTCAATAAAC

SEQ ID NO: 472

ATCATTGCTAATAGTGGTACCACATTCTACGCGAACTGGGCGAAAGGC

SEQ ID NO: 473

GAGAGTGGAATGTACAATGAATATGGTAAATTTAACATC

SEQ ID NO: 474

MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINCQASENIYSFLAWYQQKP
GQPPKLLIFKASTLASGVSSRFKGSGSGTQFTLTISDLECDDAATYYCQQGATVYDIDNN

SEQ ID NO: 475

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGIDLSAYAMIWVRQAPGEG
LEWITIIYPNGITYYANWAKGRFTVSKTSTAMDLKITSPTTEDTATYFCARDAESSKNAYWGY
FNV

SEQ ID NO: 476

QASENIYSFLA

SEQ ID NO: 477

KASTLAS

SEQ ID NO: 478

QQGATVYDIDNN

SEQ ID NO: 479

AYAMI

SEQ ID NO: 480

IIYPNGITYYANWAKG

SEQ ID NO: 481

DAESSKNAYWGYFNV

SEQ ID NO: 482

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTCTGATATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAG
TCACCATCAATTGCCAGGCCAGTGAGAACATTTATAGCTTTTTGGCCTGGTATCAGCAGAA
ACCAGGGCAGCCTCCCAAGCTCCTGATCTTCAAGGCTTCCACTCTGGCATCTGGGGTCTCA
TCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACCTGGAG
TGTGACGATGCTGCCACTTACTACTGTCAACAGGGTGCTACTGTGTATGATATTGATAATA
AT

SEQ ID NO: 483

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTTTCTGGAATCGACCTCAGTGCCTATGCAATGATCTGGGTCCGCCAGGCTCCAGGGG
AGGGGCTGGAATGGATCACAATCATTTATCCTAATGGTATCACATACTACGCGAACTGGG
CGAAAGGCCGATTCACCGTCTCCAAAACCTCGACCGCGATGGATCTGAAAATCACCAGTC
CGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGCAGAAAGTAGTAAGAATG
CTTATTGGGGCTACTTTAACGTC

SEQ ID NO: 484

CAGGCCAGTGAGAACATTTATAGCTTTTTGGCC

SEQ ID NO: 485

AAGGCTTCCACTCTGGCATCT

SEQ ID NO: 486

CAACAGGGTGCTACTGTGTATGATATTGATAATAAT

SEQ ID NO: 487

GCCTATGCAATGATC

SEQ ID NO: 488

ATCATTTATCCTAATGGTATCACATACTACGCGAACTGGGCGAAAGGC

SEQ ID NO: 489

GATGCAGAAAGTAGTAAGAATGCTTATTGGGGCTACTTTAACGTC

SEQ ID NO: 490

MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINCQASENIYSFLAWYQQKP
GQPPKLLIFRASTLASGVSSRFKGSGSGTQFTLTISDLECDDAATYYCQQGATVYDIDNN

SEQ ID NO: 491

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGIDLSAYAMIWVRQAPGEG
LEWITIIYPNGITYYANWAKGRFTVSKTSTAMDLKITSPTTEDTATYFCARDAESSKNAYWGY
FNV

SEQ ID NO: 492

QASENIYSFLA

SEQ ID NO: 493

RASTLAS

SEQ ID NO: 494

QQGATVYDIDNN

SEQ ID NO: 495

AYAMI

SEQ ID NO: 496

IIYPNGITYYANWAKG

SEQ ID NO: 497

DAESSKNAYWGYFNV

SEQ ID NO: 498

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTCTGATATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAG
TCACCATCAATTGCCAGGCCAGTGAGAACATTTATAGCTTTTTGGCCTGGTATCAGCAGAA
ACCAGGGCAGCCTCCCAAGCTCCTGATCTTCAGGGCTTCCACTCTGGCATCTGGGGTCTCA
TCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACCTGGAG
TGTGACGATGCTGCCACTTACTACTGTCAACAGGGTGCTACTGTGTATGATATTGATAATA
AT

SEQ ID NO: 499

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTTTCTGGAATCGACCTCAGTGCCTATGCAATGATCTGGGTCCGCCAGGCTCCAGGGG
AGGGGCTGGAATGGATCACAATCATTTATCCTAATGGTATCACATACTACGCGAACTGGG
CGAAAGGCCGATTCACCGTCTCCAAAACCTCGACCGCGATGGATCTGAAAATCACCAGTC
CGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGCAGAAAGTAGTAAGAATG
CTTATTGGGGCTACTTTAACGTC

SEQ ID NO: 500

CAGGCCAGTGAGAACATTTATAGCTTTTTGGCC

SEQ ID NO: 501

AGGGCTTCCACTCTGGCATCT

SEQ ID NO: 502

CAACAGGGTGCTACTGTGTATGATATTGATAATAAT

SEQ ID NO: 503

GCCTATGCAATGATC

SEQ ID NO: 504

ATCATTTATCCTAATGGTATCACATACTACGCGAACTGGGCGAAAGGC

SEQ ID NO: 505

GATGCAGAAAGTAGTAAGAATGCTTATTGGGGCTACTTTAACGTC

SEQ ID NO: 506

MDTRAPTQLLGLLLLWLPGATFAIEMTQTPSPVSAAVGGTVTINCQASESVFNNMLSWYQQK
PGHSPKLLIYDASDLASGVPSRFKGSGSGTQFTLTISGVECDDAATYYCAGYKSDSNDGDNV

SEQ ID NO: 507

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLNRNSITWVRQAPGEGL
EWIGIITGSGRTYYANWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCARGHPGLGSGNI

SEQ ID NO: 508

QASESVFNNMLS

SEQ ID NO: 509

DASDLAS

SEQ ID NO: 510

AGYKSDSNDGDNV

SEQ ID NO: 511

RNSIT

SEQ ID NO: 512

IITGSGRTYYANWAKG

SEQ ID NO: 513

GHPGLGSGNI

SEQ ID NO: 514

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCATTGAAATGACCCAGACTCCATCCCCCGTGTCTGCCGCTGTGGGAGGCACAG
TCACCATCAATTGCCAGGCCAGTGAGAGTGTTTTTAATAATATGTTATCCTGGTATCAGCA
GAAACCAGGGCACTCTCCTAAGCTCCTGATCTATGATGCATCCGATCTGGCATCTGGGGTC
CCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGTGGCGTG
GAGTGTGACGATGCTGCCACTTACTATTGTGCAGGGTATAAAAGTGATAGTAATGATGGC
GATAATGTT

SEQ ID NO: 515

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA

CAGTCTCTGGATTCTCCCTCAACAGGAATTCAATAACCTGGGTCCGCCAGGCTCCAGGGG
AGGGGCTGGAATGGATCGGAATCATTACTGGTAGTGGTAGAACGTACTACGCGAACTGGG
CAAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTC
CGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGCCATCCTGGTCTTGGTAGTG
GTAACATC

SEQ ID NO: 516

CAGGCCAGTGAGAGTGTTTTTAATAATATGTTATCC

SEQ ID NO: 517

GATGCATCCGATCTGGCATCT

SEQ ID NO: 518

GCAGGGTATAAAAGTGATAGTAATGATGGCGATAATGTT

SEQ ID NO: 519

AGGAATTCAATAACC

SEQ ID NO: 520

ATCATTACTGGTAGTGGTAGAACGTACTACGCGAACTGGGCAAAAGGC

SEQ ID NO: 521

GGCCATCCTGGTCTTGGTAGTGGTAACATC

SEQ ID NO: 522

MDTRAPTQLLGLLLLWLPGATFAQVLTQTASSVSAAVGGTVTINCQSSQSVYNNYLSWYQQK
PGQPPKLLIYTASSLASGVPSRFKGSGSGTQFTLTISEVQCDDAATYYCQGYYSGPIIT

SEQ ID NO: 523

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLNNYYIQWVRQAPGEG
LEWIGIIYAGGSAYYATWANGRFTIAKTSSTTVDLKMTSLTTEDTATYFCARGTFDGYEL

SEQ ID NO: 524

QSSQSVYNNYLS

SEQ ID NO: 525

TASSLAS

SEQ ID NO: 526

QGYYSGPIIT

SEQ ID NO: 527

NYYIQ

SEQ ID NO: 528

IIYAGGSAYYATWANG

SEQ ID NO: 529

GTFDGYEL

SEQ ID NO: 530

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCGCAAGTGCTGACCCAGACTGCATCGTCCGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAATTGCCAGTCCAGTCAGAGTGTTTATAATAACTACTTATCCTGGTATCAGC
AGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATACTGCATCCAGCCTGGCATCTGGGG

TCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGAAG
TGCAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCTATTATAGTGGTCCTATAATTAC
T

SEQ ID NO: 531

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTCAATAACTACTACATACAATGGGTCCGCCAGGCTCCAGGGGA
GGGGCTGGAATGGATCGGGATCATTTATGCTGGTGGTAGCGCATACTACGCGACCTGGGC
AAACGGCCGATTCACCATCGCCAAAACCTCGTCGACCACGGTGGATCTGAAGATGACCAG
TCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGACATTTGATGGTTATGA
GTTG

SEQ ID NO: 532

CAGTCCAGTCAGAGTGTTTATAATAACTACTTATCC

SEQ ID NO: 533

ACTGCATCCAGCCTGGCATCT

SEQ ID NO: 534

CAAGGCTATTATAGTGGTCCTATAATTACT

SEQ ID NO: 535

AACTACTACATACAA

SEQ ID NO: 536

ATCATTTATGCTGGTGGTAGCGCATACTACGCGACCTGGGCAAACGGC

SEQ ID NO: 537

GGGACATTTGATGGTTATGAGTTG

SEQ ID NO: 538

MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSVPVGDTVTISCQSSESVYSNNLLSWYQQK
PGQPPKLLIYRASNLASGVPSRFKGSGSGTQFTLTISGAQCDDAATYYCQGYYSGVINS

SEQ ID NO: 539

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFMSWVRQAPGEG
LEYIGFINPGGSAYYASWASGRLTISKTSTTVDLKITSPTTEDTATYFCARILIVSYGAFTI

SEQ ID NO: 540

QSSESVYSNNLLS

SEQ ID NO: 541

RASNLAS

SEQ ID NO: 542

QGYYSGVINS

SEQ ID NO: 543

SYFMS

SEQ ID NO: 544

FINPGGSAYYASWASG

SEQ ID NO: 545

ILIVSYGAFTI

SEQ ID NO: 546

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCCAAGTGCTGACCCAGACTCCATCCCCTGTGTCTGTCCCTGTGGGAGACACAG
TCACCATCAGTTGCCAGTCCAGTGAGAGCGTTTATAGTAATAACCTCTTATCCTGGTATCA
GCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAGGGCATCCAATCTGGCATCTGG
TGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGG
CGCACAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCTATTATAGTGGTGTCATTAAT
AGT

SEQ ID NO: 547

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTGTCTGGATTCTCCCTCAGTAGCTACTTCATGAGCTGGGTCCGCCAGGCTCCAGGGGA
GGGGCTGGAATACATCGGATTCATTAATCCTGGTGGTAGCGCATACTACGCGAGCTGGGC
GAGTGGCCGACTCACCATCTCCAAAACCTCGACCACGGTAGATCTGAAAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGATTCTTATTGTTTCTTATGGAGCC
TTTACCATC

SEQ ID NO: 548

CAGTCCAGTGAGAGCGTTTATAGTAATAACCTCTTATCC

SEQ ID NO: 549

AGGGCATCCAATCTGGCATCT

SEQ ID NO: 550

CAAGGCTATTATAGTGGTGTCATTAATAGT

SEQ ID NO: 551

AGCTACTTCATGAGC

SEQ ID NO: 552

TTCATTAATCCTGGTGGTAGCGCATACTACGCGAGCTGGGCGAGTGGC

SEQ ID NO: 553

ATTCTTATTGTTTCTTATGGAGCCTTTACCATC

SEQ ID NO: 554

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQATESIGNELSWYQQKP
GQAPKLLIYSASTLASGVPSRFKGSGSGTQFTLTITGVECDDAATYYCQQGYSSANIDNA

SEQ ID NO: 555

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLSKYYMSWVRQAPEKG
LKYIGYIDSTTVNTYYATWARGRFTISKTSTTVDLKITSPTSEDTATYFCARGSTYFTDGGHRL
DL

SEQ ID NO: 556

QATESIGNELS

SEQ ID NO: 557

SASTLAS

SEQ ID NO: 558

QQGYSSANIDNA

SEQ ID NO: 559

KYYMS

SEQ ID NO: 560

YIDSTTVNTYYATWARG

SEQ ID NO: 561

GSTYFTDGGHRLDL

SEQ ID NO: 562

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCACTGAGAGCATTGGCAATGAGTTATCCTGGTATCAGCAG
AAACCAGGGCAGGCTCCCAAGCTCCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCC
CATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCACCGGCGTGG
AGTGTGATGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTAGTGCTAATATTGATAA
TGCT

SEQ ID NO: 563

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CCGTCTCTGGATTCTCCCTCAGTAAGTACTACATGAGCTGGGTCCGCCAGGCTCCAGAGAA
GGGGCTGAAATACATCGGATACATTGATAGTACTACTGTTAATACATACTACGCGACCTG
GGCGAGAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAGATCACCAG
TCCGACAAGTGAGGACACGGCCACCTATTTCTGTGCCAGAGGAAGTACTTATTTTACTGAT
GGAGGCCATCGGTTGGATCTC

SEQ ID NO: 564

CAGGCCACTGAGAGCATTGGCAATGAGTTATCC

SEQ ID NO: 565

TCTGCATCCACTCTGGCATCT

SEQ ID NO: 566

CAACAGGGTTATAGTAGTGCTAATATTGATAATGCT

SEQ ID NO: 567

AAGTACTACATGAGC

SEQ ID NO: 568

TACATTGATAGTACTACTGTTAATACATACTACGCGACCTGGGCGAGAGGC

SEQ ID NO: 569

GGAAGTACTTATTTTACTGATGGAGGCCATCGGTTGGATCTC

SEQ ID NO: 570

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQATESIGNELSWYQQKP
GQAPKLLIYSASTLASGVPSRFKGSGSGTQFTLTITGVECDDAATYYCQQGYSSANIDNA

SEQ ID NO: 571

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLSTYNMGWVRQAPGK
GLEWIGSITIDGRTYYASWAKGRFTVSKSSTTVDLKMTSLTTGDTATYFCARILIVSYGAFTI

SEQ ID NO: 572

QATESIGNELS

SEQ ID NO: 573

SASTLAS

SEQ ID NO: 574

QQGYSSANIDNA

SEQ ID NO: 575

TYNMG

SEQ ID NO: 576

SITIDGRTYYASWAKG

SEQ ID NO: 577

ILIVSYGAFTI

SEQ ID NO: 578

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCACTGAGAGCATTGGCAATGAGTTATCCTGGTATCAGCAG
AAACCAGGGCAGGCTCCCAAGCTCCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCC
CATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCACCGGCGTGG
AGTGTGATGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTAGTGCTAATATTGATAA
TGCT

SEQ ID NO: 579

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTAACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGATTCTCCCTCAGTACCTACAACATGGGCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGAAGTATTACTATTGATGGTCGCACATACTACGCGAGCTGGGC
GAAAGGCCGATTCACCGTCTCCAAAAGCTCGACCACGGTGGATCTGAAAATGACCAGTCT
GACAACCGGGGACACGGCCACCTATTTCTGTGCCAGGATTCTTATTGTTTCTTATGGGGCC
TTTACCATC

SEQ ID NO: 580

CAGGCCACTGAGAGCATTGGCAATGAGTTATCC

SEQ ID NO: 581

TCTGCATCCACTCTGGCATCT

SEQ ID NO: 582

CAACAGGGTTATAGTAGTGCTAATATTGATAATGCT

SEQ ID NO: 583

ACCTACAACATGGGC

SEQ ID NO: 584

AGTATTACTATTGATGGTCGCACATACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 585

ATTCTTATTGTTTCTTATGGGGCCTTTACCATC

SEQ ID NO: 586

VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 587

GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTG
CCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGT
GGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG
ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACAC
AAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTC
AACAGGGGAGAGTGT

SEQ ID NO: 588

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK

SEQ ID NO: 589

GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGG
GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT
GGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAG
GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCA
AATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGAC
CGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGA
GGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGG
AGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCA
AAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAG
ATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT
GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG
GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 590

VPPGEDSKDVAAPHR

SEQ ID NO: 591

GEDSKDVAAPHRQPL

SEQ ID NO: 592

SKDVAAPHRQPLTSS

SEQ ID NO: 593

VAAPHRQPLTSSERI

SEQ ID NO: 594

PHRQPLTSSERIDKQ

SEQ ID NO: 595

QPLTSSERIDKQIRY

SEQ ID NO: 596

TSSERIDKQIRYILD

SEQ ID NO: 597

ERIDKQIRYILDGIS

SEQ ID NO: 598

DKQIRYILDGISALR

SEQ ID NO: 599

IRYILDGISALRKET

SEQ ID NO: 600

ILDGISALRKETCNK

SEQ ID NO: 601

GISALRKETCNKSNM

SEQ ID NO: 602

ALRKETCNKSNMCES

SEQ ID NO: 603

KETCNKSNMCESSKE

SEQ ID NO: 604

CNKSNMCESSKEALA

SEQ ID NO: 605

SNMCESSKEALAENN

SEQ ID NO: 606

CESSKEALAENNLNL

SEQ ID NO: 607

SKEALAENNLNLPKM

SEQ ID NO: 608

ALAENNLNLPKMAEK

SEQ ID NO: 609

ENNLNLPKMAEKDGC

SEQ ID NO: 610

LNLPKMAEKDGCFQS

SEQ ID NO: 611

PKMAEKDGCFQSGFN

SEQ ID NO: 612

AEKDGCFQSGFNEET

SEQ ID NO: 613

DGCFQSGFNEETCLV

SEQ ID NO: 614

FQSGFNEETCLVKII

SEQ ID NO: 615

GFNEETCLVKIITGL

SEQ ID NO: 616

EETCLVKIITGLLEF

SEQ ID NO: 617

CLVKIITGLLEFEVY

SEQ ID NO: 618

KIITGLLEFEVYLEY

SEQ ID NO: 619

TGLLEFEVYLEYLQN

SEQ ID NO: 620

LEFEVYLEYLQNRFE

SEQ ID NO: 621

EVYLEYLQNRFESSE

SEQ ID NO: 622

LEYLQNRFESSEEQA

SEQ ID NO: 623

LQNRFESSEEQARAV

SEQ ID NO: 624

RFESSEEQARAVQMS

SEQ ID NO: 625

SSEEQARAVQMSTKV

SEQ ID NO: 626

EQARAVQMSTKVLIQ

SEQ ID NO: 627

RAVQMSTKVLIQFLQ

SEQ ID NO: 628

QMSTKVLIQFLQKKA

SEQ ID NO: 629

TKVLIQFLQKKAKNL

SEQ ID NO: 630

LIQFLQKKAKNLDAI

SEQ ID NO: 631

FLQKKAKNLDAITTP

SEQ ID NO: 632

KKAKNLDAITTPDPT

SEQ ID NO: 633

KNLDAITTPDPTTNA

SEQ ID NO: 634

DAITTPDPTTNASLL

SEQ ID NO: 635

TTPDPTTNASLLTKL

SEQ ID NO: 636

DPTTNASLLTKLQAQ

SEQ ID NO: 637

TNASLLTKLQAQNQW

SEQ ID NO: 638

SLLTKLQAQNQWLQD

SEQ ID NO: 639

TKLQAQNQWLQDMTT

SEQ ID NO: 640

QAQNQWLQDMTTHLI

SEQ ID NO: 641

NQWLQDMTTHLILRS

SEQ ID NO: 642

LQDMTTHLILRSFKE

SEQ ID NO: 643

MTTHLILRSFKEFLQ

SEQ ID NO: 644

HLILRSFKEFLQSSL

SEQ ID NO: 645

LRSFKEFLQSSLRAL

SEQ ID NO: 646

FKEFLQSSLRALRQM

SEQ ID NO: 647

AYDMTQTPASVSAAVGGTVTIKCQASQSINNELSWYQQKPGQRPKLLIYRASTLASGVSSRFK
GSGSGTEFTLTISDLECADAATYYCQQGYSLRNIDNAFGGGTEVVVKR

SEQ ID NO: 648

AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYC

SEQ ID NO: 649

DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKVPKLLIYAASTLQSGVPSRFSG
SGSGTDFTLTISSLQPEDVATYYC

SEQ ID NO: 650

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGS
GSGTEFTLTISSLQPDDFATYYC

SEQ ID NO: 651

AIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCQQGYSLRNIDNAFGGGTKVEIKR

SEQ ID NO: 652

QSLEESGGRLVTPGTPLTLTCTASGFSLSNYYVTWVRQAPGKGLEWIGIIYGSDETAYATWAIG
RFTISKTSTTVDLKMTSLTAADTATYFCARDDSSDWDAKFNLWGQGTLVTVSS

SEQ ID NO: 653

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

SEQ ID NO: 654

EVQLVESGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

SEQ ID NO: 655

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSVIYSGGSSTYYAD
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK

SEQ ID NO: 656

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYATW
AIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSS

SEQ ID NO: 657

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYATS
AIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSS

SEQ ID NO: 658

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYVTWVRQAPGKG
LEWIGIIYGSDETAYATSAIGRFTISKTSTTVDLKMTSLTAADTATYFCARDDSSDWDAKFNLW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

SEQ ID NO: 659

IIYGSDETAYATSAIG

SEQ ID NO: 660

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQASQSINNELSWYQQKP
GQRPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISDLECADAATYYCQQGYSLRNIDNA

SEQ ID NO: 661

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYVTWVRQAPGKG
LEWIGIIYGSDETAYATWAIGRFTISKTSTTVDLKMTSLTAADTATYFCARDDSSDWDAKFNL

SEQ ID NO: 662

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGGCCAGTCAGAGCATTAACAATGAATTATCCTGGTATCAGCAG

AAACCAGGGCAGCGTCCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTC
TCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTG
GAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTGAGGAATATTGATA
ATGCT

SEQ ID NO: 663

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGAATCATTTATGGTAGTGATGAAACGGCCTACGCGACCTGGGC
GATAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCT
GACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGC
AAAATTTAACTTG

SEQ ID NO: 664

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYATW
AIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK

SEQ ID NO: 665

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYATS
AIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK

SEQ ID NO: 666

IQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGSG
SGTDFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 667

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTINCQASETIYSWLSWYQQK
PGQPPKLLIYQASDLASGVPSRFSGSGAGTEYTLTISGVQCDDAATYYCQQGYSGSNVDNV

SEQ ID NO: 668

METGLRWLLLVAVLKGVQCQEQLKESGGRLVTPGTPLTLTCTASGFSLNDHAMGWVRQAPG
KGLEYIGFINSGGSARYASWAEGRFTISRTSTTVDLKMTSLTTEDTATYFCVRGGAVWSIHSFD
P

SEQ ID NO: 669

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACA
GTCACCATCAATTGCCAGGCCAGTGAGACCATTTACAGTTGGTTATCCTGGTATCAGCAGA
AGCCAGGGCAGCCTCCCAAGCTCCTGATCTACCAGGCATCCGATCTGGCATCTGGGGTCC
CATCGCGATTCAGCGGCAGTGGGGCTGGGACAGAGTACACTCTCACCATCAGCGGCGTGC
AGTGTGACGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTGGTAGTAATGTTGATAA
TGTT

SEQ ID NO: 670

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGG
AGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTTACCT
GCACAGCCTCTGGATTCTCCCTCAATGACCATGCAATGGGCTGGGTCCGCCAGGCTCCAG
GGAAGGGGCTGGAATACATCGGATTCATTAATAGTGGTGGTAGCGCACGCTACGCGAGCT
GGGCAGAAGGCCGATTCACCATCTCCAGAACCTCGACCACGGTGGATCTGAAAATGACCA
GTCTGACAACCGAGGACACGGCCACCTATTTCTGTGTCAGAGGGGGTGCTGTTTGGAGTA
TTCATAGTTTTGATCCC

SEQ ID NO: 671

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQASQSVYDNNYLSWFQQ
KPGQPPKLLIYGASTLASGVPSRFVGSGSGTQFTLTITDVQCDDAATYYCAGVYDDDSDNA

SEQ ID NO: 672

METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSVYYMNWVRQAPGK
GLEWIGFITMSDNINYASWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCARSRGWGTMGRLD
L

SEQ ID NO: 673

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTCTGCAGCTGTGGGAGGCACAG
TCAGCATCAGTTGCCAGGCCAGTCAGAGTGTTTATGACAACAACTACTTATCCTGGTTTCA
GCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGCATCCACTCTGGCATCTGG
GGTCCCATCGCGGTTCGTGGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCACAGA
CGTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGGCGTTTATGATGATGATAGTGAT
AATGCC

SEQ ID NO: 674

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTGGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACCCCTGGGACACCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTCAGTGTCTACTACATGAACTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGATTCATTACAATGAGTGATAATATAAATTACGCGAGCTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCC

GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGAGTCGTGGCTGGGGTACAATGGG
TCGGTTGGATCTC

SEQ ID NO: 675

MDTRAPTQLLGLLLLWLPGAICDPVLTQTPSPVSAPVGGTVSISCQASQSVYENNYLSWFQQK
PGQPPKLLIYGASTLDSGVPSRFKGSGSGTQFTLTITDVQCDDAATYYCAGVYDDDSDDA

SEQ ID NO: 676

METGLRWLLLVAVLKGVQCQEQLKESGGGLVTPGGTLTLTCTASGFSLNAYYMNWVRQAPG
KGLEWIGFITLNNNVAYANWAKGRFTFSKTSTTVDLKMTSPTPEDTATYFCARSRGWGAMGR
LDL

SEQ ID NO: 677

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ATATGTGACCCTGTGCTGACCCAGACTCCATCTCCCGTATCTGCACCTGTGGGAGGCACAG
TCAGCATCAGTTGCCAGGCCAGTCAGAGTGTTTATGAGAACAACTATTTATCCTGGTTTCA
GCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGCATCCACTCTGGATTCTGG
GGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATTACAGA
CGTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGGCGTTTATGATGATGATAGTGAT
GATGCC

SEQ ID NO: 678

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTGGCTGTGCTCAAAGGTGTCCAGTGTCAGG
AGCAGCTGAAGGAGTCCGGAGGAGGCCTGGTAACGCCTGGAGGAACCCTGACACTCACCT
GCACAGCCTCTGGATTCTCCCTCAATGCCTACTACATGAACTGGGTCCGCCAGGCTCCAGG
GAAGGGGCTGGAATGGATCGGATTCATTACTCTGAATAATAATGTAGCTTACGCGAACTG
GGCGAAAGGCCGATTCACCTTCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAG
TCCGACACCCGAGGACACGGCCACCTATTTCTGTGCCAGGAGTCGTGGCTGGGGTGCAAT
GGGTCGGTTGGATCTC

SEQ ID NO: 679

MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSAAVGGTVTINCQASQSVDDNNWLGWYQ
QKRGQPPKYLIYSASTLASGVPSRFKGSGSGTQFTLTISDLECDDAATYYCAGGFSGNIFA

SEQ ID NO: 680

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGKG
LEWIGIIGGFGTTYYATWAKGRFTISKTSTTVDLRITSPTTEDTATYFCARGGPGNGGDI

SEQ ID NO: 681

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCCCAAGTGCTGACCCAGACTCCATCGCCTGTGTCTGCAGCTGTGGGAGGCACA
GTCACCATCAACTGCCAGGCCAGTCAGAGTGTTGATGATAACAACTGGTTAGGCTGGTAT
CAGCAGAAACGAGGGCAGCCTCCCAAGTACCTGATCTATTCTGCATCCACTCTGGCATCTG
GGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCG
ACCTGGAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGGTTTTAGTGGTAATATCTT
TGCT

SEQ ID NO: 682

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGTCTCTGGCTTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGAAA
GGGGCTGGAGTGGATCGGAATCATTGGTGGTTTTGGTACCACATACTACGCGACCTGGGC
GAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAGAATCACCAGTCC
GACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGTGGTCCTGGTAATGGTGGTGA
CATC

SEQ ID NO: 683

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSVPVGGTVTIKCQSSQSVYNNFLSWYQQKP
GQPPKLLIYQASKLASGVPDRFSGSGSGTQFTLTISGVQCDDAATYYCLGGYDDDADNA

SEQ ID NO: 684

METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGIDLSDYAMSWVRQAPGK
GLEWIGIIYAGSGSTWYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFCARDGYDDYGDFDR
LDL

SEQ ID NO: 685

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
ACATTTGCAGCCGTGCTGACCCAGACACCATCGCCCGTGTCTGTACCTGTGGGAGGCACA
GTCACCATCAAGTGCCAGTCCAGTCAGAGTGTTTATAATAATTTCTTATCGTGGTATCAGC
AGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACCAGGCATCCAAACTGGCATCTGGGG
TCCCAGATAGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGGCG
TGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGGTTATGATGATGATGCTGATAA
TGCT

SEQ ID NO: 686

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGT
CGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACGCTCACCTGCA
CAGTCTCTGGAATCGACCTCAGTGACTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGA
AGGGGCTGGAATGGATCGGAATCATTTATGCTGGTAGTGGTAGCACATGGTACGCGAGCT
GGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCA
GTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGATGGATACGATGACTATG
GTGATTTCGATCGATTGGATCTC

SEQ ID NO: 687

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQASQSINNELSWYQQKS
GQRPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISDLECADAATYYCQQGYSLRNIDNA

SEQ ID NO: 688

METGLRWLLLVAVLSGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYMTWVRQAPGKG
LEWIGMIYGSDETAYANWAIGRFTISKTSTTVDLKMTSLTAADTATYFCARDDSSDWDAKFN
L

SEQ ID NO: 689

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCC
AGATGTGCCTATGATATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACA

GTCACCATCAAATGCCAGGCCAGTCAGAGCATTAACAATGAATTATCCTGGTATCAGCAG
AAATCAGGGCAGCGTCCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCT
CATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGG
AGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTGAGGAATATTGATAA
TGCT

SEQ ID NO: 690

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCTCAGGTGTCCAGTGTCAGT
CGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCA
CAGCCTCTGGATTCTCCCTCAGTAACTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAA
GGGGCTGGAATGGATCGGAATGATTTATGGTAGTGATGAAACAGCCTACGCGAACTGGGC
GATAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCT
GACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGC
AAAATTTAACTTG

SEQ ID NO: 691

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYMTWVRQAPGKGLEWVGMIYGSDETAYAN
WAIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK

SEQ ID NO: 692

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYMTWVRQAPGKGLEWVGMIYGSDETAYAN
SAIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK

SEQ ID NO: 693

DIQMTQSPSTLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGS
GSGTEFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 694

CAGGCCAGTCAGAGCATTAACAATGAGTTATCC

SEQ ID NO: 695

CAACAGGGTTATAGTCTGAGGAACATTGATAATGCT

SEQ ID NO: 696

ATCATCTATGGTAGTGATGAAACCGCCTACGCTACCTCCGCTATAGGC

SEQ ID NO: 697

GATGATAGTAGTGACTGGGATGCAAAGTTCAACTTG

SEQ ID NO: 698

GCTATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCA
TCACTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAGAAACCAG
GGAAAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAA
GGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTG
ATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTT
CGGCGGAGGGACCAAGGTGGAAATCAAACGTACG

SEQ ID NO: 699

AIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGS
GSGTDFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKVEIKRT

SEQ ID NO: 700

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGTCAGGCTC
CAGGGAAGGGGCTGGAGTGGGTCGGCATCATCTATGGTAGTGATGAAACCGCCTACGCTA
CCTCCGCTATAGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTTCA
AATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGATAGTAG
TGACTGGGATGCAAAGTTCAACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC

SEQ ID NO: 701

GCTATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCA
TCACTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAGAAACCAG
GGAAAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAA
GGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTG
ATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTT
CGGCGGAGGGACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTT
CCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAAC
TTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC
TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCA
TCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 702

AIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGS
GSGTDFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 703

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGTCAGGCTC
CAGGGAAGGGGCTGGAGTGGGTCGGCATCATCTATGGTAGTGATGAAACCGCCTACGCTA
CCTCCGCTATAGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTTCA
AATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGATAGTAG
TGACTGGGATGCAAAGTTCAACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGCGC
CTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGC
ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG
AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGA
CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACA
TCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAA
TCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCG
TCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG
TCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGC
ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAG
TACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAA
GCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGAT
GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGC
CGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGC
AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGC
AGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 704

EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYATS
AIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKFNLWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK

SEQ ID NO: 705

ATGAAGTGGGTAACCTTTATTTCCCTTCTGTTTCTCTTTAGCAGCGCTTATTCCGCTATCCA
GATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGC
CAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCC
CCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCG
GCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGC
AACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTTCGGCGGAGG
GACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT

GATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCA
GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAG
AGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCT
GAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 706

MKWVTFISLLFLFSSAYSAIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKL
LIYRASTLASGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 707

ATGAAGTGGGTAACCTTTATTTCCCTTCTGTTTCTCTTTAGCAGCGCTTATTCCGAGGTGCA
GCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGC
AGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGTCAGGCTCCAGGGAAG
GGGCTGGAGTGGGTCGGCATCATCTATGGTAGTGATGAAACCGCCTACGCTACCTCCGCT
ATAGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTTCAAATGAAC
AGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGATAGTAGTGACTGG
GATGCAAAGTTCAACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGCGCCTCCACC
AAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG
GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA
GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACT
CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA
ACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTG
ACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCT
TCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATG
CGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACC
GTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGT
GCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG
GGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAG
AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAG
TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCC
GACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGC
CTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 708

MKWVTFISLLFLFSSAYSEVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGL
EWVGIIYGSDETAYATSAIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWDAKF
NLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA

PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 709

AIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPSRFSGS
GSGTDFTLTISSLQPDDFATYYCQQGYSLRNIDNAFGGGTKVEIKR

SEQ ID NO: 710

RASQGIRNDLG

SEQ ID NO: 711

RASQGISNYLA

SEQ ID NO: 712

RASQSISSWLA

SEQ ID NO: 713

AASSLQS

SEQ ID NO: 714

AASTLQS

SEQ ID NO: 715

KASSLES

SEQ ID NO: 716

SNYMS

SEQ ID NO: 717

VIYSGGSTYYADSVKG

SEQ ID NO: 718

VIYSGGSSTYYADSVKG

SEQ ID NO: 719

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK

SEQ ID NO: 720

ATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGA
AAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTT
CAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA
TTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCT

SEQ ID NO: 721

GCCTATGATATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACC
ATCAAGTGCCAGGCCAGTCAGAGCATTAACAATGAATTATCCTGGTATCAGCAGAAACCA
GGGCAGCGTCCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCTCATCGC
GGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTG
CCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTGAGGAATATTGATAATGCTTT
CGGCGGAGGGACCGAGGTGGTGGTCAAACGT

SEQ ID NO: 722

ATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA
CTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGA
AAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTT
CAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGA
TTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTTCGGC
GGAGGGACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCG
CCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT
ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC
AGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG
ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCA
GGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 723

GCTATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCA
TCACTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAGAAACCAG
GGAAAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAA
GGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTG
ATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTT
CGGCGGAGGGACCAAGGTGGAAATCAAACGT

SEQ ID NO: 724

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGTCAGGCTC
CAGGGAAGGGGCTGGAGTGGGTCGGCATCATCTATGGTAGTGATGAAACCGCCTACGCTA
CCTCCGCTATAGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACCCTGTATCTTCA
AATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGATAGTAG
TGACTGGGATGCAAAGTTCAACTTG

SEQ ID NO: 725

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACC
TGCACAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGCCAGGCTCCAG
GGAAGGGGCTGGAATGGATCGGAATCATTTATGGTAGTGATGAAACGGCCTACGCGACCT
GGGCGATAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCA
GTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGG
ATGCAAAATTTAACTTGTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGC

SEQ ID NO: 726

MEKLLCFLVLTSLSHAFGQTDMSRKAFVFPKESDTSYVSLKAPLTKPLKAFTVCLHFYTELSST
RGYSIFSYATKRQDNEILIFWSKDIGYSFTVGGSEILFEVPEVTVAPVHICTSWESASGIVEFWV
DGKPRVRKSLKKGYTVGAEASIILGQEQDSFGGNFEGSQSLVGDIGNVNMWDFVLSPDEINTI
YLGGPFSPNVLNWRALKYEVQGEVFTKPQLWP

SEQ ID NO: 727

MLAVGCALLAALLAAPGAALAPRRCPAQEVARGVLTSLPGDSVTLTCPGVEPEDNATVHWV
LRKPAAGSHPSRWAGMGRRLLLRSVQLHDSGNYSCYRAGRPAGTVHLLVDVPPEEPQLSCFR
KSPLSNVVCEWGPRSTPSLTTKAVLLVRKFQNSPAEDFQEPCQYSQESQKFSCQLAVPEGDSSF
YIVSMCVASSVGSKFSKTQTFQGCGILQPDPPANITVTAVARNPRWLSVTWQDPHSWNSSFYR
LRFELRYRAERSKTFTTWMVKDLQHHCVIHDAWSGLRHVVQLRAQEEFGQGEWSEWSPEAM
GTPWTESRSPPAENEVSTPMQALTTNKDDDNILFRDSANATSLPVQDSSSVPLPTFLVAGGSLA
FGTLLCIAIVLRFKKTWKLRALKEGKTSMHPPYSLGQLVPERPRPTPVLVPLISPPVSPSSLGSD
NTSSHNRPDARDPRSPYDISNTDYFFPR

SEQ ID NO: 728

MLTLQTWVVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNAN
YIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPK
NLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFV
NIEVWVEAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKY
NIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGIT
YEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVN
ATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQATHPVMDLKAFPKDNMLWVEWT
TPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSP
ESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNV
DSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTTL
LGVLFCFNKRDLIKKHIWPNVPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEIE
ANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTV
VHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESS
PDISHFERSKQVSSVNEEDFVRLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFE
TVGMEAATDEGMPKSYLPQTVRQGGYMPQ

CLAIMS

What is claimed is:

1.) A method of treating a patient having a disease or condition associated with hypercoagulation, comprising administering to the patient an IL-6 antagonist, whereby the patient's coagulation profile is improved or restored to normal, and monitoring the patient to assess coagulation profile.

2.) The method of claim 1 wherein the patient has elevated serum D-dimer levels prior to treatment.

3.) The method of claim 2 wherein said patient also has elevated C-reactive protein (CRP) levels prior to treatment.

4.) The method of claim 3 wherein said method further comprises the administration of at least one statin.

5.) The method of claim 1, wherein the IL-6 antagonist targets IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

6.) The method of claim 5, wherein the IL-6 antagonist comprises an antibody, an antibody fragment, a peptide, a glycoalkoid, an antisense nucleic acid, a ribozyme, a retinoid, an avemir, a small molecule, or any combination thereof.

7.) The method of claim 8, wherein the IL-6 antagonist comprises an anti-IL-6R, anti-gp130, anti-p38 MAP kinase, anti-JAK1, anti-JAK2, anti-JAK3, or anti-SYK antibody or antibody fragment.

8.) The method of claim 5, wherein the small molecule comprises thalidomide, lenalidomide, or any combination thereof.

9.) The method of claim 1, wherein the antagonist comprises an anti-IL-6 antibody or antibody fragment.

10.) The method of claim 9, wherein the anti-IL-6 antibody or antibody fragment 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 Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36.

11.) The method of claim 10, wherein the anti-IL-6 antibody 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 a fragment thereof as Ab1.

12.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment specifically binds 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36.

13.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment specifically binds to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as Ab1.

14.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment specifically binds to the same linear or conformational epitopes on an intact IL-6 polypeptide or antibody fragment thereof that is (are) specifically bound by Ab1 and wherein said epitope(s) when ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide includes one or more 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.

15.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment comprises 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, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7,

Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36.

16.) The method of claim 15, wherein the anti-IL-6 antibody or antibody fragment comprises 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.

17.) The method of claim 15, wherein all of the CDRs in the anti-IL-6 antibody or antibody fragment are identical to the CDRs contained in an anti-IL-6 antibody comprising Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36 or an antibody comprising the VH and VL sequences in SEQ ID NO:657 and SEQ ID NO:709 respectively or any of the anti-IL-6 VH and VL sequences depicted in Figures 34-37.

18.) The method of claim 15, wherein all of the CDRs in the anti-IL-6 antibody or antibody fragment are identical to the CDRs contained in Ab1.

19.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment is aglycosylated.

20.) The method of claim 18 wherein the antibody contains the variable heavy and variable light polypeptides in SEQ ID NO:657 and SEQ ID NO:709 respectively.

21.) The method of claim 18 wherein the antibody contains any combination of the variable heavy and variable light polypeptides in Figures 34-37.

22.) The method of claim 20 or 21 wherein the antibody comprises the heavy and light constant regions in SEQ ID NO:588 and SEQ ID NO:586.

23.) The method of claim 10, 20, 21 or 22, wherein the anti-IL-6 antibody or antibody fragment contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation.

24.) The method of 23 wherein the Fc region is modified to eliminate glycosylation.

25.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment is a human, humanized, single chain or chimeric antibody.

26.) The method of claim 25, wherein the anti-IL-6 antibody or antibody fragment is a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody.

27.) The method of claim 26, wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said anti-IL-6 antibody or antibody fragment 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.

28.) The method of claim 10, 20, 21 or 22 wherein the anti-IL-6 antibody or antibody fragment is administered to the patient with a frequency at most once per period of approximately four weeks.

29.) The method of claim 28, wherein the anti-IL-6 antibody or antibody fragment is administered to the patient with a frequency at most once per period of approximately eight weeks.

30.) The method of claim 29, wherein the anti-IL-6 antibody or antibody fragment is administered to the patient with a frequency at most once per period of approximately twelve weeks.

31.) The method of claim 30, wherein the anti-IL-6 antibody or antibody fragment is administered to the patient with a frequency at most once per period of approximately sixteen weeks.

32.) The method of any one of claims 27 through 30, wherein the patient's coagulation profile remains improved for an entire period intervening two consecutive anti-IL-6 antibody administrations.

33.) The method of claim 1, wherein the patient has been diagnosed with cancer selected from 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, Anaplastic 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, Klatskin 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 Müllerian 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, or any combination thereof.

34.) The method of claim 33, wherein the cancer is selected from Colorectal Cancer, Non-Small Cell Lung Cancer, Cholangiocarcinoma, Mesothelioma, Castleman's disease, Renal Cell Carcinoma, or any combination thereof.

35.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment comprises 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 comprises 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 any of the VH and VL sequences depicted in Figures 34-37 or a variant thereof wherein one or more of the framework residues (FR residues) in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-IL-6 antibody or antibody fragment that specifically binds human IL-6.

36.) The method of claim 35, wherein one or more of said FR residues are 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 V_H or V_L polypeptides have been derived or by a conservative amino acid substitution.

37.) The antibody of claim 36, wherein said anti-IL-6 antibody or antibody fragment is humanized.

38.) The antibody of claim 36, wherein said anti-IL-6 antibody or antibody fragment is chimeric.

39.) The method of claim 36 wherein the antibody contains the variable heavy and variable light polypeptides in SEQ ID NO:657 and SEQ ID NO:709 respectively.

40.) The method of claim 36 wherein the antibody contains any combination of the variable heavy and variable light polypeptides in Figures 34-37.

41.) The antibody of claim 36, 37, 38, 39 or 40, wherein said anti-IL-6 antibody or antibody fragment further comprises a human F_c.

42.) The method of claim 41, wherein said human F_c is derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19.

43.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment comprises a polypeptide having at least 90% sequence homology to one or more of the polypeptide sequences of 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, 708, 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 any of the polypeptide sequences in Figures 34-37.

44.) The method of claim 10 or 43, wherein the anti-IL-6 antibody or antibody fragment has an elimination half-life of at least about 22 days.

45.) The method of claim 44, wherein the anti-IL-6 antibody or antibody fragment has an elimination half-life of at least about 25 days.

46.) The method of claim 45, wherein the anti-IL-6 antibody or antibody fragment has an elimination half-life of at least about 30 days.

47.) The method of claim 1, wherein the IL-6 antagonist is administered as part of a regimen that includes the administration of a chemotherapy agent or another therapeutic compound.

48.) The method of claim 47, wherein the chemotherapy agent is selected from VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids,

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-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.

49.) The method of claim 48 wherein said interleukins include IL-12 and IL-2.

50.) The method of claim 48 wherein the vinca alkaloid comprises vinblastine, vincristine, vindesine or vinorelbine.

51.) The method of claim 46, wherein the another therapeutic compound is a statin.

52.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment which is directly or indirectly attached to a detectable label or therapeutic agent.

53.) The method of claim 10, wherein the anti-IL-6 antibody or antibody fragment is Ab1 or a fragment thereof.

54.) The method of claim 1, wherein the disease or condition is selected from acute venous thrombosis, pulmonary embolism, thrombosis during pregnancy, hemorrhagic skin necrosis, acute or chronic disseminated intravascular coagulation (DIC), clot formation from surgery, long bed rest, long periods of immobilization, venous thrombosis, fulminant meningococcemia, acute thrombotic stroke, acute coronary occlusion, acute peripheral arterial occlusion, massive pulmonary embolism, axillary vein thrombosis, massive iliofemoral vein thrombosis, occluded arterial cannulae, occluded venous cannulae, cardiomyopathy, venoocclusive disease of the liver, hypotension, decreased cardiac output, decreased vascular resistance, pulmonary hypertension, diminished lung compliance, leukopenia, thrombocytopenia, heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis (HITT), atrial fibrillation, implantation of a prosthetic heart valve, genetic susceptibility to thrombosis, factor V Leiden, prothrombin gene mutation,

methylenetetrahydrofolate reductase (MTHFR) polymorphism, platelet-receptor polymorphism, trauma, fractures, burns, or any combination thereof.

55.) The method of claim 1, further comprising administration of one or more anti-coagulants or statins.

56.) The method of claim 55, wherein the one or more anti-coagulants are selected from abciximab (ReoPro™), acenocoumarol, antithrombin III, argatroban, 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.

57.) The method of claim 56, wherein the one or more statins is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

58.) The method of claim 1, wherein the patient's coagulation profile is assessed by measurement of the patient's serum level of one or more of D-dimer, 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.

59.) The method of claim 1, wherein the patient's coagulation profile is assessed by a functional measurement of clotting ability.

60.) The method of claim 59, wherein the functional measurement of clotting ability is selected from prothrombin time (PT), prothrombin ratio (PR), international normalized ratio (INR), or any combination thereof.

61.) The method of claim 1, further comprising: measuring the patient's international normalized ratio (INR) prior to administration of the IL-6 antagonist, and administering to the patient an IL-6 antagonist if the patient's INR is less than about 0.9.

62.) The method of claim 1, further comprising: measuring the patient's international normalized ratio (INR) prior to administration of the IL-6 antagonist, and administering to the patient an IL-6 antagonist if the patient's INR is less than about 0.5.

63.) The method of claim 1, wherein the patient's INR is raised to more than approximately 0.9 within 4 weeks of administering to the patient an IL-6 antagonist.

64.) The method of claim 1, further comprising: measuring the patient's serum D-dimer level prior to administration of the IL-6 antagonist, and administering the IL-6 antagonist if the patient's serum D-dimer level is above the normal reference range.

65.) The method of claim 1, wherein the patient's serum D-dimer level is lowered to less than the upper limit of the normal reference range within 4 weeks of administering to the patient an IL-6 antagonist.

66.) The method of claim 1, that results in a prolonged improvement in the patient's coagulation profile.

67.) The method of claim 1, wherein the patient's coagulation profile is measurably improved within about 2 weeks of administration of the IL-6 antagonist.

68.) The method of claim 67, wherein the patient's coagulation profile remains measurably improved approximately 12 weeks after administering to the patient an IL-6 antagonist.

69.) The method of claim 1, whereby the patient's survivability is improved.

70.) The method of claim 1, wherein the IL-6 antagonist is an antisense nucleic acid or interfering RNA.

71.) The method of claim 70, wherein the antisense nucleic acid or interfering RNA (iRNA) comprises at least approximately 10 nucleotides of a sequence encoding IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.

72.) The method of claim 70, wherein the antisense nucleic acid or interfering RNA (iRNA) comprises DNA, RNA, peptide nucleic acid, locked nucleic acid,

morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, threose nucleic acid, or any combination thereof.

73.) The method of claim 1, wherein the IL-6 antagonist comprises Actemra™ (Tocilizumab), Remicade®, Zenapax™, or any combination thereof.

74.) The method of claim 1, wherein the IL-6 antagonist comprises a polypeptide having a sequence comprising a fragment of IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.

75.) The method of claim 74, wherein the IL-6 antagonist is at least 40 amino acids in length.

76.) The method of claim 74, wherein the IL-6 antagonist comprises a soluble IL-6, IL-6 receptor alpha, gp130, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

77.) The method of claim 74, wherein the IL-6 antagonist is coupled to a half-life increasing moiety.

78.) A composition comprising an IL-6 antagonist, and a statin.

79.) The composition of claim 78, wherein the statin is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

80.) A composition comprising an IL-6 antagonist, and an anti-coagulant.

81.) The composition of claim 80 wherein the one or more anti-coagulants are selected from abciximab (ReoPro™), acenocoumarol, antithrombin III, argatroban, 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.

82.) A composition comprising an IL-6 antagonist, and a chemotherapy agent.

83.) The composition of claim 82, wherein the chemotherapy agent is selected from VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids, 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-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.

84.) The method of claim 83, wherein the chemotherapy agent comprises an inhibitor of JAK1, JAK2, JAK3, or SYK.

85.) The composition of claim 84 wherein said interleukins include IL-12 and IL-2.

86.) The composition of claim 83 wherein the vinca alkaloid comprises vinblastine, vincristine, vindesine or vinorelbine.

87.) The method of any of claims 33-77 wherein the administered IL-6 antagonist includes an anti-IL-6 antibody that comprises all of the CDRs of Ab1.

88.) The method of claim 87 wherein the IL-6 antagonist antibody comprises the variable heavy sequence in SEQ ID NO:657 and the variable light sequence in SEQ ID NO:709 or any of the other variable heavy and light sequences contained in Figures 34-37.

89.) The composition of any of claims 78-83 wherein the IL-6 antagonist includes an anti-IL-6IL-6 antibody that comprises the CDRs of Ab1.

90.) The composition of claim 89 wherein the IL-6 antagonist antibody comprises the variable heavy sequence in SEQ ID NO:657 and the variable light sequence in SEQ ID NO:709 or any of the other variable heavy and light sequences contained in Figures 34-37.

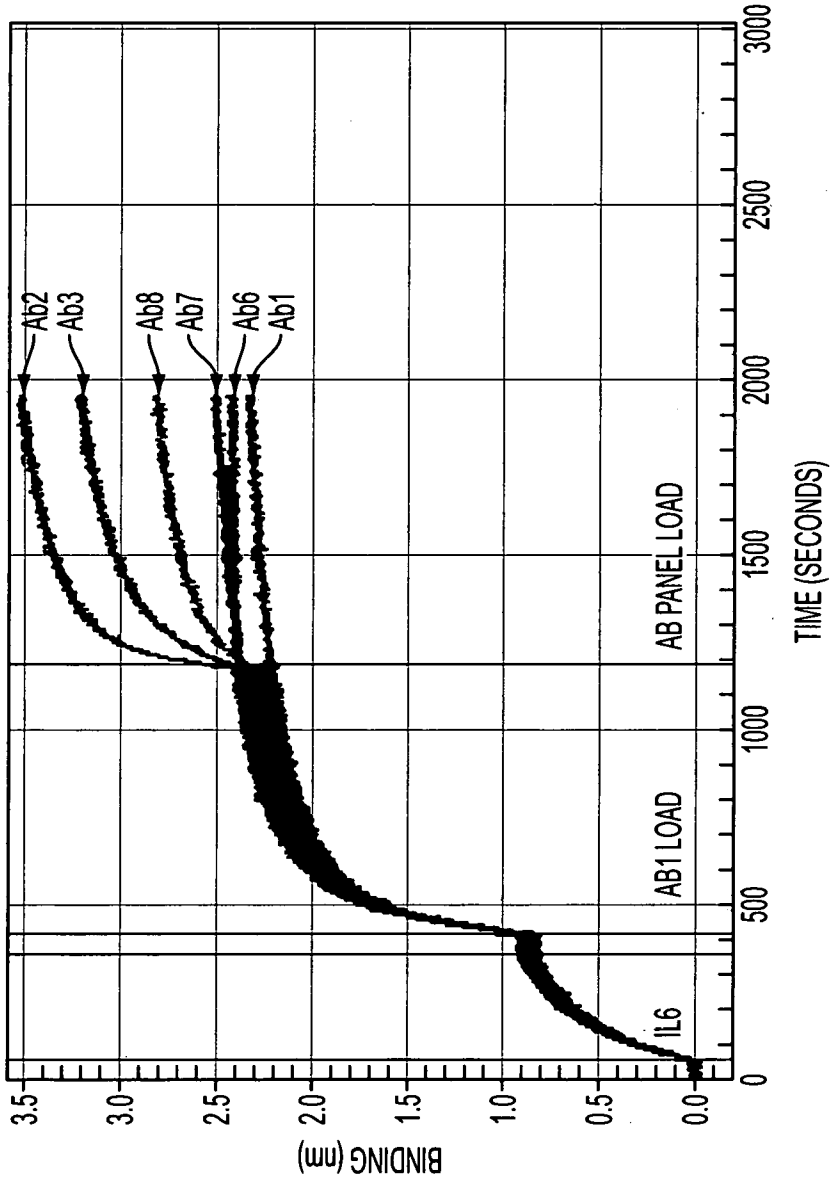

BINDING (nm)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
500
1000
1500
2000
2500
3000
TIME (SECONDS)
IL6
AB1 LOAD
AB PANEL LOAD
Ab2
Ab3
Ab8
Ab7
Ab6
Ab1

FIG. 1

```
      FR1                    CDR1        FR2             CDR2    FR3
      1                   23 24       34 35          49 50   56 57                              88
RbtVL AYDMTQTPASVEVAVGGTVTINC QASETIYSWLS WYQQKPGQPPKLLIY QASDLAS GVPSRFSGSGAGTEYTLTISGVQCDDAATYYC
L12A  DIQMTQSPSTLSASVGDRVTITC RASQSISSWLA WYQQKPGKAPKLLIY KASSLES GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC
V1    DIQMTQSPSTLSASVGDRVTITC RASQSISSWLA WYQQKPGKAPKLLIY DASSLES GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC
Vx02  DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC

VLh   DIQMTQSPSTLSASVGDRVTITC QASETIYSWLS WYQQKPGKAPKLLIY QASDLAS GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC

      CDR3         FR4
      89       100 101     111
RbtVL QQGYSGSNVDNV FGGGTEVVVKR
                   FGGGTKVEIKR

VLh   QQGYSGSNVDNV FGGGTKVEIKR
```

```
        FR1                          CDR1   FR2          CDR2            FR3
        1                         30 31 35 36          49 50            66 67                          98
RbtVH   QEQLKESGGRLVTPGTPLTLTCTASGFSLN DHAMG WVRQAPGKGLEYIG FINS-GGSARYASWAEG RFTISRTST--TVDLKMTSLTTEDTATYFCVR
3-64-04 QVQLVESGGGLVQPGGSLRLSCSASGFTFS SYAMH WVRQAPGKGLEYVS AISSNGGSTYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
3-66-04 EVQLVESGGGLVQPGGSLRLSCAASGFTVS SNYMS WVRQAPGKGLEWVS VIYS-GGSTYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
3-53-02 EVQLVETGGGLIQPGGSLRLSCAASGFTVS SNYMS WVRQAPGKGLEWVS VIYS-GGSTYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

VHh     QVQLVESGGGLVQPGGSLRLSCSASGFSLN DHAMG WVRQAPGKGLEYVG FINS-GGSARYASSAEG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

        CDR3         FR4
        99       110 111     121
RbtVH   GGAVWSIHSFDP WGPGTLVTVSS
                    WGQGTLVTVSS

VHh     GGAVWSIHSFDP WGQGTLVTVSS
```

FIG. 2

SUBSTITUTE SHEET (RULE 26)

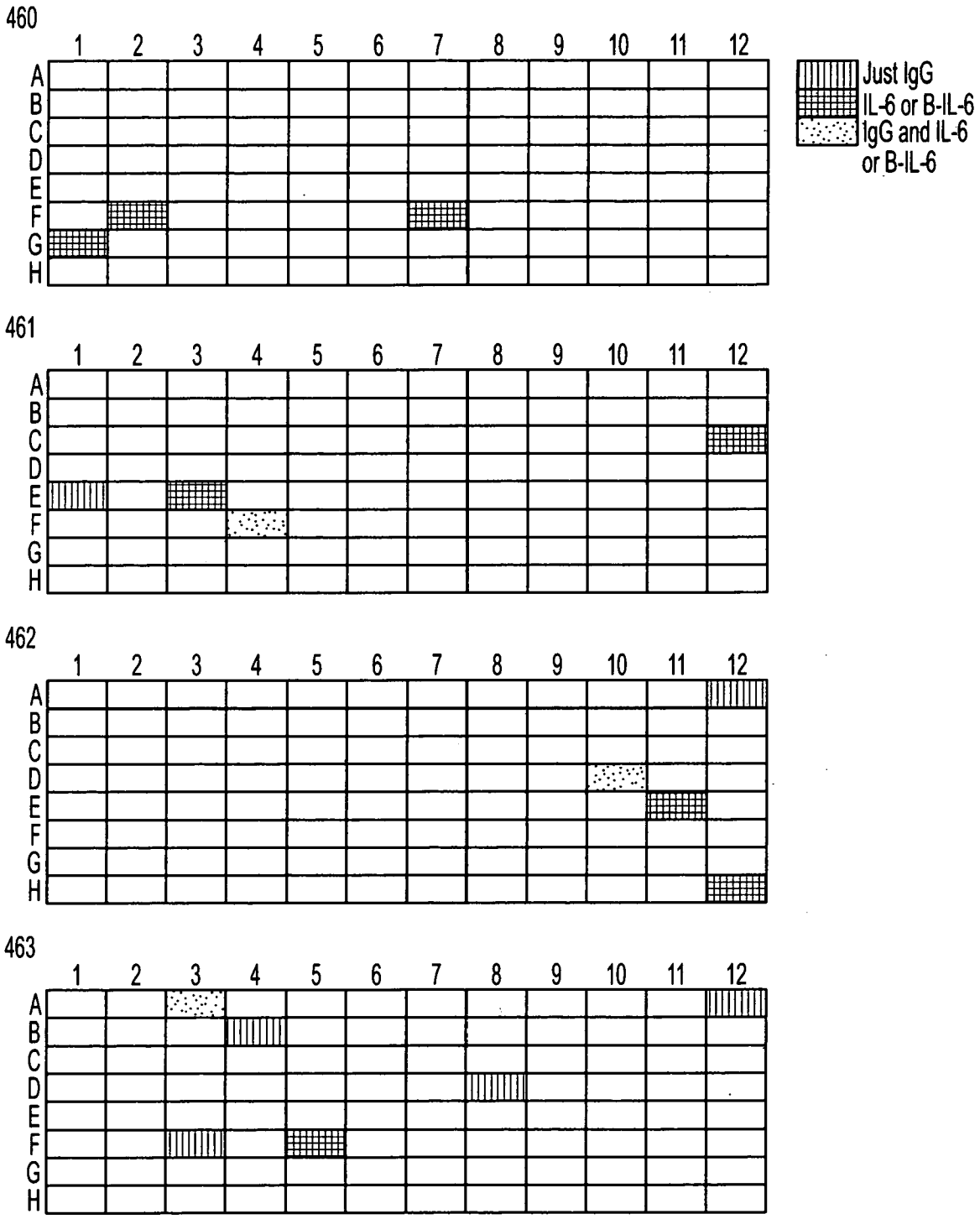

460
461
462
463
1 2 3 4 5 6 7 8 9 10 11 12
A B C D E F G H
Just IgG
IL-6 or B-IL-6
IgG and IL-6 or B-IL-6

FIG. 3

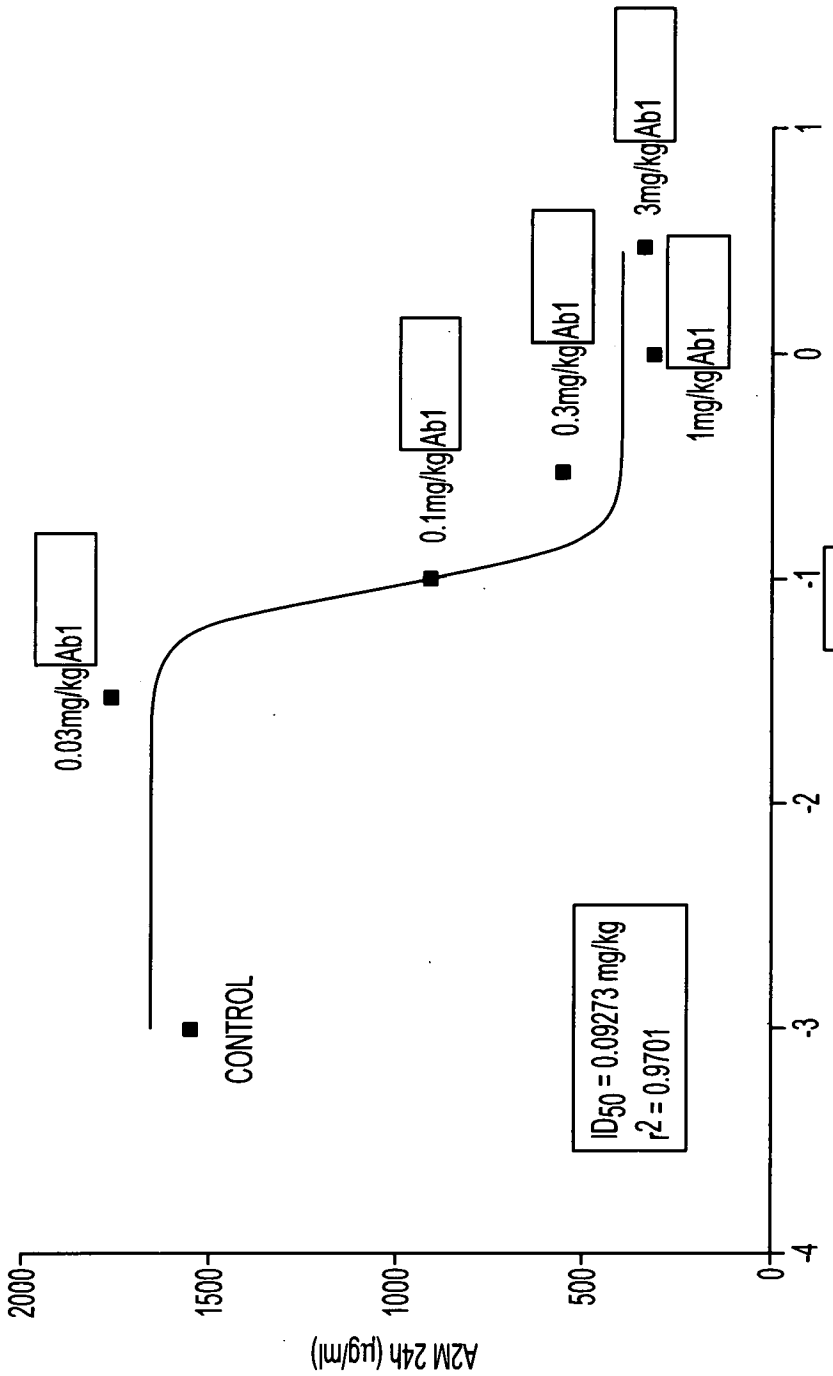

A2M 24h (µg/ml)
2000
1500
1000
500
0
-4
-3
-2
-1
0
1
LOG DOSE Ab1
CONTROL
0.03mg/kg Ab1
0.1mg/kg Ab1
0.3mg/kg Ab1
1mg/kg Ab1
3mg/kg Ab1
ID50 = 0.09273 mg/kg
r2 = 0.9701

FIG. 4

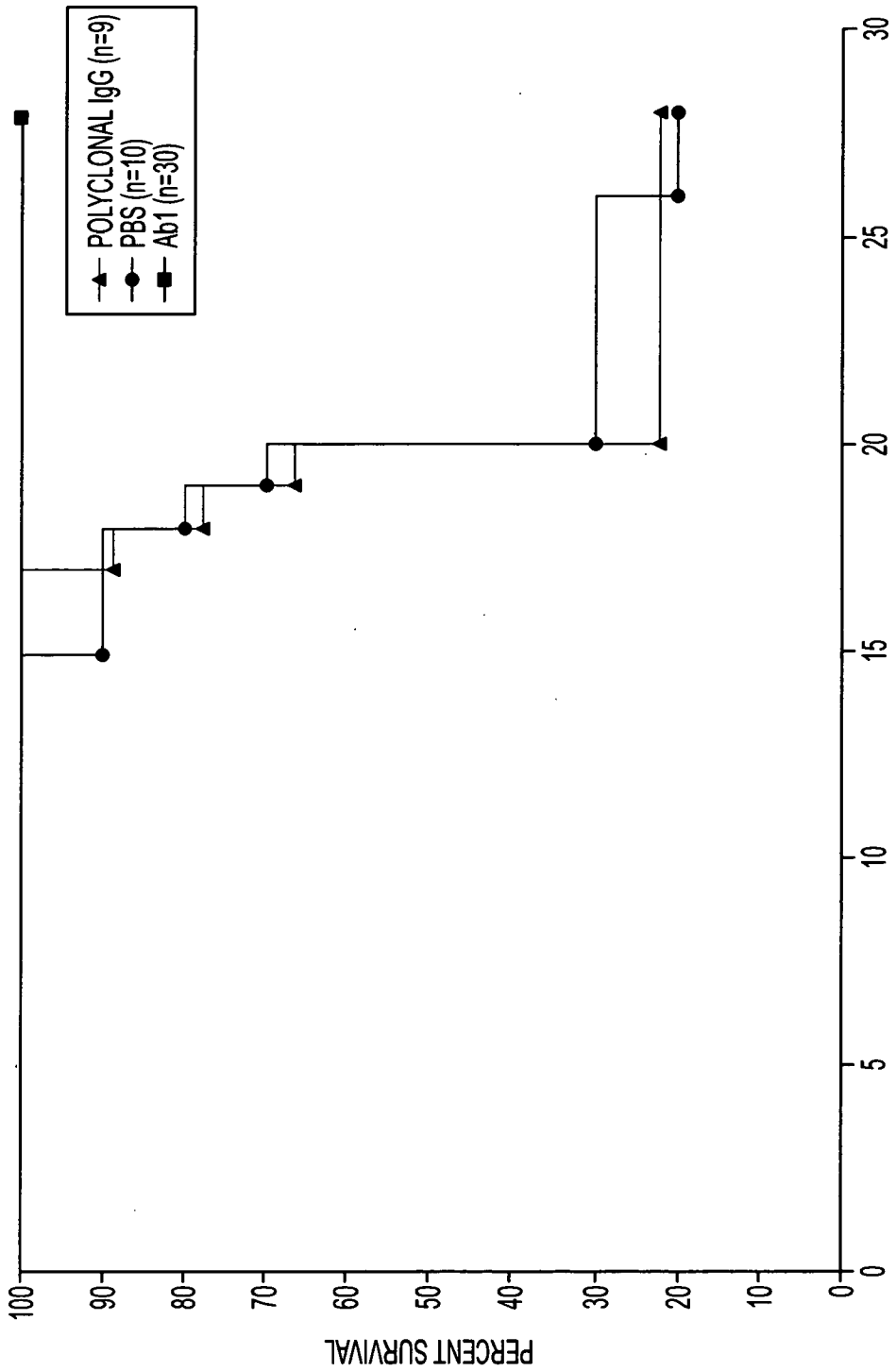

POLYCLONAL IgG (n=9)
PBS (n=10)
Ab1 (n=30)
PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
TIME (DAYS)

FIG. 5

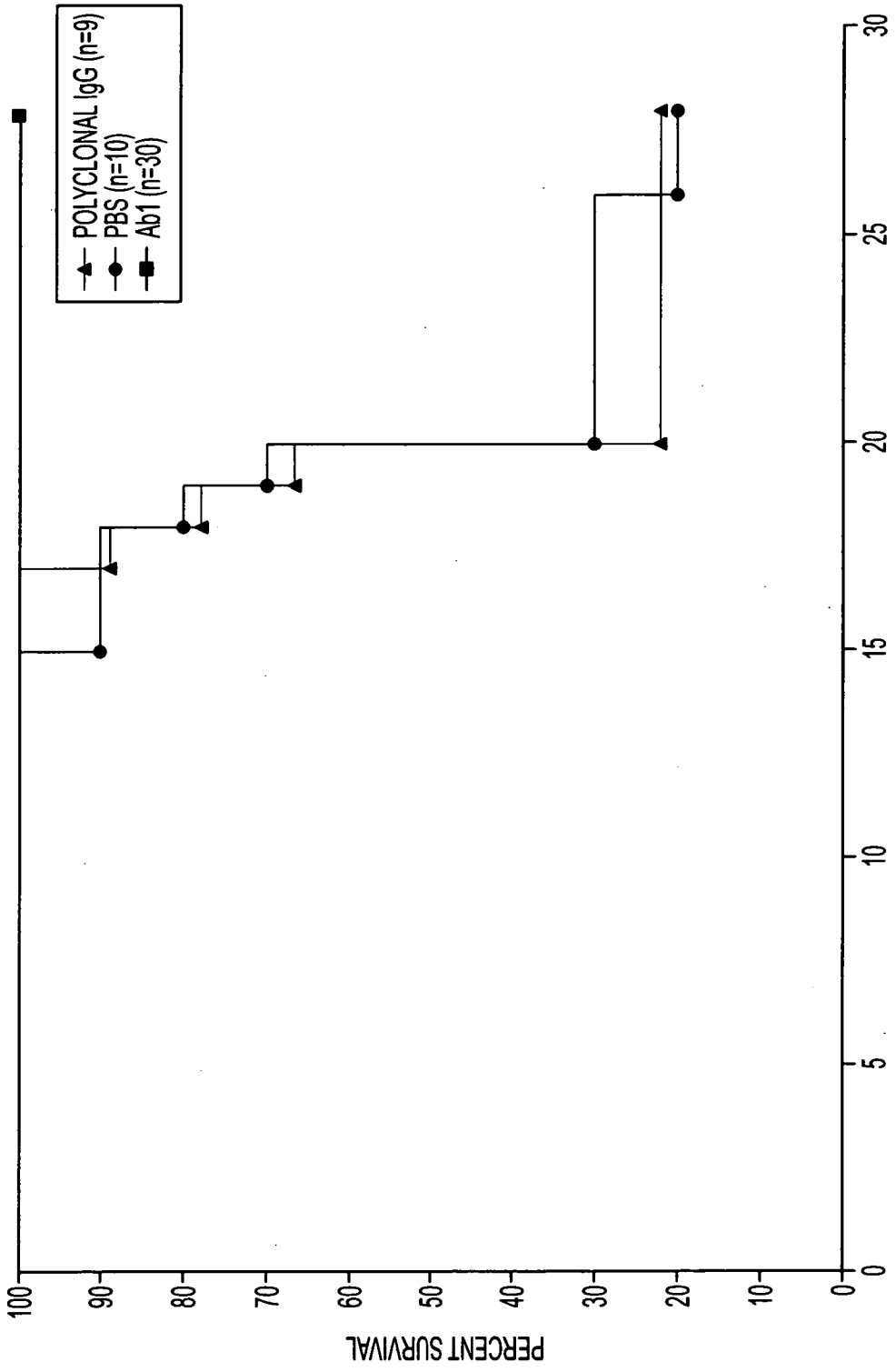

POLYCLONAL IgG (n=9)
PBS (n=10)
Ab1 (n=30)
PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
TIME (DAYS)

FIG. 6

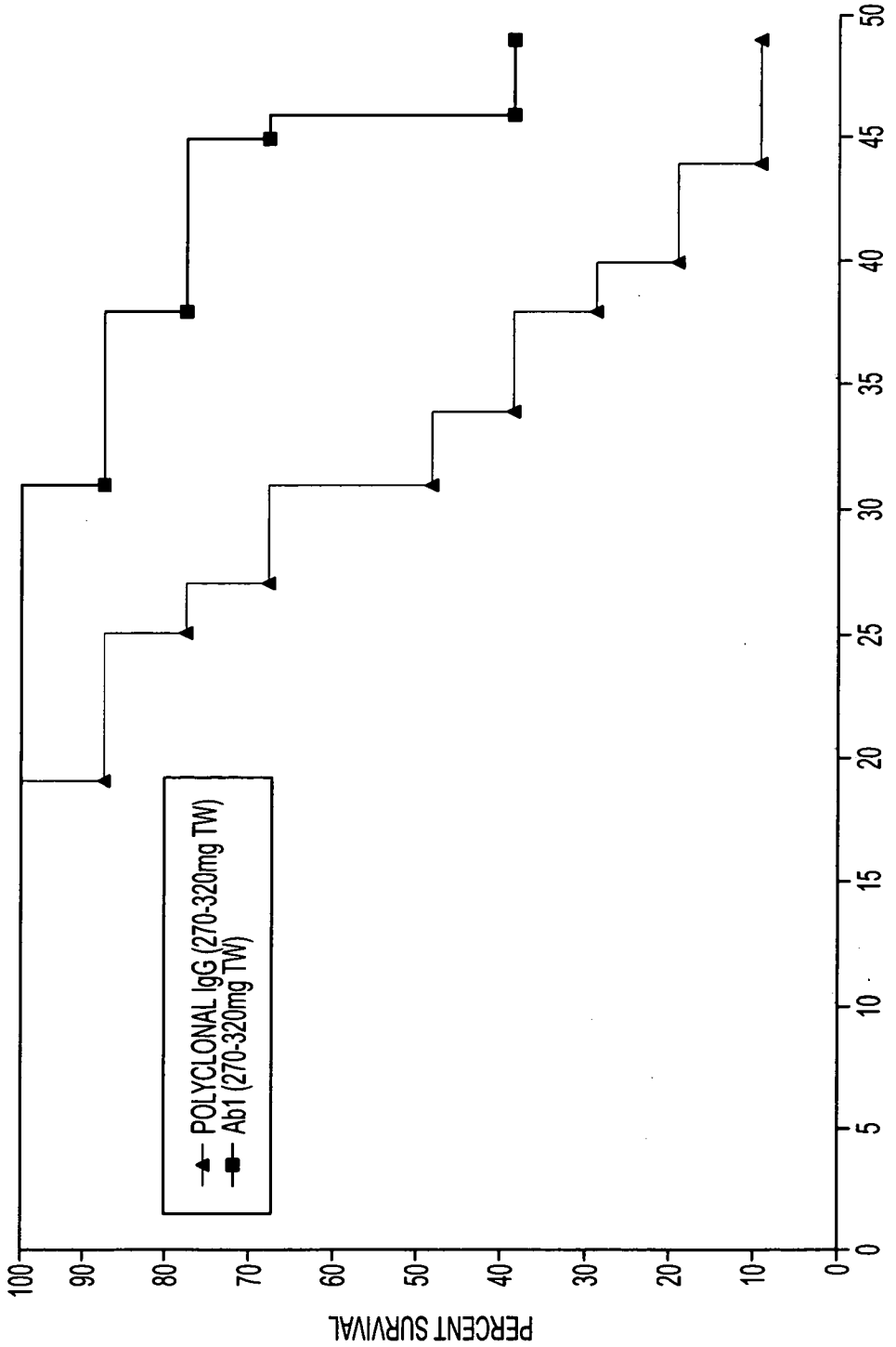

PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
TIME (DAYS)
POLYCLONAL IgG (270-320mg TW)
Ab1 (270-320mg TW)

FIG. 7

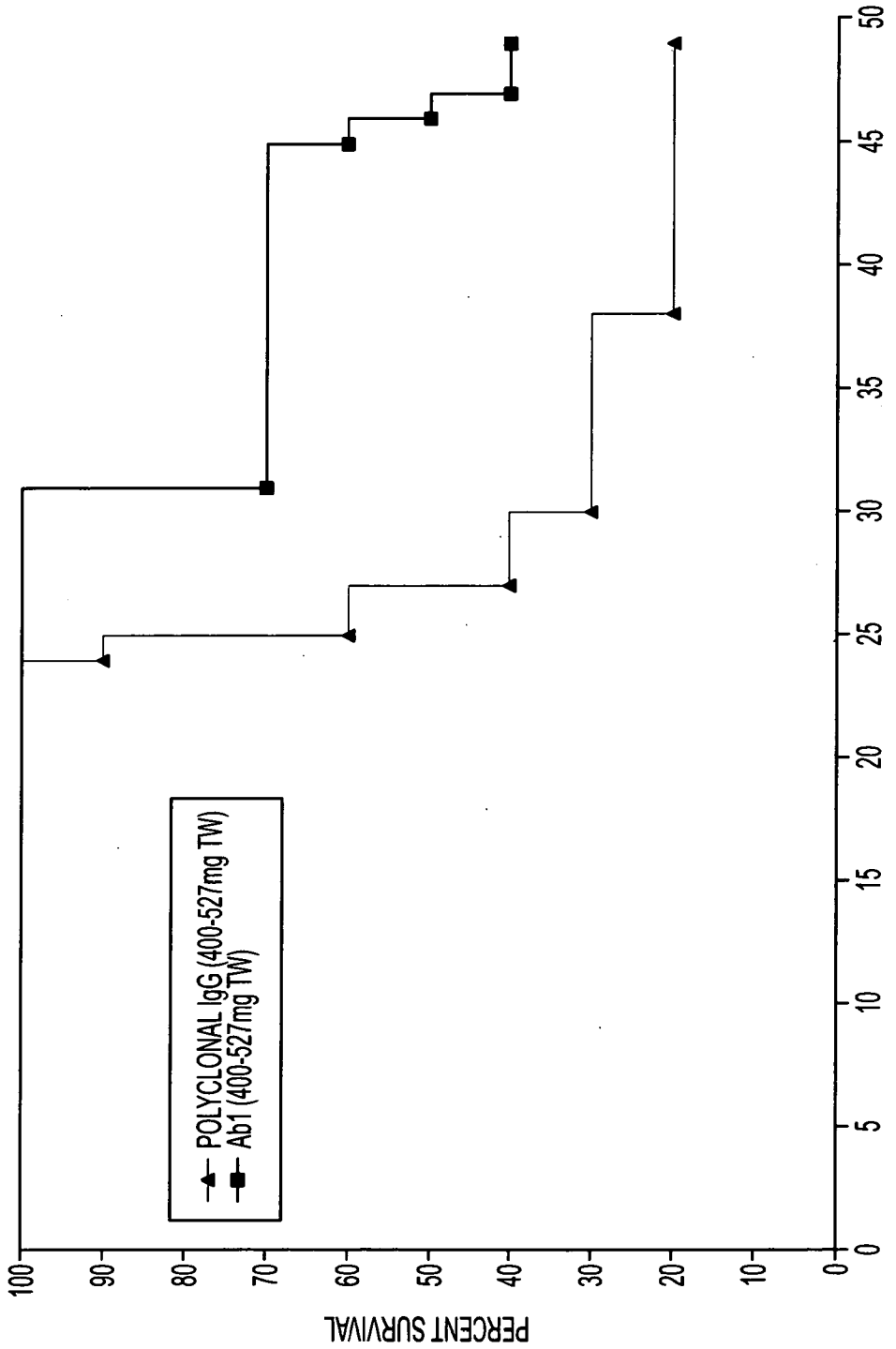

PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
TIME (DAYS)
POLYCLONAL IgG (400-527mg TW)
Ab1 (400-527mg TW)

FIG. 8

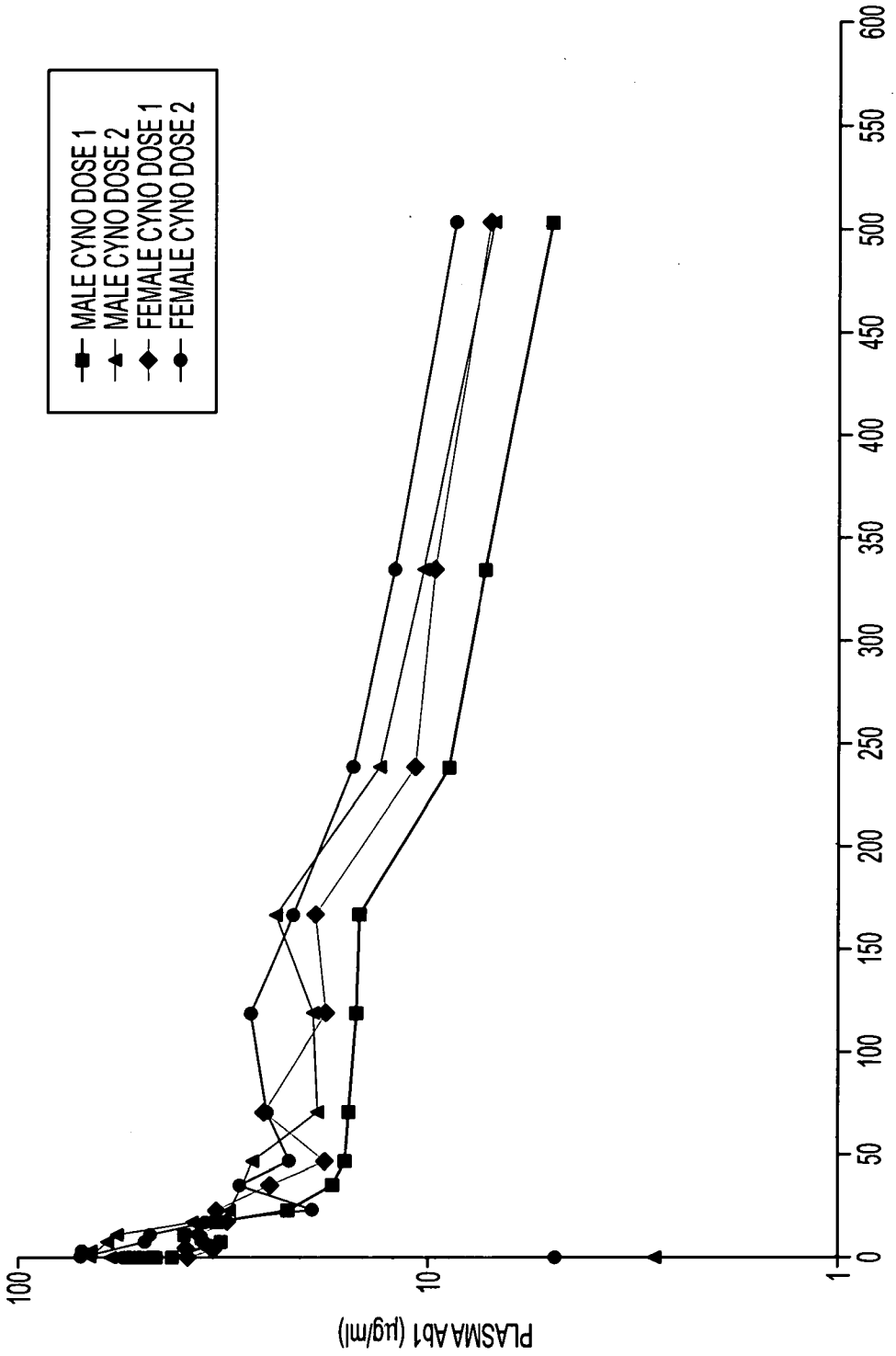

MALE CYNO DOSE 1
MALE CYNO DOSE 2
FEMALE CYNO DOSE 1
FEMALE CYNO DOSE 2
PLASMA Ab1 (µg/ml)
100
10
1
0
50
100
150
200
250
300
350
400
450
500
550
600
TIME (h)

FIG. 9

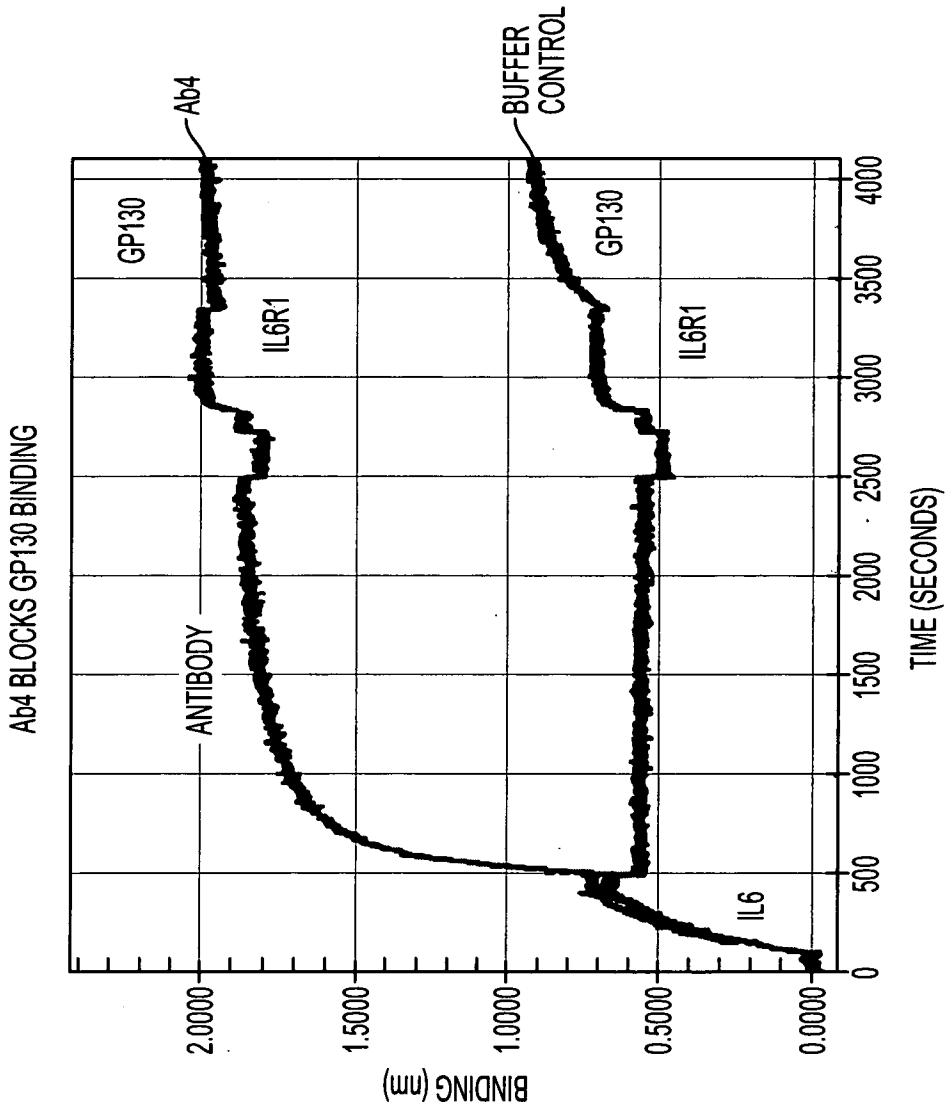

Ab4 BLOCKS GP130 BINDING
ANTIBODY
Ab4
BUFFER CONTROL
GP130
IL6R1
GP130
IL6R1
IL6
BINDING (nm)
2.0000
1.5000
1.0000
0.5000
0.0000
0
500
1000
1500
2000
2500
3000
3500
4000
TIME (SECONDS)

FIG. 10A

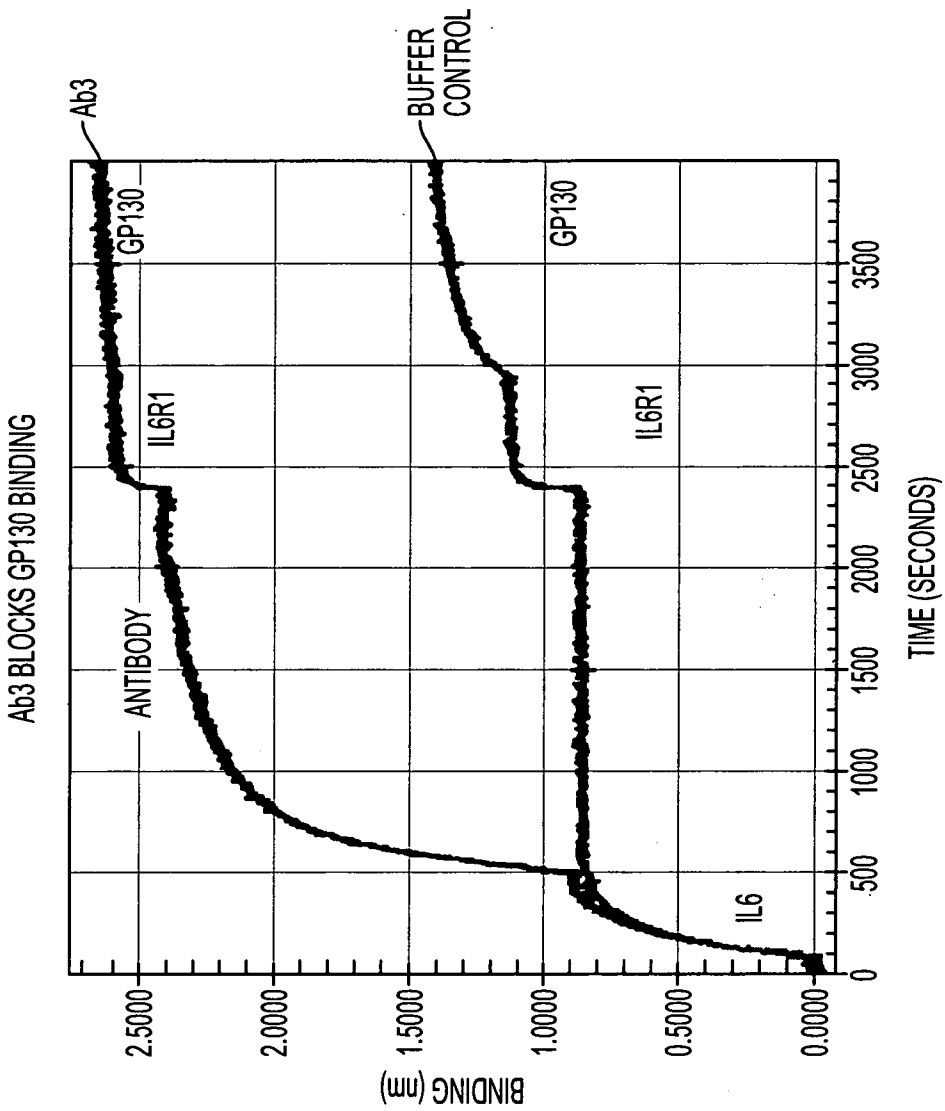

Ab3 BLOCKS GP130 BINDING
ANTIBODY
Ab3
GP130
IL6R1
BUFFER CONTROL
GP130
IL6R1
IL6
BINDING (nm)
2.5000
2.0000
1.5000
1.0000
0.5000
0.0000
0
500
1000
1500
2000
2500
3000
3500
TIME (SECONDS)

FIG. 10B

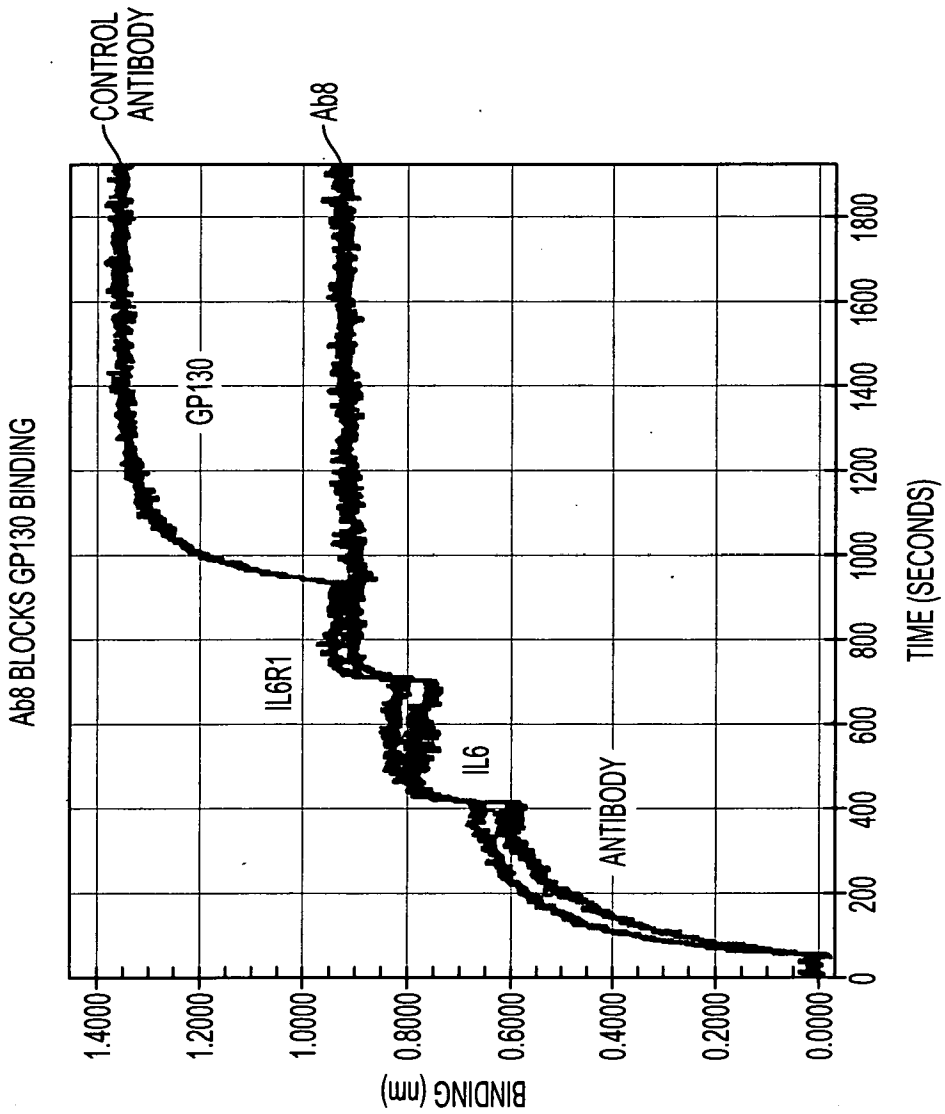

Ab8 BLOCKS GP130 BINDING
CONTROL ANTIBODY
Ab8
GP130
IL6R1
IL6
ANTIBODY
BINDING (nm)
1.4000
1.2000
1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
0
200
400
600
800
1000
1200
1400
1600
1800
TIME (SECONDS)

FIG. 10C

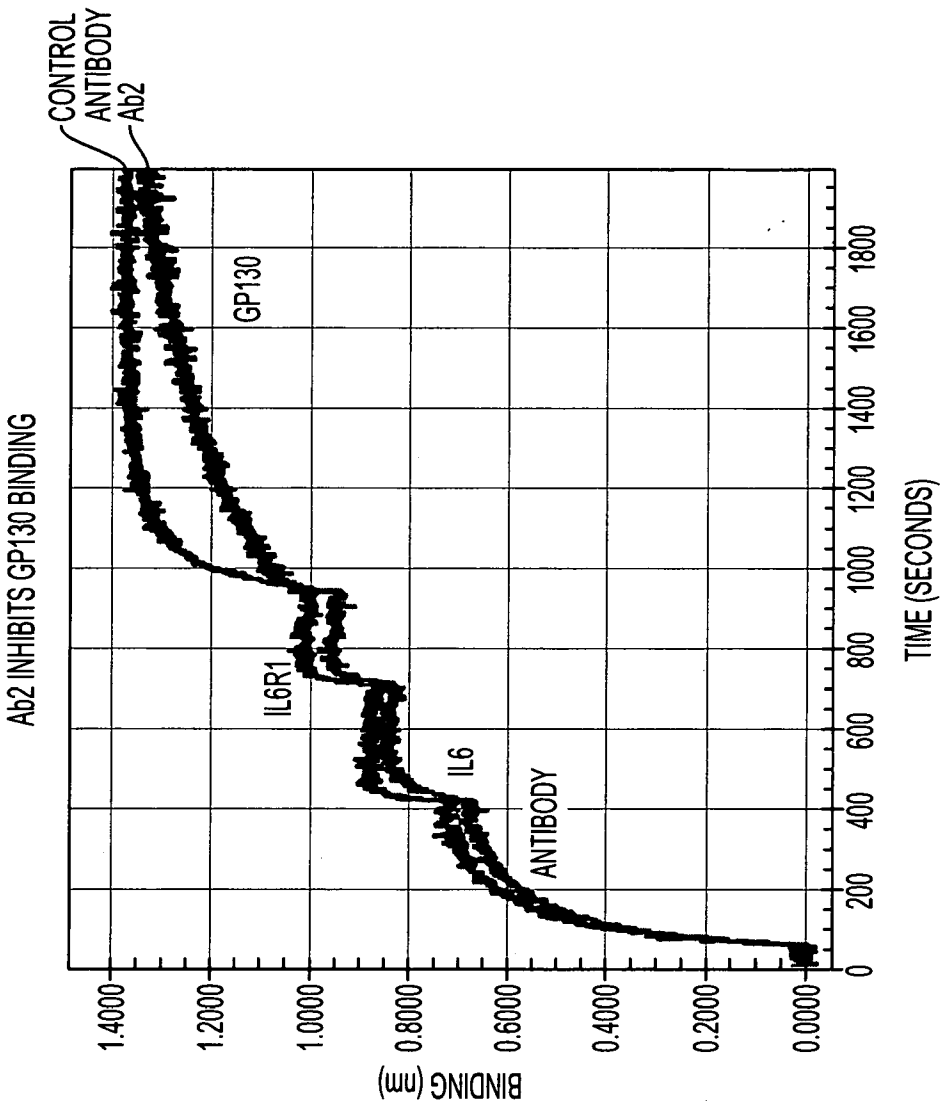

Ab2 INHIBITS GP130 BINDING
CONTROL ANTIBODY Ab2
GP130
IL6R1
IL6
ANTIBODY
BINDING (nm)
1.4000
1.2000
1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
0
200
400
600
800
1000
1200
1400
1600
1800
TIME (SECONDS)

FIG. 10D

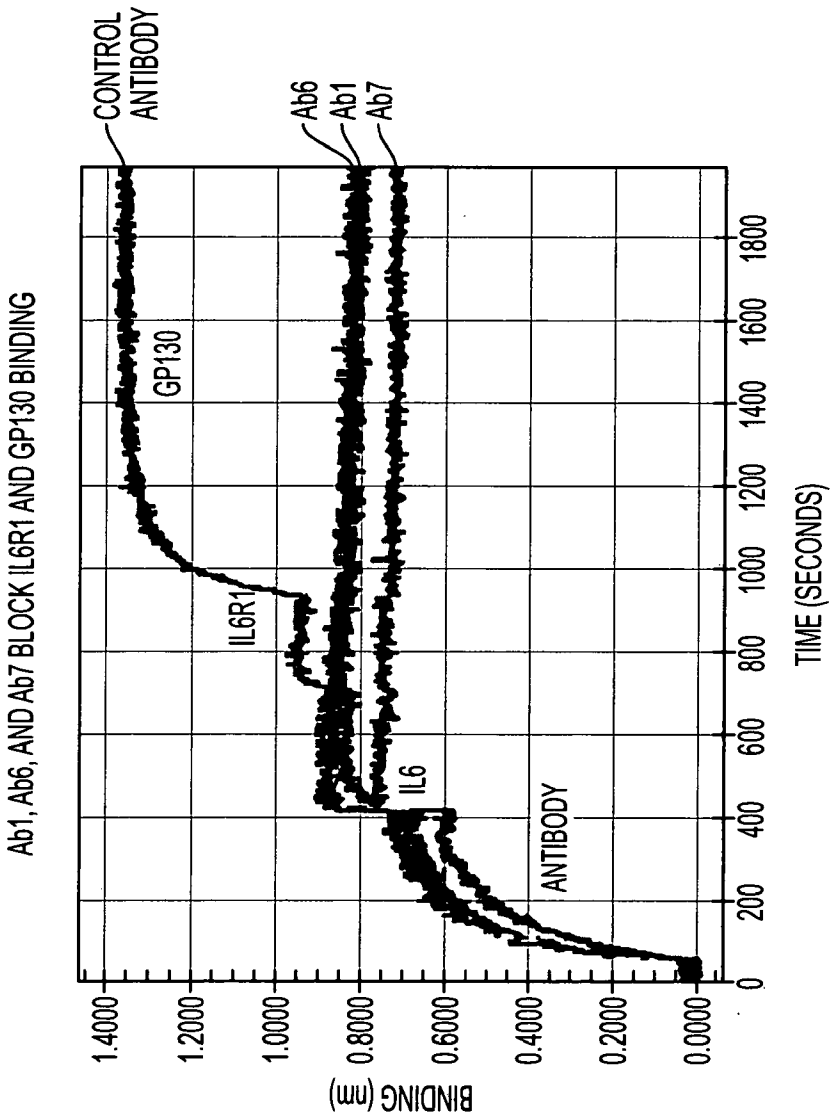

Ab1, Ab6, AND Ab7 BLOCK IL6R1 AND GP130 BINDING
CONTROL ANTIBODY
Ab6
Ab1
Ab7
GP130
IL6R1
IL6
ANTIBODY
BINDING (nm)
1.4000
1.2000
1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
0
200
400
600
800
1000
1200
1400
1600
1800
TIME (SECONDS)

FIG. 10E

ANTIBODY	BLOCKS IL6 BINDING TO R1	BLOCKS IL6 BINDING TO GP130	REFERENCE
Ab1	YES	YES	021051
Ab2	NO	PARTIAL	021050
Ab3	NO	YES	021030
Ab4	NO	YES	021050
Ab6	YES	YES	021051
Ab7	YES	YES	021051
Ab8	NO	YES	021051

FIG. 11

1 VPPGEDSKDVAAPHR	(SEQ ID NO: 590)	20 ENNLNLPKMAEKDGC	(SEQ ID NO: 609)	39 QMSTKVLIQFLQKKA	(SEQ ID NO: 628)
2 GEDSKDVAAPHRQPL	(SEQ ID NO: 591)	21 LNLPKMAEKDGCFQS	(SEQ ID NO: 610)	40 TKVLIQFLQKKAKNL	(SEQ ID NO: 629)
3 SKDVAAPHRQPLTSS	(SEQ ID NO: 592)	22 PKMAEKDGCFQSGFN	(SEQ ID NO: 611)	41 LIQFLQKKAKNLDAI	(SEQ ID NO: 630)
4 VAAPHRQPLTSSERI	(SEQ ID NO: 593)	23 AEKDGCFQSGFNEET	(SEQ ID NO: 612)	42 FLQKKAKNLDAITTP	(SEQ ID NO: 631)
5 PHRQPLTSSERIDKQ	(SEQ ID NO: 594)	24 DGCFQSGFNEETCLV	(SEQ ID NO: 613)	43 KKAKNLDAITTPDPT	(SEQ ID NO: 632)
6 QPLTSSERIDKQIRY	(SEQ ID NO: 595)	25 FQSGFNEETCLVKII	(SEQ ID NO: 614)	44 KNLDAITTPDPTTNA	(SEQ ID NO: 633)
7 TSSERIDKQIRYILD	(SEQ ID NO: 596)	26 GFNEETCLVKIITGL	(SEQ ID NO: 615)	45 DAITTPDPTTNASLL	(SEQ ID NO: 634)
8 ERIDKQIRYILDGIS	(SEQ ID NO: 597)	27 EETCLVKIITGLLEF	(SEQ ID NO: 616)	46 TTPDPTTNASLLTKL	(SEQ ID NO: 635)
9 DKQIRYILDGISALR	(SEQ ID NO: 598)	28 CLVKIITGLLEFEVY	(SEQ ID NO: 617)	47 DPTTNASLLTKLQAQ	(SEQ ID NO: 636)
10 IRYILDGISALRKET	(SEQ ID NO: 599)	29 KIITGLLEFEVYLEY	(SEQ ID NO: 618)	48 TNASLLTKLQAQNQW	(SEQ ID NO: 637)
11 ILDGISALRKETCNK	(SEQ ID NO: 600)	30 TGLLEFEVYLEYLQN	(SEQ ID NO: 619)	49 SLLTKLQAQNQWLQD	(SEQ ID NO: 638)
12 GISALRKETCNKSNM	(SEQ ID NO: 601)	31 LEFEVYLEYLQNRFE	(SEQ ID NO: 620)	50 TKLQAQNQWLQDMTT	(SEQ ID NO: 639)
13 ALRKETCNKSNMCES	(SEQ ID NO: 602)	32 EVYLEYLQNRFESSE	(SEQ ID NO: 621)	51 QAQNQWLQDMTTHLI	(SEQ ID NO: 640)
14 KETCNKSNMCESSKE	(SEQ ID NO: 603)	33 LEYLQNRFESSEEQA	(SEQ ID NO: 622)	52 NQWLQDMTTHLILRS	(SEQ ID NO: 641)
15 CNKSNMCESSKEALA	(SEQ ID NO: 604)	34 LQNRFESSEEQARAV	(SEQ ID NO: 623)	53 LQDMTTHLILRSFKE	(SEQ ID NO: 642)
16 SNMCESSKEALAENN	(SEQ ID NO: 605)	35 RFESSEEQARAVQMS	(SEQ ID NO: 624)	54 MTTHLILRSFKEFLQ	(SEQ ID NO: 643)
17 CESSKEALAENNLNL	(SEQ ID NO: 606)	36 SSEEQARAVQMSTKV	(SEQ ID NO: 625)	55 HLILRSFKEFLQSSL	(SEQ ID NO: 644)
18 SKEALAENNLNLPKM	(SEQ ID NO: 607)	37 EQARAVQMSTKVLIQ	(SEQ ID NO: 626)	56 LRSFKEFLQSSLRAL	(SEQ ID NO: 645)
19 ALAENNLNLPKMAEK	(SEQ ID NO: 608)	38 RAVQMSTKVLIQFLQ	(SEQ ID NO: 627)	57 FKEFLQSSLRALRQM	(SEQ ID NO: 646)

FIG. 12

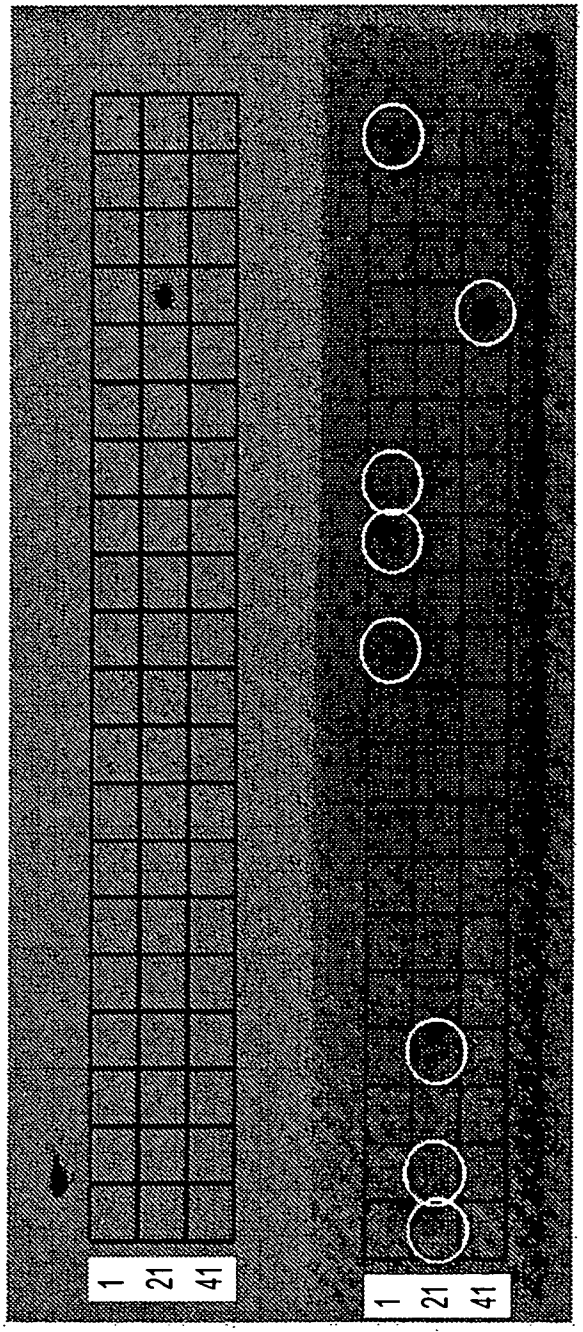


FIG. 13

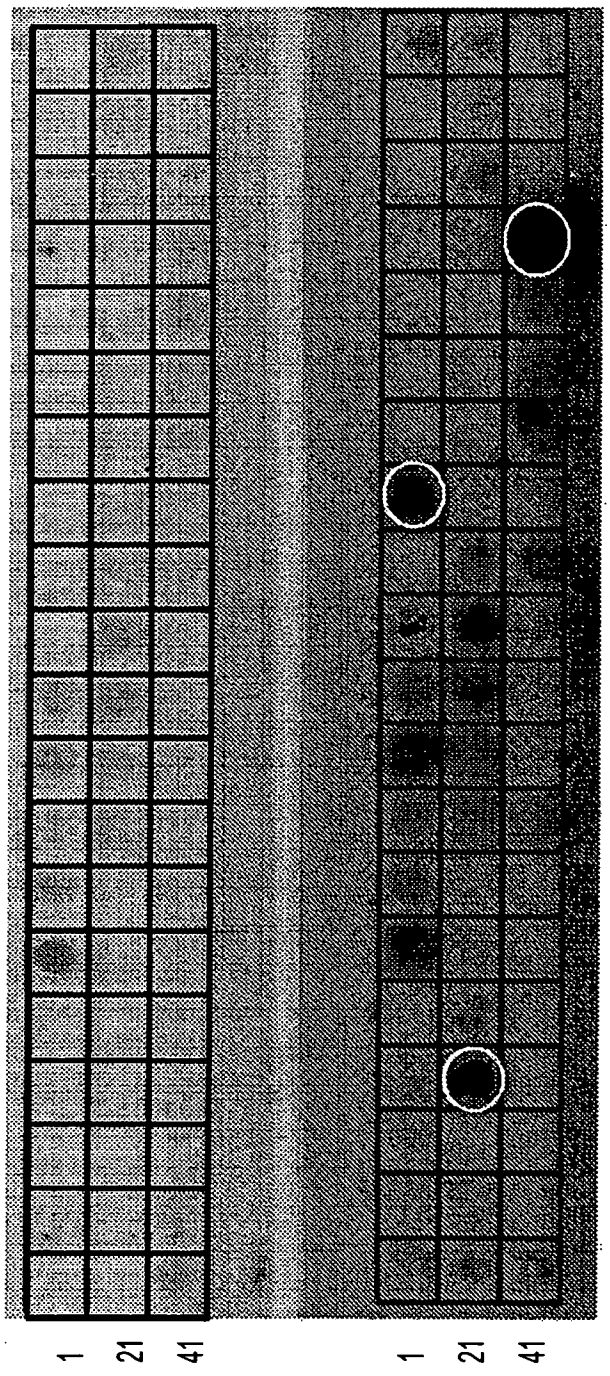


FIG. 14

A. 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_D
RAT	$1.6e^6$	$2.2e^{-3}$	1.4 nM
MOUSE	$1.1e^6$	$4.0e^{-4}$	0.4 nM
DOG	BELOW LOQ[a]	BELOW LOQ[a]	BELOW LOQ[a]
HUMAN	$1.6e^5$	$5e^{-7}$	4 pM
CYNOMOLGUS MONKEY	$9.6e^4$	$3e^{-6}$	31 pM

a. BELOW LIMIT OF QUANTITATION

B. 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

FIG. 15

SUBSTITUTE SHEET (RULE 26)

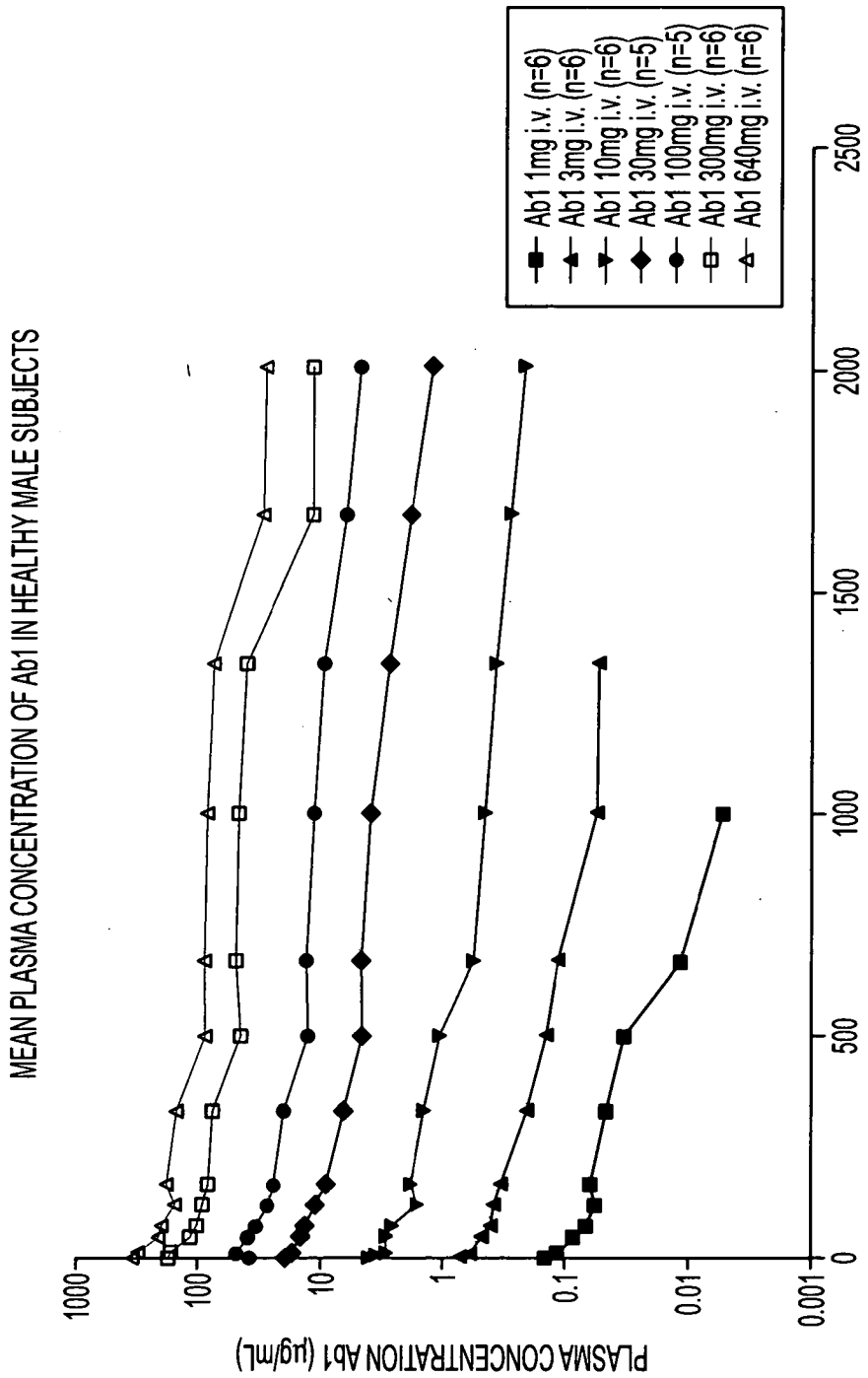

MEAN PLASMA CONCENTRATION OF Ab1 IN HEALTHY MALE SUBJECTS
PLASMA CONCENTRATION Ab1 (µg/mL)
1000
100
10
1
0.1
0.01
0.001
0
500
1000
1500
2000
2500
TIME (h)
Ab1 1mg i.v. (n=6)
Ab1 3mg i.v. (n=6)
Ab1 10mg i.v. (n=6)
Ab1 30mg i.v. (n=5)
Ab1 100mg i.v. (n=5)
Ab1 300mg i.v. (n=6)
Ab1 640mg i.v. (n=6)

FIG. 16

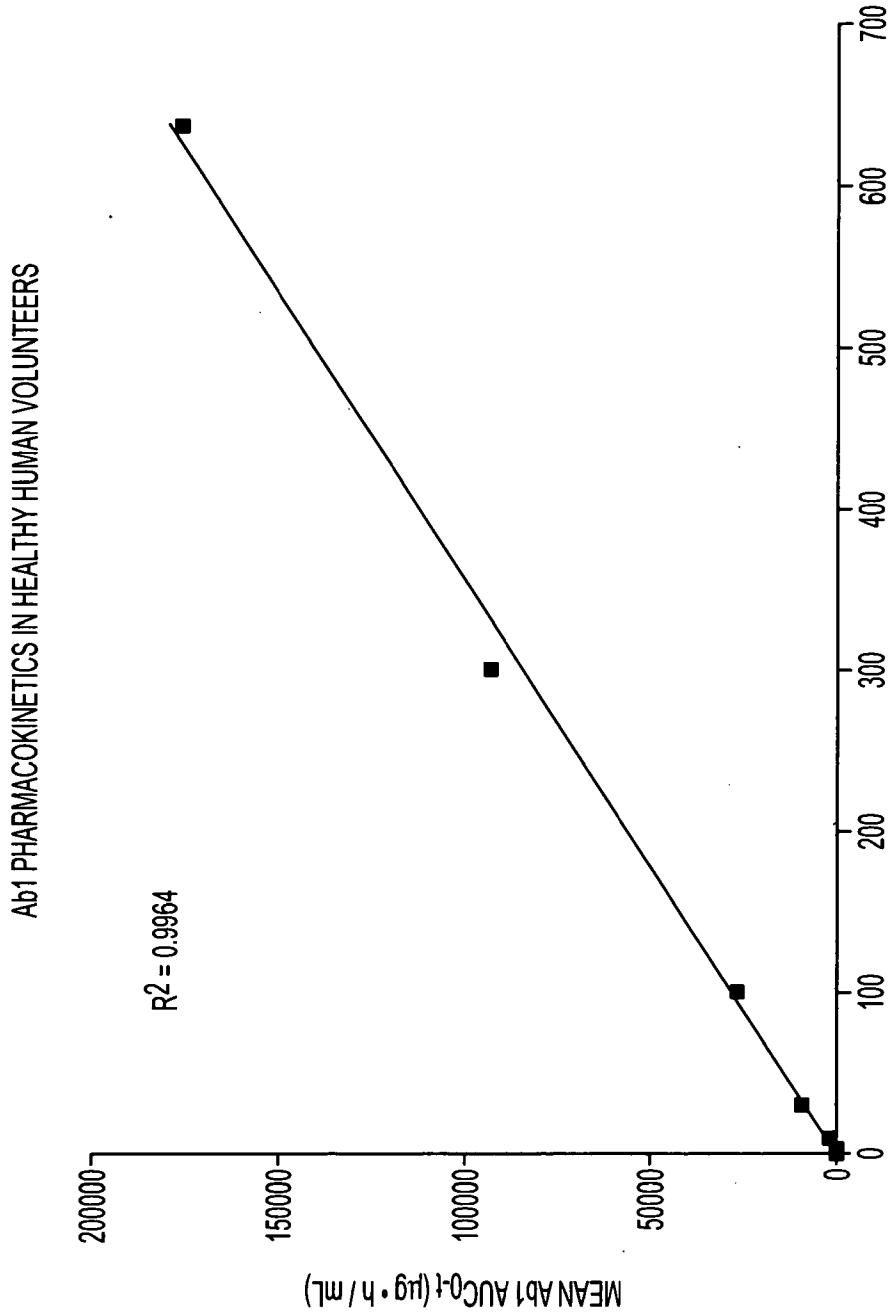

Ab1 PHARMACOKINETICS IN HEALTHY HUMAN VOLUNTEERS
R^2 = 0.9964
MEAN Ab1 AUC_{0-t} (µg • h / mL)
200000
150000
100000
50000
0
0
100
200
300
400
500
600
700
DOSE (mg)

FIG. 17

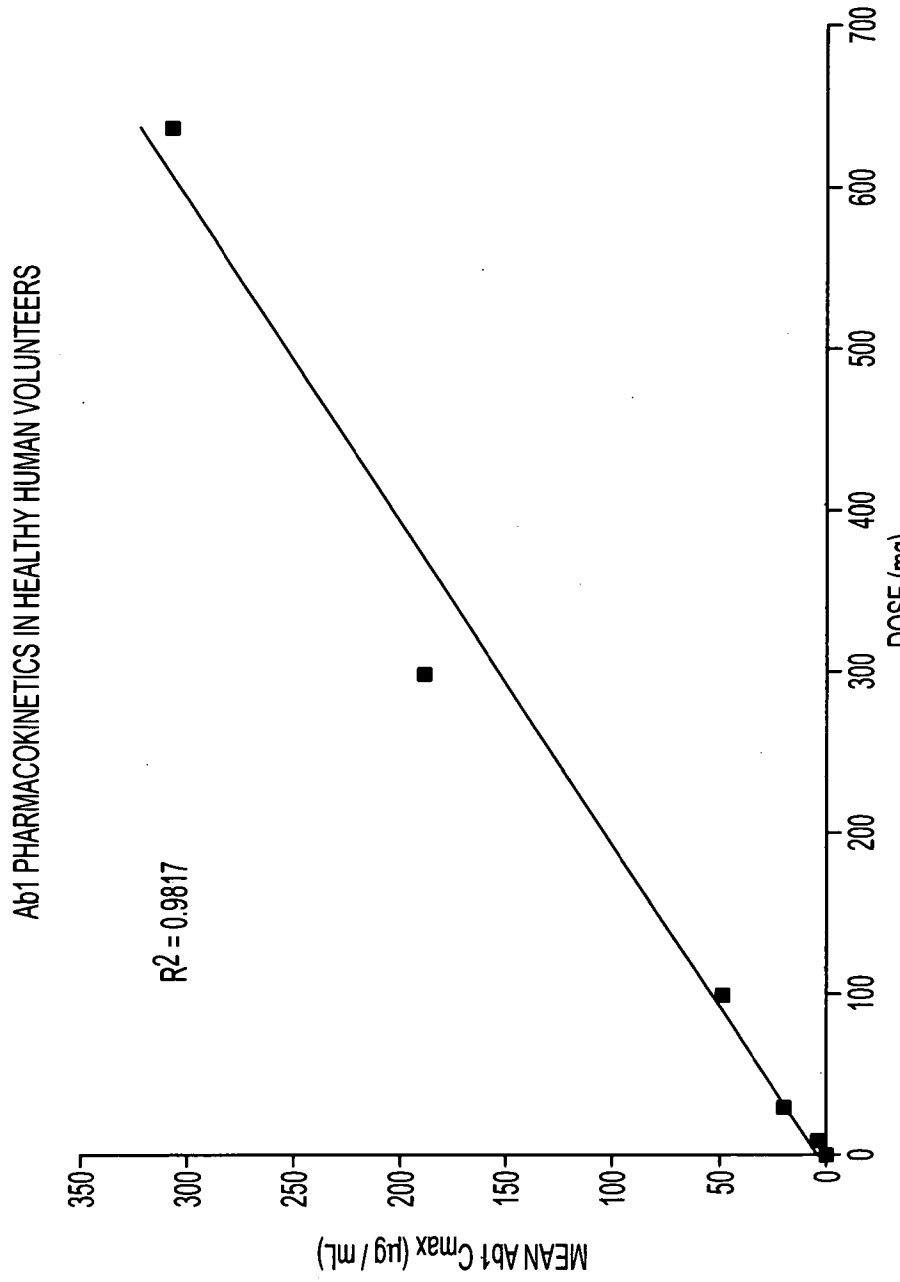

Ab1 PHARMACOKINETICS IN HEALTHY HUMAN VOLUNTEERS
$R^2 = 0.9817$
MEAN Ab1 C_{max} (µg / mL)
DOSE (mg)
0
50
100
150
200
250
300
350
0
100
200
300
400
500
600
700

FIG. 18

SUMMARY OF Ab1 PHARMACOKINETICS IN HEALTHY HUMAN VOLUNTEERS

DOSE OF Ab1	$T_{1/2}$ (DAYS)	AUC (µg • h / mL)	C_{MAX} (µg / 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	19.4	4
100mg	30.3	26128	48.0	12
300mg	26.2	92891	188.0	12
640mg	30.2	175684	306.0	12

FIG. 19

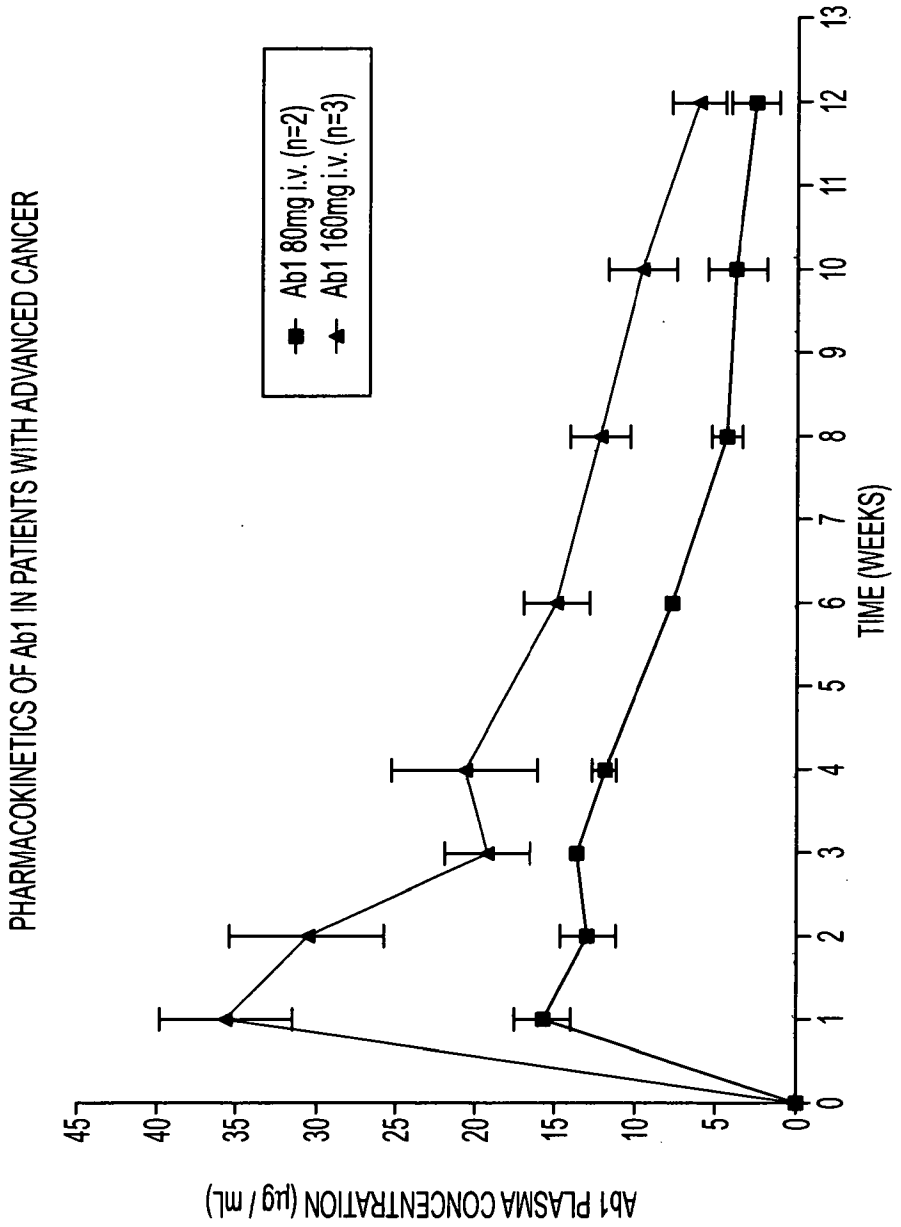

PHARMACOKINETICS OF Ab1 IN PATIENTS WITH ADVANCED CANCER
Ab1 80mg i.v. (n=2)
Ab1 160mg i.v. (n=3)
Ab1 PLASMA CONCENTRATION (µg / mL)
TIME (WEEKS)
0
5
10
15
20
25
30
35
40
45
0
1
2
3
4
5
6
7
8
9
10
11
12
13

FIG. 20

UNPRECEDENTED ELIMINATION HALF-LIFE OF Ab1

	CYNOMOLGUS MONKEY (DAYS)	HUMAN (DAYS)
Ab1	15-21	~31
ACTEMRA (TOCILIZUMAB)	7	6
REMICADE	5	8 TO 9.5
SYNAGIS	8.6	20
ERBITUX	3 TO 7	5
ZENAPAX	7	20
AVASTIN	10	20
PERTUZUMAB	10	18 TO 22

FIG. 21

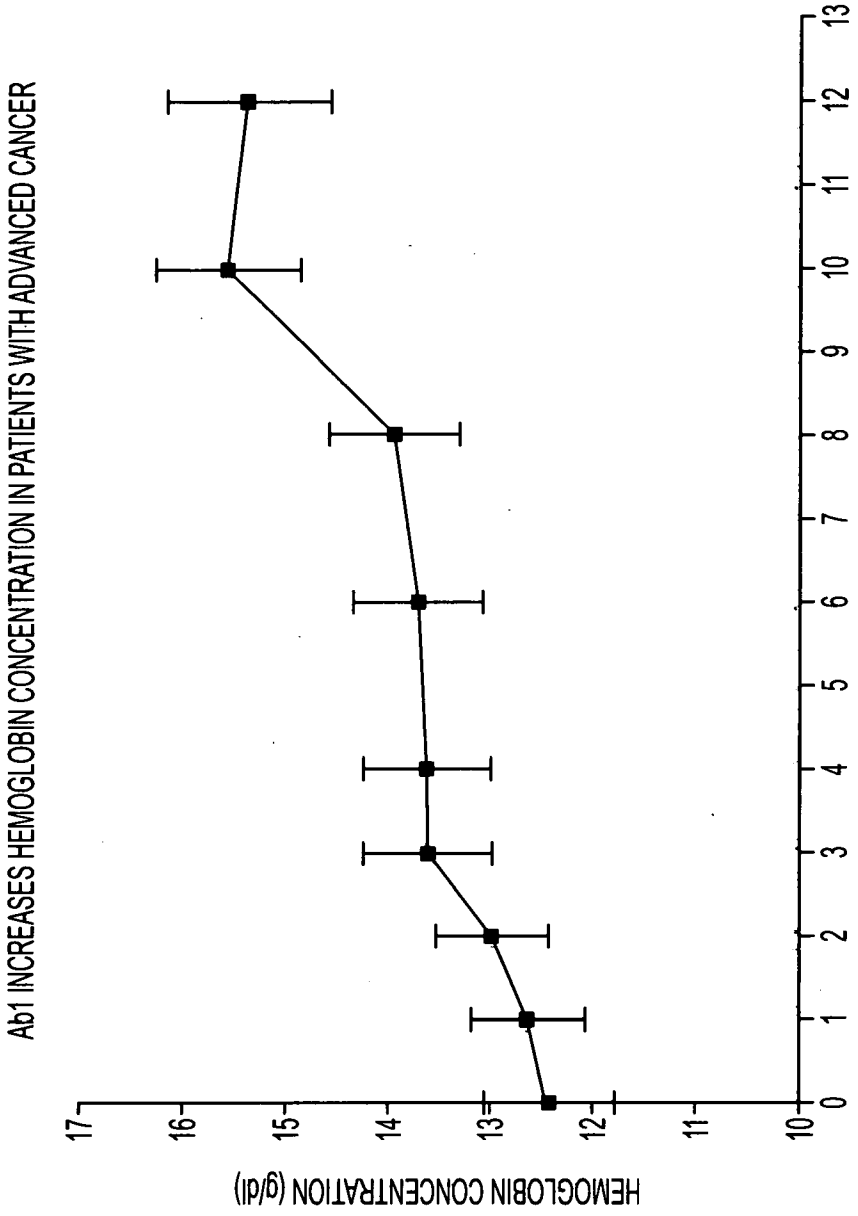

Ab1 INCREASES HEMOGLOBIN CONCENTRATION IN PATIENTS WITH ADVANCED CANCER
HEMOGLOBIN CONCENTRATION (g/dl)
TIME (WEEKS)
17
16
15
14
13
12
11
10
0
1
2
3
4
5
6
7
8
9
10
11
12
13

FIG. 22

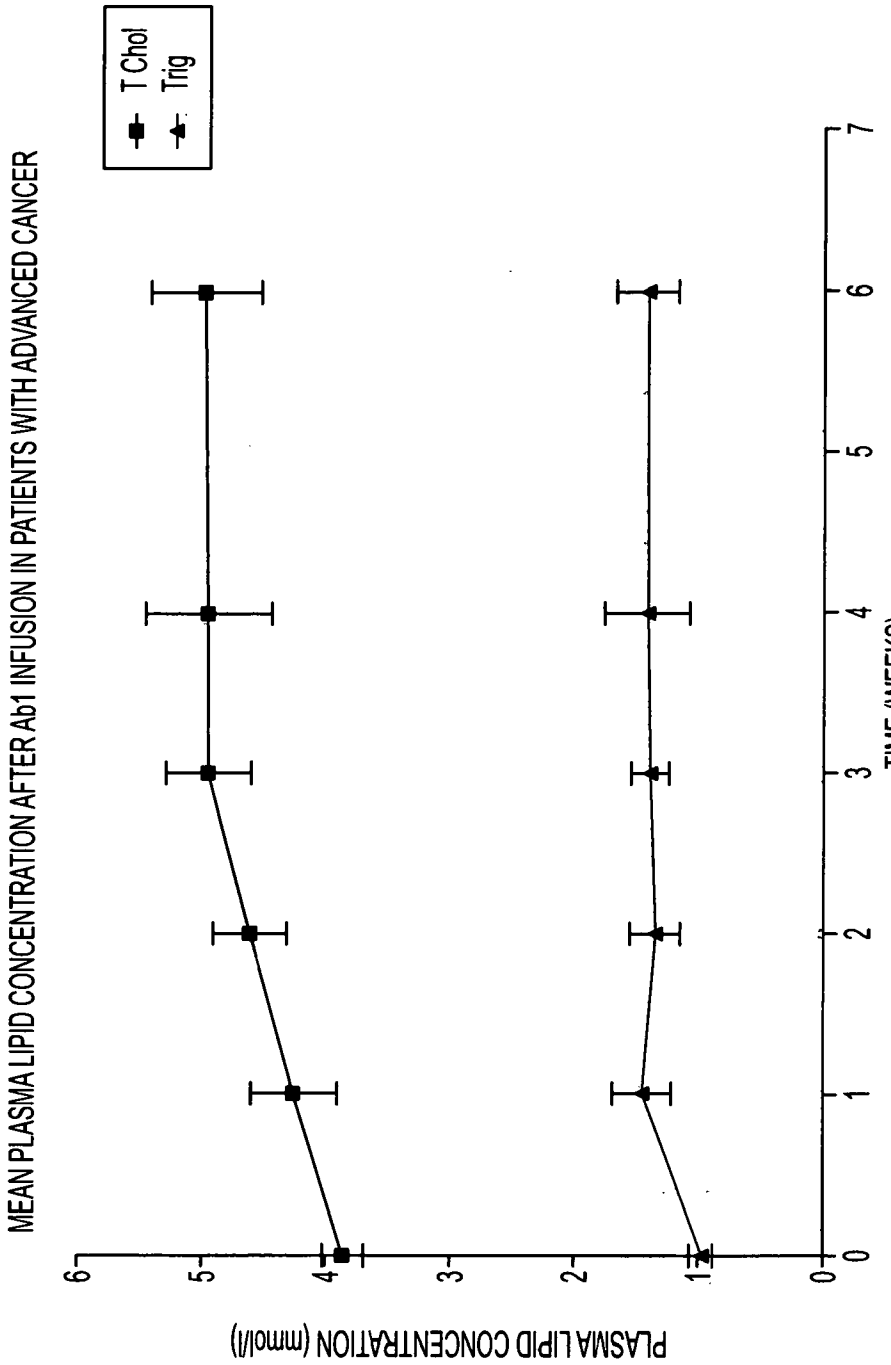

MEAN PLASMA LIPID CONCENTRATION AFTER Ab1 INFUSION IN PATIENTS WITH ADVANCED CANCER
T Chol
Trig
PLASMA LIPID CONCENTRATION (mmol/l)
TIME (WEEKS)
0
1
2
3
4
5
6
7

FIG. 23

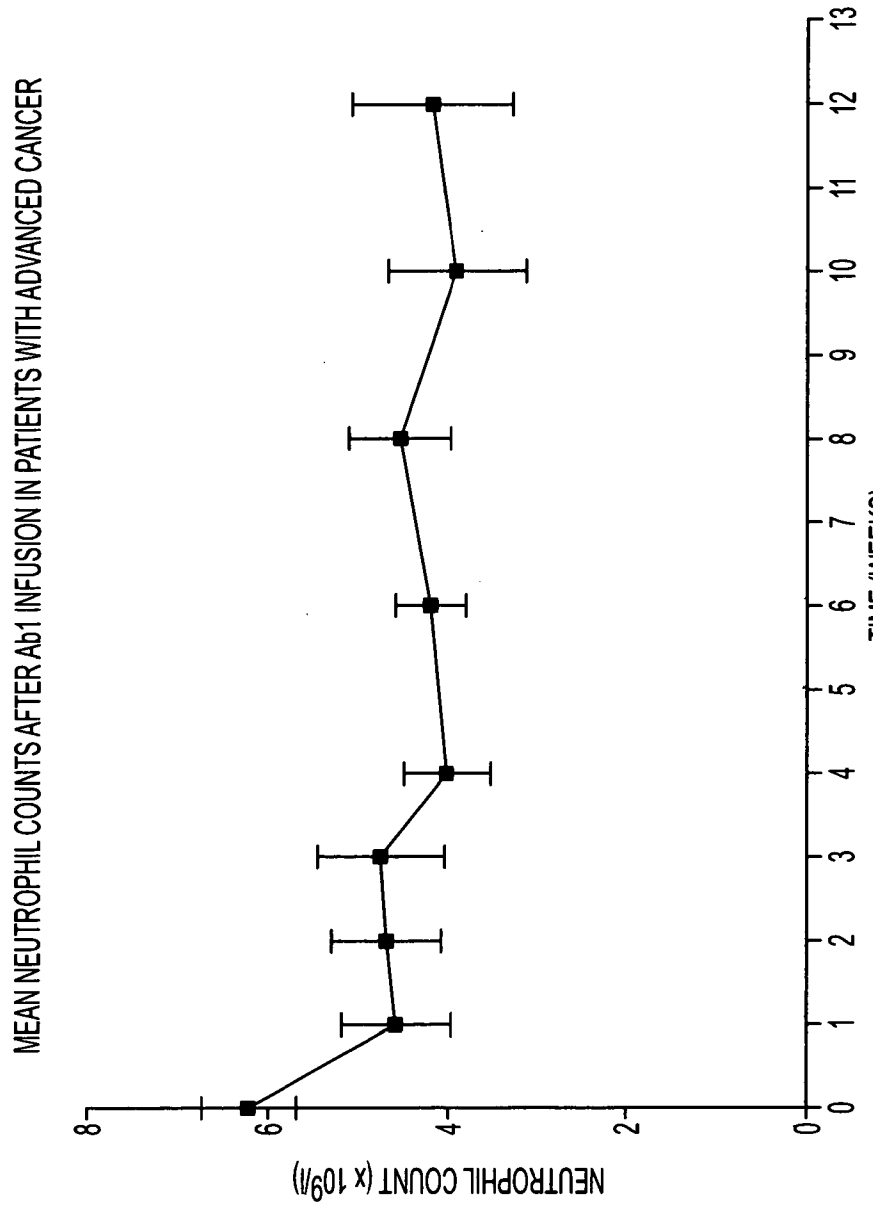

MEAN NEUTROPHIL COUNTS AFTER Ab1 INFUSION IN PATIENTS WITH ADVANCED CANCER
NEUTROPHIL COUNT (x 10⁹/l)
TIME (WEEKS)
0
2
4
6
8
0
1
2
3
4
5
6
7
8
9
10
11
12
13

FIG. 24

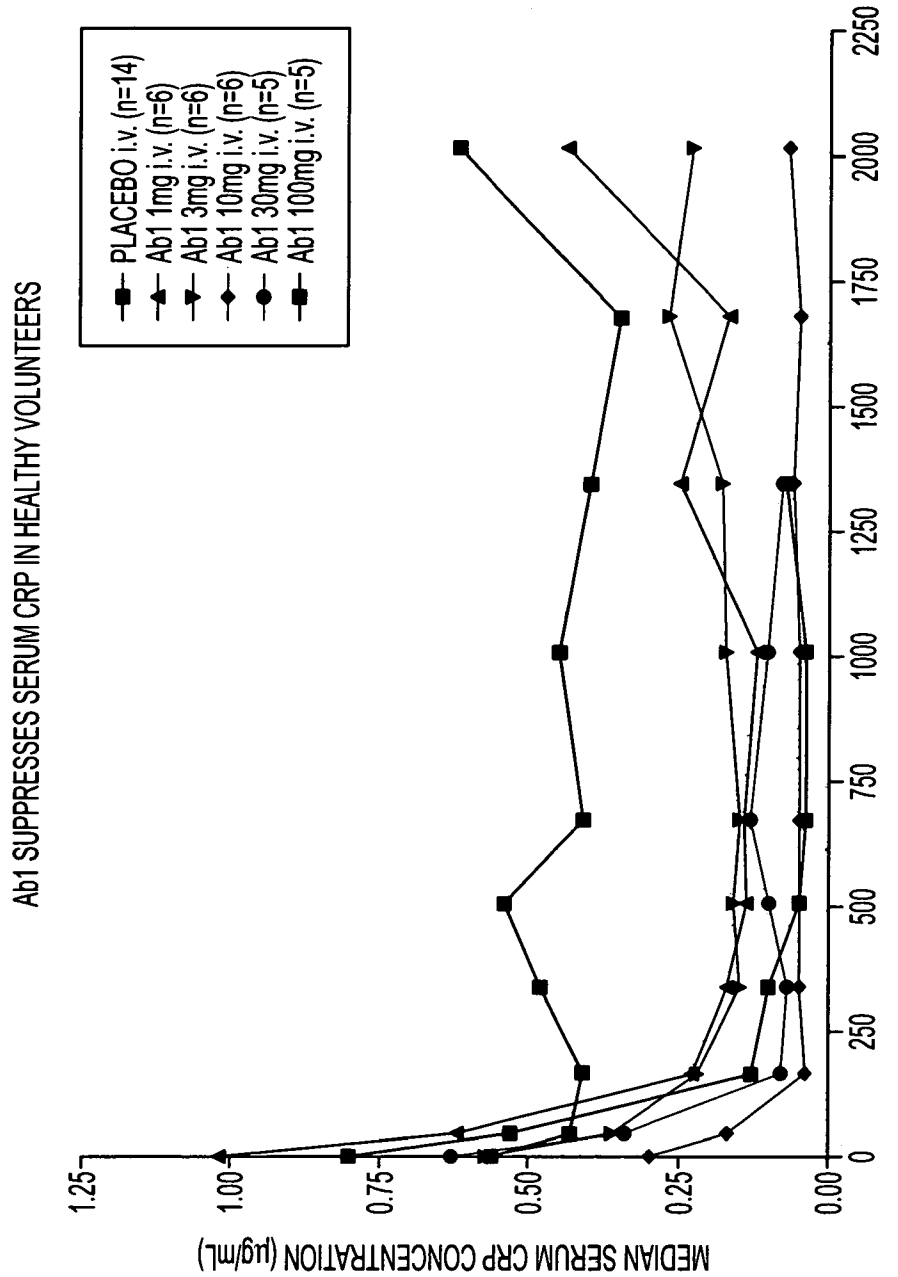

Ab1 SUPPRESSES SERUM CRP IN HEALTHY VOLUNTEERS
PLACEBO i.v. (n=14)
Ab1 1mg i.v. (n=6)
Ab1 3mg i.v. (n=6)
Ab1 10mg i.v. (n=6)
Ab1 30mg i.v. (n=5)
Ab1 100mg i.v. (n=5)
MEDIAN SERUM CRP CONCENTRATION (µg/mL)
1.25
1.00
0.75
0.50
0.25
0.00
0
250
500
750
1000
1250
1500
1750
2000
2250
TIME (h)

FIG. 25

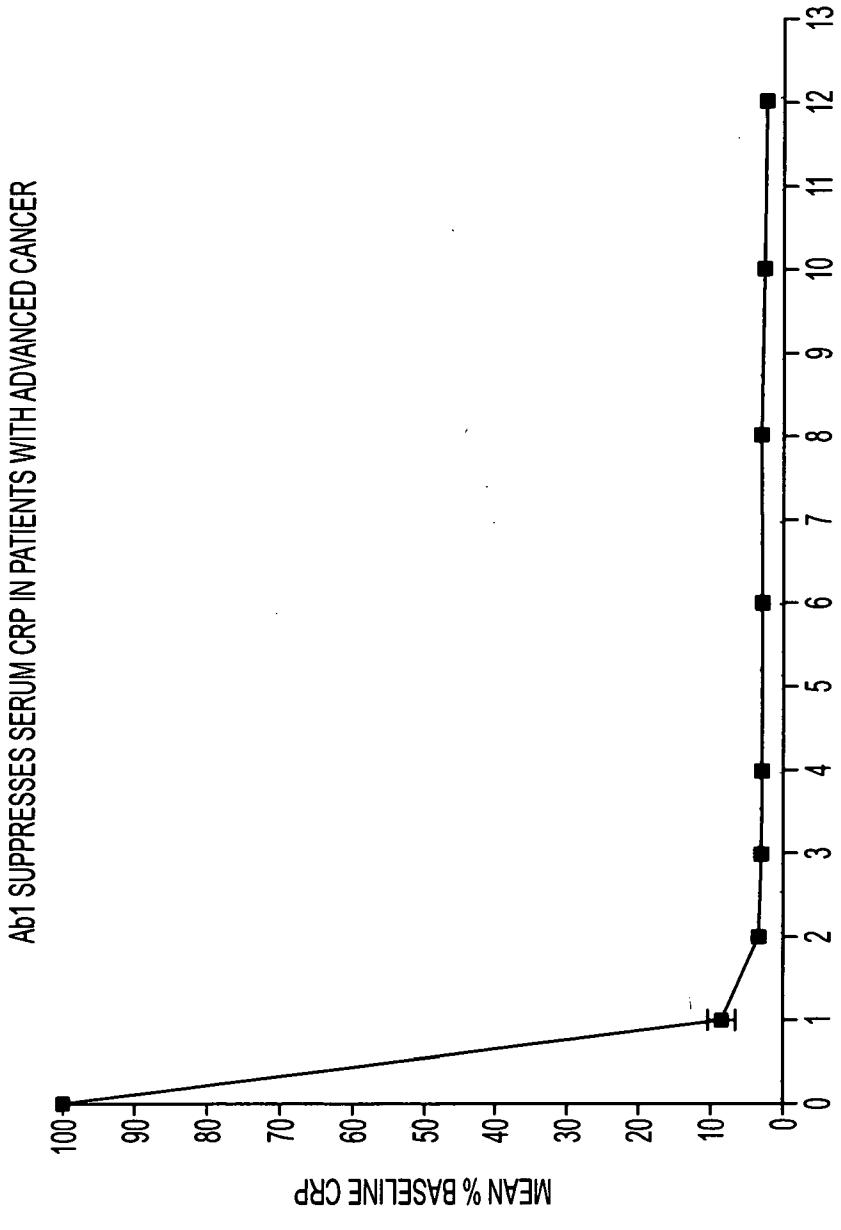

Ab1 SUPPRESSES SERUM CRP IN PATIENTS WITH ADVANCED CANCER
MEAN % BASELINE CRP
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
TIME (WEEKS)

FIG. 26A

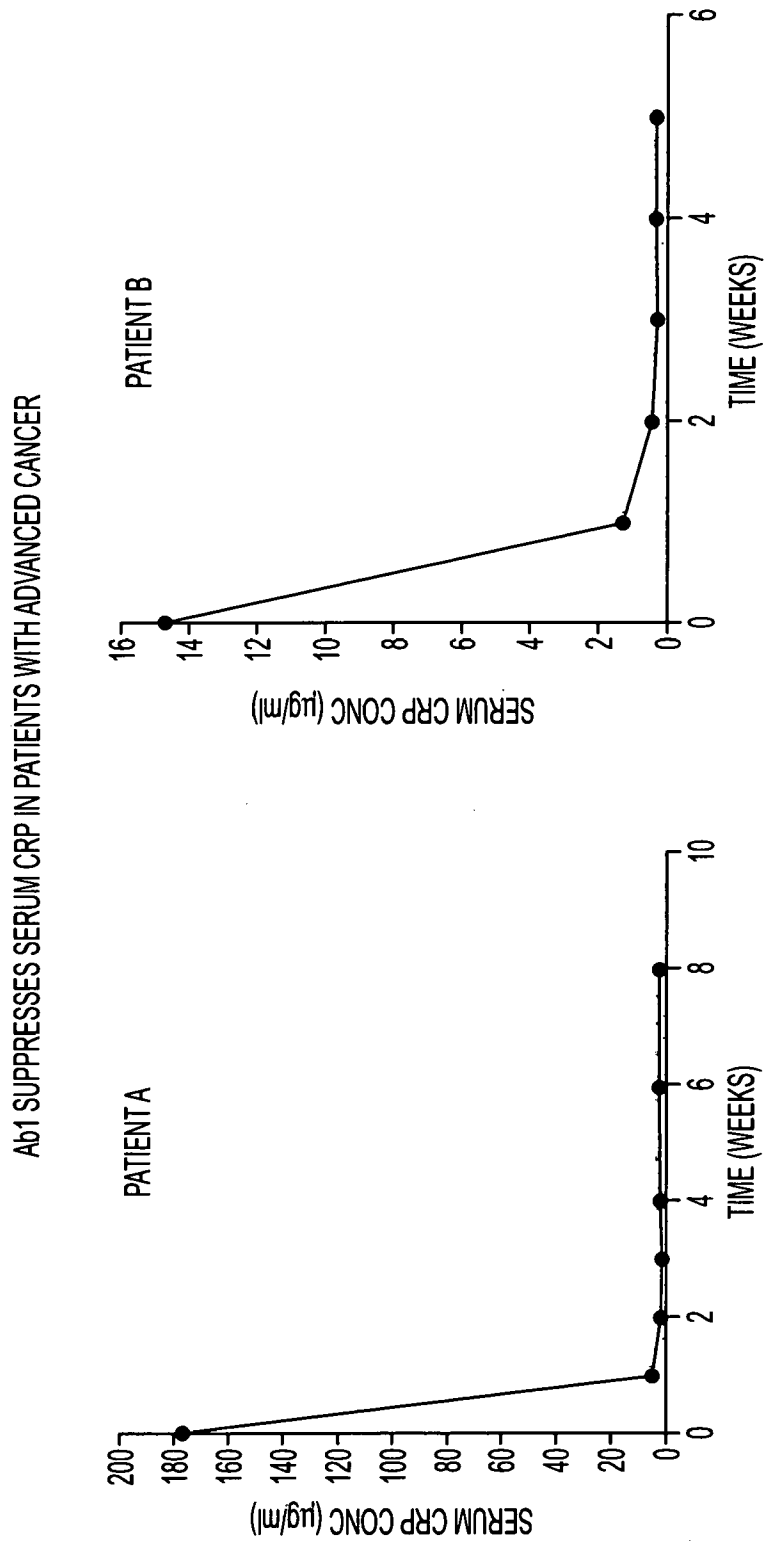

Ab1 SUPPRESSES SERUM CRP IN PATIENTS WITH ADVANCED CANCER
PATIENT A
SERUM CRP CONC (µg/ml)
200
180
160
140
120
100
80
60
40
20
0
0
2
4
6
8
10
TIME (WEEKS)
PATIENT B
SERUM CRP CONC (µg/ml)
16
14
12
10
8
6
4
2
0
0
2
4
6
TIME (WEEKS)

FIG. 26B

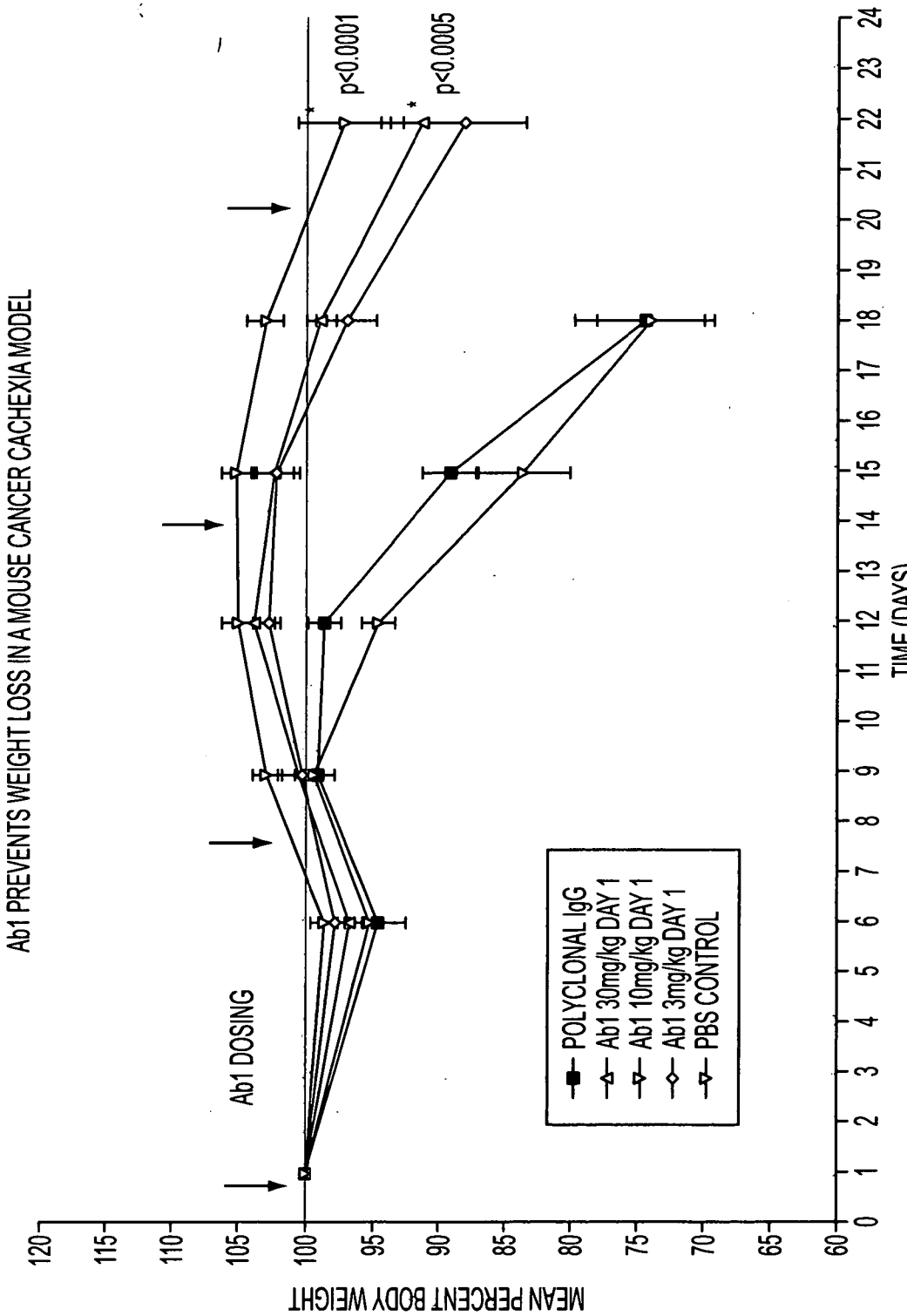

Ab1 PREVENTS WEIGHT LOSS IN A MOUSE CANCER CACHEXIA MODEL
MEAN PERCENT BODY WEIGHT
TIME (DAYS)
Ab1 DOSING
p<0.0001
p<0.0005
POLYCLONAL IgG
Ab1 30mg/kg DAY 1
Ab1 10mg/kg DAY 1
Ab1 3mg/kg DAY 1
PBS CONTROL

FIG. 27

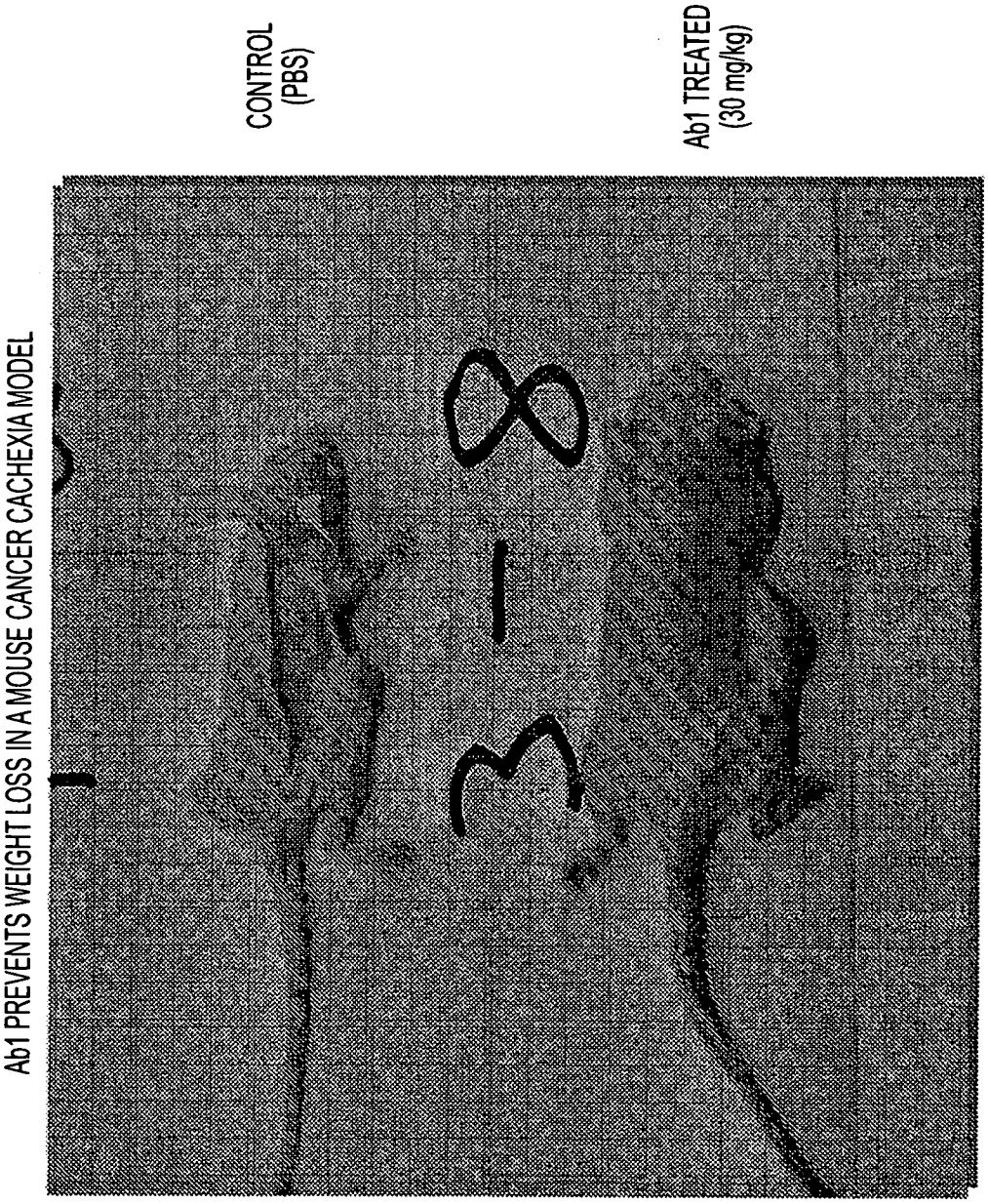

Ab1 PREVENTS WEIGHT LOSS IN A MOUSE CANCER CACHEXIA MODEL
CONTROL (PBS)
Ab1 TREATED (30 mg/kg)

FIG. 28

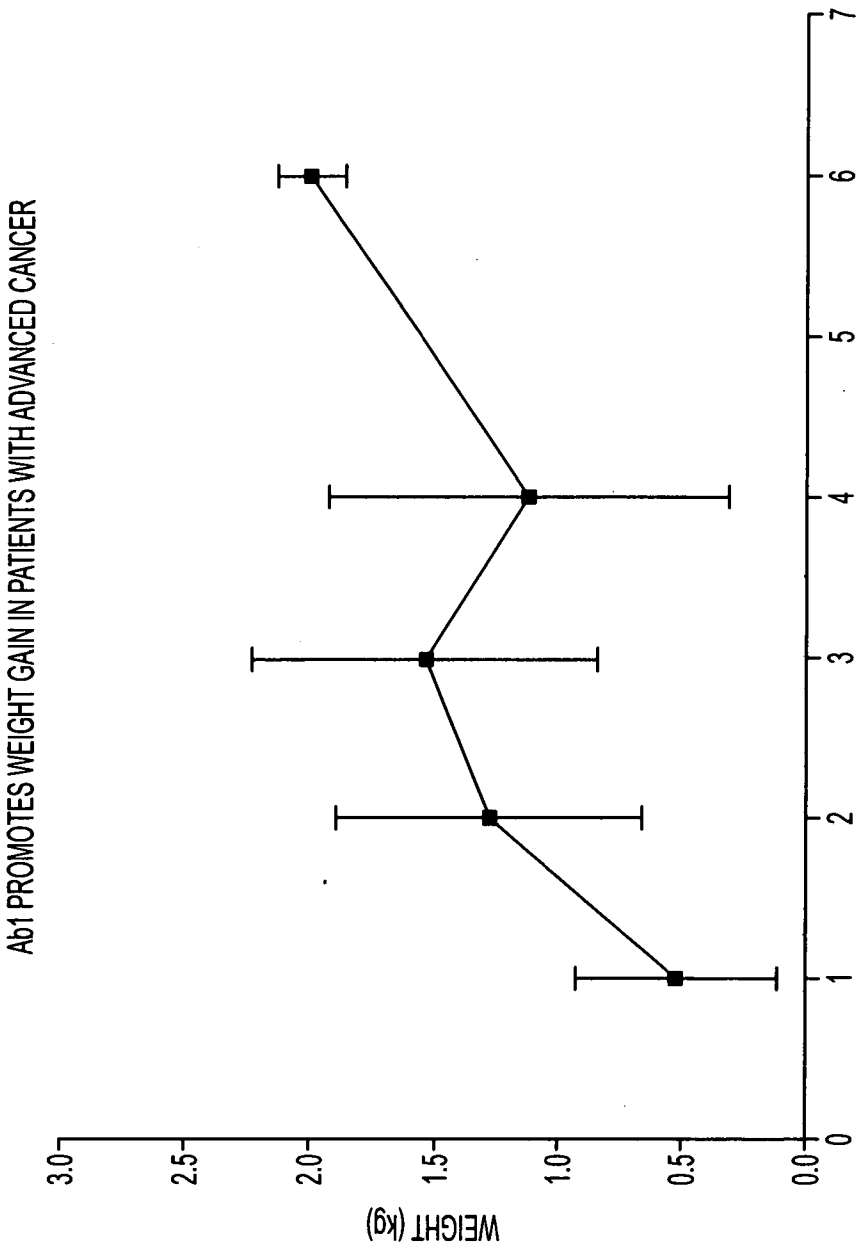

Ab1 PROMOTES WEIGHT GAIN IN PATIENTS WITH ADVANCED CANCER
WEIGHT (kg)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
TIME (WEEKS)

FIG. 29

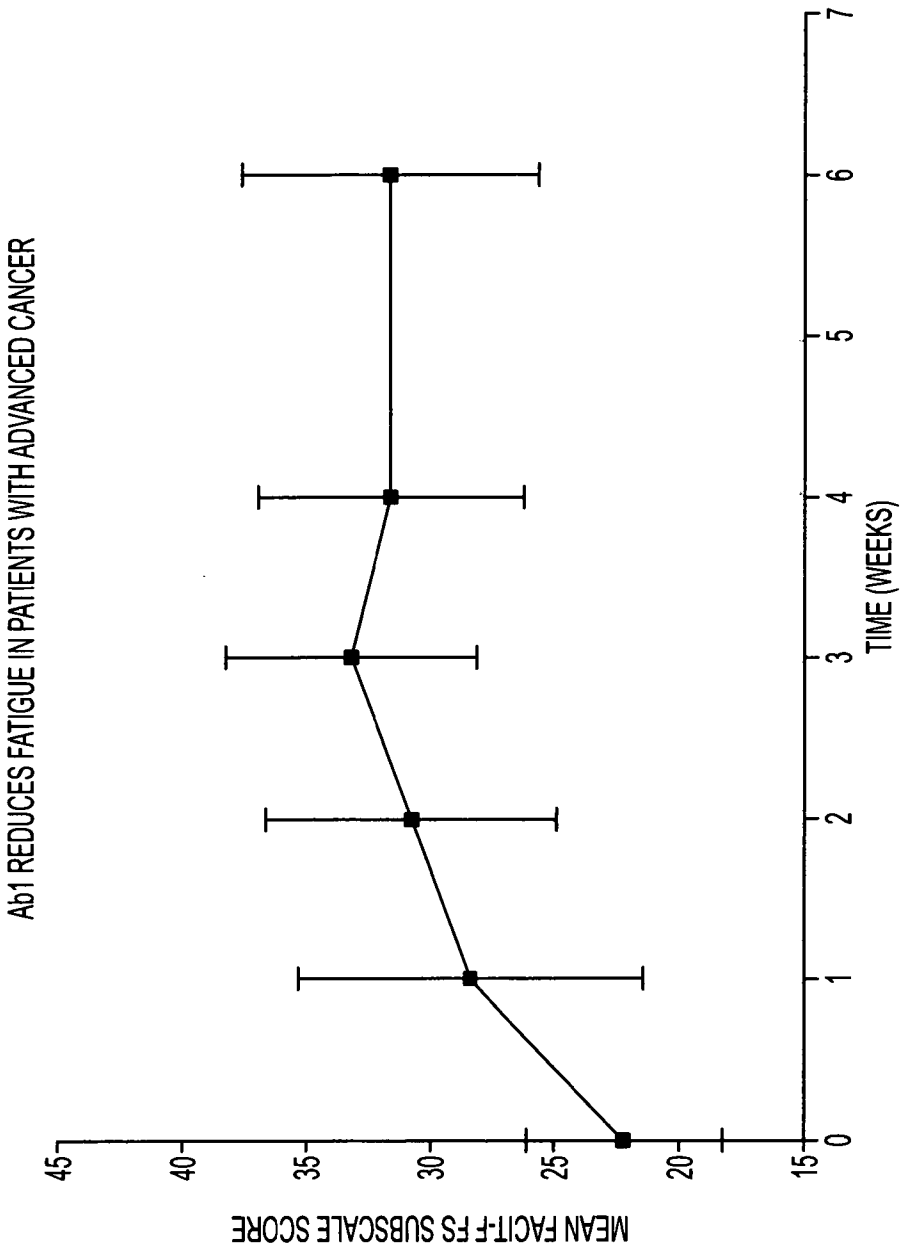

Ab1 REDUCES FATIGUE IN PATIENTS WITH ADVANCED CANCER
MEAN FACIT-F FS SUBSCALE SCORE
45
40
35
30
25
20
15
0
1
2
3
4
5
6
7
TIME (WEEKS)

FIG. 30

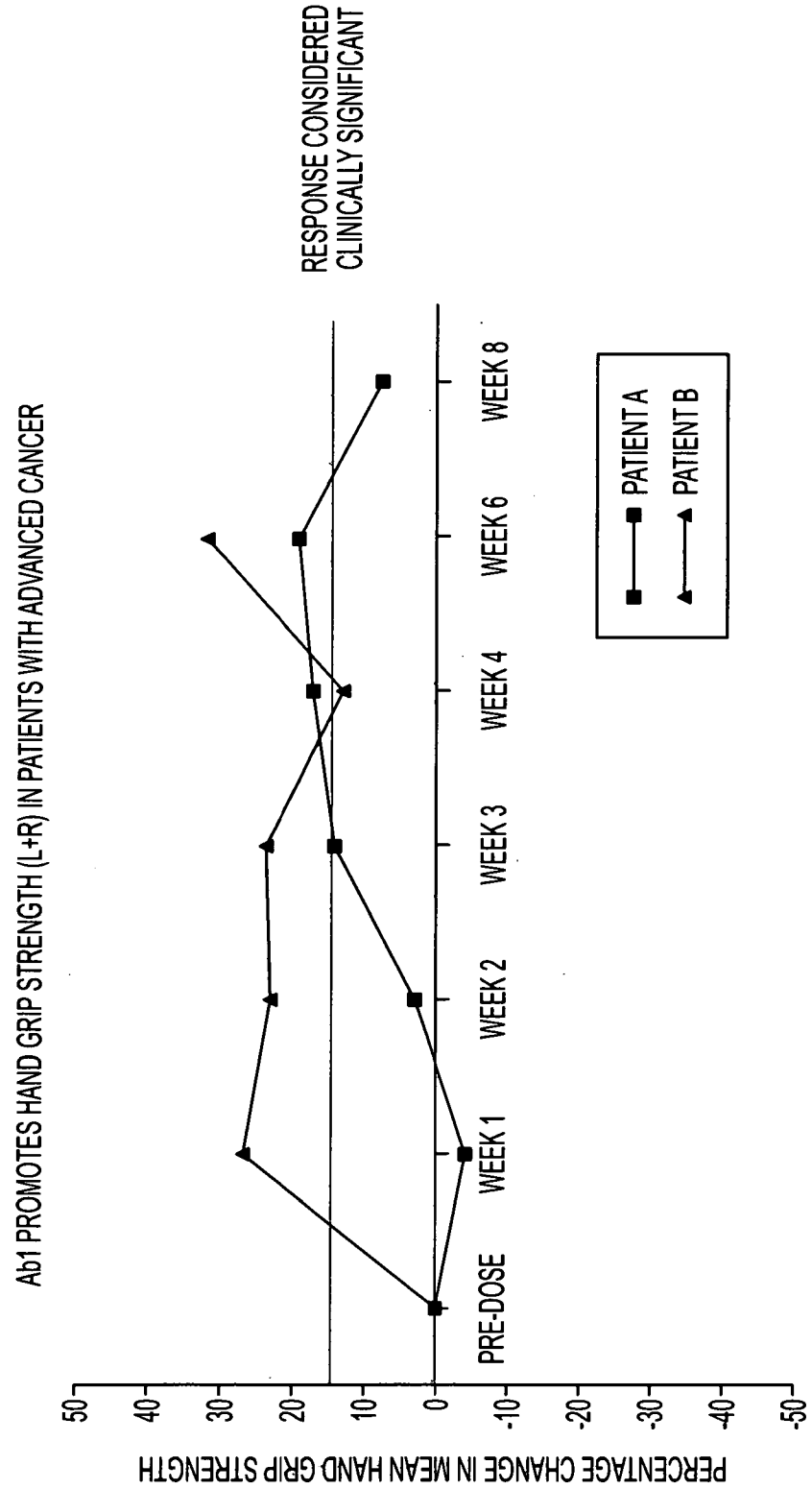

Ab1 PROMOTES HAND GRIP STRENGTH (L+R) IN PATIENTS WITH ADVANCED CANCER
RESPONSE CONSIDERED CLINICALLY SIGNIFICANT
PERCENTAGE CHANGE IN MEAN HAND GRIP STRENGTH
50
40
30
20
10
0
-10
-20
-30
-40
-50
PRE-DOSE
WEEK 1
WEEK 2
WEEK 3
WEEK 4
WEEK 6
WEEK 8
PATIENT A
PATIENT B

FIG. 31

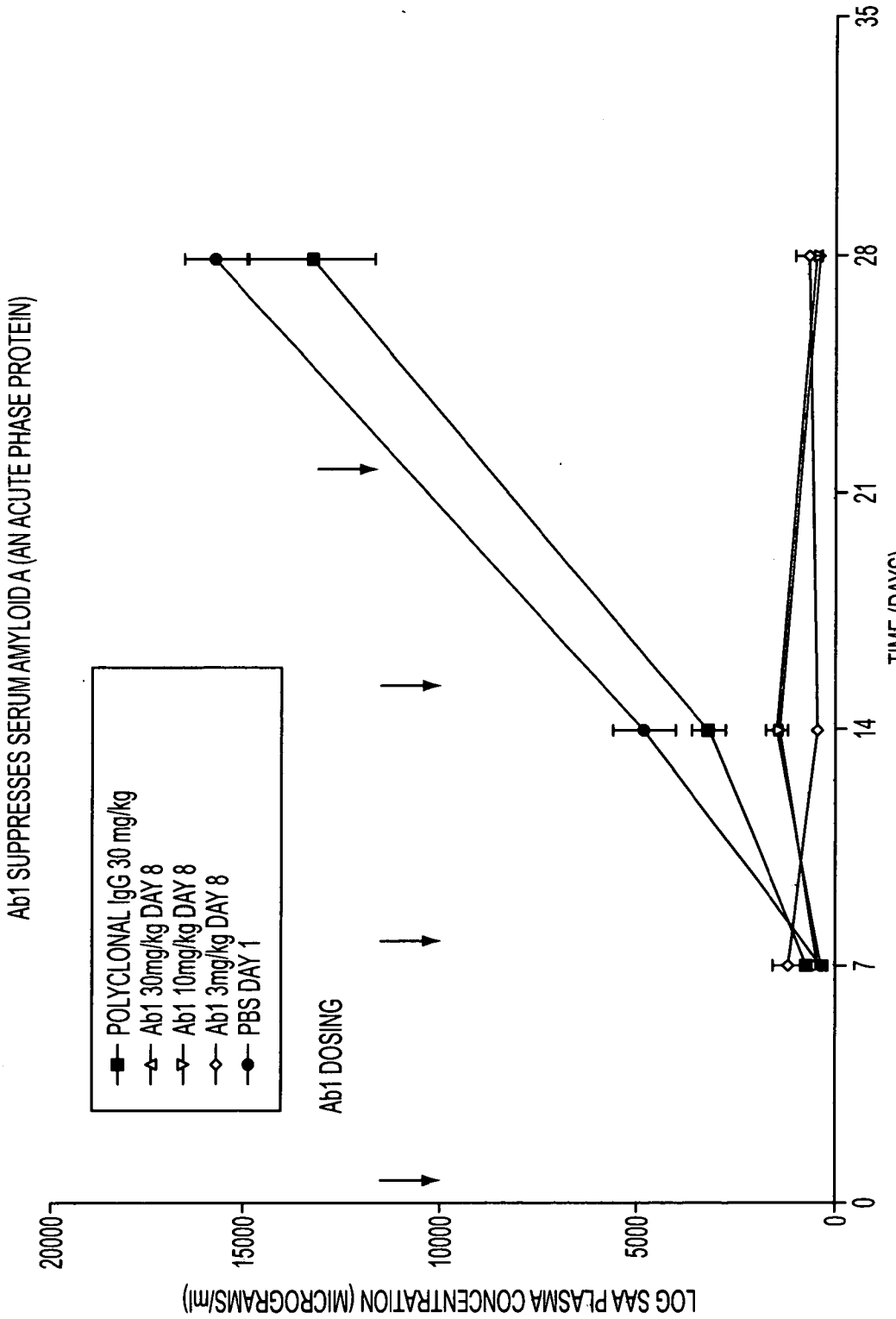

Ab1 SUPPRESSES SERUM AMYLOID A (AN ACUTE PHASE PROTEIN)
POLYCLONAL IgG 30 mg/kg
Ab1 30mg/kg DAY 8
Ab1 10mg/kg DAY 8
Ab1 3mg/kg DAY 8
PBS DAY 1
Ab1 DOSING
LOG SAA PLASMA CONCENTRATION (MICROGRAMS/ml)
20000
15000
10000
5000
0
0
7
14
21
28
35
TIME (DAYS)

FIG. 32

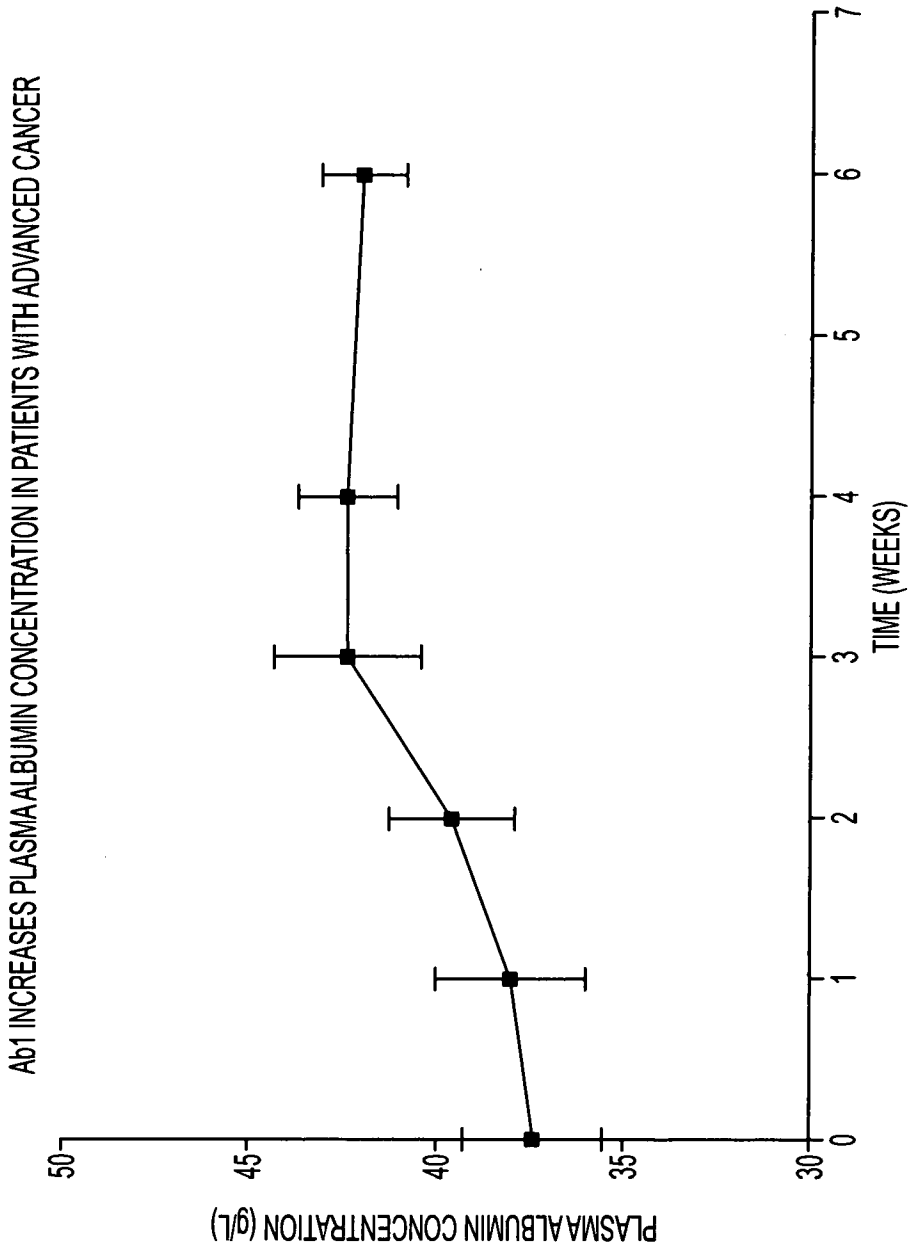

Ab1 INCREASES PLASMA ALBUMIN CONCENTRATION IN PATIENTS WITH ADVANCED CANCER
PLASMA ALBUMIN CONCENTRATION (g/L)
50
45
40
35
30
0
1
2
3
4
5
6
7
TIME (WEEKS)

FIG. 33

PREFERRED ANTI-IL-6 ANTIBODY HUMANIZATION

	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO:647	AYDMTQTPASVSAAVGGTVTIKC	QASQSINNELS	WYQQKPGQRPKLLIY	RASTLAS	GVSSRFKGSGSGTEFTLTISDLECADAATYYC
SEQ ID NO:648	AIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKLLIY	AASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
SEQ ID NO:649	DIQMTQSPSSLSASVGDRVTITC	RASQGISNYLA	WYQQKPGKVPKLLIY	AASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC
SEQ ID NO:650	DIQMTQSPSTLSASVGDRVTITC	RASQSISSWLA	WYQQKPGKAPKLLIY	KASSLES	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC
SEQ ID NO:651	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
SEQ ID NO:651	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC

	CDR3	FR4
SEQ ID NO:647	QQGYSLRNIDNA	FGGGTEVVVKR
SEQ ID NO:648		
SEQ ID NO:649		FGGGTKVEIKR
SEQ ID NO:650		
SEQ ID NO:651	QQGYSLRNIDNA	FGGGTKVEIKR
SEQ ID NO:651	QQGYSLRNIDNA	FGGGTKVEIKR

FIG. 34A

	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO:652	-QSLEESGGRLVTPGTPLTLTCTASGFSLS	NYYVT	WVRQAPGKGLEWIG	IIYG-SDETAYATWAIG	RFTISKTST--TVDLKMTSLTAADTATYFCAR
SEQ ID NO:653	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	SNYMS	WVRQAPGKGLEWVS	VIYS-GGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:654	EVQLVESGGGLIQPGGSLRLSCAASGFTVS	SNYMS	WVRQAPGKGLEWVS	VIYS-GGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:655	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	SYAMS	WVRQAPGKGLEWVS	VIYSGGSSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
SEQ ID NO:656	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG	IIYG-SDETAYATWAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:657	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

	CDR3	FR4
SEQ ID NO:652	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:653		
SEQ ID NO:654		WGQGTLVTVSS
SEQ ID NO:655		
SEQ ID NO:656	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:657	DDSSDWDAKFNL	WGQGTLVTVSS

FIG. 34B

PREFERRED ANTI-IL-6 ANTIBODY HUMANIZATION

	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO:647	AYDMTQTPASVSAAVGGTVTIKC	QASQSINNELS	WYQQKPGQRPKLLIY	RASTLAS	GVSSRFKGSGSGTEFTLTISDLECADAATYYC
SEQ ID NO:648	AIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	WYQQKPGKAPKLLIY	AASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
SEQ ID NO:649	DIQMTQSPSSLSASVGDRVTITC	RASQGISNYLA	WYQQKPGKVPKLLIY	AASTLQS	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC
SEQ ID NO:650	DIQMTQSPSTLSASVGDRVTITC	RASQSISSWLA	WYQQKPGKAPKLLIY	KASSLES	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC
SEQ ID NO:709	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC
SEQ ID NO:709	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC

	CDR3	FR4
SEQ ID NO:647	QQGYSLRNIDNA	FGGGTEVVVKR
SEQ ID NO:648		
SEQ ID NO:649		FGGGTKVEIKR
SEQ ID NO:650		
SEQ ID NO:709	QQGYSLRNIDNA	FGGGTKVEIKR
SEQ ID NO:709	QQGYSLRNIDNA	FGGGTKVEIKR

FIG. 35A

	FR1	CDR1	FR2	CDR2	FR3
SEQ ID NO:652	-QSLEESGGRLVTPGTPLTLTCTASGFSLS	NYYVT	WVRQAPGKGLEWIG	IIYG-SDETAYATWAIG	RFTISKTST--TVDLKMTSLTAADTATYFCAR
SEQ ID NO:653	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	SNYMS	WVRQAPGKGLEWVS	VIYS-GGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:654	EVQLVESGGGLIQPGGSLRLSCAASGFTVS	SNYMS	WVRQAPGKGLEWVS	VIYS-GGSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:655	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	SYAMS	WVRQAPGKGLEWVS	VIYSGGSSTYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK
SEQ ID NO:656	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG	IIYG-SDETAYATWAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR
SEQ ID NO:657	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

	CDR3	FR4
SEQ ID NO:652	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:653		
SEQ ID NO:654		WGQGTLVTVSS
SEQ ID NO:655		
SEQ ID NO:656	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:657	DDSSDWDAKFNL	WGQGTLVTVSS

FIG. 35B

ALIGNMENT OF Ab1 LIGHT CHAINS

	FR1	CDR1	FR2
SEQ ID NO:2	MDTRAPTQLLGLLLLWLPGARC AYDMTQTPASVSAAVGGTVTIKC	QASQSINNELS	WYQQKPGQRPKLLIY
SEQ ID NO:20	IQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY
SEQ ID NO:647	AYDMTQTPASVSAAVGGTVTIKC	QASQSINNELS	WYQQKPGQRPKLLIY
SEQ ID NO:651	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY
SEQ ID NO:660	MDTRAPTQLLGLLLLWLPGARC AYDMTQTPASVSAAVGGTVTIKC	QASQSINNELS	WYQQKPGQRPKLLIY
SEQ ID NO:666	IQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY
SEQ ID NO:699	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY
SEQ ID NO:702	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY
SEQ ID NO:706	MKWVTFISLLFLFSSAYS AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY
SEQ ID NO:709	AIQMTQSPSSLSASVGDRVTITC	QASQSINNELS	WYQQKPGKAPKLLIY

	CDR2	FR3	CDR3
SEQ ID NO:2	RASTLAS	GVSSRFKGSGSGTEFTLTISDLECADAATYYC	QQGYSLRNIDNA
SEQ ID NO:20	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA
SEQ ID NO:647	RASTLAS	GVSSRFKGSGSGTEFTLTISDLECADAATYYC	QQGYSLRNIDNA
SEQ ID NO:651	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA
SEQ ID NO:660	RASTLAS	GVSSRFKGSGSGTEFTLTISDLECADAATYYC	QQGYSLRNIDNA
SEQ ID NO:666	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA
SEQ ID NO:699	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA
SEQ ID NO:702	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA
SEQ ID NO:706	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA
SEQ ID NO:709	RASTLAS	GVPSRFSGSGSGTDFTLTISSLQPDDFATYYC	QQGYSLRNIDNA

FIG. 36A

ALIGNMENT OF Abl LIGHT CHAINS (CONTINUED)

FR4 kappa CONSTANT LIGHT CHAIN

SEQ ID NO:2 FGGGTEVVVKR T VAAPSVFIFPPSDEQLKSGTASVVCLLNN
SEQ ID NO:20
SEQ ID NO:647 FGGGTEVVVKR
SEQ ID NO:651 FGGGTKVEIKR
SEQ ID NO:660
SEQ ID NO:666 FGGGTKVEIKR T VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SEQ ID NO:699 FGGGTKVEIKR T
SEQ ID NO:702 FGGGTKVEIKR T VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SEQ ID NO:706 FGGGTKVEIKR T VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
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 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO:699
SEQ ID NO:702 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO:706 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO:709

FIG. 36B

ALIGNMENT OF Ab1 HEAVY CHAINS

	FR1	CDR1	FR2
SEQ ID NO:3	METGLRWLLLVAVLKGVQC -QSLEESGGRLVTPGTPLTLTCTASGFSLS	NYYVT	WVRQAPGKGLEWIG
SEQ ID NO:18	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:19	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:652	-QSLEESGGRLVTPGTPLTLTCTASGFSLS	NYYVT	WVRQAPGKGLEWIG
SEQ ID NO:656	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:657	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:658	METGLRWLLLVAVLKGVQC -QSLEESGGRLVTPGTPLTLTCTASGFSLS	NYYVT	WVRQAPGKGLEWIG
SEQ ID NO:661	METGLRWLLLVAVLKGVQC -QSLEESGGRLVTPGTPLTLTCTASGFSLS	NYYVT	WVRQAPGKGLEWIG
SEQ ID NO:664	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:665	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:704	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG
SEQ ID NO:708	MKWVTFISLLFLFSSAYS EVQLVESGGGLVQPGGSLRLSCAASGFSLS	NYYVT	WVRQAPGKGLEWVG

	CDR2	FR3	CDR3	FR4
SEQ ID NO:3	IIYG-SDETAYATWAIG	RFTISKTST--TVDLKMTSLTAADTATYFCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:18	IIYG-SDETAYATWAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	
SEQ ID NO:19	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	
SEQ ID NO:652	IIYG-SDETAYATWAIG	RFTISKTST--TVDLKMTSLTAADTATYFCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:656	IIYG-SDETAYATWAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:657	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:658	IIYG-SDETAYATSAIG	RFTISKTST--TVDLKMTSLTAADTATYFCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:661	IIYG-SDETAYATWAIG	RFTISKTST--TVDLKMTSLTAADTATYFCAR	DDSSDWDAKFNL	
SEQ ID NO:664	IIYG-SDETAYATWAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:665	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:704	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	WGQGTLVTVSS
SEQ ID NO:708	IIYG-SDETAYATSAIG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDSSDWDAKFNL	WGQGTLVTVSS

FIG. 37A

ALIGNMENT OF Abl HEAVY CHAINS, CONTINUED

gamma-1 CONSTANT HEAVY CHAIN POLYPEPTIDE

SEQ ID NO:3 ASTKGPSVFPLAPSSKSTSGGTAALGCLVK
SEQ ID NO:658 ASTKGPSVFPLAPSSKSTSGGTAALGCLVK

SEQ ID NO:664 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
SEQ ID NO:665 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
SEQ ID NO:704 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
SEQ ID NO:708 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS

gamma-1 CONSTANT HEAVY CHAIN POLYPEPTIDE, CONTINUED

SEQ ID NO:664 LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
SEQ ID NO:665 LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
SEQ ID NO:704 LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
SEQ ID NO:708 LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

gamma-1 CONSTANT HEAVY CHAIN POLYPEPTIDE, CONTINUED

SEQ ID NO:664 HEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
SEQ ID NO:665 HEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
SEQ ID NO:704 HEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
SEQ ID NO:708 HEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ

gamma-1 CONSTANT HEAVY CHAIN POLYPEPTIDE, CONTINUED

SEQ ID NO:664 PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
SEQ ID NO:665 PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
SEQ ID NO:704 PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
SEQ ID NO:708 PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

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. 37B

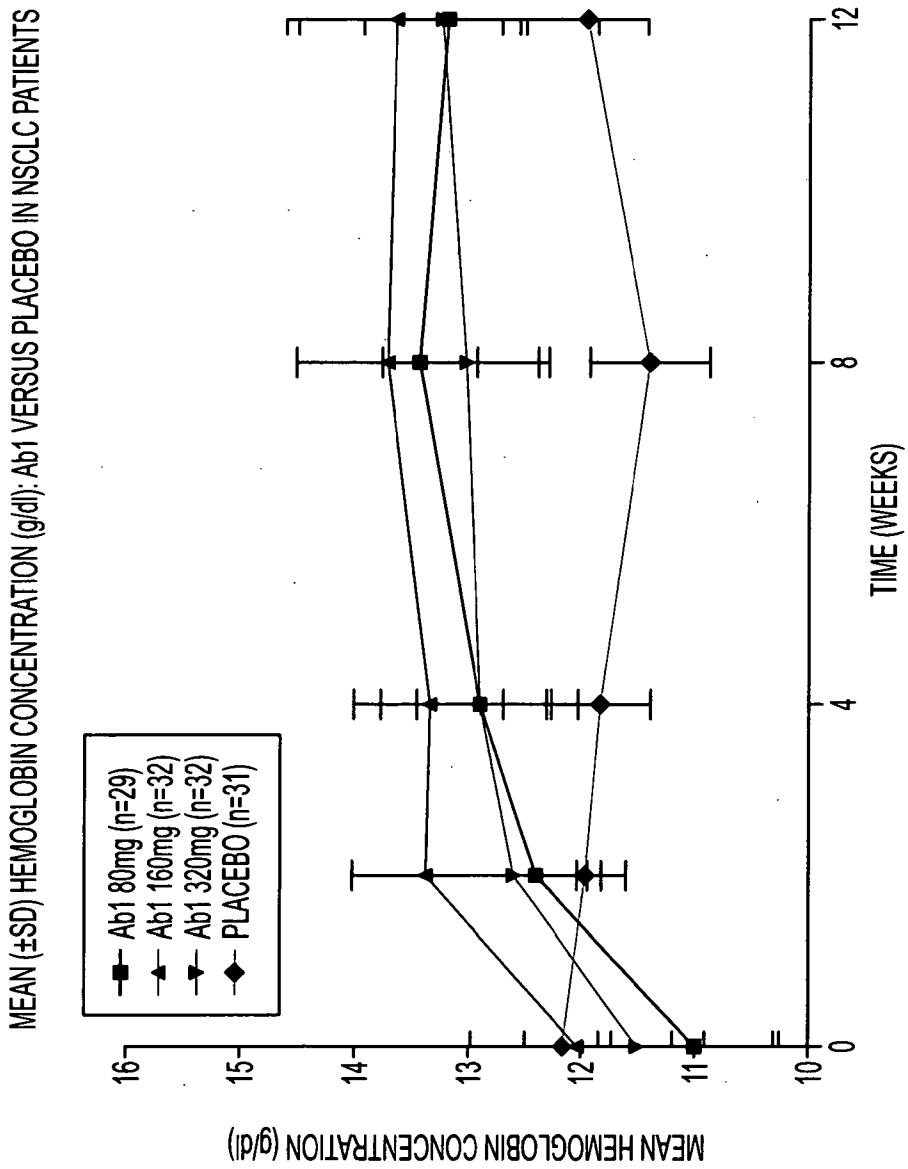

MEAN (±SD) HEMOGLOBIN CONCENTRATION (g/dl): Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
Ab1 80mg (n=29)
Ab1 160mg (n=32)
Ab1 320mg (n=32)
PLACEBO (n=31)
MEAN HEMOGLOBIN CONCENTRATION (g/dl)
16
15
14
13
12
11
10
0
4
8
12
TIME (WEEKS)

FIG. 38

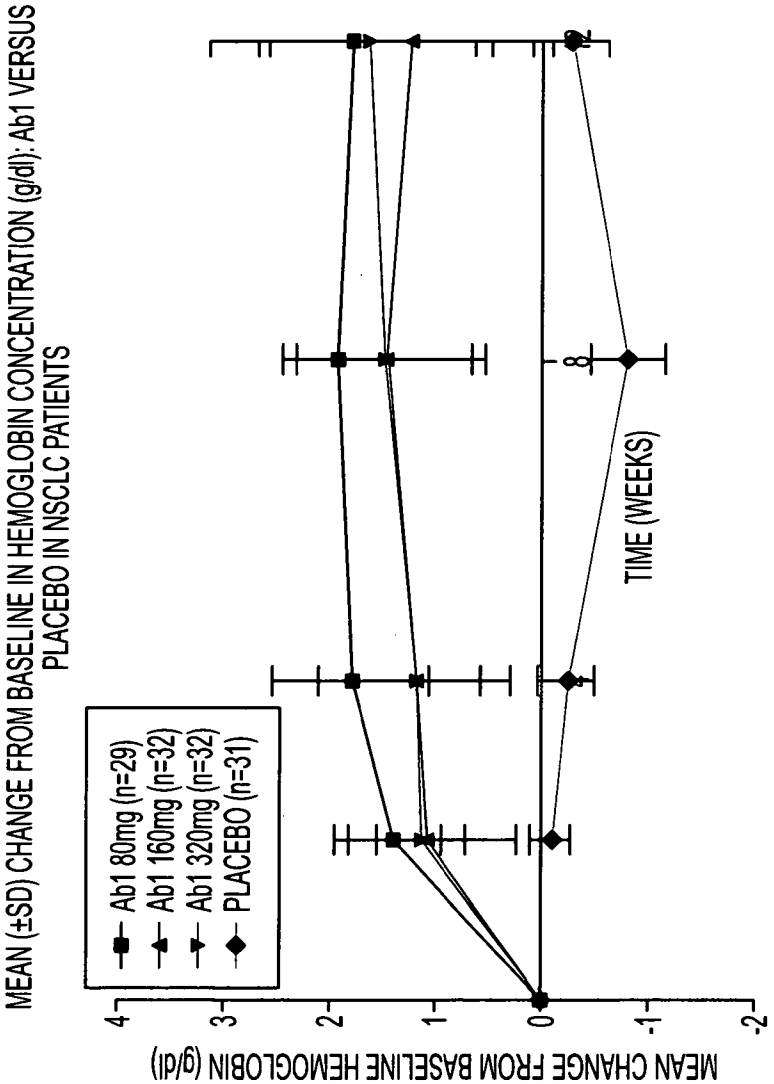

MEAN (±SD) CHANGE FROM BASELINE IN HEMOGLOBIN CONCENTRATION (g/dl): Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
Ab1 80mg (n=29)
Ab1 160mg (n=32)
Ab1 320mg (n=32)
PLACEBO (n=31)
MEAN CHANGE FROM BASELINE HEMOGLOBIN (g/dl)
4
3
2
1
0
-1
-2
TIME (WEEKS)

FIG. 39

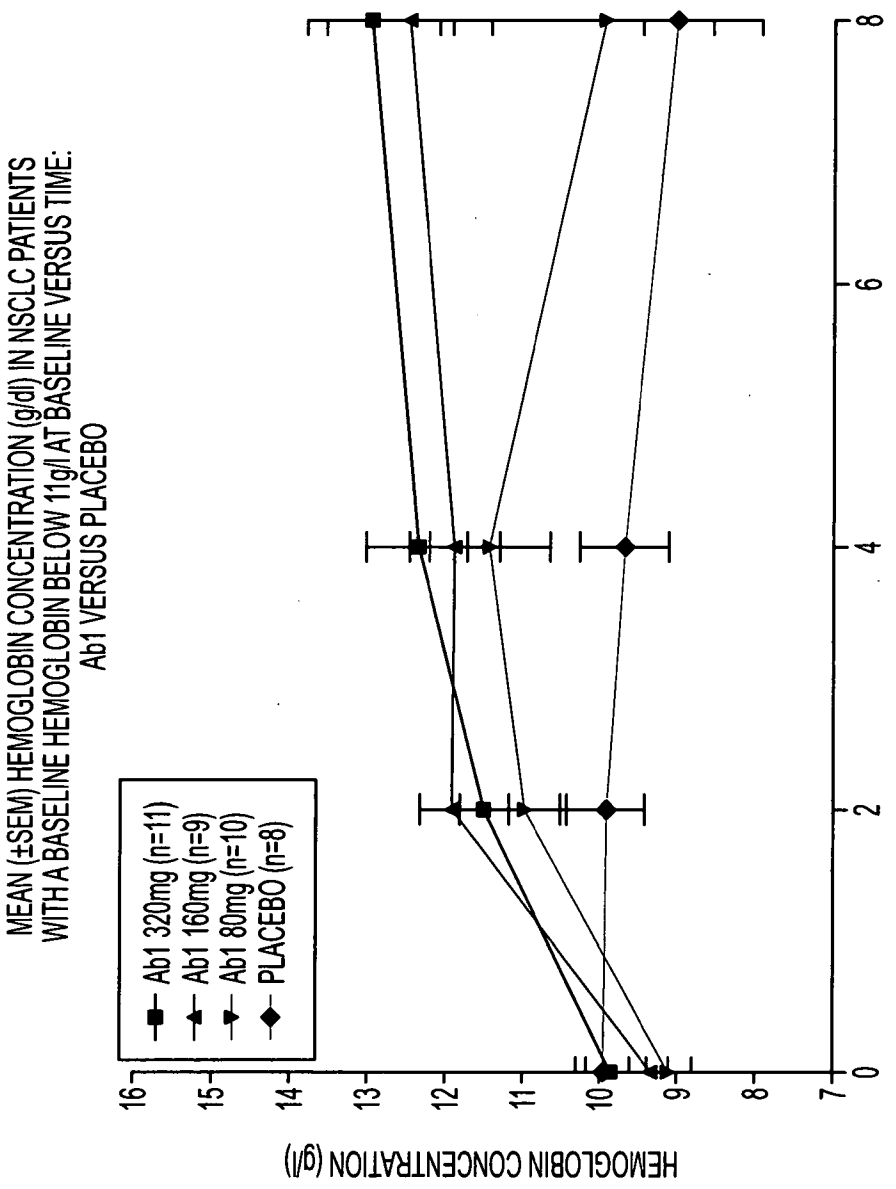

MEAN (±SEM) HEMOGLOBIN CONCENTRATION (g/dl) IN NSCLC PATIENTS
WITH A BASELINE HEMOGLOBIN BELOW 11g/l AT BASELINE VERSUS TIME:
Ab1 VERSUS PLACEBO
Ab1 320mg (n=11)
Ab1 160mg (n=9)
Ab1 80mg (n=10)
PLACEBO (n=8)
HEMOGLOBIN CONCENTRATION (g/l)
TIME (WEEKS)
16
15
14
13
12
11
10
9
8
7
0
2
4
6
8

FIG. 40

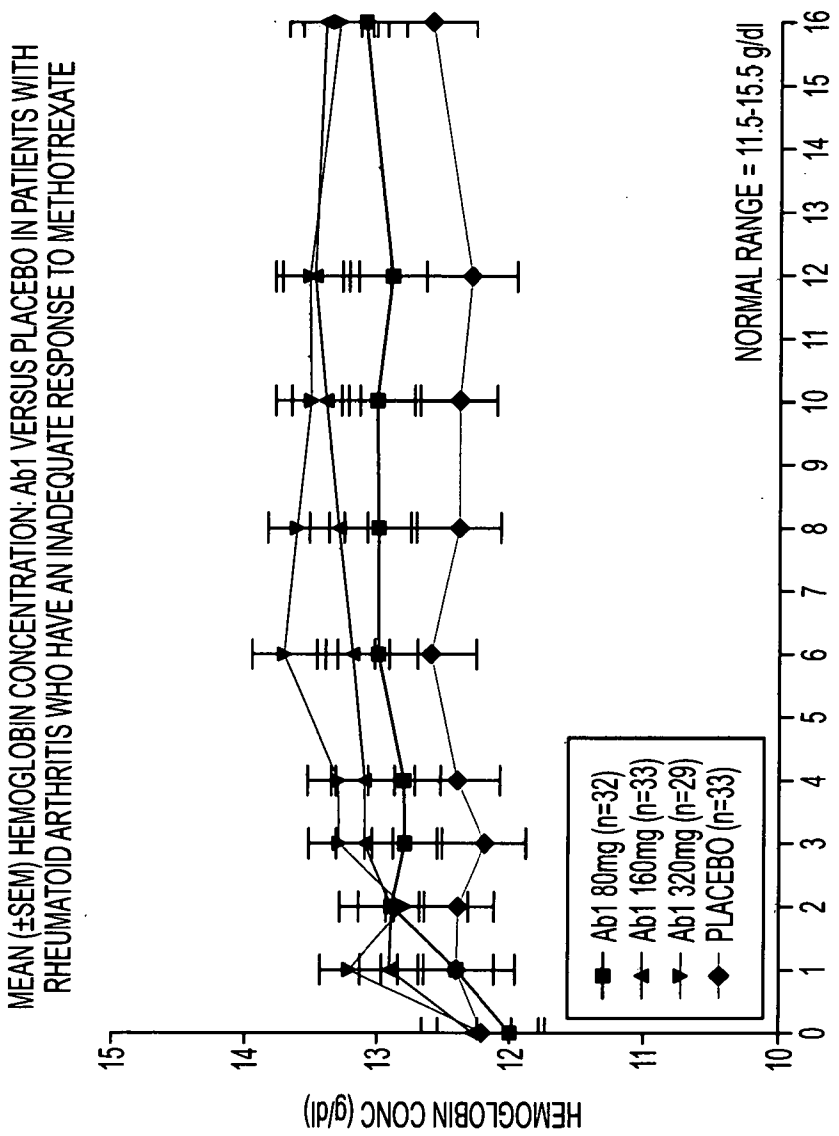

MEAN (±SEM) HEMOGLOBIN CONCENTRATION: Ab1 VERSUS PLACEBO IN PATIENTS WITH RHEUMATOID ARTHRITIS WHO HAVE AN INADEQUATE RESPONSE TO METHOTREXATE
HEMOGLOBIN CONC (g/dl)
TIME (WEEKS)
NORMAL RANGE = 11.5-15.5 g/dl
Ab1 80mg (n=32)
Ab1 160mg (n=33)
Ab1 320mg (n=29)
PLACEBO (n=33)

FIG. 41

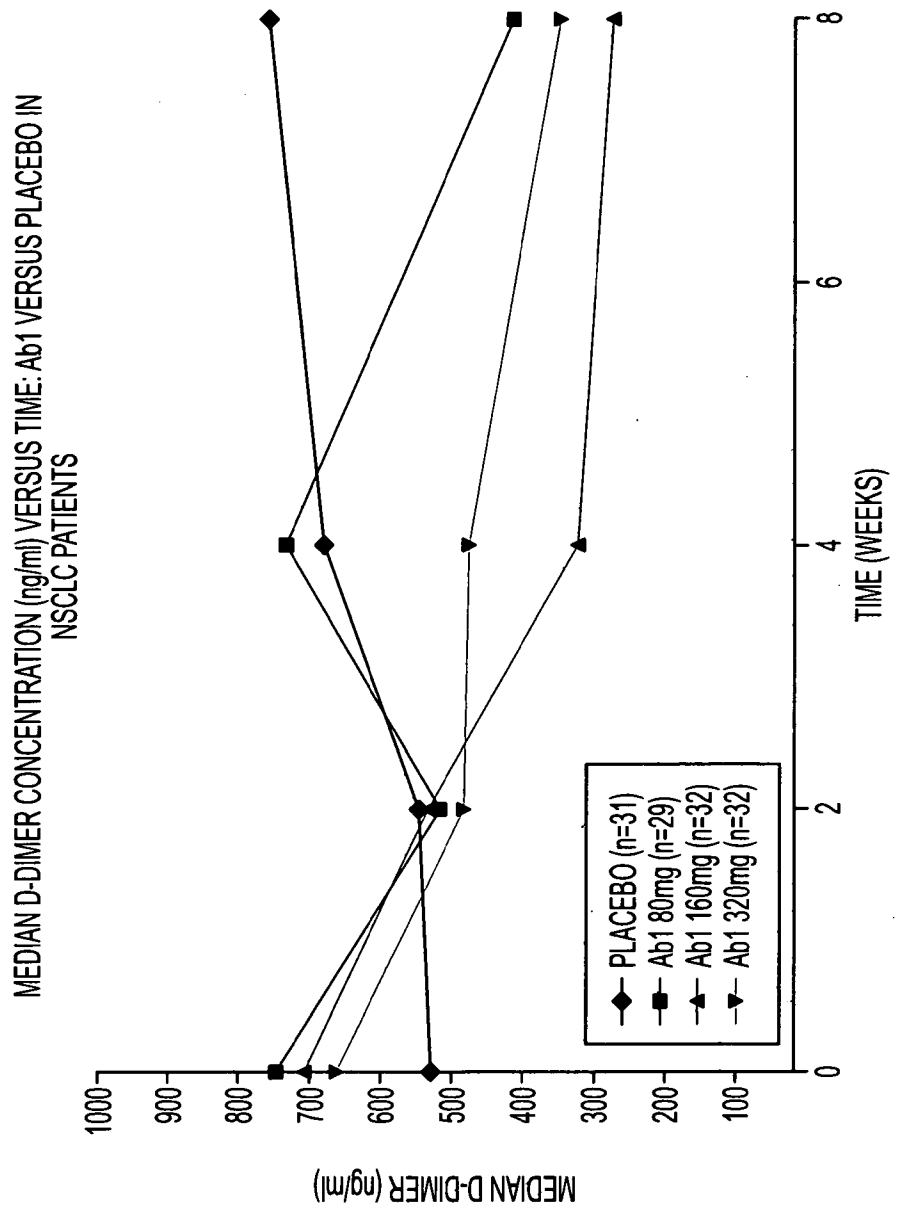

MEDIAN D-DIMER CONCENTRATION (ng/ml) VERSUS TIME: Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
MEDIAN D-DIMER (ng/ml)
1000
900
800
700
600
500
400
300
200
100
0
2
4
6
8
TIME (WEEKS)
PLACEBO (n=31)
Ab1 80mg (n=29)
Ab1 160mg (n=32)
Ab1 320mg (n=32)

FIG. 42

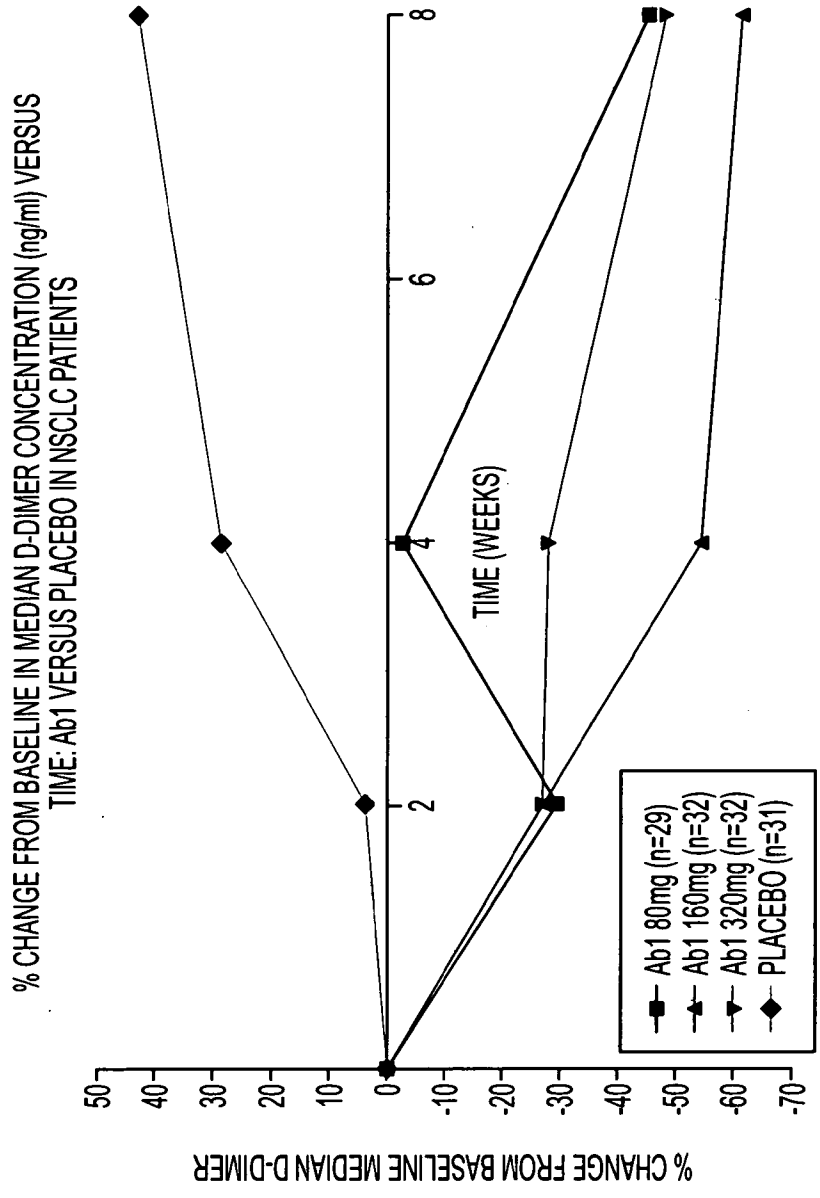

% CHANGE FROM BASELINE IN MEDIAN D-DIMER CONCENTRATION (ng/ml) VERSUS
TIME: Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
% CHANGE FROM BASELINE MEDIAN D-DIMER
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
0
2
4
6
8
TIME (WEEKS)
Ab1 80mg (n=29)
Ab1 160mg (n=32)
Ab1 320mg (n=32)
PLACEBO (n=31)

FIG. 43

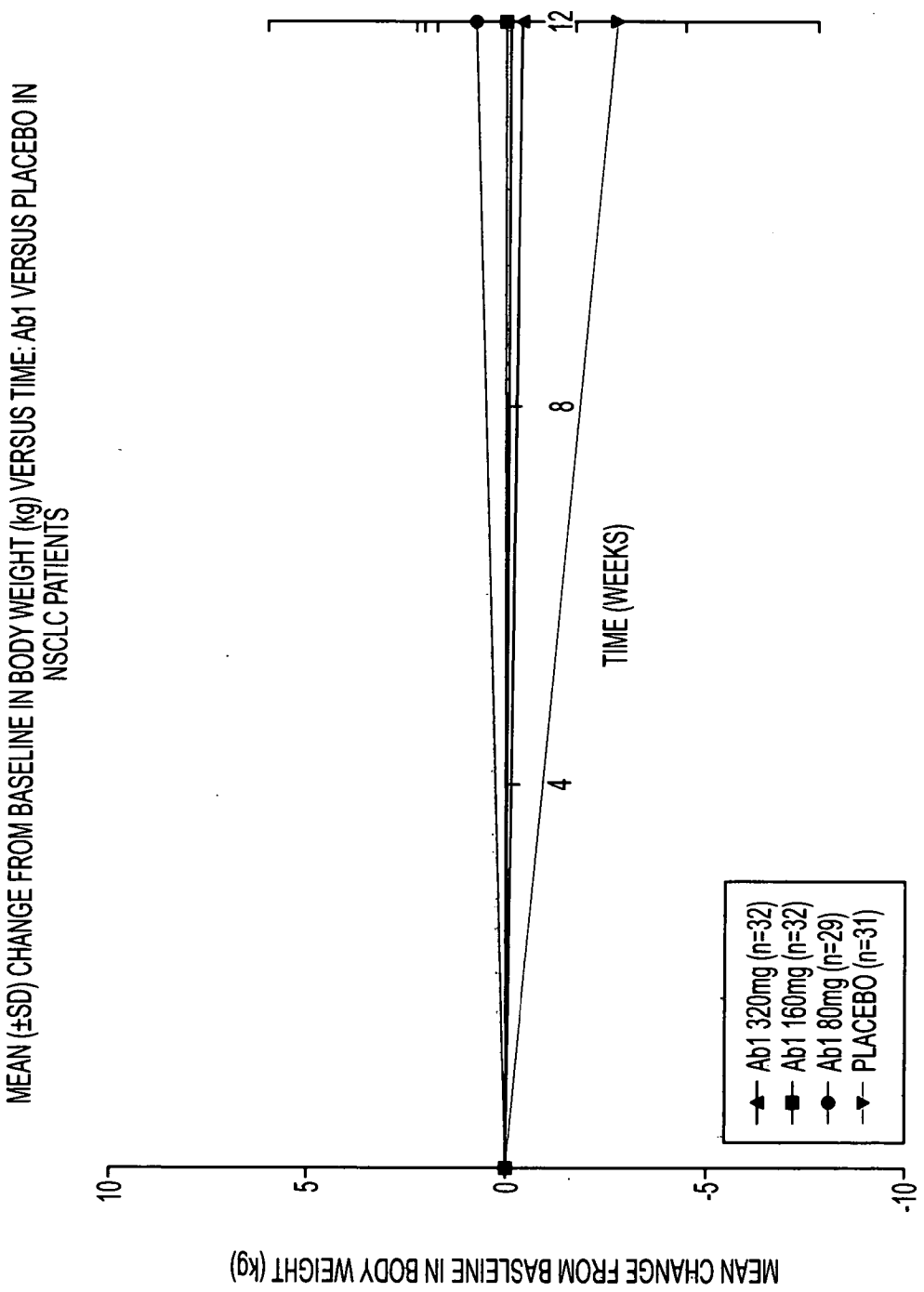

MEAN (±SD) CHANGE FROM BASELINE IN BODY WEIGHT (kg) VERSUS TIME: Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
MEAN CHANGE FROM BASELINE IN BODY WEIGHT (kg)
10
5
0
-5
-10
4
8
12
TIME (WEEKS)
Ab1 320mg (n=32)
Ab1 160mg (n=32)
Ab1 80mg (n=29)
PLACEBO (n=31)

FIG. 44

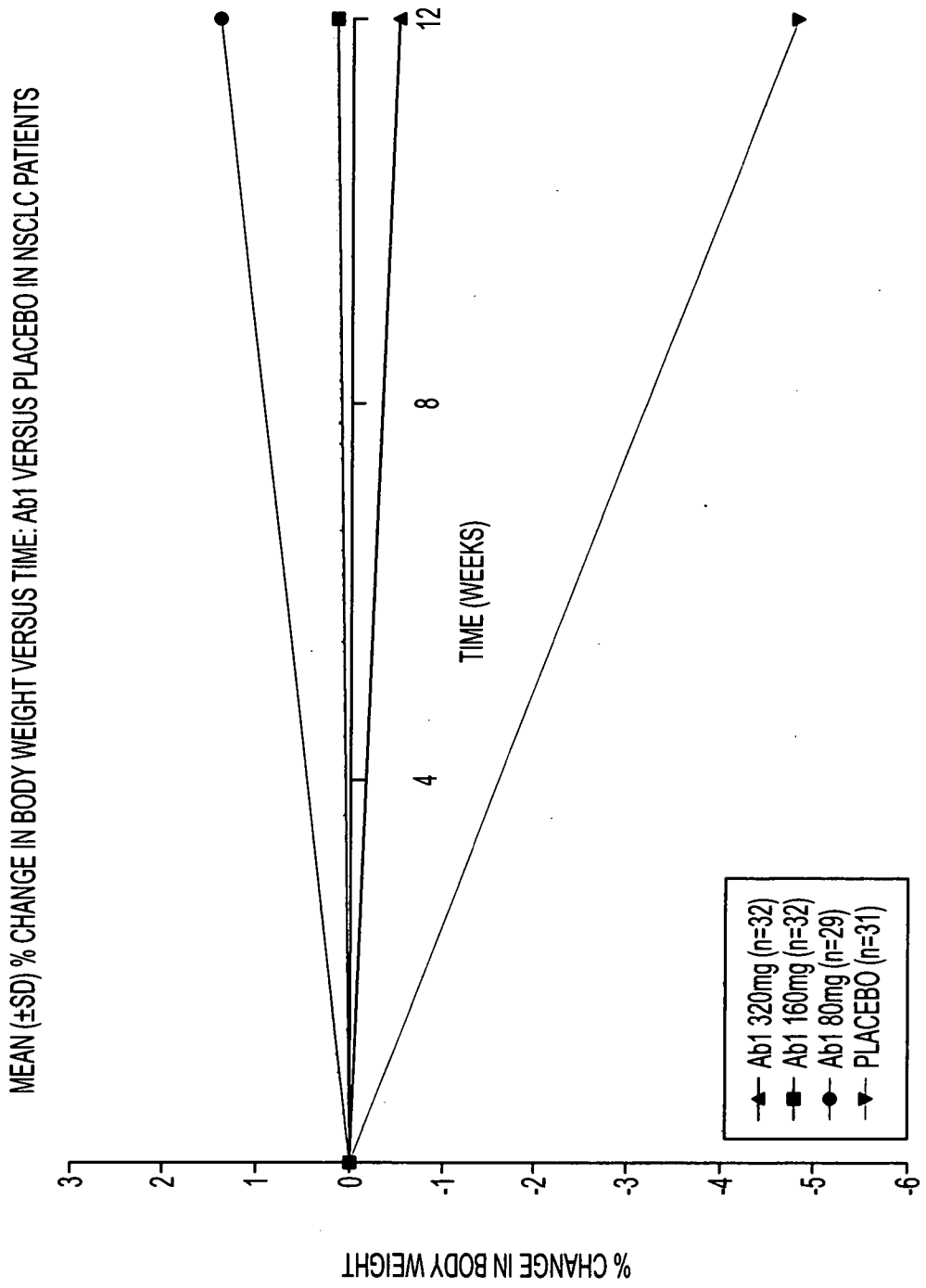

MEAN (±SD) % CHANGE IN BODY WEIGHT VERSUS TIME: Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
% CHANGE IN BODY WEIGHT
TIME (WEEKS)
3
2
1
0
-1
-2
-3
-4
-5
-6
4
8
12
Ab1 320mg (n=32)
Ab1 160mg (n=32)
Ab1 80mg (n=29)
PLACEBO (n=31)

FIG. 45

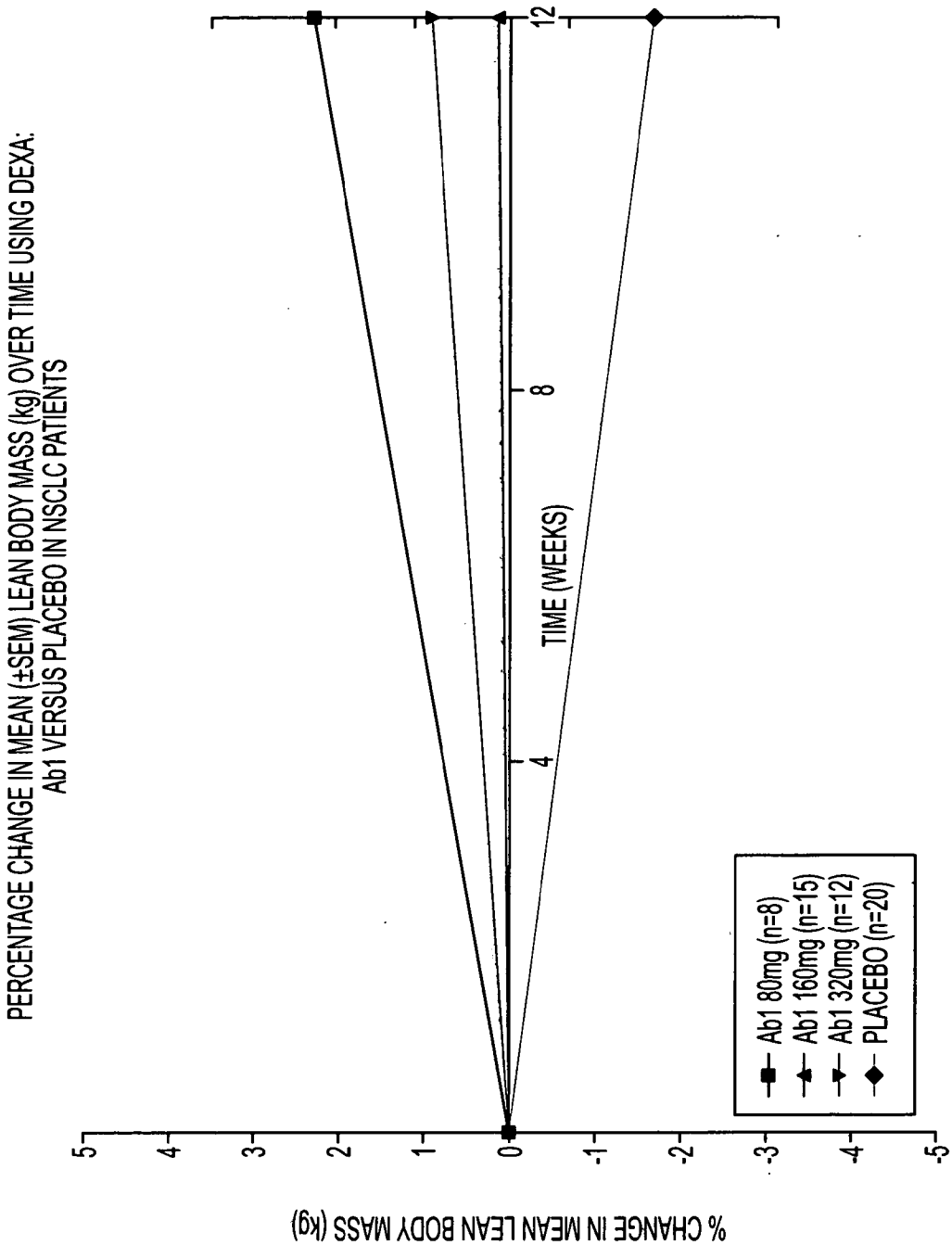

PERCENTAGE CHANGE IN MEAN (±SEM) LEAN BODY MASS (kg) OVER TIME USING DEXA:
Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
% CHANGE IN MEAN LEAN BODY MASS (kg)
TIME (WEEKS)
5
4
3
2
1
0
-1
-2
-3
-4
-5
4
8
12
Ab1 80mg (n=8)
Ab1 160mg (n=15)
Ab1 320mg (n=12)
PLACEBO (n=20)

FIG. 46

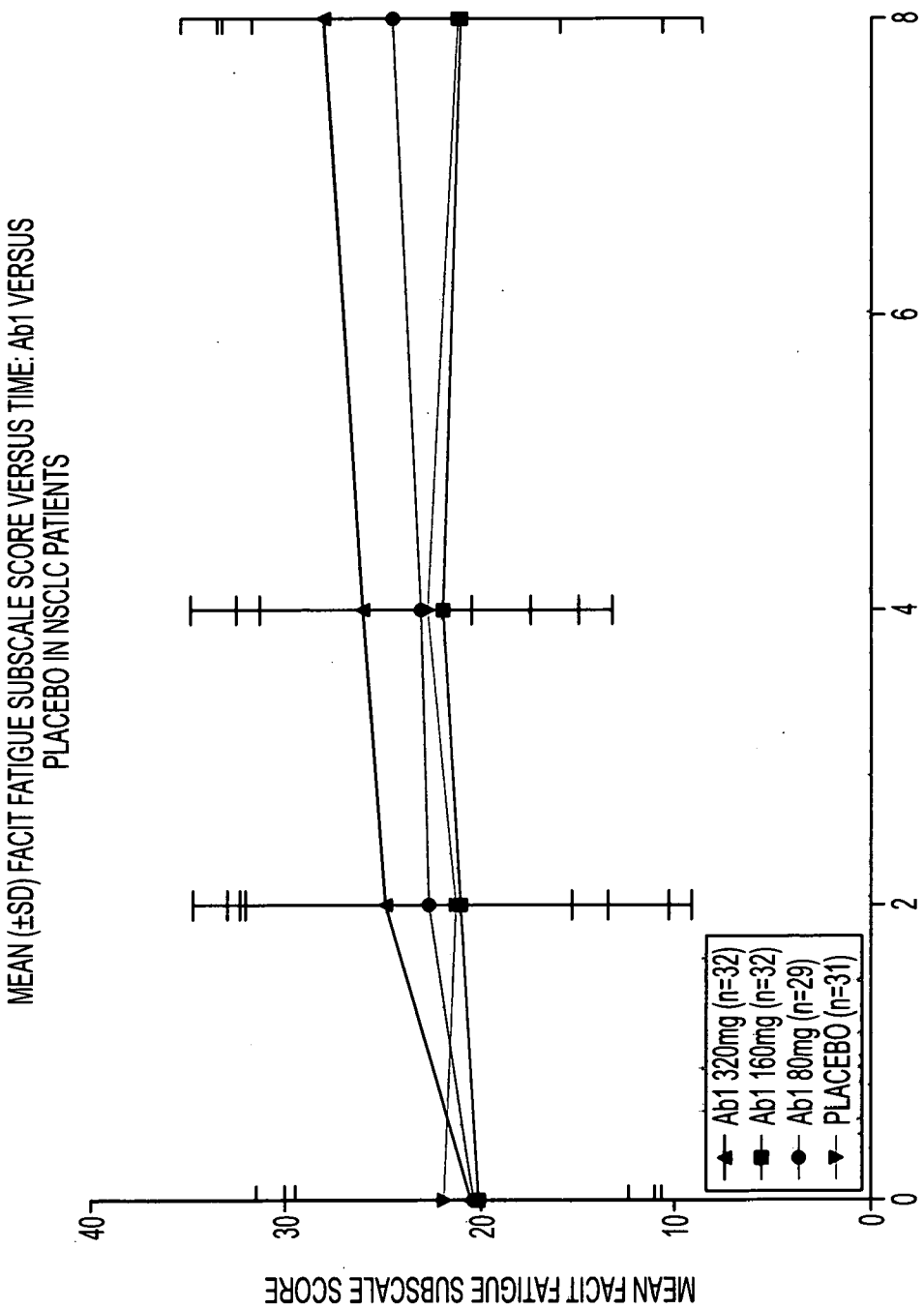

MEAN (±SD) FACIT FATIGUE SUBSCALE SCORE VERSUS TIME: Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
MEAN FACIT FATIGUE SUBSCALE SCORE
TIME (WEEKS)
Ab1 320mg (n=32)
Ab1 160mg (n=32)
Ab1 80mg (n=29)
PLACEBO (n=31)
0
10
20
30
40
0
2
4
6
8

FIG. 47

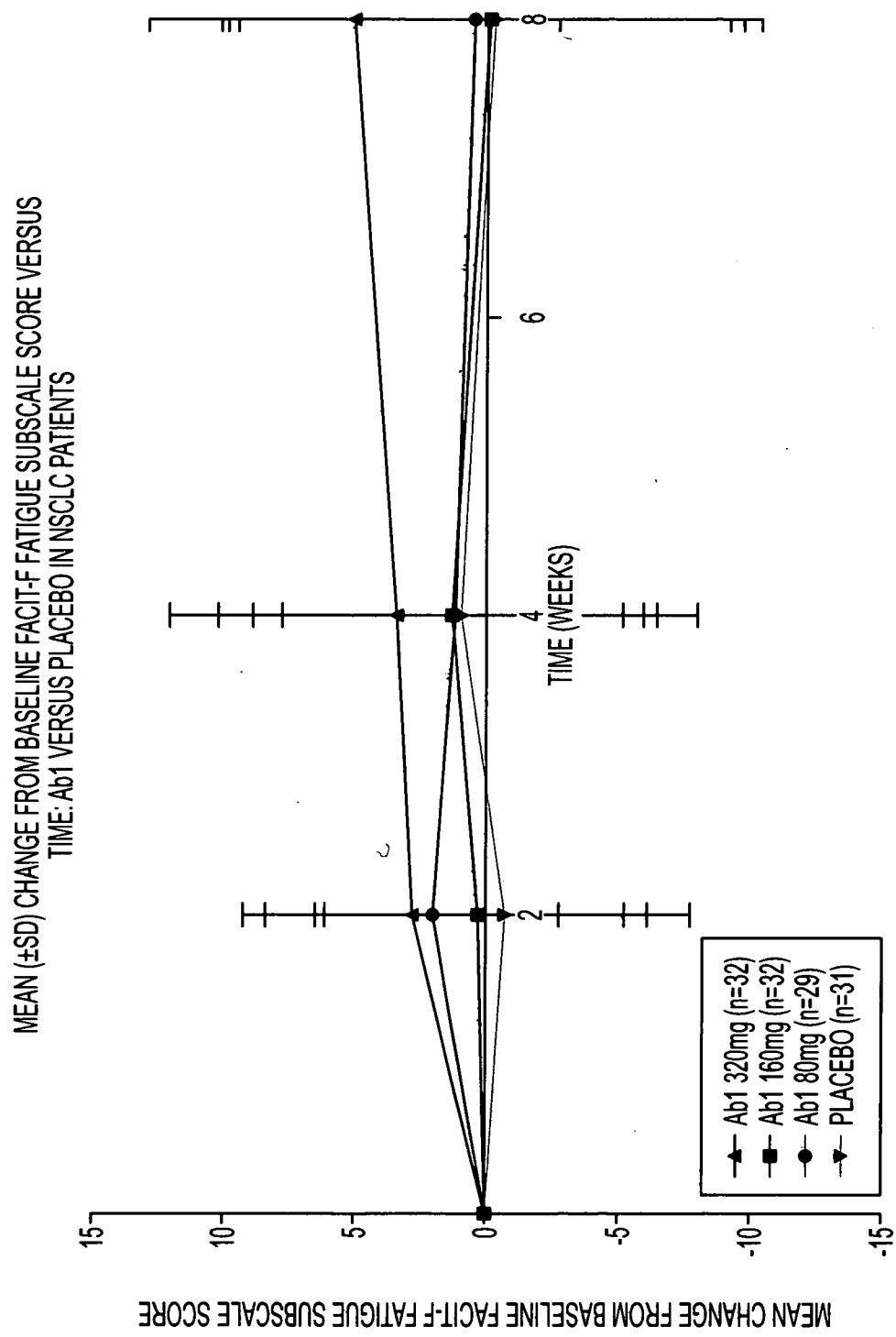

MEAN (±SD) CHANGE FROM BASELINE FACIT-F FATIGUE SUBSCALE SCORE VERSUS TIME: Ab1 VERSUS PLACEBO IN NSCLC PATIENTS
MEAN CHANGE FROM BASELINE FACIT-F FATIGUE SUBSCALE SCORE
TIME (WEEKS)
15
10
5
0
-5
-10
-15
2
4
6
8
Ab1 320mg (n=32)
Ab1 160mg (n=32)
Ab1 80mg (n=29)
PLACEBO (n=31)

FIG. 48