(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2011 (03.06.2011)

(10) International Publication Number
WO 2011/066371 A2

(51) International Patent Classification:
A61K 39/395 (2006.01)   A61P 29/00 (2006.01)
A61K 38/16 (2006.01)   A61P 25/00 (2006.01)
A61P 35/00 (2006.01)

(21) International Application Number:
PCT/US2010/057981

(22) International Filing Date:
24 November 2010 (24.11.2010)

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:
12/624,778 24 November 2009 (24.11.2009) US
12/624,816 24 November 2009 (24.11.2009) US
12/624,830 24 November 2009 (24.11.2009) US
12/624,965 24 November 2009 (24.11.2009) US
61/355,819 17 June 2010 (17.06.2010) US
61/358,615 25 June 2010 (25.06.2010) US
61/410,169 4 November 2010 (04.11.2010) US

(71) Applicant (for all designated States except US): ALDER
BIPHARMACEUTICALS, INC. [US/US]; 11804
North Creek Parkway South, Bothell, Washington 98011 (US).

(72) Inventors; and

US]; 5733 238th Place NE, Redmond, Washington 98043 (US).

(74) Agent: TESKIN, Robin L.; Hunton & Williams LLP, Inte-
lectual Property Department, 1900 K Street NW, Suite

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 417:
— as to the identity of the inventor (Rule 4.17(i))
— as to applicant’s entitlement to apply for and be granted
a patent (Rule 4.17(ii))
— as to the applicant’s entitlement to claim the priority of
the earlier application (Rule 4.17(ii))

Published:
— without international search report and to be republished
upon receipt of that report (Rule 48.2(g))
— with sequence listing part of description (Rule 5.2(a))

(54) Title: ANTIBODIES TO IL-6 AND USE THEREOF

(57) Abstract: The present invention is directed to therapeutic methods using IL-6 antagonists such as an Abl antibody or anti-
body fragment having binding specificity for IL-6 to prevent or treat disease or to improve survivability or quality of life of a pa-
tient in need thereof. In preferred embodiments these patients will comprise those exhibiting (or at risk of developing) an elevated serum C-reactive protein level, reduced serum albumin level, elevated D-dimer or other coagulation cascade related protein(s), cachexia, fever, weakness and/or fatigue prior to treatment. The subject therapies also may include the administration of other ac-
tives such as chemotherapeutics, anti-coagulants, statins, and others. Additional preferred embodiments of the subject invention relate to therapeutic compositions and methods treating or preventing rheumatoid arthritis, especially subcutaneous and intra-
venous formulations and dosage regimens using IL-6 antagonists according to the invention, as well as methods for preventing or treating GVHD or leukemia relapse in subjects receiving transplanted cells, tissue or organs, use thereof in the treatment or pre-
vention of mucositis, and use thereof to potentiate the cytotoxic, apoptotic, and anti-metastatic or anti-inflammatory effects of chemotherapeutics and radiation on cancers, especially cancers that have developed a resistance to radiation or chemotherapy, such as an EGFR inhibitor.
ANTIBODIES TO IL-6 AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to provisional application Serial No. 61/410,169, filed on November 4, 2010; provisional application Serial No 61/358,615, filed on June 25, 2010; provisional application Serial No. 61/355,819, filed on June 17, 2010 and provisional application Serial No. 61/325,547, filed on April 19, 2010. This application further claims priority to US Serial No. 12/624,965; 12/624,830; 12/624,816 and 12/624,778 all filed on November 24, 2009. The disclosure of each of the afore-mentioned provisional and non-provisional applications including all the sequence information is incorporated by reference in its entirety herein.

[0002] The sequence listing in the file named "67858o706005.txt" having a size of 332,081 bytes that was created November 23, 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, novel therapies and therapeutic protocols utilizing anti-IL-6 antibodies, and pharmaceutical formulations containing anti-IL-6 antibodies. In preferred embodiments, an anti-IL-6 antibody is Abl, which includes rabbit or humanized forms thereof, as well as heavy chains, light chains, fragments, variants, and CDRs thereof, or an antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide fragment thereof as Abl. The subject application pertains in particular to preferred formulations and therapeutic uses of an exemplary humanized antibody referred to herein as Abl and variants thereof. In preferred embodiments, the anti-IL-6 antibody has an in vivo half-life of at least about 25 days, an in vivo effect of raising albumin, has an in vivo effect of lowering C-reactive protein, has an in vivo effect of restoring a normal coagulation profile, possesses a binding affinity (Kd) for IL-6 of less than about 50 picomolar, and/or has a rate of dissociation (Kd) from IL-6 of less than or equal to $10^5$ s$^{-1}$. 

1
The invention also pertains to methods of screening for diseases and disorders associated with IL-6, and methods of preventing or treating diseases or disorders associated with IL-6 by administering said antibody or a fragment or a variant thereof.

In one aspect, this invention pertains to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an anti-IL-6 antibody, such as Abl or a fragment or variant thereof, whereby the patient's C-reactive protein ("CRP") level is lowered, and/or the patient's albumin level is raised, and optionally monitoring the patient to determine the patient's CRP and/or albumin level.

In another aspect, this invention relates to methods of lowering the C-reactive protein level in a patient in need thereof, comprising administering to the patient an IL-6 antagonist such as Abl, whereby the patient's CRP level is lowered, and monitoring the patient to assess the CRP level. In another aspect, this invention relates to methods of raising the albumin level in a patient in need thereof, comprising administering to the patient an IL-6 antagonist such as Abl, whereby the patient's serum albumin level is raised, and monitoring the patient to assess the albumin level.

In another aspect, this invention pertains to methods of preventing or treating cachexia, weakness, fatigue, and/or fever in a patient in need thereof, e.g., a patient showing elevated CRP levels, comprising administering to the patient an anti-IL-6 antibody or antibody fragment or variant thereof, whereby the patient's cachexia, weakness, fatigue, and/or fever is improved or restored to a normal condition, and optionally monitoring the patient to assess cachexia, weakness, fatigue, and/or fever. In another embodiment the present invention further relates to the use of the subject anti-IL-6 antibodies and antibody fragments for the treatment or prevention of mucositis, e.g., oral or gastrointestinal mucositis. Oral and gastrointestinal mucositis is a toxicity of many forms of radiotherapy and chemotherapy. It has a significant impact on health, quality of life and economic outcomes that are associated with treatment. It also indirectly affects the success of antineoplastic therapy by limiting the ability of patients to tolerate optimal tumoricidal treatment. The complex pathogenesis of mucositis has only recently been appreciated and reflects the dynamic interactions of all of the cells and tissue types that comprise the epithelium and submucosa. The identification of the molecular events that lead to
treatment-induced mucosal injury has provided targets for mechanistically based interventions to prevent and treat mucositis.

[0008] Historically, mucositis was thought to arise solely as a consequence of epithelial injury. It was hypothesized that radiation or chemotherapy nonspecifically targeted the rapidly proliferating cells of the basal epithelium, causing the loss of the ability of the tissue to renew itself. The atrophy, thinning and ulceration of the mucosal epithelium that is associated with mucositis was thought to be a consequence of these events. Furthermore, it was believed that the process was facilitated by trauma and oral microorganisms.

[0009] Radiation-induced mucositis was typically recognized as an Outside-in' process, in which DNA strand breaks occurred in oral basal-epithelial cells. Chemotherapy-induced mucositis has mainly been attributed to basal-cell damage that results when drugs permeate to these cells from the submucosal blood supply. A role for saliva-borne chemotherapeutic agents in the induction of mucositis has been also been proposed, but not proven. Chemotherapy-induced mucositis can be further compounded by concomitant myelosuppression.

[0010] Radiation- or chemotherapy-induced mucositis is initiated by direct injury to basal epithelial cells and cells in the underlying tissue. DNA-strand breaks can result in cell death or injury. Non-DNA injury is initiated through a variety of mechanisms, some of which are mediated by the generation of reactive oxygen species. Radiation and chemotherapy are effective activators of several injury-producing pathways in endothelia, fibroblasts and epithelia. In these cells, the activation of transcription factors such as nuclear factor-κB (NF-κB) and NRF2 leads to the upregulation of genes that modulate the damage response. Immune cells (macrophages) produce pro-inflammatory cytokines, such as tumor-necrosis factor-a (TNF-a) and interleukin 6, which causes further tissue injury. These signalling molecules also participate in a positive-feedback loop that amplifies the original effects of radiation and chemotherapy. For example, TNF-a activates NF-κB and sphingomyelinase activity in the mucosa, leading to more cell death. In addition, direct and indirect damage to epithelial stem cells results in a loss of renewal capacity. As a result, the epithelium begins to thin and patients start to experience the early symptoms of mucositis.
Mucositis is observed during chemotherapeutic or radiation treatment of many different cancers including head and neck cancer, multiple myeloma, colorectal cancers. Because of the problems caused by mucositis which may preclude further radiation or chemotherapy and also impede nutrition because of the discomfort caused by mucositis during swallowing and digestion.

The most common symptoms of mucositis include redness, dryness, or swelling of the mouth, burning or discomfort when eating or drinking, open sores in the mouth and throat, abdominal cramps, and tenderness or rectal redness or ulcers. Essentially mucositis involves the inflammation of the lining of the mouth and digestive tract, and frequently occurs in cancer patients after chemotherapy and radiation therapy. The cheek, gums, soft plate, oropharynx, top and sides of tongue, and floor of the mouth may be affected, as well as the esophagus and rectal areas. Along with redness and swelling, patients typically experience a strong, burning pain.

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

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

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

[0016] Currently there is no real cure for mucositis, treatment is aimed at prevention and management of symptoms. Mucositis typically resolves a few weeks after treatment as the cells regenerate, and treatment cessation is only occasionally required. In some cases, drug therapy will be altered so that a less toxic agent is given.

[0017] Patients at risk for mucositis should be meticulous about their oral hygiene, brushing frequently with a soft toothbrush and flossing carefully with unwaxed dental floss. If bleeding of the gums develops, patients should replace their toothbrushes with soft toothettes or gauze. Dentures should also be cleaned regularly. Patients should be well-hydrated, drinking fluids frequently and rinsing the mouth several times a day. Mouthwashes that contain alcohol or hydrogen peroxide should be avoided as they may dry out the mouth and increase pain. Lips should also be kept moist. Physical irritation to the mouth should be avoided. If time permits, dental problems, such as cavities or ill-fitting dentures, should be resolved with a dentist prior to beginning cancer treatment. Patients are generally more comfortable eating mild, medium-temperature foods. Spicy, acidic, very hot or very cold foods can irritate the mucosa. Tobacco and alcohol should also be avoided.

[0018] Hospital personnel and the patients themselves should inspect the mouth frequently to look for signs and symptoms of mucositis. Evidence of mucositis (inflammation, white or yellow shiny mucous membranes developing into red, raw, painful membranes) may be present as early as four days after chemotherapy administration. Sodium bicarbonate mouth rinses are sometimes used to decrease the amount of oral flora and promote comfort, though there is no scientific evidence that this is beneficial. Typically, patients will rinse every few hours with a solution containing 1/2 teaspoon (tsp) salt and 1/2 tsp baking soda in one cup of water.

[0019] Pain relief is often required in patients with mucositis. In some cases, rinsing with a mixture of maalox, xylocaine, and diphenhydramine hydrochloride relieves pain. However, because of xylocaine's numbing effects, taste sensation may be altered. Worse, it may reduce the body's natural gag reflex, possibly causing problems with swallowing. Coating agents such as kaopectate and aluminum hydroxide gel may also help relieve symptoms. Rinsing with
benzydamine has also shown promise, not only in managing pain, but also in preventing the
development of mucositis. More severe pain may require liquid tylenol with codeine, or even
intravenous opioid drugs. Patients with severe pain may not be able to eat, and may also require
nutritional supplements through an I.V. (intravenous line).

[0020] A treatment called cryotherapy has shown promise in patients being treated with
fluorouracil administered in the aforementioned five-day, high-dose schedule. Patients
continuously swish ice chips in their mouth during the thirty-minute infusion of the drug, causing
the blood vessels to constrict, thereby reducing the drug's ability to affect the oral mucosa.

[0021] Chamomile and allopurinol mouthwashes have been tried in the past to manage
mucositis, but studies have found them to be ineffective. Biologic response modifiers are being
evaluated to determine their possible role in managing mucositis. Recent studies using topical
antimicrobial lozenges have shown promise as well, but more research is needed.

[0022] Therefore, there is a strong need in the art for improved methods of treating and
preventing mucositis, both oral and gastrointestinal mucositis, as this condition compromises the
efficacy of chemotherapy or radiation cancer treatments as well as adversely affecting the quality
of life of cancer patients because of the extreme pain and discomfort caused by this condition.

[0023] It has been reported in the literature (Rossi et al., Bone Marrow Transplantation
36:771-779 (2005)) that patients with multiple myeloma receiving chemotherapy
(dexamethasone and melphelan) and autologous stem cell transplantation (ASCT) who were in
addition administered an anti-IL-6 antibody (BE8) had reduced CRP levels and a significant
reduction in fever as well as reduced onset and severity of mucositis. Particularly, the mucositis
in the treated patients was a lower grade of toxicity requiring no morphine infusion as compared
to patients not receiving the anti-IL-6 antibody. Also, gastrointestinal mucositis symptoms such
as diarrhea were reduced and quality of life was improved as evidenced by better oral intake of
nutrition and daily activity.

[0024] As discussed in this application the inventive anti-IL-6 antibodies and antibody
fragments effectively reduce CRP levels, cachexia and fever in treated patients as well as
providing for enhanced serum albumin levels and improved coagulation profiles and reduced
tendency of thrombosis. These antibodies elicit these activities because of their inhibitory effects on IL-6, an inflammatory cytokine eliciting many biological effects. In addition, based on these observations the inventive anti-IL-6 antibodies may be used to prevent anemia or myelosuppression that may occur during cancer treatment and may be beneficial in treatments including bone marrow or stem cell transplant.

Furthermore, because of the anti-inflammatory effects of the subject antibodies, and their beneficial effects on myelosuppression and anemia, which may otherwise occur during radiotherapy and chemotherapy, it is further anticipated that the subject antibodies may be used to treat or prevent oral and gastrointestinal mucositis, especially mucositis that occurs as a consequence of chemotherapy or radiotherapy regimens.

In this embodiment of the invention anti-IL-6 antibody or antibody fragment will be administered prophylactically to patients at significant risk of developing oral or gastrointestinal mucositis, e.g., because of a chemotherapeutic or radiotherapy regimen that are to undergo, and/or may be administered to patients already exhibiting symptoms of mucositis such as discussed above. The present antibodies because of their ameliorative effects on blood cells and inflammation will promote normal or restore tissue damage in the oral and gastrointestinal mucosa that occurs during mucositis.

Because mucositis is particularly a concern during radiotherapy or chemotherapy of some cancers wherein treatment may affect the mucosa such as head and neck cancer, esophageal cancer, throat cancer, lung cancer, gastrointestinal cancers such as stomach cancer, colorectal cancer, pancreatic cancer, as well as hematological cancers such as multiple myeloma, the present invention particularly includes prevention or treatment of mucositis that may occur in these conditions by administration of anti-IL-6 antibodies according to the invention. In addition, the present invention also embraces prevention or treatment of mucositis in patients receiving chemotherapy or radiotherapy and autologous stem cell or bone marrow transplant such as multiple myeloma and leukemias or lymphomas. It is known that mucositis is a significant concern in such patients.

In another embodiment, this invention pertains 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, such as Abl or a fragment or variant thereof, whereby the patient's coagulation profile is improved or restored to a normal condition, and optionally monitoring the patient to assess coagulation profile.

[0029] In another embodiment this invention relates to the use of anti-IL-6 antibodies according to the invention, such as Abl or humanized forms thereof for treating or preventing rheumatoid arthritis in subjects in need thereof. In this application we provide results of clinical data showing safety, pharmacokinetics, and pharmacodynamics for subcutaneous and intravenous administration of a preferred humanized antibody derived from Abl, also referred to as ALD-518, which humanized antibody contains the variable heavy and light sequences contained in SEQ ID NO: 19 and 20 (also shown below). This clinical data further demonstrates that this antibody improves disease activity in rheumatoid arthritis patients which have been subcutaneously or intravenously administered ALD-518.

SEQ ID NO: 19

EVQLVESGGGLVQPGGLRLSCAASFGSLSNYVTWVRQAPGKGLEWVGIIYGSDETA YATSAIGRFITISRDNSKNTLYLQMNSLRAEDTAVYYCARDSSDWDAAKNL

SEQ_ID_NO_20

IQMTQSPSSLSAVGDRVTITCASQSINNELSWYQQKPGKAPKLIYRASLGSVPSRF SGSGGTDFDFTLTISQLPDDFATYYCQQGYSRLNIDNA

[0030] This application provides data establishing that anti-IL-6 antibody ALD518 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC ALD518 was -60% of IV ALD518, and the half life was -30 days. Rapid and significant reductions in CRP (C-reactive protein) were observed, which were sustained over 24 weeks of assessment.

[0031] The half-life of ALD518 when administered subcutaneously (approximately 30 days) is similar to the half-life previously observed with IV administration. Additionally, subcutaneous ALD5 18 led to rapid and large reductions in serum CRP and the reductions in CRP observed during the first 12 weeks of the study were sustained over 24 weeks of assessment.
These results are also similar to those observed with IV administration. Together, these results support the use of ALD518 for the treatment of RA, as well as prevention or treatment of other IL-6 associated conditions as described herein. These therapeutic regimens may be combined with other RA therapeutics, including methotrexate or other RA drugs identified herein and generally known in the art.

[0032] In another aspect this invention provides specific dosage regimens and dosage formulations for treating rheumatoid arthritis by subcutaneous or intravenous administration of anti-IL-6 antibodies or antibody fragments according to the invention such as humanized Abl antibodies.

[0033] In another aspect the invention provides novel pharmaceutical compositions and their use in novel combination therapies and comprising administration of an anti-IL-6 antibody, such as Abl or a fragment or variant thereof, and at least one other therapeutic compound such as a statin, anti-coagulant, anti-emetic, anti-nausea agent, anti-cachexia agent, chemotherapy agent, anti-cytokine agent, etc.

[0034] Weight loss, fatigue, and 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.

(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.

[0036] 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.

[0037] Interleukin-6 (hereinafter "IL-6") (also known as interferon-β2; 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).
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).

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).

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.

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 mesangial 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.

[0042] 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.

[0043] 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.

[0044] A recent clinical trial demonstrated that administration of rosvastatin 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].

[0045] 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,


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-esophageal cancer, non-small-cell lung cancer, colorectal cancer, breast cancer, ovarian cancer, bronchogenic cancer, and metastatic renal cancer (Forrest et al, Br J

[0048] 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. 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 the above-referenced 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.

[0049] 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-PGJ2 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.

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;10(2):260-5. These results suggest that thalidomide, and possibly derivatives thereof, such as lenalidomide, may be useful antagonists of IL-6.

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.

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.

Other anti-IL-6 antibodies have been disclosed in the following U.S. patents and published patent applications: 7,482,436; 7,291,721; 6,121,423; 2008/0075726; 2007/0178098; 2007/0154481; 2006/0257407; and 2006/0188502.


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

[0058] Another cachexia-related disease is failure to thrive, also known as faltering growth, in which a child exhibits a rate of weight gain less than expected. Failure to thrive is typically defined as weight below the third percentile or a decrease in the percentile rank of 2 major growth parameters in a short period. Failure to thrive results from heterogeneous medical and psychosocial causes, and the cause sometimes eludes diagnosis. One recent study (totaling 34 patients) reported a statistically significant elevation in IL-6 levels in patients diagnosed with failure to thrive. Shaoul et al. J Pediatr Gastroenterol Nutr., 2003 Oct;37(4):487-91.
BRIEF SUMMARY OF THE INVENTION

[0059] The present invention is an extension of Applicants' previous invention which is directed to specific antibodies, humanized or chimeric or single chain antibodies and fragments and variants 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 invention encompasses specific humanized antibodies and fragments and variants 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/gpl30 complexes and/or multimers of IL-6/IL-6R/gpl30. The present invention relates to novel therapies and therapeutic protocols using anti-IL-6 antibodies, preferably those described 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 (such as Abl) or antibody fragment or variant thereof, 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 such as Abl and thereby more effectively treat or prevent thrombosis.

[0060] The present invention also pertains to methods of improving survivability or quality of life of a patient in need thereof, e.g., a patient showing elevated CRP levels and/or lowered albumin levels, comprising administering to the patient an IL-6 antagonist, such as those identified infra, e.g., an anti-IL-6 antibody (e.g., Abl) or antibody fragment or variant thereof, whereby the patient's C-reactive protein ("CRP") level is lowered, and/or the patient's albumin level is raised. 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 such as Abl and thereby more effectively treat the patient.
Another embodiment of the invention relates to Abl, including rabbit and humanized forms thereof, as well as heavy chains, light chains, fragments, variants, and CDRs thereof. In the human clinical trial data presented, a humanized form of Abl was administered.

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, or humanized or chimeric or single chain versions thereof containing one or more of the CDRs of the exemplified anti-IL-6 antibody sequences and the polynucleotides encoding them. Preferably these antibodies will be aglycosylated. In more specific embodiments of the invention these antibodies will block gpl30 activation and/or possess binding affinities (Kds) less than 50 picomolar and/or $K_{eq}$ values less than or equal to $10^{-7}$ S$^{-1}$.

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. In exemplary embodiments these humanized antibodies will comprise human frameworks which are highly homologous (possess high level of sequence identity) to that of a parent (e.g. rabbit) antibody as described infra.

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 or variants or fragments thereof, 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/gpl30 complexes and/or multimers thereof.

The invention also contemplates the administration of conjugates of anti-IL-6 antibodies and humanized, chimeric or single chain versions thereof and other binding fragments and variants thereof conjugated to 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 and variants thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, Fv and scFv fragments.

[0066] 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 or variants 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, especially humanized, chimeric and single chain antibodies are the treatment and prevention of cancer associated fatigue, and/or cachexia and rheumatoid arthritis.

[0067] 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.

[0068] In another embodiment the present invention also relates to the use of anti-IL-6 antibodies and antibody fragments according to the invention for preventing or alleviating the onset of graft-versus-host disease (GVHD), or leukemia relapse in subjects receiving transplanted cells, tissues or organs such as subjects receiving hematopoietic stem cell transplants (HCTs), bone marrow transplants (BMTs) and other transplanted cells, tissues or organs, especially transplanted cells, tissues or organs, especially wherein the transplant may contain dendritic cells, especially BDCAA4+ plasmacytoid dendritic cells.

[0069] It has been reported in the literature (Perez-Martinez et al., "Blood dendritic cells suppress NK cell function and increase the risk of leukemia relapse after hematopoietic cell transplantation" , Biology of Blood and Marrow Transplantation, Available online 25 October 2010) that leukemic subjects receiving transplanted HCTs containing greater numbers of BDCAA4+ plasmacytoid dendritic cells (as well as BDCA1+ myeloid dendritic cells ) exhibit a higher propensity to leukemia relapse and exhibit poorer survival. These transplant subjects typically exhibit an inflammatory environment characterized by abundant pathogen associated molecular patterns (PAMPS) derived from endogenous pathogens and host tissues as a consequence of tissues damaged by high-dose chemotherapy and radiation (as a result of disease treatment, such as cancer prior to the need for transplant).
Particularly, the authors explain that while NK cells normally induce DC maturation and the DCs in turn increase the expression of activating markers in NK cells that paradoxically both BDCAA4+ plasmacytoid dendritic cells and BDCA1+ myeloid dendritic cells suppressed the function of NK cells in both in vitro assays and in vivo mouse models when TLR ligands were used to mimic the microbe-associated inflammatory environment in allogeneic HCT. They theorize that this phenomena may explain why patients who received HCTS containing greater numbers of these cells had a high risk of leukemia relapse. They further teach that detailed mechanistic findings suggest that these dendritic cells elicit this inhibitory effect on NK cytotoxicity cells through IL-10 and IL-6 (as incubation of NK cells with these cytokines has a dose-dependent suppressive effect on NK cell cytotoxicity).

Based on these findings, and the potent ability of antibodies according to the invention to suppress IL-6 production in vitro and in vivo the present invention provides methods and compositions for preventing leukemia relapse, or graft versus host disease, by the use of an anti-IL-6 antibody or antibody fragment according to the invention as an adjunct to therapies wherein transplanted cells, tissues or organs are used. Most particularly, the invention provides methods of reducing or preventing GVHD, or leukemia relapse in patients receiving bone marrow transplants, hematopoietic cell transplants, pancreatic or liver transplants, and other cell, tissue and organ transplants wherein the transplant may comprise dendritic cells, especially BDCAA4+ plasmacytoid dendritic cells and/or BDCA1+ myeloid dendritic cells.

The present invention is especially suitable for treating transplant patients already prone to having an inflammatory milieu, such as subjects who have already undergone or are still undergoing chemotherapy and/or radiation. Essentially, the subject anti-IL-6 antibodies and antibody fragments will act to suppress already high IL-6 levels in these transplant recipients and thereby help to alleviate the undesired effect of such dendritic cells on NK cells. This is clinically advantageous as NK cells play an important role in hematopoietic stem cell transplantation and in cross talk with dendritic cells to induce primary responses against infection. Also, it has been demonstrated that donor NK cells may promote engraftment, prevent GVHD, control infections, and reduce the risk of leukemia relapse.
Accordingly, based on the foregoing the present invention provides methods of promoting transplant engraftment, controlling or reducing the risk of infection, and/or reducing or preventing GVHD, and/or leukemia relapse in a subject receiving transplanted cells, tissues or organs by administering prior, concurrent of after transplant at least one anti-IL-6 antibody or antibody fragment according to the invention. In preferred embodiments these subjects will comprise individuals who have cancer, and/or subjects who have already received a therapeutic regimen or have an underlying condition that results in an endogenous inflammatory milieu such as subjects who have received chemotherapy or radiation prior to transplant.

The subject therapy will typically administer the antibody prior or concurrent to transplant, e.g. on the order of from about a month, several weeks, or a week prior to transplant so as to reduce circulating levels of IL-6 antibody when transplant is effected. However, alternatively the subject anti-IL-6 antibodies or antibody fragments may be administered concurrent to the transplanted cell, tissues or organ or shortly thereafter, e.g. preferably within several hours or days of transplant. If these moieties are administered concurrently the IL-6 antibody or antibody fragment may be combined with the transplanted cells, tissues or organ or they may be administered in separate medicament compositions.

In some instances, e.g., in the case of hematopoietic stem cell or bone marrow transplants it may be desirable to contact the cells, tissue or organ prior to transplant with an anti-IL-6 antibody or antibody fragment according to the invention so as to suppress the production of IL-6 by any dendritic cells contained therein prior to transplantation.

In addition, it may be further desirable to further administer to the subject or pretreat the cells, tissue or organ prior to transplant with an IL-10 antagonist, e.g., an anti-IL-10 antibody or antibody fragment.

The present invention therefore further provides compositions containing at least one anti-IL-6 antibody or antibody fragment according to the invention in association with cells, tissues or an organ which is to be transplanted and further optionally also including at least one IL-10 antagonist.
The invention also provides methods of reducing the risk of infection in subjects receiving transplanted cells, tissues or organs, especially those potentially containing dendritic cells by administering prior, concurrent or after transplant an amount of at least one anti-IL-6 antibody or antibody fragment according to the invention sufficient to prevent or reduce the risk of infection.

The invention also provides methods of reducing the risk of GVHD in subjects receiving transplanted cells, tissues or organs, especially those potentially containing dendritic cells by administering to a patient prior, concurrent or after transplant, e.g., BMT or HCT, an amount of at least one anti-IL-6 antibody or antibody fragment according to the invention sufficient to prevent or reduce the risk of GVHD. In some embodiments these subjects will have received chemotherapy and/or radiation or such chemotherapy and/or radiation may be ongoing.

The invention also provides methods of reducing the risk of leukemia relapse in leukemia subjects receiving transplanted cells, tissues or organs, especially those potentially containing dendritic cells by administering prior, concurrent or after transplant an amount of at least one anti-IL-6 antibody or antibody fragment according to the invention sufficient to prevent or reduce the risk of leukemia relapse. Examples of such leukemias include Chronic Leukemias, Acute Leukemias such as Myelogenous Leukemia which is a disease that develops from myeloid cells and can either be chronic or acute, referred as chronic myelogenous leukemia(CML), or acute myelogenous leukemia (AML), Lymphocytic Leukemia which develops from cells called lymphoblasts or lymphocytes in the blood marrow and which disease similarly can be acute or chronic, referred as chronic lymphocytic leukemia (CLL) or acute lymphocytic leukemia (ALL), hairy cell leukemia, T cell prolymphocytic leukemia, (T-PLL) which is a very rare and aggressive leukemia affecting adults, large granular lymphocytic leukemia which disease may involve either T-cells or NK cells which like hairy cell leukemia, involves solely B cells, and is a rare and indolent (not aggressive) leukemia.

The present invention also provides methods of reducing the risk of GVHD in subjects receiving transplanted pancreatic or liver cells, tissues or organs, especially those potentially containing dendritic cells by administering prior, concurrent or after transplant an amount of at
least one anti-IL-6 antibody or antibody fragment according to the invention sufficient to prevent or reduce the risk of GVHD.

[0082] The present invention also relates to the use of the subject anti-IL-6 antibodies and antibody fragments for the treatment of specific cancers in combination with chemotherapeutics, preferably EGFR inhibitors, and/or radiation wherein this combination is administered using a dosage regimen whereby the anti-IL-6 antibody or anti-IL-6 antibody fragment renders the cancer cells more sensitive to the action of the chemotherapeutic or radiation. These methods in particular include treatment of any cancer, especially cancers wherein an EGFR inhibitor is useful for treatment of cancer. Non-limiting examples thereof include advanced and non-advanced cancers including metastasized cancers such as metastatic and non-metastatic lung cancer, breast cancer, head and neck cancer, (FNSCC), pancreatic cancer, pharyngeal cancer, colorectal cancer, anal cancer, glioblastoma multiforme, epithelial cancers, renal cell carcinomas, acute or chronic myelogenous leukemia and other leukemias.

[0083] With respect to this embodiment of the invention it has been reported in the literature that IL-6 upregulation contributes to the resistance of some cancers to chemotherapeutics such as EGFR inhibitors and that this resistance involves elevated IL-6 at the site of the cancer. For example, Yao et al, Proc. Natl. Acad. Sci., USA, PNAS August 31, 2010 vol. 107 No. 35 15535-15540 teach that IL-6 is expressed at high levels in erlotinib-resistant lung cancer cells and is required for their survival.


[0085] In addition an earlier study Gao et al. (2007) "Mutations in the EGFR kinase domain mediate STAT3 activation via IL-6 production in human lung adenocarcinomas", J Clin Invest
and the authors showed that NSCLC cells expressing mutant EGFR are dependent on the IL-6 axis for their long-term proliferation and survival.

[0086] More particularly, Yao et al. (Id) showed that the reduction of the level of IL-6 by siRNA as well as inhibition of the IL-6 axis by means of an IL-6 neutralizing antibody or a JAK1/2 inhibitor not only significantly decreased IL-6-mediated signaling but also affected cell viability and revealed that IL-6 was sufficient for modifying the sensitivity of cancer cells to the EGFR inhibitor erlotinib. They showed this by measuring the effect of IL-6 on the viability of multiple NSCLC cell lines (HCC827, PC9, and HCC4006) that express mutant EGFR. They found that likely as a consequence of the accumulation of different genetic and epigenetic abnormalities, these cell lines, despite harboring somatic-activating EGFR mutations, displayed different erlotinib sensitivities with IC50s ranging from 5 µM in the case of H1650 to 0.001 µM in the case of HCC827. Despite these differences, in all cases the presence of IL-6 in the medium was sufficient to diminish the sensitivity of various cell lines to erlotinib. They further observed that IL-6 treatment did not substantially affect the cell-proliferation rates but rather, decreased their apoptotic response and that the effect of IL-6 was caused by the activation of the gpl30-STAT3 axis and not a decreased bioavailability of erlotinib. Based on these results they hypothesized a tumor model in which paracrine or autocrine stimulation of the TGF-β axis (and increased IL-6 production) is sufficient for acquisition of mesenchymal-like morphology, increased motility and invasion ability, and increased erlotinib resistance.

[0087] Others have also reported the effects of increased IL-6 levels on the resistance of tumors to EGFR inhibitors. For example, Nishioka et al., in Leukemia (2009) 23:2304-2308 teach that AML cell lines acquire drug resistance to receptor tyrosine kinases such as sunitibib and imatinib, apparently because of aberrantly secretion of inflammatory cytokines such as IL-6 and further show that treatment of these cells with IL-6 blunted the efficacy of these compounds against these cancer cell lines. In addition they disclose that a humanized antibody against the IL-6 receptor, tocilizumab, or AG490 blocked JAK2/STAT5 signaling and restored the sensitivity of the cells to sunitinib.

[0088] Therefore, based on the potent IL-6 inhibitory properties of anti-IL-6 antibodies and antibody fragments according to the invention, the present invention in another embodiment
relates to treatment regimens using chemotherapeutics and/or radiation whereby resistance against the chemotherapeutic or radiation may involves increased IL-6 production at the tumor site, and whereby this resistance is blocked or inhibited by administering the chemotherapeutic and/or radiation in association with an anti-IL-6 antibody or antibody fragment according to the invention. In particular such chemotherapeutics include EGFR inhibitors as it has been reported that cancers may become resistant to these drugs based on increased IL-6 levels at the tumor site, likely as a consequence of an inflammatory response elicited as a result of prolonged chemotherapy and/or radiation.

[0089] Examples of EGFR inhibitors that may be administered in therapeutic regimens with anti-IL-6 antibodies or antibody fragments according to the invention include by way of example Cetuximab (Erbitux) available from ImClone, Erlotinib (Tarceva) available from OSI Pharmaceuticals, Gefitinib (Iressa) available from AstraZeneca, Lapatinib (Tykerb) available from Glaxo, Panitumumab (Vectibix) available from Amgen, Sunitinib or Sutent (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-lH-indol-3-ylidene)methyl]-2,4-dimethyl-lH-pyrrole-3-carboxamide) marketed by Pfizer, Gefitinib or N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine marketed by AstraZeneca, Zalutumumab in clinical development by GenMab, and others.

[0090] According to this embodiment of the invention an anti-IL-6 antibody or antibody fragment according to the invention will be administered prior, concurrent or after administration of the chemotherapeutic, e.g., an EGFR inhibitor or radiation. In a preferred embodiment the anti-IL-6 antibody or antibody fragment will be administered to individuals whereby their cancer, e.g., a leukemia such as AML, pharyngeal cancer, or a lung cancer such as nonsmall cell lung cancer (NSCLC) has developed a resistance to the drug, e.g., as a consequence of the inflammatory environment around the cancer resulting in increased IL-6 levels. In addition, the subject IL-6 antibodies may be used to enhance the efficacy of radiation against radiation resistant tumors in instances wherein the tumor resistance similarly involves an inflammatory tumor environment associated with elevated proinflammatory cytokines, and in particular elevated IL-6.
In a preferred embodiment the invention will administer an anti-IL-6 antibody or antibody fragment according to the invention to potentiate the efficacy of an EGFR inhibitor, especially in patients who have developed a resistance or weakened sensitivity of the treated cancer to the drug because of an inflammatory response involving increased IL-6 levels. Specific EGFR inhibitors which may be used in combination with antibodies according to the invention are identified above. In addition, specific examples of FDA-approved EGFR inhibitors and indications and dosage regimens are provided in the table below.

It is anticipated that when these drugs when used in conjunction with the subject anti-IL-6 antibodies or antibody fragments, that the same chemotherapeutic dosage regimens may be used, but with greater cytotoxicity to the cancer cells, based on the sensitizing effect of the IL-6 antibody on the treated cancer cells (because of the antibody's inhibitory effect on IL-6 levels at the site of the cancer or tumor which when elevated "protect" the cancer from the effects of the drug).

<table>
<thead>
<tr>
<th>Drug (Trade name)</th>
<th>Class</th>
<th>Target</th>
<th>Initial Approval Date</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>mAb</td>
<td>EGFR</td>
<td>02/2004</td>
<td>In combination with radiation therapy for locally or regionally advanced</td>
<td>Intravenous 400 mg/m² initial dose then</td>
</tr>
<tr>
<td>ImClone, Bristol-Myers</td>
<td></td>
<td></td>
<td></td>
<td>HNSCC</td>
<td>250 mg/m² weekly</td>
</tr>
<tr>
<td>Squibb</td>
<td></td>
<td></td>
<td></td>
<td>Recurrent or metastatic HNSCC progressing after platinum-based therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Single agent in metastatic CRC (EGFR-expressing) after failure of irinotecan-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and oxaliplatin-based regimen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metastatic CRC (EGFR-expressing) in combination with irinotecan for</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>irinotecan-refractory patients</td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>TKI</td>
<td>EGFR</td>
<td>11/2004</td>
<td>Second-line therapy in locally advanced or metastatic NSCLC</td>
<td>Oral 150 mg daily</td>
</tr>
<tr>
<td>OSI Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td>First line, in combination with gemcitabine in locally advanced or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>metastatic pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>TKI</td>
<td>EGFR</td>
<td>05/2003</td>
<td>Monotherapy for the treatment of patients with advanced or metastatic</td>
<td>Oral 250 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In a preferred embodiment the treated cancer will be a lung cancer such as a non-small lung cancer e.g., squamous cell carcinoma, large cell carcinoma or adenocarcinoma or a small cell lung cancer such as small cell carcinoma (oat cell cancer) or combined small cell carcinoma. In a particularly preferred embodiment the treated lung cancer will comprise squamous cell carcinoma and the treated patient will be one receiving erlotinib or sunitinib. These patients will include individuals whose tumors have developed a resistance to these drugs after one or more rounds of chemotherapy.

However, as noted above any cancer wherein these EGFR inhibitory drugs are potentially useful is contemplated such as advanced or non-advanced, non-metastatic and metastatic forms of colorectal cancer, pancreatic cancer, breast cancer, head and neck cancer, esophageal cancer, lung cancer, ovarian cancer, cervical cancer, renal cancer, prostate cancer, testicular cancer, brain cancer, and others.

In this embodiment of the invention the subject anti-IL-6 antibodies or antibody fragments will be administered at dosages effective to render the treated tumor more sensitive to the effects of the drug and/or radiation, e.g., dosages ranging from about 25-500 mg, more typically about 120, 160, 240 or 320 mg dosages. The antibody will be administered before, concurrent or after administration of the chemotherapeutic, e.g., from about a month, several weeks or a week prior or after chemotherapy. Preferably the antibody will be administered prior to chemotherapy or radiation in order to render the cancer more sensitive to the effects of the drug or radiation.
As it has been shown that drug resistant cancer cells have a higher invasive or metastatic capacity and reduced apoptosis relative to non-resistant cancer cells, the present invention should further reduce the risk of invasion or metastasis of the cancer cells to other sites and/or potentially reverse or prevent metastasis. Also, the present invention should result in increased apoptosis of the drug resistant cancer cells.

In some instances it may be possible to co-administer the anti-IL-6 antibody or antibody fragment, e.g., in instances wherein the EGFR inhibitor is also a biologic such as an antibody. However, in most instances the antibody and the EGFR inhibitor which may be a biologic or small molecule will be administered in separate compositions, even in instances wherein administration of these moieties is effected concurrently. 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 or variant thereof, whereby the patient’s serum C-reactive protein ("CRP") level is stabilized and preferably 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 or variant thereof 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 antibody fragment or variant thereof as an anti-IL-6 antibody comprising Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.

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 or variant thereof, 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 or variant thereof 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 Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, 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 or variant thereof, 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 or variant thereof, as measured by the Hand Grip Strength test.

[0099] 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 or variant thereof, 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 or variant thereof 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 antibody fragment or variant thereof as an anti-IL-6 antibody comprising Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, 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 5-10 g/L, preferably 7-8 g/L, within approximately 6 weeks of administering the anti-IL-6 antibody or antibody fragment or variant thereof. 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.

[00100] In an embodiment of the invention, the patient may have been diagnosed with 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.

[00101] In an embodiment of the invention, the patient may have an elevated C-reactive protein (CRP) level prior to treatment.

[00102] Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an IL-6 antagonist such as Abl, 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.

[00103] Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an IL-6 antagonist such as Abl, whereby the patient's serum albumin level is increased, and monitoring the patient to assess the increase in the patient's serum albumin level.

[00104] Another embodiment of the invention relates to methods of improving survivability or quality of life of a patient in need thereof, comprising administering to the patient an IL-6 antagonist such as Abl, whereby the patient's serum CRP level is reduced and the patient's serum albumin level is increased, and monitoring the patient to assess the reduction in the patient's serum CRP level and the increase in the patient's serum albumin level.

[00105] Another embodiment of the invention relates to methods of preventing or treating thrombosis in a patient in a state of hypercoagulation, comprising administering to the patient an IL-6 antagonist, e.g. an anti-IL-6 antibody (e.g., Abl) and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified
antibodies) that specifically bind IL-6, which preferably are aglycosylated, whereby the patient's coagulation profile is improved or restored to a normal condition, and monitoring the patient to assess coagulation profile. As discussed infra in a preferred exemplary embodiment the anti-IL-6 antibody will comprise a humanized antibody containing the CDRs of Abl and more preferably will comprise the variable heavy and light chain in SEQ ID NO: 657 and SEQ ID NO: 709 respectively and the constant regions in SEQ ID NO: 588 and 586 respectively or variants thereof wherein one or more amino acids are modified by substitution or deletion without substantially disrupting IL-6 binding affinity.

[00106] In such methods if the IL-6 antagonist is an anti-IL-6 antibody or antibody fragment or variant thereof 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 Abl and fragments and variants thereof. 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 or variant thereof 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.

[00107] 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 such as Abl, whereby the patient's coagulation profile is improved or restored to normal, and monitoring the patient to assess coagulation profile.

[00108] In an embodiment of the invention, the patient may have elevated serum D-dimer levels prior to treatment.
In an embodiment of the invention, the patient may have a reduced serum albumin level prior to treatment.

In an embodiment of the invention, the patient's Glasgow Prognostic Score (GPS) may be improved following the treatment.

In an embodiment of the invention, the patient may have an elevated serum CRP level prior to treatment.

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

In an embodiment of the invention, the IL-6 antagonist may target IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

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.

In an embodiment of the invention, the IL-6 antagonist may comprise an anti-IL-6R, anti-gpl30, anti-p38 MAP kinase, anti-JAK1, anti-JAK2, anti-JAK3, or anti-SYK antibody or antibody fragment.

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

In an embodiment of the invention, the antagonist may comprise an anti-IL-6 antibody (e.g., Abl) or antibody fragment or variant thereof.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.
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 Abl.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof 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 Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may specifically bind to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as Abl.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may specifically bind to the same linear or conformational epitopes on an intact IL-6 polypeptide or fragment thereof that is (are) specifically bound by Abl 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.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof 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 Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated. In certain embodiments, antibodies containing these CDRs may be constructed using appropriate human frameworks based on the humanization methods disclosed herein.
In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof 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 Abl.

In an embodiment of the invention, all of the CDRs in the anti-IL-6 antibody or antibody fragment or variant thereof may be identical to the CDRs contained in an anti-IL-6 antibody comprising Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated.

In an embodiment of the invention, all of the CDRs in the anti-IL-6 antibody or antibody fragment or variant thereof may be identical to one or more of the CDRs contained in Abl.

In a preferred exemplary embodiment, the anti-IL-6 antibody will comprise all the CDRs in Abl. In a more preferred embodiment the anti-IL-6 antibody will comprise the variable heavy and light chain sequences in SEQ ID NO: 657 and SEQ ID NO: 709 (humanized Abl), or variants thereof.

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, 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.
[00129] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be aglycosylated.

[00130] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation. Preferably the Fc region is modified to eliminate glycosylation.

[00131] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be a human, humanized, single chain or chimeric antibody.

[00132] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be a humanized antibody derived from a rabbit (parent) anti-IL-6 antibody.

[00133] In an embodiment of the invention, the framework regions (FRs) in the variable light region and the variable heavy regions of said anti-IL-6 antibody or antibody fragment or variant thereof respectively may be human FRs which are unmodified or which have been modified by the substitution of at most 2 or 3 human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and the human FRs may have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library. As disclosed in detail infra in a preferred embodiment the antibody will comprise human FRs which are selected based on their high level of homology (degree of sequence identity) to that of the parent antibody that is humanized.

[00134] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may be administered to the patient with a frequency at most once per period of approximately four weeks, approximately eight weeks, approximately twelve weeks, approximately sixteen weeks, approximately twenty weeks, or approximately twenty-four weeks.

[00135] 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.
In an embodiment of the invention, the patient's serum CRP level may remain decreased and/or serum albumin level may remain raised for an entire period intervening two consecutive anti-IL-6 antibody administrations.

In an embodiment of the invention, the patient's cachexia, weakness, fatigue, and/or fever may remain improved for an entire period intervening two consecutive anti-IL-6 antibody administrations.

Cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, Wilms' tumor, or any combination thereof.

[00139] 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.

[00140] In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof may comprise a heavy chain polypeptide sequence comprising: SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708; and may further comprise a VL polypeptide sequence comprising: SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709 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 or variant thereof that specifically binds human IL-6, or may comprise a polypeptide wherein the CDRs therein are incorporated into a human framework homologous to said sequence. Preferably the variable heavy and light sequences comprise those in SEQ ID NO: 657 and 709 (humanized Ab).

[00141] 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.

[00142] In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment or variant thereof may be humanized.

[00143] In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment or variant thereof may be chimeric.

[00144] In an embodiment of the invention, said anti-IL-6 antibody or antibody fragment or variant thereof further may comprise a human Fc, e.g., an Fc region comprised of the variable heavy and light chain constant regions contained in SEQ ID NO: 704 and 702.
In an embodiment of the invention, said human Fc may be derived from IgGl, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19.

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment or variant thereof 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, 652, 656, 657, 658, 661, 664, 665, 704, 708, 2, 20, 647, 651, 660, 666, 699, 702, 706, and 709.

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

In an embodiment of the invention, the IL-6 antagonist such as Abl may be co-administered with a chemotherapy agent. In an embodiment of the invention, the chemotherapy agent include 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.

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

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

In an embodiment of the invention, the anti-IL-6 antibody or antibody fragment may be Abl or a humanized, chimeric, single chain or fragment thereof comprising all or most of the CDRs of Abl.
[00152] 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.

[00153] In an embodiment of the invention, the disease or condition may be selected from 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), or any combination thereof.

[00154] In an embodiment of the invention, the method may include administration of an antagonist of a cachexia-associated factor, weakness-associated factor, fatigue-associated factor, and/or fever-associated factor. The cachexia-associated factor, weakness-associated factor, fatigue-associated factor, and/or fever-associated factor may be selected from tumor necrosis factor-alpha, Interferon gamma, Interleukin 1 alpha, Interleukin 1 beta, Interleukin 6, proteolysis inducing factor, leukemia-inhibitory factor, or any combination thereof.

[00155] In an embodiment of the invention, the method may include administration of an anti-cachexia agent selected from cannabis, dronabinol (Marinol™), nabilone (Cesamet), cannabidiol, cannabichromene, tetrahydrocannabinol, Sativex, megestrol acetate, or any combination thereof.
[00156] In an embodiment of the invention, the method may include administration of an anti-nausea or antiemetic agent selected from 5-HT3 receptor antagonists, ajwain, alizapride, anticholinergics, antihistamines, aprepitant, benzodiaxepines, cannabichromene, cannabidiol, cannabinoids, cannabis, casopitant, chlorpromazine, cyclizine, dexamethasone, dexamethasone, dimenhydrinate (Gravol™), diphenhydramine, dolasetron, domperidone, dopamine antagonists, doxylamine, dronabinol (Marinol™), droperidol, emetrol, ginger, granisetron, haloperidol, hydroxyzine, hyoscine, lorazepam, meclizine, metoclopramide, midazolam, muscimol, nabilone (Cesamet), nkl receptor antagonists, ondansetron, palonosetron, peppermint, Phenergan, prochlorperazine, Promacot, promethazine, Pentazine, propofol, sativex, tetrahydrocannabinol, trimethobenzamide, tropisetron, nandrolone, stilbestrol, thalidomide, lenalidomide, ghrelin agonists, myostatin antagonists, anti-myostatin antibodies, selective androgen receptor modulators, selective estrogen receptor modulators, angiotensin All antagonists, beta two adenergic receptor agonists, beta three adenergic receptor agonists, or any combination thereof.

[00157] In an embodiment of the invention, the method may include administration of an anti-nausea or antiemetic agent selected from 5-HT3 receptor antagonists, ajwain, alizapride, anticholinergics, antihistamines, aprepitant, benzodiaxepines, cannabichromene, cannabidiol, cannabinoids, cannabis, casopitant, chlorpromazine, cyclizine, dexamethasone, dexamethasone, dimenhydrinate (Gravol™), diphenhydramine, dolasetron, domperidone, dopamine antagonists, doxylamine, dronabinol (Marinol™), droperidol, emetrol, ginger, granisetron, haloperidol, hydroxyzine, hyoscine, lorazepam, meclizine, metoclopramide, midazolam, muscimol, nabilone (Cesamet), nkl receptor antagonists, ondansetron, palonosetron, peppermint, Phenergan, prochlorperazine, Promacot, promethazine, Pentazine, propofol, sativex, tetrahydrocannabinol, trimethobenzamide, tropisetron, nandrolone, stilbestrol, thalidomide, lenalidomide, ghrelin agonists, myostatin antagonists, anti-myostatin antibodies, selective androgen receptor modulators, selective estrogen receptor modulators, angiotensin All antagonists, beta two adenergic receptor agonists, beta three adenergic receptor agonists, or any combination thereof.

[00158] In an embodiment of the invention, the patient's fever may be assessed by measurement of patient's body temperature.
[00159] In an embodiment of the invention, the method may include measuring the patient's body temperature prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment or variant thereof if the patient's body temperature is higher than about 38 °C.

[00160] In an embodiment of the invention, the method may include measuring the patient's body temperature within 24 hours prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment or variant thereof if the patient's body temperature measurement indicates that a fever was present.

[00161] In an embodiment of the invention, the method may further include measuring the patient's body weight prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment or variant thereof if the patient's weight has declined by greater than approximately 5% within approximately 30 days, or if the patient's lean body mass index is less than about 17 kg / m² (male patient) or less than about 14 kg / m² (female patient).

[00162] In an embodiment of the invention, the method may include measuring the patient's muscular strength prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment or variant thereof if the patient's muscular strength has declined by greater than approximately 20% within approximately 30 days.

[00163] In an embodiment of the invention, the method may result in a prolonged improvement in cachexia, weakness, fatigue, and/or fever in the patient.

[00164] In an embodiment of the invention, the patient's body mass may be raised by approximately 1 kilogram within approximately 4 weeks of administration of the anti-IL-6 antibody or antibody fragment or variant thereof.

[00165] In an embodiment of the invention, the patient's cachexia may be measurably improved within about 4 weeks of anti-IL-6 antibody administration.

[00166] In an embodiment of the invention, the patient's cachexia may be assessed by measurement of the patient's total body mass, lean body mass, lean body mass index, and/or appendicular lean body mass.
In an embodiment of the invention, the measurement of the patient's body mass may discount (subtract) the estimated weight of the patient's tumor(s) and/or extravascular fluid collection(s).

In an embodiment of the invention, the patient's cachexia may remain measurably improved approximately 8 weeks after anti-IL-6 antibody administration.

In an embodiment of the invention, the patient's weakness may be measurably improved within about 4 weeks of anti-IL-6 antibody administration.

In an embodiment of the invention, the patient's weakness may be measured by the hand grip strength test.

In an embodiment of the invention, the patient's hand grip strength may be improved by at least about 15%, or at least about 20%.

In an embodiment of the invention, the patient's weakness may remain measurably improved approximately 8 weeks after anti-IL-6 antibody administration.

In an embodiment of the invention, the patient's fatigue may be measurably improved within about 1 week of anti-IL-6 antibody administration.

In an embodiment of the invention, the patient's fatigue may be measured by the FACIT-F FS test.

In an embodiment of the invention, the patient's FACIT-F FS score may be improved by at least about 10 points.

In an embodiment of the invention, the patient's fatigue may remain measurably improved approximately 8 weeks after anti-IL-6 antibody administration.

In an embodiment of the invention, the patient's fever may be measurably improved within about 1 week of anti-IL-6 antibody administration.

In an embodiment of the invention, the patient's fever may remain measurably improved approximately 8 weeks after anti-IL-6 antibody administration.
In an embodiment of the invention, the patient's quality of life may be improved.

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

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.

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.

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.

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

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.

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 such as Abl if the patient's INR is less than about 0.9.
In a 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 such as Abl if the patient's INR is less than about 0.5.

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.

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 such as Abl if the patient's serum D-dimer level is above the normal reference range.

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.

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

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.

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.

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

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

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, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.
In an embodiment of the invention, the antisense nucleic acid may comprise DNA, RNA, peptide nucleic acid, locked nucleic acid, morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, threose nucleic acid, or any combination thereof.

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

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, gpl30, 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.

In an embodiment of the invention, the IL-6 antagonist may comprise a soluble IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

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

In an embodiment of the invention, the method may include measuring the patient's serum CRP level prior to administration of the anti-IL-6 antibody, and administering the anti-IL-6 antibody or antibody fragment or variant thereof if the patient's serum CRP level is at least approximately 5 mg/L.

In an embodiment of the invention, the patient's serum CRP level may be reduced to less than approximately 5 mg/L within 1 week of administration of the IL-6 antagonist.

In an embodiment of the invention, the patient's serum CRP level may be reduced to below 1 mg/L within 1 week of administration of the IL-6 antagonist.

In an embodiment of the invention, treatment may result in a prolonged reduction in serum CRP level of the patient.

In an embodiment of the invention, the patient's serum CRP level may be reduced to below 10 mg/L within about 1 week of IL-6 antagonist administration.
In an embodiment of the invention, 14 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 21 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 28 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 35 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 42 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 49 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, 56 days after IL-6 antagonist administration the patient's serum CRP level may remain below 10 mg/L.

In an embodiment of the invention, the patient's survivability is improved.

In an embodiment of the invention, the method may include measuring the patient's serum albumin level prior to administration of the IL-6 antagonist, and administering the IL-6 antagonist such as Abl if the patient's serum albumin level is less than approximately 35 g/L.

In an embodiment of the invention, the patient's serum albumin level may be increased to more than approximately 35 g/L within about 5 weeks of administration of the IL-6 antagonist.

In an embodiment of the invention, treatment may result in a prolonged increase in serum albumin level of the patient.

In an embodiment of the invention, 42 days after IL-6 antagonist administration the patient's serum albumin level may remain above 35 g/L.
In an embodiment of the invention, 49 days after IL-6 antagonist administration the patient’s serum albumin level may remain above 35 g/L.

In an embodiment of the invention, 56 days after IL-6 antagonist administration the patient’s serum albumin level may remain above 35 g/L.

In an embodiment of the invention, the patient’s serum albumin level may be increased by about 5 g/L within approximately 5 weeks of administering the IL-6 antagonist.

In an embodiment of the invention, the patient may have been 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.

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.

Another embodiment of the invention relates to a composition comprising an IL-6 antagonist such as Abl, 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.

Another embodiment of the invention relates to a composition comprising an IL-6 antagonist such as Abl, 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, vincedesine 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 DRAWINGS**

[00226] 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).

[00227] 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 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.
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.

FIG. 4 provides the α/β/γ-2-macroglobulin (A2M) dose response curve for antibody Abl administered intravenously at different doses one hour after a 10(^g/kg s.c. dose of human IL-6.

FIG. 5 provides survival data for the antibody Abl progression groups versus control groups.

FIG. 6 provides additional survival data for the antibody Abl regression groups versus control groups.

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 Abl at 10 mg/kg i.v. every three days (270-320 mg tumor size).

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 Abl at 10 mg/kg i.v. every three days (400-527 mg tumor size).

FIG. 9 provides a pharmacokinetic profile of antibody Abl in cynomolgus monkey. Plasma levels of antibody Abl 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.

FIG. 10 (A-D) provides binding data for antibodies Ab4, Ab3, Ab8 and Ab2, respectively. FIG. 10 E provides binding data for antibodies Abl, Ab6 and Ab7.

FIG. 11 summarizes the binding data of FIG. 10 (A-E) in tabular form.

FIG. 12 presents the sequences of the 15 amino acid peptides used in the peptide mapping experiment of Example 14.
FIG. 13 presents the results of the blots prepared in Example 14.

FIG. 14 presents the results of the blots prepared in Example 14.

FIG. 15A shows affinity and binding kinetics of Abl for IL-6 of various species.

FIG. 15B demonstrates inhibition of IL-6 by Abl in the T165 cell proliferation assay.

FIG. 16 shows the mean plasma concentration of Abl resulting from a single administration of Abl to healthy male subjects in several dosage groups.

FIG. 17 shows mean area under the plasma Abl concentration time curve (AUC) for the dosage groups shown in FIG. 16.

FIG. 18 shows mean peak plasma Abl concentration (C_max) for the dosage groups shown in FIG. 16.

FIG. 19 summarizes Abl pharmacokinetic measurements of the dosage groups shown in FIG. 16.

FIG. 20 shows the mean plasma concentration of Abl resulting from a single administration of Abl to patients with advanced cancer.

FIG. 21 illustrates the unprecedented elimination half-life of Abl compared with other anti-IL-6 antibodies.

FIG. 22 shows increased hemoglobin concentration following administration of Abl to patients with advanced cancer.

FIG. 23 shows mean plasma lipid concentrations following administration of Abl to patients with advanced cancer.

FIG. 24 shows mean neutrophil counts following administration of Abl to patients with advanced cancer.

FIG. 25 demonstrates suppression of serum CRP levels in healthy individuals.
FIG. 26 (A-B) demonstrates suppression of serum CRP levels in advanced cancer patients.

FIG. 27 shows prevention of weight loss by Abl in a mouse cancer cachexia model.

FIG. 28 shows the physical appearance of representative Abl-treated and control mice in a cancer cachexia model.

FIG. 29 demonstrates that Abl promotes weight gain in advanced cancer patients.

FIG. 30 demonstrates that Abl reduces fatigue in advanced cancer patients.

FIG. 31 demonstrates that Abl promotes hand grip strength in advanced cancer patients.

FIG. 32 demonstrates that Abl suppresses an acute phase protein (Serum Amyloid A) in mice.

FIG. 33 demonstrates that Abl increase plasma albumin concentration in advanced cancer patients.

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

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

FIG. 38 shows the mean CRP values for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Abl monoclonal antibody.

FIG. 39 shows the change in median values of CRP from each dosage concentration group corresponding to Fig. 38.
FIG. 40 shows a reduction in serum CRP levels in patients with various cancers after dosing at 80, 160 or 320 mg for 12 weeks.

FIG. 41 shows a reduction in serum CRP levels in the patient population with rheumatoid arthritis after dosing at 80, 160 and 320 mg for 12 weeks.

FIG. 42 demonstrates that Abl increases mean hemoglobin at 80, 160 and 320 mg after 12 weeks of dosing.

FIG. 43 demonstrates mean change from baseline hemoglobin for the data presented in Figure 42.

FIG. 44 demonstrates that Abl increases mean hemoglobin at 160 and 320 mg after 12 weeks of dosing in patients having baseline hemoglobin below 11 g/l.

FIG. 45 demonstrates that Abl increases mean hemoglobin at 80, 160 and 320 mg after 16 weeks of dosing.

FIG. 46 demonstrates that Abl increases mean albumin concentration at 80, 160 and 320 mg after 12 weeks of dosing.

FIG. 47 demonstrates the change from baseline for mean albumin concentration from each dosage concentration group corresponding to Figure 46.

FIG. 48 demonstrates that Abl provides sustained increases in mean albumin concentration at 160 and 320 mg after 12 weeks of dosing in patients having baseline albumin below 35 g/l.

FIG. 49 demonstrates the averaged weight change data from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Abl monoclonal antibody over 12 weeks.

FIG. 50 demonstrates the averaged percent change in body weight from each dosage concentration group corresponding to Fig. 49.

FIG. 51 demonstrates the change in averaged lean body mass data for the dosage concentration groups corresponding to Figure 49.
FIG. 52 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.

FIG. 53 demonstrates the change from baseline Facit-F FS subscale score corresponding to Fig. 52.

FIG. 54 demonstrates that Abl drops D-dimer levels over placebo at 80, 160 and 320 mg after 16 weeks of dosing.

FIG. 55 demonstrates the percent change from baseline in D-dimer concentration from each dosage concentration group corresponding to Figure 54.

FIG. 56 demonstrating that treatment of patients with rheumatoid arthritis produced significant improvement over placebo based upon ACR metrics.

FIG. 57 demonstrates patients achieving ACR 20 over placebo at 80, 160, and 320 mg after 16 weeks of dosing.

FIG. 58 demonstrates patients achieving ACR 50 over placebo at 80, 160, and 320 mg after 16 weeks of dosing.

FIG. 59 demonstrates patients achieving ACR 70 over placebo at 80, 160, and 320 mg after 16 weeks of dosing.

FIG. 60 demonstrates the change from baseline for the components of the ACR metric for placebo, 80, 160, and 320 mg dosage concentration groups.

FIG. 61 demonstrates the change in HAQ-DI scores for placebo, 80, 160, and 320 mg dosage concentration groups.

FIG. 62 demonstrates the change in DAS28 scores for placebo, 80, 160, and 320 mg dosage concentration groups.

FIG. 63 demonstrates the change in percentage of patients achieving EULAR good or moderate responses for placebo, 80, 160, and 320 mg dosage concentration groups.
FIG. 64 schematically shows a clinical study relating to the use of humanized Abl for treatment of rheumatoid arthritis.

FIG. 65 shows plasma concentrations of humanized Abl in rheumatoid arthritis patients after subcutaneous (SC) or intravenous (iv) dosing with humanized Abl.

FIG. 66 shows plasma CRP level concentrations after subcutaneous or intravenous dosing of humanized Ab1.

FIG. 67 contains a table enumerating adverse events in patients administered humanized Abl through week 24.

FIG. 68 contains a Table enumerating injection site reactions to humanized Abl through week 12 after antibody administration.

FIG. 69 tabulates clinical laboratory evaluations (ALT, AST, bilirubin, neutrophil counts, and platelet counts) for patients subcutaneously or intravenously administered humanized Abl and controls through week 12 after humanized Abl administration.

FIG. 70 tabulates plasma pharmacokinetic parameters in patients through week 24 after subcutaneous or intravenous administration of humanized Abl.

FIG. 71 shows the effect of subcutaneous and intravenous administration of ALD518 through week 12 after antibody dosing at 50 or 100 mg.

DETAILED DESCRIPTION

Definitions

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.
The term "variants" (as applied to antibodies including Abl) includes single-chain antibodies, dimers, multimers, sequence variants, domain substitution variants, etc. Single-chain antibodies such as SMIPs, shark antibodies, nanobodies (e.g., Camelidiae antibodies). Sequence variants can be specified by percentage identity (or similarity) e.g., 99%, 95%, 90%>, 85%, 80%, 70%, 60%, etc. or by numbers of permitted conservative or non-conservative substitutions. Domain substitution variants include replacement of a domain of one protein with a similar domain of a related protein. A similar domain may be identified by similarity of sequence, structure (actual or predicted), or function. For example, domain substitution variants include the substitution of one or more CDRs and/or framework regions.

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.

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: MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPPGEMSKDVAAHRQPLTSSERIDKQIRYIL DGISALRKECNKSNMCESSKEALENAENLNLKMAEKDFQSGFNEETCLVKIITGLLE FEVYLEYLQRNFRSEEEQARAVQSTMSTKVLIQFLQKKAKNLDAITTPDPTTNASLLTQLA QNQWLQDMTHILRSHFKEFLQSSLRALRM (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.

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, gpl30, 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 US200700 10529 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-gpl30 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 gpl30, which may be native, mutant, or variant sequence, and may optionally be coupled to other moieties (such as half-life-increasing moieties, e.g. an Fc domain). For example, an IL-6 antagonist may be a soluble IL-6 receptor or fragment, a soluble IL-6 receptor:Fc fusion protein, a small molecule inhibitor of IL-6, an anti-IL-6 receptor antibody or antibody fragment or variant thereof, antisense nucleic acid, 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 Vase Biol. 2006 May;26(5):1 177-83). 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.

[00301] 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 and the risk of developing thrombosis or hypercoagulation 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, conditions that preclude or restrict movement such as partial or complete paralysis, morbid obesity, disorders that impede oxygen uptake and absorption such as lung disorders including lung cancer, COPD, emphysema, drug related fibrosis, cystic fibrosis, 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.

[00302] 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 Vase Med, 2005 Nov;5(4):3 15-20). 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.

[00303] 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.

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.
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(1):1385-8.

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.

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.,

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.

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.

[00310] 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:

```
MEKLLCFLVLTSLSHAFGQTDMRSKAVFPKESDTSYVSLKAPLT
ELSTRGYSYSATKRQDNEILIFWSDKIGYSFTVGGSEILFEVPEVT
VHICTSWESASGIHEFWVDGKRVRKSLKGGYTVGAEASIILGQEQD
FSGNFGSGLVGDIGNVNWDFVLSPDEINTIYLGGPPSNVLNW
RALKYEVeQGEVF
```

(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.

[00311] 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:

```
MLAVGCALLAAPGAALAPRCPAEVaRGLTSLPGDVTLTCPGVEPEDNATVHWVLKPANGSHPSRWAGMRRLLLRSVQLHDGNYSYCRAGRAPTVHLLVDVPPE
```
EPQLSCFRKSPLSNVVCEWGPSTPSLTTKAFLVRKFQNPSAEDFQEPQCYSQESQKFS
CQLAVPEGDSSFYIVSMCVASSVGSKFSKTRTTFQGCGLQDPPANITVTAVARNPRWLS
HTWQDHPHSWNSSFYRLFELRYAERSTFTTWMVKDLQHCVIHDAWSGLRHVQ
RAQEEFGQGEWSEAMTPWTSRSPPAEVENSTPMQLTTNDDNILFRDSAN
ATSLPVQDSSVPLPTFLVGGLAFGLTCLIAVLRFKTKWKLRLALKEGTKSMHPPSL
GQLVPERPRPVTPLVPLSPPVSLGSNTSSHNRDPARDPRSPYDISNTDYFFPR (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.

[00312] gp/l30: As used herein, gp/l30 (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:
MLTLQTWVVQALFIIITTESTGELDCPGYISPESVPVQLHSNFTAVCVALKEKCMYFH
VNANYIVWKTNHTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFQGQLEQNVYGITISS
GLPPEKPKNLSCIYVNEKCMRRCEWDGGRETHTLETNFTLKEWATHKFADECKTKRDTPT
SCTVDYSTVYFVNEVWEAENLGLKVTSDHINFDPVKVKNPPNHLSVINSEELSSIL
KLTWNTNSIKSVIILKYJNIQYRTKDASTWSQIPPETDASTRSSFTVQDLKPFETYVFRIRC
MKEDGKGYWDWSEEASIGITYEDRPSKSAPSFVYKIDPSHTQGYRTVQLVWKTLPPFEA
NGKILDYEVTLTRWKSHEQYNTVNAKTCLTVNLTNDRLLATLTVNLVGKSDAAVLTIP
ACDFQATHPVMDDKAPKDNMLWVEWTTPRESVKKYILEDWCVLSDKAPCITWDQQED
GTTHYRTHLRGNLAESKCYLITVPVYADPGSPESIKAYLQAPPSKGPTVRTKKGK
EAVLEWDQLPVDVNNFIRNNTFYRTIIGNETAVNVDSSHTEYTLSLTSDTLYVMRM
AAAYDEGKDGPEFTFTPFAQGEIEAVVPVCLAFLLTLLGVLFCFNKDRLKHHWP
NVPDSKSIAQWSSPTPRHNFNSKDHQMYSDGNTVDVVEIEANDKKPFPEDLKL
LFKKEKINTEGRIGCGGSSCMSSRSSPISISDENSEQTSSTVQYSTVHSKHYQVPS
VQVFSRSESTQPLLSEPEDLQVLVDHVGKDGDILPRQYFKQNCQHESSPDISHF
ERSKQVSSVNEEDFVRLKQQIDHISQCGSAGQMKMFQEVSAAADAFPGTEGQVERFETVG
MEATDEGMPKSYLPQTVQGGYMPQ (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.
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.

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. Similarly, "an amount of an anti-IL-6 antibody effective to reduce serum CRP levels" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable decrease in serum CRP levels, or prevent, slow, delay, or arrest, an increase in serum CRP levels for which the subject is at risk. Similarly, "an amount of an anti-IL-6 antibody effective to increase serum albumin levels" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable increase in serum albumin levels, or prevent, slow, delay, or arrest, a decrease in serum albumin levels for which the subject is at risk. Similarly, "an amount of an anti-IL-6 antibody effective to reduce weakness" and similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable decrease in weakness as determined by the hand grip strength test. Similarly, "an amount of an anti-IL-6 antibody effective to increase weight" and
similar phrases refer to an amount of anti-IL-6 antibody that, when administered to a subject, will cause a measurable increase in a patient's weight. An effective amount will vary according to the weight, sex, age and medical history of the individual, as well as the severity of the patient's condition(s), the type of disease(s), mode of administration, and the like. An effective amount may be readily determined using routine experimentation, e.g., by titration (administration of increasing dosages until an effective dosage is found) and/or by reference to amounts that were effective for prior patients. Generally, the anti-IL-6 antibodies of the present invention will be administered in dosages ranging between about 0.1 mg/kg and about 20 mg/kg of the patient's body-weight.

[00315] 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 such as Abl) 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.

[00316] 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 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.

[00317] 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 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.

[00318] 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.

[00319] 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.

[00320] 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.

[00321] 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.)
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.

[00322] **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.

[00323] In one embodiment of the invention, the mating competent yeast is a member of the *Saccharomycetaceae* family, which includes the genera *Arxizyma; Ascobotryozyma; Citeromyces; Debaryomyces; Dekkera; Eremothecium; Issatchenka; 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*.

[00324] 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*.

[00325] **Haploid Yeast Cell:** A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[00326] **Polyploid Yeast Cell:** A cell having more than one copy of its normal genomic (chromosomal) complement.
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.

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.

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

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.

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.

**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.

**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.

**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.

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

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.

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.

Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PH03, PH05, 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.

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).

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.

[00343] 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.

[00344] 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.

[00345] 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. 55:913-949; 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.21 1-250. 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.

[00346] 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.

[00347] 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.

[00348] 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.

[00349] 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.

[00350] 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.

[00351] 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')\textsubscript{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(1):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.

[00352] For example, antibodies or antigen binding fragments or variants thereof may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected
into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[00353] 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.

[00354] 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 IgGl, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgGlO, IgGl 1, IgGl2, IgGl3, IgGl4, IgGl5, IgGl6, IgGl7, IgGl8 or IgGl9 constant regions.

[00355] 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. In a preferred embodiment, humanization may be effected as disclosed in detail infra. This scheme grafts CDRs onto human FRs highly homologous to the parent antibody that is being humanized.

[00356] 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.

[00357] 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.

[00358] 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.

[00359] 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.

[00360] 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.

[00361] 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.

[00362] 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.
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).

For example, a liposomes or other lipid aggregate may comprise a lipid such as phosphatidylcholines (lecithins) (PC), phosphatidylethanolamines (PE), lysolecithins, lysophosphatidylethanolamines, phosphatidylserines (PS), phosphatidylglycerols (PG), phosphatidylinositol (PI), sphingomyelins, cardiolipin, phosphatidic acids (PA), fatty acids, gangliosides, glucolipids, glycolipids, mono-, di or triglycerides, ceramides, cerebrosides and combinations thereof; a cationic lipid (or other cationic amphiphile) such as 1,2-dioleoyloxy-3-(trimethylamino) propane (DOTAP); N-cholesteryloxy carbaryl-3,7,12-triazapentadecane-1,15-diamine (CTAP); N-[1-(2,3, -ditetradecyloxy)propyl]-N,N-dimethyl-N-hydroxyethylammonium bromide (DMRIE); N-[1-(2,3,-dioleoyloxy)propyl]-N,N-dimethyl-N-hydroxy ethylammonium bromide (DORIE); N-[1-(2,3-dioleoyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA); 3 beta [N-(N',N'-dimethylaminoethane)carbamoly] cholesterol (DC-Choi); and dimethyldioctadecylammonium (DDAB); dioleoylphosphatidyl ethanolamine (DOPE),
cholesterol-containing DOPC; and combinations thereof; and/or a hydrophilic polymer such as polyvinylpyrrolidone, polyvinylmethylene, polymethoxyzoline, polyethylenezoline, polyhydroxypropyloxsoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, 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.

[00365] "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.

[00366] 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 Fab region; the stem portion of the "Y" configuration is designated the Fc region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y"
configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses
the variable region having specificity for the antigen that elicited it, and is approximately 100
amino acids in length, there being slight variations between light and heavy chain and from
antibody to antibody.

[00367] 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.

[00368] 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.

[00369] 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)). CDRs for exemplary anti-IL-6 antibodies are provided herein.

[00370] 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. As mentioned in the preferred embodiments, the FRs will comprise human FRs highly homologous to the parent antibody (e.g., rabbit antibody).

**Abl Anti-IL-6 Antibodies and Binding Fragments Thereof**

[00371] The invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below: MDTRAPTQLLGLLLLWLPGARCAVDMTQTPASVSAAVGGTVTIKCQASQINNELSWY QQKPGQRRPKLLYIRASTLASGVSSRFKGSQSGTEFLTISDLECADAATYYCYQQGYSRNI DNAFGGGTEVVKRTVAAPSVFIFPSDEQLKSGTASVVCLLNN (SEQ ID NO: 2) or AIQMTQSPSSLSASVGDRVITITCQASQINNELSWYQQPGKAPKLLYIRASTLASGVPS RFSGSNGSTDFTLTISSLQPDDFATYYCQQGYSRNI DNAFGGGTKVEIKR (SEQ ID NO: 709) and humanized versions and variants thereof including those set forth in FIGS. 2 and 34-37, and those identified in Table 1.
The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
METGLRWLLLVAVLGQCSLEESGGLVTPGTPPLCTCTASGFLSNYYVTWVRQA
PGKGLEWGIYGSDEYATWAIGRTISKTSTTVLDKMTSLTAADTATYFCARDDSD
WDAKFNWQGQTLLVTSSASTKPSVFPLAPSSKSTSNGTAALGCLVK (SEQ ID NO: 3)
```

or

```
EVQLVSEGGGLVQPGGLRLSCAASGFLSNYYVTWVRQAPGKGGLEWGIYGSDEYATWAIGRTISRDNSKNTLYLQMNLSRAEDTAVYYCARDDSDLWDADKNWQGQTLLVTSSASTKPSVFPLAPSSKSTSNGTAALGCLVLV (SEQ ID NO: 657)
```

and humanized versions and variants thereof including those set forth in FIGS. 2 and 34-37, and those identified in Table 1.

The invention further includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence which is a modified version of SEQ ID NO: 3 wherein the tryptophan residue in CDR2 is changed to a serine as set forth below:

```
METGLRWLLLVAVLGQCSLEESGGLVTPGTPPLCTCTASGFLSNYYVTWVRQA
PGKGLEWGIYGSDEYATWAIGRTISKTSTTVLDKMTSLTAADTATYFCARDDSD
WDAKFNWQGQTLLVTSSASTKPSVFPLAPSSKSTSNGTAALGCLVK (SEQ ID NO: 658)
```

and humanized versions and variants thereof including those set forth in FIGS. 2 and 34-37, and those identified in Table 1.

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, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8 or 120; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or 19, 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.

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, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8 or 120; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or 19, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and humanized versions of the variable heavy and light chain sequences set forth above.

[00376] 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, humanized versions of the polypeptide sequence of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, humanized versions of the polypeptide sequence of SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, or 708.

[00377] 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.

[00378] 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 or SEQ ID NO: 120; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 and 657 or 19.

[00379] 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; the variable heavy chain region of SEQ ID NO: 3; the complementarity-
determining regions (SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6) of the variable light chain region of SEQ ID NO: 2; and the complementarity-determining regions (SEQ ID NO: 7; SEQ ID NO: 8 or SEQ ID NO: 120; and SEQ ID NO: 9) of the variable heavy chain region of SEQ ID NO: 3 and 657 or 19.

[00380] 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 SEQ ID NO: 709; and the heavy chain CDR sequence of SEQ ID NO: 120 is substituted for the heavy chain CDR sequence of SEQ ID NO: 8.

[00381] In a preferred embodiment of the invention, the anti-IL-6 antibody is Abl, 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 a humanized sequence as shown in Figures 34-37.

[00382] Sequences of anti-IL-6 antibodies of the present invention are shown in Table 2. Exemplary sequence variants other alternative forms of the heavy and light chains of Abl 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.

[00383] Exemplary Abl embodiments include an antibody comprising a variant of the light chain and/or heavy chain. Exemplary variants of the light chain of Abl include the sequence of any of the Abl 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).

Exemplary variants of the heavy chain of Abl include the sequence of any of the Abl 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 Abl 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).

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.

[00386] 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.

[00387] 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.

[00388] 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.

[00389] 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.

[00390] 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.

[00391] 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.

[00392] 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

[00393] 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.

[00394] 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.

[00395] 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 Abl \( \text{in vitro} \) and/or \( \text{upon in vivo} \) administration.

[00396] These \( \text{in vitro} \) and \( \text{in vivo} \) properties are described in more detail in the examples below and include: competing with Abl 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 (Kd) from IL-6 of less than or equal to \( 10^{-4} \text{ S}^{-1} \); having an \( \text{in-vivo} \) half-life of at least about 22 days in a healthy human subject; ability to prevent or treat hypoalbuminemia; ability to prevent or treat elevated CRP; ability to prevent or treat abnormal coagulation; and/or ability to decrease the risk of thrombosis in an individual having a disease or condition associated with increased risk of thrombosis. Additional non-limiting examples of anti-IL-6 activity are set forth herein, for example, under the heading "Anti-IL-6 Activity."

[00397] In another embodiment the anti-IL-6 antibody includes one or more of the Abl light-chain and/or heavy chain CDR sequences (see Table 1) or variant(s) thereof which has one or more of the properties of Abl \( \text{in vitro} \) and/or \( \text{upon in vivo} \) 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:

- 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;

- a polypeptide having at least 81.8% (i.e., 9 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;
a polypeptide having at least 90.9% (i.e., 10 out of 11 amino acids) identity to the light chain CDR1 of SEQ ID NO: 4;

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

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

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

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

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;

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

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

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

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;

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

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;
a polypeptide having 100% (i.e., 5 out of 5 amino acids) identity to the heavy chain CDR1 of SEQ ID NO: 7;
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;
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;
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;
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;
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;
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;
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;
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;
a polypeptide having 100% (i.e., 16 out of 16 amino acids) identity to the heavy chain CDR2 of SEQ ID NO: 120;
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;
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;
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;

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;

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;

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;

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;

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;

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

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;

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

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;

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

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;
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;

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;

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;

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

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;

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

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;

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;

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;

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;

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;

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;
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;

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

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;

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;

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;

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;

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;

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;

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

[00398] 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:

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;

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;
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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;
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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;
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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;
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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;
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;

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;

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;

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;

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;

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;

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;

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;

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.

Table 2. Sequences of exemplary anti-IL-6 antibodies.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antibody chains</th>
<th>CDR1</th>
<th>CDR2</th>
<th>CDR3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRT.</td>
<td>Nuc.</td>
<td>PRT.</td>
<td>Nuc.</td>
</tr>
<tr>
<td>Ab1 light chains *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>4</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>720</td>
<td>4</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>647</td>
<td>721</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td>651</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>660</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>666</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>699</td>
<td>4</td>
<td>694</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>702</td>
<td>4</td>
<td>694</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>706</td>
<td>4</td>
<td>694</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>709</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

**Human light chains used in Ab1 humanization**

<table>
<thead>
<tr>
<th></th>
<th>648</th>
<th>710</th>
<th>713</th>
</tr>
</thead>
<tbody>
<tr>
<td>649</td>
<td>7</td>
<td>11</td>
<td>714</td>
</tr>
<tr>
<td>650</td>
<td>712</td>
<td>715</td>
<td></td>
</tr>
</tbody>
</table>

**Ab1 heavy chains**

<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>11</th>
<th>7</th>
<th>15</th>
<th>8</th>
<th>16</th>
<th>9</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>724</td>
<td>7</td>
<td>15</td>
<td>120</td>
<td>696</td>
<td>9</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>652</td>
<td>725</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>656</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>657</td>
<td>700</td>
<td>7</td>
<td>15</td>
<td>120</td>
<td>696</td>
<td>9</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>658</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>659</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>665</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>704</td>
<td>703</td>
<td>7</td>
<td>15</td>
<td>120</td>
<td>696</td>
<td>9</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>708</td>
<td>707</td>
<td>7</td>
<td>15</td>
<td>120</td>
<td>696</td>
<td>9</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

**Human heavy chains used in Ab1 humanization**

<table>
<thead>
<tr>
<th></th>
<th>653</th>
<th>716</th>
<th>717</th>
</tr>
</thead>
<tbody>
<tr>
<td>654</td>
<td>7</td>
<td>16</td>
<td>717</td>
</tr>
<tr>
<td>655</td>
<td>74</td>
<td>82</td>
<td>718</td>
</tr>
</tbody>
</table>

**Ab2 light chains**

<table>
<thead>
<tr>
<th></th>
<th>21</th>
<th>29</th>
<th>23</th>
<th>31</th>
<th>24</th>
<th>32</th>
<th>25</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>667</td>
<td>23</td>
<td>31</td>
<td>24</td>
<td>32</td>
<td>25</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

101
<table>
<thead>
<tr>
<th></th>
<th>22</th>
<th>30</th>
<th>26</th>
<th>34</th>
<th>27</th>
<th>35</th>
<th>28</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab2 heavy chains</td>
<td>668</td>
<td>670</td>
<td>26</td>
<td>34</td>
<td>27</td>
<td>35</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Ab3 light chains</td>
<td>37</td>
<td>45</td>
<td>39</td>
<td>47</td>
<td>40</td>
<td>48</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>Ab3 heavy chains</td>
<td>671</td>
<td>673</td>
<td>39</td>
<td>47</td>
<td>40</td>
<td>48</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>Ab4 light chains</td>
<td>38</td>
<td>46</td>
<td>42</td>
<td>50</td>
<td>43</td>
<td>51</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>Ab4 heavy chains</td>
<td>672</td>
<td>674</td>
<td>42</td>
<td>50</td>
<td>43</td>
<td>51</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>Ab5 light chains</td>
<td>53</td>
<td>61</td>
<td>55</td>
<td>63</td>
<td>56</td>
<td>64</td>
<td>57</td>
<td>65</td>
</tr>
<tr>
<td>Ab5 heavy chains</td>
<td>675</td>
<td>677</td>
<td>55</td>
<td>63</td>
<td>56</td>
<td>64</td>
<td>57</td>
<td>65</td>
</tr>
<tr>
<td>Ab6 light chains</td>
<td>54</td>
<td>62</td>
<td>58</td>
<td>66</td>
<td>59</td>
<td>67</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Ab6 heavy chains</td>
<td>676</td>
<td>678</td>
<td>58</td>
<td>66</td>
<td>59</td>
<td>67</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Ab7 light chains</td>
<td>69</td>
<td>77</td>
<td>71</td>
<td>79</td>
<td>72</td>
<td>80</td>
<td>73</td>
<td>81</td>
</tr>
<tr>
<td>Ab7 heavy chains</td>
<td>679</td>
<td>681</td>
<td>71</td>
<td>79</td>
<td>72</td>
<td>80</td>
<td>73</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>78</td>
<td>74</td>
<td>82</td>
<td>75</td>
<td>83</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>680</td>
<td>682</td>
<td>74</td>
<td>82</td>
<td>75</td>
<td>83</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>93</td>
<td>87</td>
<td>95</td>
<td>88</td>
<td>96</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>683</td>
<td>685</td>
<td>87</td>
<td>95</td>
<td>88</td>
<td>96</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>94</td>
<td>90</td>
<td>98</td>
<td>91</td>
<td>99</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>684</td>
<td>686</td>
<td>90</td>
<td>98</td>
<td>91</td>
<td>99</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>109</td>
<td>103</td>
<td>111</td>
<td>104</td>
<td>112</td>
<td>105</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>103</td>
<td>111</td>
<td>104</td>
<td>112</td>
<td>105</td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>687</td>
<td>689</td>
<td>103</td>
<td>111</td>
<td>104</td>
<td>112</td>
<td>105</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>693</td>
<td>103</td>
<td>111</td>
<td>104</td>
<td>112</td>
<td>105</td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>110</td>
<td>106</td>
<td>114</td>
<td>107</td>
<td>115</td>
<td>108</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>117</td>
<td>106</td>
<td>114</td>
<td>107</td>
<td>115</td>
<td>108</td>
<td>116</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>106</td>
<td>114</td>
<td>121</td>
<td>107</td>
<td>115</td>
<td>108</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>688</td>
<td>690</td>
<td>106</td>
<td>114</td>
<td>121</td>
<td>107</td>
<td>115</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>691</td>
<td>106</td>
<td>114</td>
<td>121</td>
<td>107</td>
<td>115</td>
<td>108</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>692</td>
<td>106</td>
<td>114</td>
<td>121</td>
<td>107</td>
<td>115</td>
<td>108</td>
<td>116</td>
</tr>
<tr>
<td>Ab8 light chain</td>
<td>122</td>
<td>130</td>
<td>124</td>
<td>132</td>
<td>125</td>
<td>133</td>
<td>126</td>
<td>134</td>
</tr>
<tr>
<td>Ab8 heavy chain</td>
<td>123</td>
<td>131</td>
<td>127</td>
<td>135</td>
<td>128</td>
<td>136</td>
<td>129</td>
<td>137</td>
</tr>
<tr>
<td>Ab9 light chain</td>
<td>138</td>
<td>146</td>
<td>140</td>
<td>148</td>
<td>141</td>
<td>149</td>
<td>142</td>
<td>150</td>
</tr>
<tr>
<td>Ab9 heavy chain</td>
<td>139</td>
<td>147</td>
<td>143</td>
<td>151</td>
<td>144</td>
<td>152</td>
<td>145</td>
<td>153</td>
</tr>
<tr>
<td>Ab10 light chain</td>
<td>154</td>
<td>162</td>
<td>156</td>
<td>164</td>
<td>157</td>
<td>165</td>
<td>158</td>
<td>166</td>
</tr>
<tr>
<td>Ab10 heavy chain</td>
<td>155</td>
<td>163</td>
<td>159</td>
<td>167</td>
<td>160</td>
<td>168</td>
<td>161</td>
<td>169</td>
</tr>
<tr>
<td>Ab11 light chain</td>
<td>170</td>
<td>178</td>
<td>172</td>
<td>180</td>
<td>173</td>
<td>181</td>
<td>174</td>
<td>182</td>
</tr>
<tr>
<td>Ab11 heavy chain</td>
<td>171</td>
<td>179</td>
<td>175</td>
<td>183</td>
<td>176</td>
<td>184</td>
<td>177</td>
<td>185</td>
</tr>
<tr>
<td>Ab12 light chain</td>
<td>186</td>
<td>194</td>
<td>188</td>
<td>196</td>
<td>189</td>
<td>197</td>
<td>190</td>
<td>198</td>
</tr>
<tr>
<td>Ab12 heavy chain</td>
<td>187</td>
<td>195</td>
<td>191</td>
<td>199</td>
<td>192</td>
<td>200</td>
<td>193</td>
<td>201</td>
</tr>
<tr>
<td>Ab13 light chain</td>
<td>202</td>
<td>210</td>
<td>204</td>
<td>212</td>
<td>205</td>
<td>213</td>
<td>206</td>
<td>214</td>
</tr>
<tr>
<td>Ab13 heavy chain</td>
<td>203</td>
<td>211</td>
<td>207</td>
<td>215</td>
<td>208</td>
<td>216</td>
<td>209</td>
<td>217</td>
</tr>
<tr>
<td>Ab14 light chain</td>
<td>218</td>
<td>226</td>
<td>220</td>
<td>228</td>
<td>221</td>
<td>229</td>
<td>222</td>
<td>230</td>
</tr>
<tr>
<td>Ab14 heavy chain</td>
<td>219</td>
<td>227</td>
<td>223</td>
<td>231</td>
<td>224</td>
<td>232</td>
<td>225</td>
<td>233</td>
</tr>
<tr>
<td>Ab15 light chain</td>
<td>234</td>
<td>242</td>
<td>236</td>
<td>244</td>
<td>237</td>
<td>245</td>
<td>238</td>
<td>246</td>
</tr>
<tr>
<td>Ab15 heavy chain</td>
<td>235</td>
<td>243</td>
<td>239</td>
<td>247</td>
<td>240</td>
<td>248</td>
<td>241</td>
<td>249</td>
</tr>
<tr>
<td>Ab16 light chain</td>
<td>250</td>
<td>258</td>
<td>252</td>
<td>260</td>
<td>253</td>
<td>261</td>
<td>254</td>
<td>262</td>
</tr>
<tr>
<td>Ab16 heavy chain</td>
<td>251</td>
<td>259</td>
<td>255</td>
<td>263</td>
<td>256</td>
<td>264</td>
<td>257</td>
<td>265</td>
</tr>
<tr>
<td>Ab17 light chain</td>
<td>266</td>
<td>274</td>
<td>268</td>
<td>276</td>
<td>269</td>
<td>277</td>
<td>270</td>
<td>278</td>
</tr>
<tr>
<td>Ab17 heavy chain</td>
<td>267</td>
<td>275</td>
<td>271</td>
<td>279</td>
<td>272</td>
<td>280</td>
<td>273</td>
<td>281</td>
</tr>
<tr>
<td>Ab18 light chain</td>
<td>282</td>
<td>290</td>
<td>284</td>
<td>292</td>
<td>285</td>
<td>293</td>
<td>286</td>
<td>294</td>
</tr>
<tr>
<td>Ab18 heavy chain</td>
<td>283</td>
<td>291</td>
<td>287</td>
<td>295</td>
<td>288</td>
<td>296</td>
<td>289</td>
<td>297</td>
</tr>
<tr>
<td>Ab19 light chain</td>
<td>298</td>
<td>306</td>
<td>300</td>
<td>308</td>
<td>301</td>
<td>309</td>
<td>302</td>
<td>310</td>
</tr>
<tr>
<td>Ab19 heavy chain</td>
<td>299</td>
<td>307</td>
<td>303</td>
<td>311</td>
<td>304</td>
<td>312</td>
<td>305</td>
<td>313</td>
</tr>
<tr>
<td>Ab20 light chain</td>
<td>314</td>
<td>322</td>
<td>316</td>
<td>324</td>
<td>317</td>
<td>325</td>
<td>318</td>
<td>326</td>
</tr>
<tr>
<td>Ab20 heavy chain</td>
<td>315</td>
<td>323</td>
<td>319</td>
<td>327</td>
<td>320</td>
<td>328</td>
<td>321</td>
<td>329</td>
</tr>
<tr>
<td>Ab21 light chain</td>
<td>330</td>
<td>338</td>
<td>332</td>
<td>340</td>
<td>333</td>
<td>341</td>
<td>334</td>
<td>342</td>
</tr>
<tr>
<td>Ab21 heavy chain</td>
<td>331</td>
<td>339</td>
<td>335</td>
<td>343</td>
<td>336</td>
<td>344</td>
<td>337</td>
<td>345</td>
</tr>
<tr>
<td></td>
<td>Ab22 light chain</td>
<td>346</td>
<td>354</td>
<td>348</td>
<td>356</td>
<td>349</td>
<td>357</td>
<td>350</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab22 heavy chain</td>
<td>347</td>
<td>355</td>
<td>351</td>
<td>359</td>
<td>352</td>
<td>360</td>
<td>353</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab23 light chain</td>
<td>362</td>
<td>370</td>
<td>364</td>
<td>372</td>
<td>365</td>
<td>373</td>
<td>366</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab23 heavy chain</td>
<td>363</td>
<td>371</td>
<td>367</td>
<td>375</td>
<td>368</td>
<td>376</td>
<td>369</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab24 light chain</td>
<td>378</td>
<td>386</td>
<td>380</td>
<td>388</td>
<td>381</td>
<td>389</td>
<td>382</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab24 heavy chain</td>
<td>379</td>
<td>387</td>
<td>383</td>
<td>391</td>
<td>384</td>
<td>392</td>
<td>385</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab25 light chain</td>
<td>394</td>
<td>402</td>
<td>396</td>
<td>404</td>
<td>397</td>
<td>405</td>
<td>398</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab25 heavy chain</td>
<td>395</td>
<td>403</td>
<td>399</td>
<td>407</td>
<td>400</td>
<td>408</td>
<td>401</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab26 light chain</td>
<td>410</td>
<td>418</td>
<td>412</td>
<td>420</td>
<td>413</td>
<td>421</td>
<td>414</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab26 heavy chain</td>
<td>411</td>
<td>419</td>
<td>415</td>
<td>423</td>
<td>416</td>
<td>424</td>
<td>417</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab27 light chain</td>
<td>426</td>
<td>434</td>
<td>428</td>
<td>436</td>
<td>429</td>
<td>437</td>
<td>430</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab27 heavy chain</td>
<td>427</td>
<td>435</td>
<td>431</td>
<td>439</td>
<td>432</td>
<td>440</td>
<td>433</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab28 light chain</td>
<td>442</td>
<td>450</td>
<td>444</td>
<td>452</td>
<td>445</td>
<td>453</td>
<td>446</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab28 heavy chain</td>
<td>443</td>
<td>451</td>
<td>447</td>
<td>455</td>
<td>448</td>
<td>456</td>
<td>449</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab29 light chain</td>
<td>458</td>
<td>466</td>
<td>460</td>
<td>468</td>
<td>461</td>
<td>469</td>
<td>462</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab29 heavy chain</td>
<td>459</td>
<td>467</td>
<td>463</td>
<td>471</td>
<td>464</td>
<td>472</td>
<td>465</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab30 light chain</td>
<td>474</td>
<td>482</td>
<td>476</td>
<td>484</td>
<td>477</td>
<td>485</td>
<td>478</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab30 heavy chain</td>
<td>475</td>
<td>483</td>
<td>479</td>
<td>487</td>
<td>480</td>
<td>488</td>
<td>481</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab31 light chain</td>
<td>490</td>
<td>498</td>
<td>492</td>
<td>500</td>
<td>493</td>
<td>501</td>
<td>494</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab31 heavy chain</td>
<td>491</td>
<td>499</td>
<td>495</td>
<td>503</td>
<td>496</td>
<td>504</td>
<td>497</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab32 light chain</td>
<td>506</td>
<td>514</td>
<td>508</td>
<td>516</td>
<td>509</td>
<td>517</td>
<td>510</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab32 heavy chain</td>
<td>507</td>
<td>515</td>
<td>511</td>
<td>519</td>
<td>512</td>
<td>520</td>
<td>513</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab33 light chain</td>
<td>522</td>
<td>530</td>
<td>524</td>
<td>532</td>
<td>525</td>
<td>533</td>
<td>526</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab33 heavy chain</td>
<td>523</td>
<td>531</td>
<td>527</td>
<td>535</td>
<td>528</td>
<td>536</td>
<td>529</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab34 light chain</td>
<td>538</td>
<td>546</td>
<td>540</td>
<td>548</td>
<td>541</td>
<td>549</td>
<td>542</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab34 heavy chain</td>
<td>539</td>
<td>547</td>
<td>543</td>
<td>551</td>
<td>544</td>
<td>552</td>
<td>545</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab35 light chain</td>
<td>554</td>
<td>562</td>
<td>556</td>
<td>564</td>
<td>557</td>
<td>565</td>
<td>558</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Ab35 heavy chain</td>
<td>555</td>
<td>563</td>
<td>559</td>
<td>567</td>
<td>560</td>
<td>568</td>
<td>561</td>
</tr>
</tbody>
</table>
**Ab36 light chain** 570 578 572 580 573 581 574 582
**Ab36 heavy chain** 571 579 575 583 576 584 577 585

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

PRT.: Polypeptide sequence.

Nuc: Exemplary coding sequence.

[00399] For reference, sequence identifiers other than those included in Table 2 are summarized in Table 3.

**Table 3.** Summary of sequence identifiers in this application.

<table>
<thead>
<tr>
<th>SEQ ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Human IL-6</td>
</tr>
<tr>
<td>586</td>
<td>kappa constant light chain polypeptide sequence</td>
</tr>
<tr>
<td>587</td>
<td>kappa constant light chain polynucleotide sequence</td>
</tr>
<tr>
<td>588</td>
<td>gamma-1 constant heavy chain polypeptide sequence</td>
</tr>
<tr>
<td>589</td>
<td>gamma-1 constant heavy chain polynucleotide sequence</td>
</tr>
<tr>
<td>590 - 646</td>
<td>Human IL-6 peptides (see FIG. 12 and Example 14)</td>
</tr>
<tr>
<td>719</td>
<td>gamma-1 constant heavy chain polypeptide sequence</td>
</tr>
<tr>
<td></td>
<td>(differs from SEQ ID NO: 518 at two positions)</td>
</tr>
<tr>
<td>726</td>
<td>C-reactive protein polypeptide sequence</td>
</tr>
<tr>
<td>727</td>
<td>IL-6 receptor alpha</td>
</tr>
<tr>
<td>728</td>
<td>IL-6 receptor beta / gp130</td>
</tr>
</tbody>
</table>

[00400] Such antibody fragments or variants thereof 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:

VAAPSVFIFPPSDEQLKSGTASVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRC (SEQ ID NO: 586).
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:

ASTKGPSVFPLAPSSKSTSGTAALGCLVQKVFDYFPEPVTVSWNSGALTSSGVHHTFPAPLVQSS GLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEKPDVKSCDKTHTCPPCPAPELLEGG PSVFLFPPKPDTPDSRTPEEVTCVVVDVSHEDPEVKFNWYVDGEVEHNAKTKPREEQY ASTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQQGNVFCMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 588)

and

ASTKGPSVFPLAPSSKSTSGTAALGCLVQKVFDYFPEPVTVSWNSGALTSSGVHHTFPAPLVQSS GLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEKPDVKSCDKTHTCPPCPAPELLEGG PSVFLFPPKPDTPDSRTPEEVTCVVVDVSHEDPEVKFNWYVDGEVEHNAKTKPREEQY ASTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQQGNVFCMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 719).

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.
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; and further comprising a $V_L$ polypeptide sequence comprising: SEQ ID NO: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 or a variant thereof wherein one or more of the framework residues (FR residues) or CDR residues in said $V_H$, $V_L$ polypeptide has been substituted with another amino acid residue resulting in an anti-IL-6 antibody that specifically binds IL-6. The invention contemplates humanized and chimeric forms of these antibodies wherein preferably the FR will comprise human FRs highly homologous to the parent antibody. The chimeric antibodies may include an Fc derived from IgGl, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgGl 1, IgGl 2, IgGl 3, IgGl 4, IgGl15, IgGl 6, IgGl 7, IgGl 8 or IgGl 9 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.

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.

In another embodiment of the invention, the anti-IL-6 antibodies and fragments and variants thereof have binding specificity for primate homologs of the human IL-6 protein. Non-limiting examples of primate homologs of the human IL-6 protein are IL-6 obtained from Macaca fascicularis (also known as the cynomolgus monkey) and the Rhesus monkey. In another embodiment of the invention, the anti-IL-6 antibodies and fragments and variants thereof inhibits the association of IL-6 with IL-6R, and/or the production of IL-6/IL-6R/gpl30 complexes and/or the production of IL-6/IL-6R/gpl30 multimers and/or antagonizes the biological effects of one or more of the foregoing.
As stated above, antibodies and fragments and variants thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, 3,4-dioxygenase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent 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 (125I), Carbon 14 (14C), Sulfur 35 (35S), Tritium (3H) and Phosphorus 32 (32P).

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, thioea chlorambucil, melphalan, carmustine (BCNU), mitomycin C, lomustine (CCNU), 1-methyl nitrosourea, cyclophosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mitomycin, and anthramycin (AMC); and antimyotic 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 (0,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.
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. Nafl Acad. Sci. USA 77:5483 (1980); GiUiland, et al, Proc. Nafl Acad. Sci. USA 77:4539 (1980); Krollick, et al, Proc. Nafl Acad. Sci. USA 77:5419 (1980)).

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).

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).
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.

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.

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.

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.

[00416] 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. As noted preferred anti-IL-6 antibodies or fragments or variants thereof may contain a variable heavy and/or light sequence as shown in FIG. 34 or 35, such as SEQ ID NO: 651, 657, 709 or variants thereof wherein one or more CDR or FR residues are modified without adversely affecting antibody binding to IL-6 or other desired functional activity.

Polynucleotides Encoding Anti-IL-6 Antibody Polypeptides

[00417] 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:

ATGGACACGAGGCCCCCACCTCAGCTGCTGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCAGATGTGCTATGATATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACCACATCAAAGTGGCCAGGCCAGTCAAGCATTAACAAATGAAATTATCTCAGGTATCAGCAAAACCAGGGCGAGCTCCCAAGCTCCTGTCTCTATAGGGCATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTAGTCTGAGGAATATTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCCATCTGTAGCGACAGTTGAAT

111
CTGGAACTGCCTCTGTTGTGCTGCTGAATAACTT (SEQ ID NO: 10) or the polynucleotide sequence of SEQ ID NO: 662, 698, 701, or 705.

[00418] 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:

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTGACTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGCCAGGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATCATTTATGGTAGTGATGAAACGGCCTACGCGACCTGGGCGATAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGAGCTGAAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGCAAAATTTAACTTGTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG (SEQ ID NO: 11) or the polynucleotide sequence of SEQ ID NO: 663, 700, 703, or 707.

[00419] In a further embodiment of the invention, polynucleotides encoding fragments or variants 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 or 694; SEQ ID NO: 13; and SEQ ID NO: 14 or 695 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 2.

[00420] In a further embodiment of the invention, polynucleotides encoding fragments or variants 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 or 696; and SEQ ID NO: 17 or 697 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 3 or SEQ ID NO: 661 or SEQ ID NO: 657 or others depicted in Figs. 34 or 35.
The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments or variants described herein. In one embodiment of the invention, polynucleotides encoding fragments or variants 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 SEQ ID NO: 720 encoding the light chain polypeptide of SEQ ID NO: 20; the polynucleotide SEQ ID NO: 721 encoding the light chain polypeptide of SEQ ID NO: 647; the polynucleotide SEQ ID NO: 662 encoding the light chain polypeptide of SEQ ID NO: 660; the polynucleotide SEQ ID NO: 722 encoding the light chain polypeptide of SEQ ID NO: 666; the polynucleotide SEQ ID NO: 698 encoding the light chain polypeptide of SEQ ID NO: 699; the polynucleotide SEQ ID NO: 701 encoding the light chain polypeptide of SEQ ID NO: 702; the polynucleotide SEQ ID NO: 705 encoding the light chain polypeptide of SEQ ID NO: 706; the polynucleotide SEQ ID NO: 723 encoding the light chain polypeptide of SEQ ID NO: 709; the polynucleotide SEQ ID NO: 724 encoding the heavy chain polypeptide of SEQ ID NO: 19; the polynucleotide SEQ ID NO: 725 encoding the heavy chain polypeptide of SEQ ID NO: 652; the polynucleotide SEQ ID NO: 700 encoding the heavy chain polypeptide of SEQ ID NO: 657; the polynucleotide SEQ ID NO: 663 encoding the heavy chain polypeptide of SEQ ID NO: 661; the polynucleotide SEQ ID NO: 703 encoding the heavy chain polypeptide of SEQ ID NO: 704; the polynucleotide SEQ ID NO: 707 encoding the heavy chain polypeptide of SEQ ID NO: 708; the polynucleotides of SEQ ID NO: 12, 13, 14, 694 and 695 encoding the complementarity-determining regions of the aforementioned light chain polypeptides; and the polynucleotides of SEQ ID NO: 15, 16, 17, 696 and 697 encoding the complementarity-determining regions of the aforementioned heavy chain polypeptides, and polynucleotides encoding the variable heavy and light chain sequences in SEQ ID NO: 657 and SEQ ID NO: 709 respectively, e.g., the nucleic acid sequences in SEQ ID NO: 700 and SEQ ID NO: 723 and fragments or variants thereof, e.g., based on codon degeneracy. These nucleic acid sequences encoding variable heavy and light chain sequences may be expressed alone or in combination and these sequences preferably are fused to suitable variable constant sequences, e.g., those in SEQ ID NO: 589 and SEQ ID NO: 587.
Exemplary nucleotide sequences encoding anti-IL-6 antibodies of the present invention are identified in Table 1, above. The polynucleotide sequences shown are to be understood to be illustrative, rather than limiting. One of skill in the art can readily determine the polynucleotide sequences that would encode a given polypeptide and can readily generate coding sequences suitable for expression in a given expression system, such as by adapting the polynucleotide sequences provided and/or by generating them de novo, and can readily produce codon-optimized expression sequences, for example as described in published U.S. Patent Application no. 2008/0120732 or using other methods known in the art.

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:

```
GTGGCTGCACCACATCTGCTCTCCTTCCCCGCCCACATCTGTAGAGCGAGTTGAAATCTGGACTGCCTCTGTTGTGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCA
```

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:

```
GCCTCCACCAAGGGCCCATCGTCTTTCCCCCTCGCACCCTCTCTCCAAGAGCACCCTCTGTAGAGCGAGTTGAAATCTGGACTGCCTCTGTTGTGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCA
```

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:
CAAGACAAAGCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCC
TCACCGCTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCC
AACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACC
AGGTCAGCCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCGCTCCCGTGCTGGAC
TCCGACGGCTTCTTCTCTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG
CAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACG
CAGAAGAGCCTCTCCTCCGTCTCCGGGTAAA (SEQ ID NO: 589).

[00425] 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, 652, 656, 657, 658, 661, 664, 665, 704, and 708 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_H polypeptide or a conservative amino acid substitution. In addition, the invention specifically encompasses humanized anti-IL-6 antibodies or humanized antibody binding fragments or variants thereof and nucleic acid sequences encoding the foregoing comprising the humanized variable heavy chain and/or light chain polypeptides depicted in the sequences contained in FIG. 2 or 34-37, or those identified in Table 1, or variants thereof wherein one or more framework or CDR residues may be modified. Preferably, if any modifications are introduced they will not affect adversely the binding affinity of the resulting anti-IL-6 antibody or fragment or variant thereof.

[00426] 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 selected from SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, and 709 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_L polypeptide or a conservative amino acid substitution.

[00427] 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: 2 and SEQ ID NO: 18; SEQ ID NO: 2 and SEQ ID NO: 19; SEQ ID NO: 20 and SEQ ID NO: 3; SEQ ID NO: 20 and SEQ ID NO: 18; or SEQ ID NO: 20 and SEQ ID NO: 19.

[00428] 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 V₉ or V₉ polypeptides contained in SEQ ID NO: 3, 18, 19, 652, 656, 657, 658, 661, 664, 665, 704, 708, 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709.

[00429] Host cells and vectors comprising said polynucleotides are also contemplated.

[00430] 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.

[00431] 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*.

[00432] In some instances, more than one exemplary polynucleotide encoding a given polypeptide sequence is provided, as summarized in Table 4.

**Table 4.** Multiple exemplary polynucleotides encoding particular polypeptides.

<table>
<thead>
<tr>
<th>Polypeptide SEQ ID NO</th>
<th>Exemplary coding SEQ ID NOs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12, 111, 694</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
</tr>
<tr>
<td>5</td>
<td>13, 112, 389, 501</td>
</tr>
<tr>
<td>6</td>
<td>14, 113, 695</td>
</tr>
<tr>
<td>9</td>
<td>17, 116, 697</td>
</tr>
<tr>
<td>39</td>
<td>47, 260</td>
</tr>
<tr>
<td>40</td>
<td>48, 261</td>
</tr>
<tr>
<td>60</td>
<td>68, 265</td>
</tr>
<tr>
<td>72</td>
<td>80, 325, 565, 581</td>
</tr>
<tr>
<td>89</td>
<td>97, 134, 166</td>
</tr>
<tr>
<td>103</td>
<td>12, 111, 694</td>
</tr>
<tr>
<td>104</td>
<td>13, 112, 389, 501</td>
</tr>
<tr>
<td>105</td>
<td>14, 113, 695</td>
</tr>
<tr>
<td>108</td>
<td>17, 116, 697</td>
</tr>
<tr>
<td>126</td>
<td>97, 134, 166</td>
</tr>
<tr>
<td>158</td>
<td>97, 134, 166</td>
</tr>
<tr>
<td>190</td>
<td>198, 214</td>
</tr>
<tr>
<td>191</td>
<td>199, 215</td>
</tr>
<tr>
<td>205</td>
<td>213, 469, 485</td>
</tr>
<tr>
<td>206</td>
<td>198, 214</td>
</tr>
<tr>
<td>207</td>
<td>199, 215</td>
</tr>
<tr>
<td>252</td>
<td>47, 260</td>
</tr>
<tr>
<td>253</td>
<td>48, 261</td>
</tr>
<tr>
<td>257</td>
<td>68, 265</td>
</tr>
<tr>
<td>317</td>
<td>80, 325, 565, 581</td>
</tr>
<tr>
<td>333</td>
<td>341, 533</td>
</tr>
<tr>
<td>381</td>
<td>13, 112, 389, 501</td>
</tr>
<tr>
<td>415</td>
<td>423, 439</td>
</tr>
<tr>
<td>431</td>
<td>423, 439</td>
</tr>
<tr>
<td>461</td>
<td>213, 469, 485</td>
</tr>
<tr>
<td>475</td>
<td>483, 499</td>
</tr>
<tr>
<td>476</td>
<td>484, 500</td>
</tr>
<tr>
<td>477</td>
<td>213, 469, 485</td>
</tr>
<tr>
<td>478</td>
<td>486, 502</td>
</tr>
<tr>
<td>479</td>
<td>487, 503</td>
</tr>
<tr>
<td>480</td>
<td>488, 504</td>
</tr>
<tr>
<td>481</td>
<td>489, 505</td>
</tr>
<tr>
<td>491</td>
<td>483, 499</td>
</tr>
<tr>
<td>492</td>
<td>484, 500</td>
</tr>
<tr>
<td>493</td>
<td>13, 112, 389, 501</td>
</tr>
<tr>
<td>494</td>
<td>486, 502</td>
</tr>
<tr>
<td>495</td>
<td>487, 503</td>
</tr>
<tr>
<td>496</td>
<td>488, 504</td>
</tr>
<tr>
<td>497</td>
<td>489, 505</td>
</tr>
<tr>
<td>525</td>
<td>341, 533</td>
</tr>
</tbody>
</table>
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.

Table 5. Repeated sequences. Each cell lists a group of repeated sequences included in the sequence listing.

<table>
<thead>
<tr>
<th>SEQ ID NOs of repeated sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>4, 103</td>
</tr>
<tr>
<td>5, 104, 381, 493</td>
</tr>
<tr>
<td>6, 105</td>
</tr>
<tr>
<td>9, 108</td>
</tr>
<tr>
<td>12, 111</td>
</tr>
<tr>
<td>13, 112</td>
</tr>
<tr>
<td>14, 113</td>
</tr>
<tr>
<td>17, 116</td>
</tr>
<tr>
<td>39, 252</td>
</tr>
<tr>
<td>40, 253</td>
</tr>
<tr>
<td>48, 261</td>
</tr>
<tr>
<td>60, 257</td>
</tr>
<tr>
<td>68, 265</td>
</tr>
<tr>
<td>72, 317, 557, 573</td>
</tr>
<tr>
<td>80, 325, 565, 581</td>
</tr>
<tr>
<td>89, 126, 158</td>
</tr>
<tr>
<td>97, 134, 166</td>
</tr>
<tr>
<td>120, 659</td>
</tr>
<tr>
<td>190, 206</td>
</tr>
<tr>
<td>191, 207</td>
</tr>
<tr>
<td>198, 214</td>
</tr>
</tbody>
</table>
[00434] 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.

[00435] 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, 5xSSC, and 1% SDS, incubating at 42 °C, or, 5xSSC, 1% SDS, incubating at 65 °C, with wash in 0.2xSSC, and 0.1% SDS at 65 °C. Such hybridizations and wash steps can be carried out for, e.g., 1, 2, 5, 10, 15, 30, 60; or more minutes.

[00436] 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 1xSSC 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.

Additional Exemplary Embodiments of the Invention

[00437] In another embodiment, the invention contemplates one or more anti-IL-6 antibodies or antibody fragments or variants thereof which may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational
epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-IL-6 antibody comprising Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-identified antibodies) that specifically bind IL-6, which preferably are aglycosylated. In a preferred embodiment, the anti-IL-6 antibody or fragment or variant thereof may specifically bind to the same linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated.

[00438] In another embodiment of the invention, the anti-IL-6 antibody which may specifically bind to the same linear or conformational epitopes on an intact IL-6 polypeptide or fragment thereof that is (are) specifically bound by Abl may bind to an IL-6 epitope(s) ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide. 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.

[00439] 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 Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated.

[00440] In another embodiment, the invention is also directed to an isolated anti-IL-6 antibody or antibody fragment or variant thereof 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\textsubscript{L} polypeptide sequence consisting of: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 647, 651, 660, 666, 667, 671, 675, 679, 683, 687, 693, 699, 702, 706, or 709 and the VH and VL sequences depicted in the antibody alignments comprised in Figures 34-37 of this application.

[00441] 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 Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated.

[00442] 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 Abl. 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 Abl and chimeric, humanized, single chain antibodies and fragments thereof (containing one or more CDRs of the afore-mentioned antibody) that specifically bind IL-6, which preferably are aglycosylated. In a preferred embodiment of the invention, all of the CDRs of the anti-IL-6 antibody discussed above are identical to the CDRs contained in Abl, e.g., an antibody comprised of the VH and VL sequences comprised in SEQ ID NO: 657 and SEQ ID NO: 709 respectively.

[00443] 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 encoded by the nucleic acid sequences in SEQ ID NO: 589 and SEQ ID NO: 587.
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.

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

In another embodiment, the disease is selected from general fatigue, exercise-induced fatigue, cancer-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.

[00447] The invention further contemplates anti-IL-6 antibodies or fragments or variants thereof directly or indirectly attached to a detectable label or therapeutic agent.

[00448] The invention also contemplates one or more nucleic acid sequences which result in the expression of an anti-IL-6 antibody or antibody fragment or variant thereof as set forth above, including those comprising, or alternatively consisting of, yeast or human preferred codons. 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.

[00449] 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 or variant thereof. 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.

[00450] 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.

**Anti-IL-6 Activity**

[00451] 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 gpl30 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 gpl30.

[00452] It is believed that the anti-IL-6 antibodies of the invention, or IL-6 binding fragments or variants thereof, are useful by exhibiting anti-IL-6 activity. In one non-limiting embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments or variants thereof, exhibit anti-IL-6 activity by binding to IL-6 which may be soluble IL-6 or cell surface expressed IL-6 and/or may prevent or inhibit the binding of IL-6 to IL-6R and/or activation (dimerization) of the gpl30 signal-transducing glycoprotein and the formation of IL-6/IL-6R/gpl30 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/gpl30 or IL-6/IL-6R/gpl30 multimers is a desired therapeutic outcome. This can be determined in binding and other assays.

[00453] The anti-IL-6 activity of the anti-IL-6 antibody of the present invention, and fragments and variants thereof having binding specificity to IL-6, may also be described by their strength of
binding or their affinity for IL-6. This also may affect their therapeutic properties. In one embodiment of the invention, the anti-IL-6 antibodies 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 and variants thereof bind IL-6 with a dissociation constant of less than or equal to 5x10^-10.

[00454] In another embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments and variants thereof having binding specificity to IL-6, bind to IL-6 with an off-rate of less than or equal to 10^-2 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 and variants thereof having binding specificity to IL-6, bind to a linear or conformational IL-6 epitope.

[00455] In a further embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments and variants thereof having binding specificity to IL-6, exhibit anti-IL-6 activity by ameliorating or reducing the symptoms of, or alternatively treating, or preventing, diseases and disorders associated with IL-6. Non-limiting examples of diseases and disorders associated with IL-6 are set forth infra. As noted cancer-related fatigue, cachexia and rheumatoid arthritis are preferred indications for the subject anti-IL-6 antibodies.

[00456] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments and variants thereof, do not have binding specificity for IL-6R or the gp-130 signal-transducing glycoprotein.

B-cell Screening and Isolation

[00457] 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.

[00458] In one embodiment, the present invention provides a method comprising the steps of:

a. preparing a cell population comprising at least one antigen-specific B cell;

b. enriching the cell population, e.g., by chromatography, to form an enriched cell population comprising at least one antigen-specific B cell;

c. isolating a single B cell from the enriched B cell population; and

d. determining whether the single B cell produces an antibody specific to the antigen.

[00459] 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.

[00460] 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.

[00461] 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.

[00462] 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:

a. harvesting a cell population from an immunized host to obtain a harvested cell population;

b. creating at least one single cell suspension from the harvested cell population;

c. enriching at least one single cell suspension to form a first enriched cell population;

d. enriching the first enriched cell population to form a second enriched cell population;

e. enriching the second enriched cell population to form a third enriched cell population; and

f. selecting an antibody produced by an antigen-specific cell of the third enriched cell population.

[00463] 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.

[00464] 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%.

[00465] 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.
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.

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-alpha, IFN-gamma, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF) and Hepcidin. Preferred antigens include IL-6, IL-13, TNF-alpha, VEGF-alpha, 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.

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.

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.

[00470] 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.

[00471] 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.

[00472] 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.

[00473] 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.

[00474] 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.

[00475] 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).

[00476] 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.

[00477] 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 1x10⁻¹⁵ 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™ (bevacizumab), 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.

[00478] 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).

[00479] 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.

[00480] 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:

[00481] First, it has been found that when these selection procedures are utilized with a desired antigen such as IL-6 or TNF-alpha, 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.

[00482] 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.

[00483] 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.

[00484] 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.

[00485] 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.

[00486] 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.
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:

a. immunizing a host against an antigen;

b. harvesting B cells from the host;

c. enriching the harvested B cells to increase the frequency of antigen-specific cells;

d. creating at least one single cell suspension;

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;

f. isolating B cells from the sub-population; and

g. determining whether the single B cell produces an antibody specific to the antigen.

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.

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.

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.

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.
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.

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%.

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 subpopulation 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.

[00495] 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.

[00496] 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.

[00497] The identified antigen-specific cell can be used to derive the corresponding nucleic acid sequences encoding the desired monoclonal antibody. (An Alul 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.

[00498] 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.

[00499] Thus, in one embodiment, the present invention provides a method comprising:

a. harvesting a cell population from an immunized host to obtain a harvested cell population;

b. creating at least one single cell suspension from a harvested cell population;

c. enriching at least one single cell suspension, preferably by chromatography, to form a first enriched cell population;

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;

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

f. selecting an antibody produced by an antigen-specific cell isolated from the third enriched cell population.
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.

Similarly, the method can include one or more steps of screening the second enriched cell population for antibody binding strength and/or antibody functionality.

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, chimerization, 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.

In one embodiment, the method comprises:

a. immunizing a host against an antigen to yield host antibodies;

b. screening the host antibodies for antigen specificity and neutralization;

c. harvesting B cells from the host;
d. enriching the harvested B cells to create an enriched cell population having an increased frequency of antigen-specific cells;

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;

f. determining whether the clonal population produces an antibody specific to the antigen;

g. isolating a single B cell; and

h. sequencing the nucleic acid sequence of the antibody produced by the single B cell.

**Methods of Humanizing Antibodies**

[00504] 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:

**Light Chain**

[00505] 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.

[00506] Example: RbtVL Amino acid residue 1 in Fig. 2, starting 'AYDM. ..'

[00507] 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.

[00508] Example: RbtVL amino acid residue 88 in Fig. 2, ending as 'TYYC
3. Use the rabbit light chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be a search against human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be found from various sources such as NCBI (National Center for Biotechnology Information).

Example: RbtVL amino acid sequence from residues numbered 1 through 88 in Fig. 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.

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

Example: In Fig. 2, L12A was the most homologous human germline variable light chain sequence and is used as the basis for the humanization of RbtVL.

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

Example: In Fig. 2, the RbtVL sequence is aligned with the human homologous sequence L12A, and the framework and CDR domains are indicated.

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

[00516] 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.

[00517] 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.

[00518] 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.

[00519] 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.
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.

In addition, Figs. 34 and 35 depict preferred humanized anti-IL-6 variable heavy and variable light chain sequences humanized from the variable heavy and light regions in Abl according to the invention. These humanized light and heavy chain regions are respectively contained in the polypeptides contained in SEQ ID NO: 647, or 651 and in SEQ ID NO: 652, 656, 657 or 658. The CDR2 of the humanized variable heavy region in SEQ ID NO: 657 (containing a serine substitution in CDR2) is contained in SEQ ID NO: 658. Alignments illustrating variants of the light and heavy chains are shown in Figs. 36 and 37, respectively, with sequence differences within the CDR regions highlighted. Sequence identifiers of CDR sequences and of exemplary coding sequences are summarized in Table 1, above.

**Heavy Chain**

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

Example: RbtVH Amino acid residue 1 in Fig. 2, starting 'QEQL…'

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

Example: RbtVH amino acid residue 98 in Fig. 2, ending as '…FCVR'.

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

Example: RbtVH amino acid sequence from residues numbered 1 through 98 in Fig. 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.

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

Example: 3-64-04 in Fig. 2 was the most homologous human germline variable heavy chain sequence and is used as the basis for the humanization of RbtVH.

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

Example: In Fig. 2, the RbtVH sequence is aligned with the human homologous sequence 3-64-04, and the framework and CDR domains are indicated.

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

[00533] 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.

[00534] 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.

[00535] Example: The CDR3 of RbtVH (amino acid residues numbered 99-1 10) is added after the end of framework 3 in the humanized sequence indicated as VHh.

[00536] 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.

[00537] 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**

[00538] 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).

[00539] 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.

[00540] 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.

[00541] 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.

[00542] 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.

[00543] 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).

[00544] 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, adel, 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.
[00545] 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.

[00546] 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.

[00547] 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.

[00548] 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.

[00549] 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.

[00550] 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.
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.

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.

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.

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.

[00555] 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.

[00556] 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).


[00558] 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.
[00559] 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.

[00560] 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.

[0100] 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.

[00561] 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.

[00562] 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.
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.

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.

Exemplary Embodiments of Heavy and Light Chain Polypeptides and Polynucleotides

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.

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 Abl (e.g. cachexia, cancer fatigue, arthritis, etc.) comprising administration of a composition comprising such a polynucleotide and/or polypeptide.
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.

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.

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 Abl light chain polypeptides is recited, e.g. any of SEQ ID NO: 2, 20, 647, 651, 660, 666, 699, 702, 706, or 709, another Abl light chain polypeptide may be substituted unless the context indicates otherwise. Similarly, wherever one of the Abl 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 Abl heavy chain polypeptide may be substituted unless the context indicates otherwise. Likewise, wherever one of the Abl light chain polynucleotides is recited, e.g. any of SEQ ID NO: 10, 662, 698, 701, or 705, another Abl light chain polynucleotide may be substituted unless the context indicates otherwise. Similarly, wherever one of the Abl heavy chain polynucleotides is recited, e.g. any of SEQ ID NO: 11, 663, 700, 703, or 707, another Abl
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); Abl Light Chain CDR1 polynucleotides (SEQ ID NO: 12 and 694); Abl Light Chain CDR3 polynucleotides (SEQ ID NO: 14 and 695); Abl Heavy Chain CDR2 polynucleotides (SEQ ID NO: 16 and 696) and Abl Heavy Chain CDR3 polynucleotides (SEQ ID NO: 17 and 697).

[00570] Exemplary Abl -encoding polynucleotide sequences are recited as follows:

[00571] SEQ ID NO: 662:

ATGGACACGAGGCCCCACTCAGCTGCTGGGCTCTGCTGTGGCTCCCAGGT
GCCAGATGTGCTATGATATGACCCAGACTCCAGGTGCTGCTGAACGCTGGGGA
GGCCAGTCCACCATCAAGTGCCAGCCAGTCAGACGCTATTACGATGAGATATTATCTTG
GTATCGCAGAAACCAGGGCAGCGTCCCAAGCTCCTGATCTATAGGGCAGCAGTT
GGCATCTGGGGTCTCATCGGTTCAAAAGGCAGTGGATCTGGGACAGAGTTCACTCT
CACCACGACGACCTGGAGGTGTGCCGATGCTGCCACTTACTCTGCAACAGGGTTA
TAGTCTGAGGAATATTGATAATGCT

[00572] SEQ ID NO: 663:
ATGGAGACTGGGCTGCGCTGGCTTCTCCTTGGTGCTCTGTCAAAAGGTGTCAGTGT
CAGTCGCTGGAGAGGTCCGGGGGTGGCCTGTCACGCTGGGACACCCCTGACACT
CACCTGCACAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGCA
GGCTCCAGGGAAGGGGCTGGAATGGATCGGGAATTTGATGTGAGAAGCG
CCTACGCGACCTGGGCGATAAGCGGAATTTGATGTGAGAAGCG
GATCTGAAAATGACCTGCTGACAGCCCGGAGACACCGGACCTTCTCTTCTGTGAGCCAG
AGATGATAGTGTAGCTGGGATGGAGATGTG

[00573] SEQ ID NO: 698:
GCTATCCAGATGACCCAGTCTCCTTCCCTCCTCCTGCTGTAGTACCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAG
AAACCAGGGAAAGCCCTTGAAGCTCCTGTATTATAGGGGCTCCACCCCTTGCGCTGAG
GGTCCCATCAAGGTGCAGGGCACTGGGACAGACTTCACTCTCACCATCAG
CAGCCTGCAGCTGATATTGGCAACTTATTACTGCAAACAGGGTTATAGTCTGAG
GAACATTTGATAATGCTTCTGGGAGGAGCATGGGAATACAAACGTAGC

[00574] SEQ ID NO: 700:
GAGGTGCAGCTGGAGTGGTTCCTGGGAGGCTTGGGTCCAGGCTGGGAGGTCCCTGAG
ACTCTCCTGTGCAAGCTCTTGATTTCTCCTCAGTAAACTACTACGTGCCTGGGCTCCTGAG
CAGGCTCCAGGGAAGGGGCTGAGGCTGGGCTCCGCACTGATCATCTATAGTGATGAAAC
CGCCTACGCTACCTCCCAGGATGAGGTTGACCATCTCCAGAGGACATTTCCAAGAA
CACCCGCTATCTCTCAATGAAAGGGCTGAGGAGCTGGAGCAACTTCTGTGTGATTTGAT
TGCTAGAGATGATAGTGTAGTCCTGCAGGGATTACACCTTCTTCTGAGGGCCAAGGGA
CCCTGCTACCCCTTGCAGC

[00575] SEQ ID NO: 701:
GCTATCCAGATGACCCAGTCTCCTTCTTCCCTGCTGTAGTACCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAG
AAACCAGGGAAAGCCCTTGAAGCTCCTGTATTATAGGGGCTCCACCCCTTGCGCTGAG
AGATGATAGTGTAGCTGGGATGGAGATGTG
GGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTTCGGCGGAGGGACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAAGAGAGCCAAAGTACAGTGGGACGGAACAGCAGACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

[00576] SEQ ID NO: 703:
GAGGTGCAAGTGTTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGTACGAGGTCCAGGGAAGGGGCTGGAGTGGGTCGGCATCATCTATGGTAGTGATGAAACCGCCTACGCTACCTCCGCTATAGGCCGATTCACCATCTCCAGAGACAATTCCAAGAAACCCTGTAATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTACTGTGCTAGAGATGATAGTAGTGACTGGGATGCAAAGTTCAACTTGTGGGGCCAAGGGACCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCTGCAACCCTTGCAGTTCCCTGGGGGACCGTCAGTCTTCCTCTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC

GGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAACATTGATAATGCTTTCGGCGGAGGGACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAAGAGAGCCAAAGTACAGTGGGACGGAACAGCAGACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
AGACCACGCCTCCCGTCTGGGACTCCGACGGCTCCTTCTTCTTCTACAGCTCATGAGCTCA
CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
TGAGCTTCTGCACAACCACACTACAGCAGAAGAGCTCCTCCCTGTCTCCGGGTAAA

[00577] SEQ ID NO: 705:
ATGAAGTGGGTAACCTTTATTTCCCTTCTGTTTCTTTTACAGCAGCGCTTATTCGGCTA
TCCAGATGACCCACTCTCTCTCTCTCTCTCTCTGCTCTGTCTGACTCTGAAGGAGACAGAGTCACCA
TC.ACTTGCCAGGCGAGTCAGACATTAACAATGAGTTATCTGTGTATTCAGCAGAAAC
CAGGGAAAGGCCCTAAGCTCTGTCTGCTATAGGGGACATCCACTCTGGCATCTGGGGTC
CATCAAGGTTCAGCGGAGTTGCTTCTGGGACAGACTTCCACTCTCACACTACAGCAGCC
TGAGCCTGTAGTATTTGICAACAATTATATTGTCTGGAACAGGGTTATAGGCTCTGGAACAGGAAACA
TTGATAATGCTTTCCGCGAGGGAACCAAGGTGGAAATAACGTCAGGCTCGTGAACA
CCATCTGTCTCTACGCTCTCCGGCATCTGATGAGCAGTTGAACTGGAACTGCCTCTGTTGTGC
CCTGCTGAATAACTTCTATCCCGAGAGGGCACAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGATACTCCCGAGAGTGCTACAGAGCAGAGCAAGGACAGCC
GACAGCAGCTACTACAGCCCTACAGCCACCTCTCCGAGCTCAGGAAATACGTCAGGCTCG
ACAGAGCTTCAACAGGGGAGAGTGT

[00578] SEQ ID NO: 707:
ATGAAGTGGGTAACCTTTATTTCCCTTCTGTTTCTTTTACAGCAGCGCTTATTCGGCTA
TGAGCCTGTAGTATTTGICAACAATTATATTGTCTGGAACAGGGTTATAGGCTCTGGAACAGGAAACA
TTGATAATGCTTTCCGCGAGGGAACCAAGGTGGAAATAACGTCAGGCTCGTGAACA
CCATCTGTCTCTACGCTCTCCGGCATCTGATGAGCAGTTGAACTGGAACTGCCTCTGTTGTGC
CCTGCTGAATAACTTCTATCCCGAGAGGGCACAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGATACTCCCGAGAGTGCTACAGAGCAGAGCAAGGACAGCC
GACAGCAGCTACTACAGCCCTACAGCCACCTCTCCGAGCTCAGGAAATACGTCAGGCTCG
ACAGAGCTTCAACAGGGGAGAGTGT
AGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACAC
ATGCCCACCGTGCCACGACCACTCTAGCTGAGGAGACAGTCAGTCTCCCTCTTTCC
CCCAAACCAAGAGACACCCTATGCTTCCCGGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGACGCAAGACAGCCCTTGGTCAAGTTGTCGTCGTCGTCGTCGTCG
TGAGGAGTGGCAGCAGGGGAACGTCTTCTGTCCGGGTAAA

[00579] SEQ ID NO: 720:
ATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGGACAGTCAC
CCAGGGAAAGGCCCCCTAAGCTCCTGTGATCTATAGGGCATCCACTCTGGCATCTGGG
CCATCAAGTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGGACAGTCAC
CCATCAAGTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGGACAGTCAC
CAGCGTGGTCTCACTGCCGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCAC
CATGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTGAG
GAATATTGATAATGCT

[00580] SEQ ID NO: 721:
GCCTATGATATGACCCAGACTCCAGCCTCGGTGTCTCGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGGATCAGTCAC
CCAGGGAAAGGCCCCCTAAGCTCCTGTGATCTATAGGGCATCCACTCTGGCATCTGGG
CCATCAAGTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGGACAGTCAC
CCATCAAGTGCCAGGCCAGTCAGAGCATTAACAATGAGTTATCCTGGGACAGTCAC
CAGCGTGGTCTCACTGCCGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCAC
CATGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTGAG
GAATATTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGT

[00581] SEQ ID NO: 722:
ATCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCAGGCAGTCAGACATTAAACATGAGTTATCCTGTATATCAGCAGAAA
CCAGGGAAAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTC
CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGC
CTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAGGAAC
ATTGATAATGCTTTCGGCGGAGGGACACGGAATCTAAACGTACGGTGGCTGC
ACCATCTGTCTTCTTCTCCCAGCATCTGATGACGAGCTGAAATCTGGAAGCTGCCTCT
GTTGTGTGCTGCTGAAATATCTCTATCCAGAGAGGCAAGATACAGTGAAGGTG
GATAACGCCTCCAAATCGGTAACCTCCAGAGAGGTGCTACAGACAGGAGAA
GGAGACAGCACCTAAGCAGCAGCAGGACCTCGAAGCAGACTACGAGAGAGACAGACGAA
AACACAAAGTCTAAGCCTGCAAGTCATCCCACCTGCAGGCTGCCCGTCAACA
AAGAGCTTCAACAGGGAGAGTG

[00582] SEQ ID NO: 723:
GCTATCCAGATGACCCAGTCTCCTTCCTCCCTGCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCAGGCAGTCAGAGCATTAACAATGAGTTATCCTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGG
GGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAG
CAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTCTGAG
GAACATGGATAATGCTTTCGGCGGAGGGACCAAGGTGGAAATCAAACGTACGGTGGCTGC
ACCATCTGTCTTCTTCTCCCAGCATCTGATGACGAGCTGAAATCTGGAAGCTGCCTCT
GTTGTGTGCTGCTGAAATATCTCTATCCAGAGAGGCAAGATACAGTGAAGGTG
GATAACGCCTCCAAATCGGTAACCTCCAGAGAGGTGCTACAGACAGGAGAA
GGAGACAGCACCTAAGCAGCAGCAGGACCTCGAAGCAGACTACGAGAGAGACAGACGAA
AACACAAAGTCTAAGCCTGCAAGTCATCCCACCTGCAGGCTGCCCGTCAACA
AAGAGCTTCAACAGGGAGAGTG

[00583] SEQ ID NO: 724:
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAG
ACTCTCTGTGCGACGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGT
CAGGCTCCAGGAAGGGCTGAGTGGGTCCGGCATCATCTATGTTAGTGATGAAAC
CGCCTACGCTACCTCCGCTATAGGGCCAGATTCCACACGAGAAGATATTCCAAGAA
CACCCGTATCTTCAATGAACAGCCTGAGAGCTGAGGACACTGCTGATTTACTG
TGCTAGAGATGATGATGACTGGGTCAAGATGTTCAACTTG

[00584] SEQ ID NO: 725:
CAGTCGCTGGAGAGGGGCTCCTCCTGCTGACGCCTCTGGGACACCCCTGCACACT
CACCCGAGAGCCCTCTGGAATTCCCTCAGTAACTACGAGCTGCTGAAAACGG
AGGCTCCAGGAAGGGCTGAGATCCAGGAAATCATTTATGTTATGTGATGAAACGG

162
Screening Assays

[00585] 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.

[00586] In one embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments or variants thereof, are used to detect the presence of IL-6 in a biological sample obtained from a patient exhibiting symptoms of a disease or disorder associated with IL-6. The presence of IL-6, or elevated levels thereof when compared to pre-disease levels of IL-6 in a comparable biological sample, may be beneficial in diagnosing a disease or disorder associated with IL-6.

[00587] 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 or variant thereof. The anti-IL-6 antibody or binding fragment or variant thereof may be post-translationally modified to include a detectable moiety such as set forth previously in the disclosure.

[00588] The IL-6 level in the biological sample is determined using a modified anti-IL-6 antibody or binding fragment or variant thereof as set forth herein, and comparing the level of IL-6 in the biological sample against a standard level of IL-6 (e.g., the level in normal biological samples). The skilled clinician would understand that some variability may exist between normal biological samples, and would take that into consideration when evaluating results.
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.

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 or variant thereof.

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

In an embodiment of the invention, IL-6 antagonists such as Abl 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 (e.g., Abl) 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.

In one embodiment of the invention, IL-6 antagonists described herein (e.g., Abl) 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 erythematosus, 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.

[00594] In one embodiment of the invention, IL-6 antagonists described herein, such as anti-IL-6 antibodies (e.g., Abl), variants thereof, or fragments thereof, 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.

[00595] In another embodiment of the invention, IL-6 antagonists described herein are administered to a patient in combination with another active agent. For example, an IL-6 antagonist such as Abl 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.


[00597] In a preferred embodiment of the invention, anti-IL-6 antibodies described herein, or fragments or variants 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

[00598] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments or variants 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 or variants thereof, are useful for ameliorating or

[00599] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments or variants 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 or variants 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

[00600] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments or variants 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, Blastaoma, 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,

[00601] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments or variants 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;112(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


[00603] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments or variants thereof, are useful as a wakefulness aid.
Administration

[00604] In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, 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 or variants thereof, as well as combinations of said antibody fragments or variants, 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 or variants thereof, as well as combinations of said antibody fragments or variants, 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 or variants 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.

[00605] 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.,

[00606] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, are administered to a subject in a pharmaceutical formulation.

[00607] 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.

[00608] In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments or variants thereof, as well as combinations of said antibody fragments or variants, may be optionally administered in combination with 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-alpha, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-alpha, IFN-gamma, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, including antibodies reactive against any of the foregoing, and antibodies reactive against any of their receptors. Active agents also include 2-Arylpropionic acids, Aceclofenac, Acemetacin, Acetylsalicylic acid (Aspirin), Alclofenac, Alminoprofen, Amoxiprin, Ampyrone, Arylalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxaprofen, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofezone, COX-2 inhibitors, Dexibuprofen, Dextropropfen, Diclofenac, Diflunisal, Droxidone, Ethenzamide, Etodolac, Etoricoxib, Faislamine, fenamic acids, Fenbufen,
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, nelfmavir, nevirapine, nexitavir, nucleoside analogues, oseltamivir, penciclovir, peramivir, pleconaril, podophyllotoxin, protease inhibitor, reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, saquinavir, stavudine, tenofovir, tenofor 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.

[00609] 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 or variants thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[00610] 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. Pharmacologically 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.
In one embodiment of the invention that may be used to intravenously administer antibodies of the invention, including Abl, 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.

In another embodiment of the invention that may be used to intravenously administer antibodies of the invention, including Abl, 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.

In another embodiment the present invention also relates to the use of the subject anti-IL-6 antibodies and antibody fragments for treatment of specific cancers in combination with chemotherapeutics, preferably EGFR inhibitors, and/or radiation and preferably wherein this combination is administered using a dosage regimen whereby the anti-IL-6 antibody or anti-IL-6 antibody fragment renders the cancer cells more sensitive to the action of the radiation or chemotherapeutic. These methods in a preferred embodiment will comprise the treatment of cancer using an EGFR inhibitor and an anti-IL-6 antibody according to the invention such as humanized Abl or ALD518. Non-limiting examples of cancers which may be treated using this combination include advanced and non-advanced, including metastatic lung cancers, breast cancer, head and neck cancer, (HNSCC), pancreatic cancer, colorectal cancer, anal cancer, glioblastoma multiforme, epithelial cancers, renal cell carcinomas, chronic myelogenous leukemia and other leukemias.

Examples of EGFR inhibitors that may be administered in therapeutic regimens with anti-IL-6 antibodies or antibody fragments according to the invention include by way of example Cetuximab (Erbitux) available from ImClone, Erlotinib (Tarceva) available from OSI Pharmaceuticals, Lapatinib (Tykerb) available from Glaxo, Panitumumab (Vectibix) available from Amgen, Sunitinib or Sutent (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-lH-indol-3-ylidene)methyl]-2,4-dimethyl-lH-pyrrole-3-carboxamide) marketed by Pfizer, Gefitinib (Iressa) or N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-y propoxy)quinazolin-4-amine marketed by AstraZeneca, Zalutumumab in clinical development by GenMab, and others.
The amount of antibody administered in combination with the chemotherapeutic may range from about 5-1000 mg, more typically from about 25-500 mg, e.g., 50, 80, 100, 150, 160, 200, 240, 250, 300, 320, 350, 400, 480 mg dosage regimens. The antibody may be administered by different means, e.g., intravenously or subcutaneously and may be administered together (in same or different dosage compositions) or separate from the chemotherapeutic such as an EGFR inhibitor.

In a preferred embodiment the treated cancer will be a lung cancer such as a non-small lung cancer e.g., squamous cell carcinoma, large cell carcinoma or adenocarcinoma or a small cell lung cancer such as small cell carcinoma (oat cell cancer) or combined small cell carcinoma. In a preferred embodiment the treated lung cancer will comprise squamous cell carcinoma. In some instances these methods will be used to treat cancer patients wherein the patient has manifested a tolerance for the particular chemotherapeutic such as an EGFR inhibitor, e.g., Erlotinib or sunitinib or imatinib, perhaps as a result of a mutant EGFR. As disclosed in Yao et al, Proc.Natl. Acad. Sci., USA and Nishioka et al, Leukemia 23:2304-2308 (2009) resistance of some tumors and cell lines such as leukemic and lung cancers to chemotherapeutics may involve inflammatory responses that result in the aberrant expression of IL-6 that may render the tumor resistant to chemotherapy. In addition the subject anti-IL-6 antibodies and fragments may be used to treat cancers that have become resistant to radiotherapy by administering an anti-IL-6 antibody according to the invention prior, concurrent or after radiation.

In a preferred embodiment of the invention wherein the antibodies may be used to subcutaneously administer antibodies of the invention, including Abl, 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. In another embodiment of the invention that may be used to subcutaneously administer antibodies of the invention, including Abl, 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.
[00618] 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.

[00619] 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.

[00620] 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.

[00621] 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.

[00622] 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.

[00623] 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.

[00624] 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.

[00625] 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.

[00626] 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.

[00627] 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.
[00628] Certain teachings related to anti-IL-6 antibodies and methods of using those antibodies or fragments thereof to address certain diseases and/or disorders were disclosed in U.S. provisional patent application nos. 61/117,839, 61/117,861, and 61/117,811, all filed on November 25, 2008, the disclosures of each of which are herein incorporated by reference in their entireties.

[00629] 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.

[00630] The entire disclosure of each document cited herein (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) is herein incorporated by reference in its entirety.

[00631] 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

[00632] In the following examples, the term "Ab1" refers to an antibody containing the light chain sequence of SEQ ID NO: 702 and the heavy chain sequence of SEQ ID NO: 704, except where the context indicates otherwise.

Example 1 Production of Enriched Antigen-Specific B Cell Antibody Culture

[00633] 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.

[00634] 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.

[00635] 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

[00636] 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**

[00637] 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**

[00638] 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**

[00639] 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 Alul 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**

[00640] 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**

[00641] 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 (T1 165 and HepG2). Furthermore, the collection of antibodies displays distinct modes of antagonism toward IL-6-driven processes.

**Immunization Strategy**

[00642] 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 T1 165 cell line.

**Antibody Selection Titer Assessment**

[00643] 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.

Functional Titer Assessment

[00644] The functional activity of the samples was determined by a T1 165 proliferation assay. T1 165 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.

[00645] 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% CO2. 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.

**Tissue Harvesting**

[00646] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[00647] 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.

[00648] 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.

**B cell culture**

[00649] 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 µT 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 µT 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.

[00650] 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% CO₂.

Identification of Selective Antibody Secreting B Cells

[00651] Cultures were tested for antigen recognition and functional activity between days 5 and 7.

Antigen Recognition Screening
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.

**Functional Activity Screening**

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.

**B cell recovery**

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.

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.

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% CO₂ in the dark.
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

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

Expression vector: The vector contains the following functional components: 1) a mutant ColEl 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).

P. pastoris strains: P. pastoris strains metl, lys3, ura3 and adel 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 adel or ura3 cells remain present in a culture or arise through meiosis or other mechanism, the diploid strain should outgrow them in culture.
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 adel 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 adel and ura3, one can readily monitor the sexual state of the resulting antibody-producing diploid strains (haploid versus diploid).

Methods

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 AGCGCTTATTCGCTATCCAGATGACCCAGTC-the Afel 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 CGTACGTTTTGATTTCCACCTTG.

Variable light chain reverse primer. BsiWI site is underlined, followed by the reverse complement for the 3' end of the variable light chain. Upon restriction enzyme digest with Afel and BsiWI this enable insertion in-frame with the pGAPZ vector using the human HAS leader sequence in frame with the human kapp light chain constant region for export. (2) A similar strategy is performed for the heavy chain. The forward primer employed is AGCGCTTATTCGAGGTGCAGCTGGTGGAGTC. The Afel site is single underlined. The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable heavy chain (not underlined). The reverse heavy chain primer is CTCGAGACGGTGACGAGGGT. The Xhol 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-γI CH1-CH2-CH3 region previous inserted within pGAPZ using a comparable directional cloning strategy.


[00665] 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 adel, ura3, metl 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 adel, metl 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.

[00666] 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 adel (or metl 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.

[00667] 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.

[00668] 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 adel and ura3 strains are spheroplasted and their resulting spheroplasts fused using polyethylene glycol/CaCl₂. The fused haploid strains are then embedded in agar containing 1 M sorbitol and minimal medium to allow diploid strains to regenerate their cell wall and grow into visible colonies. Resulting colonies are picked from the agar, streaked onto a minimal medium plate, and the plates are incubated for two days at 30 °C to generate colonies from single cells of diploid cell lines. The resulting putative diploid cell lines are then examined for diploidy and antibody production as described above.

[00669] 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.

[00670] 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 stained SDS-PAGE and immunoblotting for antibody protein. Antibody is characterized using the ELISA described above for IL-6 recognition.

[00671] 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 Abl.

[00672] Human IL-6 can provoke an acute phase response in rats, and one of the major acute phase proteins that is stimulated in the rat is alpha-2 macroglobulin (A2M). A study was designed to assess the dose of antibody Abl 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 Abl 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-Abl). The results are presented in Fig. 4.

[00673] The ID50 for antibody Abl 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 Abl.

**Example 10** RXF393 Cachexia Model Study 1.

Introduction
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 10 ng/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 Abl, on survival, body weight, serum amyloid A protein, hematology parameters, and tumor growth in athymic nude mice transplanted with the human renal cell cancer cell line, RXF393.

Methods

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 Abl 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 Abl 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.

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

Results - Survival

[00677] No animals were euthanized or died in any of the antibody Abl 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.

[00678] The survival curves for the two control groups and the antibody Abl progression (dosed from day 1 of the study) groups are presented in Fig. 5.

[00679] The survival curves for the two control groups and the antibody Abl regression (dosed from day 8 of the study) groups are presented in Fig. 6.

[00680] 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 Abl groups. There was no statistically significant difference between the two control groups (p=0.97).

Results - Tumor Size

[00681] 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 Abl 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.

[00682] As administration of antibody Abl 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 support the hypothesis that antibody Abl can promote
cancer patient survivability without directly affecting tumor growth, possibly by enhancing
general patient well-being.

Results - Weight Loss

Mean Percent Body Weight (MPBW) (± SEM) versus time is shown in Fig. 27. Compared to controls, mice dosed with Abl 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.

Representative photographs of control and Abl-treated mice (Fig. 28) illustrate the emaciated condition of the control mice, compared to the normal appearance of the Abl-treated mouse, at the end of the study (note externally visible tumor sites in right flank).

These results suggest that Abl may be useful to prevent or treat cachexia caused by elevated IL-6 in humans.

Results - Plasma Serum Amyloid A

The mean (± SEM) plasma serum amyloid A concentration versus time for the two control groups and the antibody Abl 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 Abl, all groups versus control groups

<table>
<thead>
<tr>
<th></th>
<th>Mean Plasma SAA±SEM Day 5 (µg/mL)</th>
<th>Mean Plasma SAA±SEM Day 13 (µg/mL)</th>
<th>Mean Plasma SAA±SEM Terminal Bleed (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyclonal IgG iv weekly from day 1</td>
<td>675 ± 240 (n=5)</td>
<td>3198 ± 628 (n=4)</td>
<td>13371 ± 2413 (n=4)</td>
</tr>
<tr>
<td>PBS iv weekly from day 1</td>
<td>355 ± 207 (n=5)</td>
<td>4844 ± 1126 (n=5)</td>
<td>15826 ± 802 (n=3)</td>
</tr>
<tr>
<td>Ab1 30 mg/kg iv weekly from day 1</td>
<td>246 ± 100 (n=5)</td>
<td>2979 ± 170 (n=5)</td>
<td>841 ± 469 (n=10)</td>
</tr>
<tr>
<td>Ab1 10 mg/kg iv weekly from day 1</td>
<td>3629 ± 624 (n=5)</td>
<td>3096 ± 690 (n=5)</td>
<td>996 ± 348 (n=10)</td>
</tr>
<tr>
<td>Ab1 3 mg/kg iv weekly from day 1</td>
<td>106 ± 9 (n=5)</td>
<td>1623 ± 595 (n=4)</td>
<td>435 ± 70 (n=9)</td>
</tr>
<tr>
<td>Ab1 30 mg/kg iv weekly from day 8</td>
<td>375 ± 177 (n=5)</td>
<td>1492 ± 418 (n=4)</td>
<td>498 ± 83 (n=9)</td>
</tr>
<tr>
<td>Ab1 10 mg/kg iv weekly from day 8</td>
<td>487 ± 170 (n=5)</td>
<td>1403 ± 187 (n=5)</td>
<td>396 ± 58 (n=10)</td>
</tr>
<tr>
<td>Ab1 3 mg/kg iv weekly from day 8</td>
<td>1255 ± 516 (n=5)</td>
<td>466 ± 157 (n=5)</td>
<td>685 ± 350 (n=5)</td>
</tr>
</tbody>
</table>

[S00687] 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 Abl displays in vivo efficacy.

Example 11 RXF393 Cachexia Model Study 2.

Introduction

[S00688] A second study was performed in the RXF-393 cachexia model where treatment with antibody Abl 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 Abl 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 Abl.

Methods

[00689] 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 Abl 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 Abl 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).

[00690] Animals were weighed every 3-4 days from day 1 to day 49 after transplantation. Mean Percent Body Weight (MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows: ((Body Weight - Tumor Weight)/Baseline Body Weight) x 100. Tumor weight was measured every 3-4 days from day 5 to day 49 after transplantation. Food consumption was measured (amount consumed in 24 hours by weight (g) by each treatment group) every day from day 10 for the 270-320 mg tumor groups and day 13 for the 400-527 mg tumor groups.

Results -survival

[00691] The survival curves for antibody Abl 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.

[00692] Median survival for the antibody Abl 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).
The survival curves for the antibody Abl 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 Abl 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 Abl in Non-human Primates.

Antibody Abl 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 Abl was quantitated through the use of an antigen capture ELISA assay. Biotinylated IL-6 (50 μl of 3 μg/mL) was captured on Streptavidin coated 96 well microtiter plates. The plates were washed and blocked with 0.5% Fish skin gelatin. Appropriately diluted plasma samples were added and incubated for 1 hour at room temperature. The supematants removed and an anti-hFc-HRP conjugated secondary antibody applied and left at room temperature.

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 Abl 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.

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.

IL-6 signaling is dependent upon interactions between IL-6 and two receptors, IL-6R1 (CD126) and gpl30 (IL-6 signal transducer). To determine the antibody mechanism of action, mechanistic studies were performed using bio-layer interferometry with an Octet QK instrument.
Studies were performed in two different configurations. In the first orientation, biotinylated IL-6 (R&D systems part number 206-IL-OOIMG/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.

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 gpl30 (R&D systems 228-GP-OIO/CF) in the presence of IL-6R1 for stability purposes. If gpl30 did not bind, it was concluded that the antibody blocked gpl30 interactions with IL-6.

In the second orientation, the antibody was bound to a biosensor coated with an anti-human IgGl 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 gpl30 in the presence of IL-6R1. If gpl30 did not interact, then it was concluded that the antibody blocked IL-6/gpl30 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).

Results are presented in Fig. 10 (A-E) and Fig. 11.

**Example 14 Peptide Mapping.**

In order to determine the epitope recognized by Abl 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 is shown in Fig. 12 and correspond to SEQ
Blots were prepared and probed according to the manufacturer's recommendations.

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 Abl 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 (Alphalnnotec). The results of the blots is shown in Fig. 13 and Fig. 14.

The sequence of the form of human IL-6 utilized to generate peptide library is set forth:

VPPGEDSKDVAAPHRQPLTSERIDKQIRYILDGISALRKETCNKSNMCESSKEALAEENN
LNLPKMAEKDGCFQSGFNEETCLVKIITGLLEFEYLEYLQNRFESSEEQARAVQMSTK
VLIQFLQKKAKNLDAITTPDPTNASLLTKLQAQNLQDMTTHLILRSFKELQSSLRA
LRQM (SEQ ID NO: 1).

Example 15 Abl has high affinity for IL-6.

Surface plasmon resonance was used to measure association rate ($K_a$), dissociation rate ($K_d$) and dissociation constant ($K_D$) for Abl 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 Abl for IL-6 of cynomolgus monkey, rat, and mouse were 31 pM, 1.4 nM, and 0.4 nM, respectively. Abl affinity for dog IL-6 below the limit of quantitation of the experiment.

The high affinity of Abl for mouse, rat, and cynomolgus monkey IL-6 suggest that Abl 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 Abl could inhibit 50% of proliferation (IC50) was measured. Inhibition was consistent with the measured dissociation constants (Fig. 15B). These
results demonstrate that Abl 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 Abl.

**Example 16 Multi-dose Pharmacokinetic Evaluation of Antibody Abl in Healthy Human Volunteers.**

[00706] Antibody Abl 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 Abl using a monoclonal antibody specific for Abl, as follows. A 96 well microtiter plate was coated overnight with the monoclonal antibody specific for Abl in IX 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 IX 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.

[00707] Average plasma concentration of Abl for each dosage group versus time is shown in Fig. 16. Mean AUC and $C_{\text{max}}$ increased linearly with dosage (Fig. 17 and Fig. 18, respectively). For dosages of 30 mg and above, the average Abl half-life in each dosage group was between approximately 25 and 30 days (Fig. 19).

**Example 17 Pharmacokinetics of Abl in patients with advanced cancer.**

[00708] Antibody Abl 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 Abl. Plasma samples were drawn weekly, and the level of antibody Abl was quantitated as in Example 16.
Average plasma concentration of Abl in these individuals as a function of time is shown in Fig. 20. The average Abl half-life was approximately 31 days.

**Example 18 Unprecedented half-life of Abl.**

Overall, the average half-life of Abl was approximately 31 days in humans (for dosages of 10 mg and above), and approximately 15-21 days in cynomolgus monkey. The Abl half-life in humans and cynomolgus monkeys are unprecedented when compared with the half-lives of other anti-IL-6 antibodies (Fig. 21). As described above, Abl 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 Abl from interacting with the Fc receptor or complement. Without intent to be limited by theory, it is believed that the unprecedented half-life of Abl is at least partially attributable to the humanization and/or the lack of glycosylation. The particular sequence and/or structure of the antigen binding surfaces may also contribute to Abl's half-life.

**Example 19 Abl Effect on Hemoglobin Concentration, Plasma Lipid Concentration, and Neutrophil Counts in Patients with Advanced Cancer.**

Antibody Abl 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 Abl. 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).

These results further demonstrate some of the beneficial effects of administration of Abl 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 Abl 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 Abl inhibits IL-6. Finally, IL-6 causes anorexia as well as cachexia in these patients; neutralization of IL-6 by Abl results in the return of appetite and reversal of cachexia. The increase in plasma lipid concentrations reflect the improved nutritional status of the patients. Taken together, these results further demonstrate that Abl effectively reverses these adverse consequences of IL-6 in these patients.

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

Introduction

[00713] 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 or poor prognosis and early recurrence in patients with hepatocellular carcinoma.

[00714] 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.

Methods
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 Abl 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 Abl monoclonal antibody. No further dosages of the Abl monoclonal antibody were administered to the test population.

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

Results

Healthy Volunteers

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 Abl 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).

Cancer Patients

Five advanced cancer patients (colorectal cancer, cholangiocarcinoma, or NSCLC) having elevated serum CRP levels were dosed with 80 mg or 160 mg of Abl. 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 Abl 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 Abl to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

**Example 21** Abl Improved Muscular Strength, Improved Weight, and Reduced Fatigue in Patients with Advanced Cancer

Introduction

[00719] Weight loss and fatigue (and accompanying muscular weakness) are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue, weight loss and muscular weakness can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue, weight loss and muscular weakness include regular routines of fitness and exercise, methods of conserving the patient's energy, and treatments that address anemia-induced fatigue and muscular weakness. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue, weight loss and muscular weakness in cancer patients.

Methods

[00720] 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 Abl monoclonal antibody. No further dosages of the Abl monoclonal antibody were administered to the test population.

[00721] 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

Results

Weight Change

[00722] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Abl monoclonal antibody demonstrated an increase of about 2 kilograms of weight per patient over the period of 6 weeks (Fig. 29).

Fatigue

[00723] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Abl 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).

Hand-Grip Strength

[00724] The averaged data for both dosage concentrations (80 mg and 160 mg) of the Abl 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  Abl For Prevention of Thrombosis

[00725] 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.
[00726] 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 Abl, 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.

[00727] 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 Abl Increases Plasma Albumin Concentration in Patients with Advanced Cancer

[00728] Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbuminemia 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.
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)).

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 "albumin 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)).

Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

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 Abl monoclonal antibody. No further dosages of the Abl monoclonal antibody were administered to the test population.

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

Results

The averaged data for both dosage concentrations (80 mg and 160 mg) of the Abl 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 Abl Suppresses Serum CRP in Patients with Advanced Cancer.
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.

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.

Methods

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

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

Results

The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Abl monoclonal antibody are plotted in Figure 38. All dosage levels of Abl antibody demonstrated an immediate drop in CRP concentrations relative to placebo over the period of 12 weeks. CRP levels displayed breakthrough at 8 weeks post-dosing. The CRP levels fell below 5 mg/L by week 12. Median values of CRP demonstrated rapid and sustained decreases for all dosage concentrations relative to placebo (Fig. 39). Thus, administration of Abl to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.

Example 25 Abl Suppresses Serum CRP in Patients with Advanced Cancers.

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.

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.

Methods

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

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

Results

Serum CRP levels were greatly reduced in all patients studied (Fig. 40). The reduction in serum CRP levels was rapid, with approximately 90% of the decrease occurring within one week of Abl administration, and prolonged diminished levels continued at least until the final measurement was taken (up to twelve weeks). In all cases except one patient with colorectal cancer, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. The colorectal cancer patient achieved similar normal levels by week 4 of the study. Thus, administration of Abl to advanced cancer patients can cause a rapid and sustained suppression of serum CRP levels.
**Example 26  Abl Suppresses Serum CRP in Patients with Rheumatoid Arthritis.**

[00745] Serum CRP concentrations have been identified as a strong prognostic indicator in patients with rheumatoid arthritis. Patients suffering from rheumatoid arthritis with high levels of CRP demonstrated almost universal deterioration. Amos et al., 1 Br. Med. J. 195-97 (1977). Conversely, patients with low CRP levels showed no disease progression, suggesting that sustaining low levels of CRP is necessary for effectively treating rheumatoid arthritis. *Id.* Tracking of CRP during rheumatoid arthritis treatment regimes of gold, D-penicillamine, chloroquine, or dapsone indicated that radiological deterioration was impeded after the first 6 months of treatment when CRP levels were consistently controlled. Dawes et al., 25 Rheumatology 44-49 (1986). A highly significant correlation between CRP production and radiological progression was identified. van Leeuwen et al., 32 (Supp. 3) Rheumatology 9-13 (1997). Another study revealed that for patients with active rheumatoid arthritis, suppression of abnormally elevated CRP led to improvement in functional testing metrics, whereas sustained CRP elevation associated with deterioration in the same metrics. Devlin et al., 24 J. Rheumatol. 9-13 (1997). No further deterioration was observed without CRP re-elevation, indicating CRP suppression as a viable candidate for rheumatoid arthritis treatment. *Id.* Accordingly, there remains a need in the art for methods and/or treatments that reduce serum C-Reactive Protein (CRP) concentrations in rheumatoid arthritis patients.

Methods

[00746] One-hundred twenty-seven patients with active rheumatoid arthritis and CRP >10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Abl monoclonal antibody, once at the start of the 16 week trial and again at week 8. CRP concentration was quantitated by a C-reactive protein particle-enhanced immunoturbidimetric assay using latex-attached anti-CRP antibodies (i.e. Roche CRP Tinaquant®). Briefly, about 1.0 mL of patient sample serum was collected and stored in a plastic collection tube. Sample was placed into appropriate buffer, and anti-CRP antibody coupled to latex microparticles was added to the sample to start the reaction. These anti-CRP antibodies with conjugated latex microparticles react with antigen in the sample to form an
antigen/antibody complex. Following agglutination, this was measured turbidimetrically using a Roche/Hitachi Modular P analizer. Data on CRP concentration was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16.

Results

[00747] Serum CRP levels were greatly reduced in all patients studied (Fig. 41). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Abl administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Abl to rheumatoid arthritis patients can cause a rapid and sustained suppression of serum CRP levels and presents an effective treatment regime.

Example 27  Abl Increases Hemoglobin in Patients with Advanced Cancer

[00748] Antibody Abl was dosed at 80 mg, 160 mg, or 320 mg of Abl in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the hemoglobin concentration was determined. Mean hemoglobin concentration rose for those receiving antibody Abl, 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. 42 and 43).

[00749] 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 Abl at dosages of 160 mg and 320 mg, while mean hemoglobin concentration of those receiving antibody Abl at dosages of 80 mg or placebo did not rise above 11 g/l after eight weeks (Fig. 44).

[00750] These results further demonstrate some of the beneficial effects of administration of Abl 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 Abl increases hemoglobin concentration in these individuals.

**Example 28 Abl Increases Hemoglobin in Patients with Rheumatoid Arthritis.**

[00751] Hemoglobin levels were analyzed in patients with rheumatoid arthritis during treatment with Abl antibody. Abl 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 Abl, 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. 45).

[00752] These results further demonstrate some of the beneficial effects of administration of Abl 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 Abl increases hemoglobin concentration.

**Example 29 Abl Increases Albumin in Patients with Advanced Cancer**

[00753] Serum albumin concentrations are recognized as predictive indicators of survival and/or recovery success of cancer patients. Hypoalbuminemia 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.*

[00754] Similarly, Senior and Maroni state that "*[t]he recent appreciation that hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease"

[00755] 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)).

[00756] Accordingly, there remains a need in the art for methods and/or treatments that improve serum albumin concentrations in cancer patients and address hypoalbuminemic states in cancer patients, particularly those with advanced cancers.

Methods

[00757] Antibody Abl was dosed at 80 mg, 160 mg, or 320 mg of Abl in phosphate buffered saline to 93 individuals with non-small cell lung carcinoma. Each individual received a dosage of. The placebo group of 31 individuals with non-small cell lung carcinoma was dosed with phosphate buffered saline only. Blood samples were removed just prior to dosing (zero week), and at two, four, eight and twelve weeks, and the albumin concentration was determined.

Results

[00758] Mean albumin concentration rose for those receiving antibody Abl, while mean albumin concentration of those receiving placebo did not rise after twelve weeks when compared to the concentration just prior to dosing (zero week) (Fig. 46). The change from baseline albumin values for all dosage concentration groups is plotted in Figure 47.

[00759] A subset of the study population began the study with low levels of albumin, defined as a baseline albumin concentration less than or equal to 35 g/L. Mean albumin concentration initially rose with all dosages of antibody Abl over placebo, but only patients receiving 160 mg or 320 mg demonstrated sustained albumin levels above 35 g/L over 8 weeks of the study (Fig.
48). The 80 mg dosage group demonstrated an initial increase, but gradually declined after week 2 and never rose above 35 g/L during the 8 weeks where data was available (Id.).

Example 30 Abl Improved Weight and Reduced Fatigue in Patients with Advanced Cancer

[00760] Weight loss and fatigue are very common symptoms of patients with advanced forms of cancer, and these symptoms can worsen as the cancer continues to progress. Fatigue and weight loss can have significant negative effects on the recovery of patients with advanced forms of cancer, for example by disrupting lifestyles and relationships and affecting the willingness or ability of patients to continue cancer treatments. Known methods of addressing fatigue and weight loss include regular routines of fitness and exercise, methods of conserving the patient's energy, and treatments that address anemia-induced fatigue. Nevertheless, there remains a need in the art for methods and/or treatments that improve fatigue and weight loss in cancer patients.

Methods

[00761] 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 Abl monoclonal antibody every 8 weeks over a 24 week duration for a total of 3 doses.

[00762] 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.).

Results
Weight Change

[00763] The averaged weight change data from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Abl monoclonal antibody over 12 weeks is plotted in Figure 49. The average percent change in body weight from each dosage concentration is plotted in Fig. 50. The averaged lean body mass data for the dosage concentration groups is plotted in Figure 51.

Fatigue

[00764] The averaged fatigue from each dosage concentration group (placebo, 80 mg, 160 mg, and 320 mg) of the Abl 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. 52). The change from baseline Facit-F subscale score is plotted in Figure 53.

Example 31 Abl Decreases D-dimer Levels in Patients with Advanced Cancer

[00765] 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))

[00766] 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)
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))

Accordingly, there remains a need in the art for methods and/or treatments of thrombosis that improve D-dimer concentrations in cancer patients and address elevated D-dimer states in cancer patients, particularly those with advanced cancers.

Methods

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 Abl 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.

Results
The averaged data for each dosage concentrations (placebo, 80 mg, 160 mg, and 320 mg) of the Abl monoclonal antibody are plotted in Figure 54. Error bars were omitted from the graph for clarity purposes. The percent change from baseline in D-dimer concentration is plotted in Figure 55. All dosage levels of Abl antibody demonstrated a drop in D-dimer levels over placebo over the period of 8 weeks.

Example 32 Abl Efficacy and Safety in Patients with Advanced NSCLC

The primary objective of this study was to determine the efficacy and safety of ALD518 or humanized Abl in patients with advanced NSCLC.

Methods: 124 patients (pts) with NSCLC, ECOG 0-3, weight loss in the preceding 3 months of >5% body weight, hemoglobin (Hb) >7g/dL, and C-reactive protein (CRP) >10mg/L were dosed. Pts were randomized to 1 of 4 groups (n~30/group). Placebo or ALD518 80mg, 160mg, or 320mg was administered intravenously every 8 weeks. Pts were followed up for 24 weeks. Data included hematology, clinical chemistry, CRP and adverse events (AEs).

Results: 29 pts completed the study treatments and evaluations, 38 failed to complete every visit, 52 died of progressive disease, and 5 withdrew because of adverse events. There were no dose limiting toxicities (DLTs) or infusion reactions. 84 pts had serious AEs of which 1 was deemed to be possibly related to administration of ALD518 (rectal hemorrhage). The mean (±SD) values for Hb, hematocrit (Hct), mean corpuscular Hb (MCH), and albumin are below:

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Hb (g/dL)</th>
<th>Hct (%)</th>
<th>MCH (pg)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD518</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>93</td>
<td>11.5 (±2.1)</td>
<td>37.9 (±6.2)</td>
<td>28.4 (±2.8)</td>
<td>37.3 (±5.3)</td>
</tr>
<tr>
<td>Week 4</td>
<td>69</td>
<td>13.0 (±1.6)</td>
<td>42.5 (±5.0)</td>
<td>29.2 (±2.5)</td>
<td>43.6 (±4.7)</td>
</tr>
<tr>
<td>Week 12</td>
<td>39</td>
<td>13.4 (±1.6)</td>
<td>42.5 (±4.7)</td>
<td>29.8 (±2.8)</td>
<td>45.2 (±4.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>31</td>
<td>12.2 (±1.8)</td>
<td>39.0 (±5.9)</td>
<td>29.0 (±2.8)</td>
<td>37.5 (±5.7)</td>
</tr>
<tr>
<td>Week 4</td>
<td>29</td>
<td>11.8 (±2.0)</td>
<td>39.5 (±6.4)</td>
<td>28.0 (±2.8)</td>
<td>37.3 (±6.8)</td>
</tr>
<tr>
<td>Week 12</td>
<td>21</td>
<td>12.0 (±2.5)</td>
<td>39.6 (±7.4)</td>
<td>27.8 (±3.0)</td>
<td>37.0 (±7.5)</td>
</tr>
</tbody>
</table>

\[ a p<0.0001 \quad b p=0.0002 \quad c p<0.001 \] (paired t-test compared to pre-dose)
38/93 pts treated ALD518 and 10/31 given placebo has a pre-dose Hb ≤ 11g/dL. 24 of these pts on ALD518 and 7 of these pts on placebo remained in the study at week 4. 14/24 pts on ALD518 and 0/7 on placebo had raised their Hb from ≤ 11g/dL to ≥ 12g/dL.

[00774] **Conclusion:** ALD518 increased Hb, Hct, MCH and albumin in NSCLC pts and raised Hb to ≥ 12g/dL in 58% of pts with a Hb ≤ 11g/dL at baseline. This further indicates that ALD518 can be administered as a non-erythropoietic stimulating agent for treating cancer-related anemia.

**Example 33** Abl achieved ACR 20/50/70 in Patients with Rheumatoid Arthritis.

[00775] Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology ("ACR") released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement of the disease in clinical trials. Felson et al., 36 Arthritis & Rheumatism 729-40 (1993).

Methods

[00776] One-hundred twenty-seven patients with active rheumatoid arthritis and CRP >10 mg/L were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Abl monoclonal antibody, once at the start of the 16 week trial and again at week 8. Data on CRP concentration was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16.

[00777] Assessment under the standardized protocols from the American College of Rheumatology were employed in determining the percentage of improvement of patients during the clinical trial and conducted by a person trained in the ordinary art of evaluating rheumatoid arthritis. The evaluation was based upon activity measures, including tender joint count, swollen
joint count, the patient's assessment of pain, the patient's and physician's global assessments of disease activity, and laboratory evaluation of either erythrocyte sedimentation rate or CRP level. 

**Id.** The patient's assessment of pain was based upon the Stanford Health Assessment Questionnaire Disability Index (HAQ DI). Patients that achieve a 20% increase in activity measures for rheumatoid arthritis during a clinical trial are categorized as achieving ACR 20. Similarly, patients achieving 50% and 70% improvements are categorized as ACR 50 and ACR 70, respectively.

**Results**

[00778] A significant portion of patients suffering from rheumatoid arthritis achieved ACR 20 or greater during the course of the study (Fig. 56). Patients observed rapid improvement in systems within the first 4 weeks of the study, as well as continued, steady improvement throughout the course of the 16 week evaluation (Figs. 57, 58, and 59). The greatest results where exhibited by patients receiving the 320 mg dosage level, with 43% achieving ACR 70 status during the study (Fig. 59).

[00779] Analysis of the individual components of the ACR evaluation demonstrated gains in every component (Fig. 60). HAQ DI scores demonstrated clinically meaningful change over placebo during the course of the evaluation (Fig. 61). Serum CRP levels were greatly reduced in all patients studied (Fig. 61). The reduction in serum CRP levels was rapid, with immediate reduction in CRP levels relative to placebo within one week of Abl administration, and prolonged diminished levels continued at least until the final measurement was taken (up to sixteen weeks). In all cases, CRP levels fell to at or below the normal reference range (less than 5-6 mg/L) within one week. Thus, administration of Abl can cause a rapid and sustained improvement rheumatoid arthritis patients, as evidenced by the significant improvement in ACR scores during clinical evaluation, and presents an effective treatment regime.

**Example 34** Abl Achieved Improved DAS28 and EULAR Scores in Patients with Rheumatoid Arthritis

**Introduction**
Rheumatoid arthritis is a chronic, systemic inflammatory disorder that principally attack synovium of joints. The disease causes painful and potentially disabling inflammation, with onset typically occurring between 40 and 50 years of age. Interpretation of drug treatment efficacy in rheumatoid arthritis is made difficult by the myriad of subjective and objective assessment tools made available over the years. The American College of Rheumatology ("ACR") released a standardized set of rheumatoid arthritis measures to facilitate evaluation of improvement of the disease in clinical trials. Felson et al., 36 Arthritis & Rheumatism 729-40 (1993).

Inflammatory activity associated with rheumatoid arthritis is measured using numerous variables through validated response criteria such as Disease Activity Score (DAS), DAS28 and EULAR. The DAS is a clinical index of rheumatoid arthritis disease activity that combines information from swollen joints, tender joints, the acute phase response, and general health. Fransen, J., et al, Clin. Exp. Rheumatol, 23 (Suppl. 39): S93-S99 (2005). The DAS 28 is an index similar to the original DAS, but utilizes a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR (erythrocyte sedimentation rate), and an optional general health assessment on a visual analogue scale (range 0-100). Id. The European League against Rheumatism (EULAR) response criteria classify patients using the individual amount of change in the DAS and the DAS value (low, moderate, high) reached into one of the following classifications: Good; Moderate; or Non-Responders. Id.

Methods

One-hundred twenty-seven patients with active rheumatoid arthritis were divided into 4 treatment groups. Patients in one group received one 1-hour intravenous (IV) infusion of either placebo (n=33), 80 mg (n=32), 160 mg (n=34), or 320 mg (n=28) of the Abl monoclonal antibody, once at the start of the 16 week trial and again at week 8. Data on the DAS28 and EULAR scores was collected every week for the first 4 weeks, every two weeks between weeks 4 and 12, and at the conclusion of the test at week 16. Assessment under the standardized DAS28 and EULAR protocols were employed in determining the respective scores of patients during the clinical trial and conducted by a person trained in the ordinary art of evaluating rheumatoid arthritis.
Results

[00783] Patients receiving 80 mg, 160 mg or 320 mg of Abl demonstrated improved DAS28 scores relative to those patients receiving placebo over the course of 16 weeks, as presented in Fig. 62 as a mean change from the baseline DAS28 score. Furthermore, a significant percentage of patients receiving 80 mg, 160 mg or 320 mg of Abl achieved "Good" or "Moderate" classifications relative to those patients receiving placebo over the course of 16 weeks. (Fig. 63).

[00784] Thus, administration of Abl can result in improved DAS28 and EULAR scores in rheumatoid arthritis when compared to those patients receiving placebo.

Example 35 Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Abl in Human Subjects

[00785] As described herein a humanized antibody derived from Abl (humanized Abl or ALD518) containing the variable heavy and light sequences in SEQ ID NO: 19 and 20 was administered to rheumatoid arthritis patients. This antibody is a humanized, asialated, IgGl monoclonal antibody against IL-6 which has been shown to have a half-life (t½) of approximately 30 days in humans. In studies in patients with RA, intravenous (IV) with this antibody (humanized Abl) has demonstrated: efficacy over 16 weeks with rapid American College of Rheumatology (ACR) responses; Complete and durable suppression of C-reactive protein (CRP); Good tolerability, and a safety profile consistent with the biology of IL-6 blockade. This humanized antibody binds to IL-6 with high affinity, preventing interaction and signalling mediated via IL-6R. Rapid and significant treatment responses have been demonstrated with intravenous (IV) administration of humanized Abl in patients with RA. In this example we study the safety, pharmacokinetics and pharmacodynamics of subcutaneous (SC) administration of humanized Abl in healthy subjects.

[00786] The objective of this study was to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of a single SC injection of this humanized antibody in healthy male subjects.

Methods:
In this Phase I, double-blind, placebo-controlled study, 27 subjects were randomized 2:1 to receive a single dose of humanized Abl or placebo in the following groups: humanized Abl 50 mg SC, humanized Abl 100 mg SC or humanized Abl 100 mg IV (n=6 active and n=3 placebo per group). The primary objective was to assess safety of SC humanized Abl versus placebo over 12 weeks. Plasma concentrations of humanized Abl and serum concentrations of C-reactive protein (CRP) were assessed as secondary objectives. Assessments were performed daily in Week 1 and then on Day 10, Weeks 2, 4, 6 and 8, and then monthly to Week 12. The study was unblinded at Week 12, and humanized Abl subjects were monitored to Week 24.

Study design and population

The study included 27 healthy male subjects (aged 18-65 years). Subjects were dosed in three treatment groups of nine subjects each, randomized 2:1 to receive a single dose of humanized Abl or placebo on Day 1 (Figure 64). Humanized Abl treatments per group were:

- humanized Abl IV 100 mg infusion over 60 minutes
- humanized Abl SC 50 mg injection (1 mL)
- humanized Abl 100 mg injection (1 mL)

The study was unblinded at Week 12, after which placebo subjects discontinued the trial and BMS-945429 subjects were monitored to Week 24 (Figure 64).

Safety and immunogenicity assessments

The primary objective of the study was to assess the safety of SC humanized Abl compared with placebo over 12 weeks. Safety was monitored over 12 weeks for all subjects. The study was unblinded at Week 12, and Humanized Abl subjects were monitored to Week 24.

Laboratory safety tests were performed pre-dose at screening and Day -1, and post dose on Days 2 and 7, Weeks 2, 4, 6, 8 and 12 for all subjects, and Weeks 16, 20 and 24 post-dose for those randomized to Humanized Abl. Anti-Humanized Abl antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Blood samples were collected at Day 1 (pre-
dose) and Week 12 post-dose for all subjects, and Week 24 post-dose for those randomized to Humanized Abl.

Pharmacokinetic and pharmacodynamic assessments

[00791] Plasma Humanized Abl and serum CRP concentrations were assessed by ELISA. For all subjects, samples were collected at screening, pre-dose on Day 1, and post-dose on Days 2 and 7 and Weeks 2, 4, 6, 8 and 12. For subjects randomized to Humanized Abl, further samples were collected at Weeks 16, 20 and 24 post-dose.

Statistical analysis

[00792] All subjects who received a dose of Humanized Abl or placebo were included in the safety analysis. All subjects who received a dose of Humanized Abl or placebo were included in PD and immunogenicity analyses. All subjects who received a dose of Humanized Abl were included in PK analyses (n=18). All PK samples for placebo subjects were confirmed as below quantification.

[00793] Descriptive statistics were generated for baseline demographics, safety data, plasma Humanized Abl parameters and serum CRP concentrations. Wilcoxon Rank Sum test was used to compare CRP concentrations for Humanized Abl treatments versus placebo.

Results:

Summary

[00794] Over 24 weeks, there were no deaths or serious AEs, and no withdrawals due to AEs. Nearly all subjects (89%) experienced AEs, which were mild or moderate except one event of severe gastroenteritis in the Humanized Abl SC 50 mg group. Injection site reactions occurred in 5/12 Humanized Abl SC subjects, 1/6 placebo SC subjects and 1/3 placebo IV subjects (none were reported in Humanized Abl IV subjects). These were mild except one case of moderate erythema and pruritis in the Humanized Abl 100 mg SC group. Increases in direct bilirubin and neutrophil counts below the limit of normal were more common in subjects receiving Humanized Abl than placebo; all were CTC Grade 1 or 2. The half life of Humanized Abl was similar across all groups (mean range: 30.7-33.6 days). The median T_max of Humanized Abl was
longer after SC (~1 week) than after IV administration (-end of infusion). The PK of SC Humanized Abl was dose-proportional in terms of AUC and $C_{\text{max}}$ at doses of 50 mg and 100 mg. Based on $AUC_{\text{0-\infty}}$ (day*µg/mL) of 237, 452 and 764 for the Humanized Abl 50 mg SC, 100 mg SC and 100 mg IV groups, respectively, the bioavailability of Humanized Abl was -60% for the SC versus IV groups. Subjects receiving Humanized Abl experienced rapid and sustained reductions in serum CRP (Figure 66).

**Subject disposition and baseline demographics**

[00795] A total of 27 subjects were enrolled and completed the study (n=18 Humanized Abl and n=9 placebo). No subjects were withdrawn for any reason.

[00796] All subjects were male; 23/27 subjects were Caucasian and 4/27 were Asian. Mean age was 29 (range 20-59) and was similar across the groups. Mean height and weight were also generally comparable across groups, although the IV placebo group were slightly lighter.

**Safety and immunogenicity to Week 12 for Humanized Abl and placebo**

[00797] A summary of safety is presented in Figure 67. For the SC Humanized Abl groups, a total of 11/12 (91%) patients experienced an adverse event (AE) compared with:

6/6 (100%) for the IV Humanized Abl group;

4/6 (66.6%) for the SC placebo group; and

3/3 (100%) for the IV placebo group.

[00798] Across groups:

No deaths or serious AEs were reported and there were no withdrawals due to AEs.

Most AEs were mild or moderate in intensity.

One case of gastroenteritis in a SC Humanized Abl 50 mg subject was considered severe, but not serious, and not related to study medication.

No anti-Humanized Abl antibodies were detected in any subject during this period.
Injection site reactions

Injection site reactions were reported in 26% (7/27) of subjects, and all occurred prior to Week 12 (Figure 68). Injection site reactions occurred in 5/12 SC Humanized Abl subjects and 1/6 SC placebo subjects. In the IV groups, 0/6 Humanized Abl subjects and 1/3 placebo subjects experienced injection site reactions. All injection site reactions were mild except in one SC Humanized Abl 100 mg subject with moderate injection site erythema and pruritis. No injection site reactions occurred after Week 12 in any of the Humanized Abl groups. Infusion site reactions were reported in 0/6 subjects receiving IV Humanized Abl and 1/3 IV placebo subjects (infusion site pruritis)

Clinical laboratory evaluations

Figure 69 shows incidences of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and bilirubin levels across the Humanized Abl and placebo groups. All ALT and AST levels were Grade 1 by the Common Terminology Criteria for Adverse Events (CTCAE), and no levels were >3 times the upper limit of normal (ULN). All increases in total and direct bilirubin were CTCAE Grade 1 or 2 and no subject met criteria for drug-induced liver damage. Only one subject (SC Humanized Abl 100 mg group) had total bilirubin out of range (26 µmol/L, range 0-24 µmol/L), at Week 24.

Sporadic decreases in neutrophil and platelet counts were also observed in the Humanized Abl and placebo groups (Figure 69). Neutrophil counts below the lower limit of normal were more common in subjects receiving Humanized Abl than placebo but all decreases were CTCAE Grade 1 or 2. Only one subject (SC Humanized Abl 50 mg group) had consistent mild neutropenia to Week 24 (1.6 x 10^9/L at Week 24). Reductions in platelet counts were all CTCAE Grade 1 (lowest level 134 x 10^9/L) and no subject had a low platelet count past Week 8.

Pharmacokinetics

Bioavailability of Humanized Abl was 60% for SC Humanized Abl 50 and 100 mg versus IV Humanized Abl 100 mg groups based on the mean AUCo (Figure 70). The half-life of Humanized Abl was similar across all groups (mean range: 30.7-33.6 days) (Figure 70). Peak plasma concentration (Cmax) of SC Humanized Abl was reduced as compared to IV
Median time to maximum plasma concentration ($T_{\text{max}}$) of Humanized Abl was longer after SC Humanized Abl (at approximately one week) than after IV Humanized Abl administration (at approximately the end of infusion).

**Pharmacodynamics**

CRP levels were reduced in all subjects who received Humanized Abl irrespective of dose or administration route. (Figures 66 and 71) From Weeks 4 to 12, CRP levels were significantly lower in subjects who received Humanized Abl compared with placebo (unadjusted p-value <0.05; Figure 66). In Humanized Abl subjects, CRP levels were lowered to <20% of pre-dose levels in:

- 72% (13/18) of subjects at Week 1;
- 73% (11/15) of subjects at Week 12; and
- 56% (10/18) of subjects at Week 24.

**Conclusions:**

In this Phase I study, the anti-IL-6 antibody Humanized Abl was generally well tolerated when administered in a single SC dose in healthy male subjects. Injection site reactions were generally mild. No anti-Humanized Abl antibodies were detected. Changes in liver enzymes, neutrophil and platelet counts were reversible. The bioavailability of SC Humanized Abl was approximately 60% of that observed with IV Humanized Abl. The half-life of Humanized Abl was approximately 30 days, irrespective of route of administration. These data concur with previous data using IV Humanized Abl. Subcutaneous Humanized Abl led to rapid and large reductions in serum CRP. Reductions in CRP observed during the first 12 weeks of the study were sustained over 24 weeks of assessment. These preliminary data support the continued development and evaluation of SC Humanized Abl for the treatment of patients with RA.

In summary, in this Phase I study, the anti-IL-6 antibody Humanized Abl was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC Humanized Abl was ~60% of IV Humanized Abl, and the half life
was -30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

**Example 36  Effect of Abl on DAS28-Assessed Disease Activity**

[00806] As discussed above, ALD518* is an asialated, humanized anti-IL-6 monoclonal antibody with a half-life of ~30 days containing the humanized variable heavy and light sequences contained in SEQ ID NO: 19 and 20. These humanized heavy and light sequences are derived from a parent rabbit antibody that specifically binds human IL-6 which antibody is referred to in said incorporated application as Abl. ALD518 binds to IL-6 with high affinity, preventing interaction and signalling mediated via soluble and membrane-bound IL-6R. Rapid and significant ACR responses have been demonstrated with ALD518* in patients with RA. In this example we report the impact of ALD518 on DAS28-assessed disease activity over 16 weeks.

[00807] **Methods:** Patients with active RA and an inadequate response to MTX were randomized 1:1:1:1 to intravenous ALD518* 80, 160 or 320 mg or placebo during this 16-week, double-blind, placebo-controlled Phase II study. Patients received two IV infusions of ALD518 (Day 1 and Week 8), while continuing on stable doses of MTX. The primary efficacy endpoint was the proportion of patients achieving ACR20 at Week 12; disease activity was assessed via Disease Activity Score (DAS28) based on C-reactive protein (CRP) as a secondary endpoint. The proportion of patients achieving DAS28-defined remission (score <2.6), low disease activity state (LDAS; score <3.2) and good EULAR responses (current DAS28 <3.2 and improvement from baseline >1.2) were assessed for the modified intent-to-treat population, and are presented for patients with available data (as observed). P-values are based on Chi-square tests.

[00808] **Results:** Of 127 randomized and treated patients, 116 completed the trial. At baseline, mean age was 52.3 years and RA duration was 6.8 years. At Weeks 4, 12 and 16, the proportion of patients achieving LDAS and remission was greater than placebo for all ALD518* doses; differences were significant versus placebo (p<0.05) for all assessments except ALD518* 80 mg at Week 4 (p=0.056). Similarly, EULAR responses were significantly better for all ALD518* doses versus placebo (p<0.01) at Weeks 4, 12 and 16. There was a trend toward greater responses with higher ALD518* doses.
Proportion of patients achieving DAS28-defined remission, LDAS and good EULAR responses

<table>
<thead>
<tr>
<th></th>
<th>ALD518* 80 mg (N=32)</th>
<th>ALD518* 160 mg (N=34)</th>
<th>ALD518* 320 mg (N=28)</th>
<th>Placebo - (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAS28-defined remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>10.0</td>
<td>8.8</td>
<td>17.9</td>
<td>0</td>
</tr>
<tr>
<td>Week 12</td>
<td>17.2</td>
<td>21.2</td>
<td>34.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Week 16</td>
<td>13.8</td>
<td>28.1</td>
<td>44.0</td>
<td>0</td>
</tr>
<tr>
<td><strong>LDAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>10.0</td>
<td>23.5</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>Week 12</td>
<td>20.6</td>
<td>33.3</td>
<td>46.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Week 16</td>
<td>20.7</td>
<td>50.0</td>
<td>52.0</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Good EULAR response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>10.0</td>
<td>23.5</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>Week 12</td>
<td>20.7</td>
<td>33.3</td>
<td>46.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Week 16</td>
<td>20.7</td>
<td>50.0</td>
<td>52.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

DAS28=Disease Activity Score 28; LDAS=low disease activity state

[00809] SAEs were reported in two ALD518 patients (both had significant increases in liver enzymes, and discontinued treatment). Overall, elevations in liver enzymes >2xULN occurred in 17% of ALD518* versus 0% placebo-treated patients; the frequency was highest in the 320 mg dose group. Modest increases in total cholesterol were observed (mean increase by Week 16=1.1 mmol/L for ALD518* versus 0.2 mmol/L for placebo). Nine ALD518 patients had transient Grade II and two had transient Grade III neutropenias. There were no serious infections or infusion reactions in any treatment group, and no evident immunogenicity.

[00810] Conclusions: In this Phase II study, the novel IL-6 inhibitor ALD518 resulted in rapid and significant improvements in disease activity sustained over 16 weeks of assessment in
patients with RA and an inadequate response to MTX. ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

**Example 37 Abl Administration**

Methods: Patients with active RA were randomized into a 16 week, double-blind, placebo-controlled trial comparing multiple iv infusions of ALD518 (80, 160 or 320mg). Patients received an infusion every 8 weeks and were maintained on a stable dose of MTX throughout the trial. Assessments included ACR 20/50/70 responses and DAS28. All patients were evaluated for safety. For early withdrawals, LOCF analysis was used for continuous variables and non-responder imputation for categorical variables.

**Results:** 132 patients were randomized; 127 were dosed. Mean disease duration was 6.6 years; mean DAS28 score was 6.2 and mean HAQ-DI was 1.72. 11 patients did not complete the 16-week trial: 320mg-3, 160mg-1, 80mg-3, placebo-4: 4 discontinued due to adverse events (80mg-2, 320mg-2), with 2 SAEs (80mg-1, 320mg-1). Elevations in liver enzymes (LFTs) >2xULN were observed in 17% ALD518 versus 0% placebo. There were modest increases in total cholesterol (mean increase by week 16 = 1.1 mmol/L ALD518 versus 0.2 mmol/L placebo). 9 patients on ALD518 had transient grade 2 neutropenias; 2 pts transient grade 3 neutropenias. There were no serious infections reported in any treatment group. Infusions of ALD518 were well tolerated without infusion reactions or evident immunogenicity. At weeks 4 and 16, ACR responses (non responder imputation analysis) and improvements in DAS28 scores were:

<table>
<thead>
<tr>
<th>Week 4</th>
<th>80mg (n=32)</th>
<th>160mg (n=34)</th>
<th>320mg (n=28)</th>
<th>PBO+MTX (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>50% (16)*</td>
<td>56% (19)*</td>
<td>71% (20)*</td>
<td>23% (8)</td>
</tr>
<tr>
<td>ACR50</td>
<td>9% (3)</td>
<td>15% (5)</td>
<td>29% (8)†</td>
<td>3% (1)</td>
</tr>
<tr>
<td>ACR70</td>
<td>6% (2)</td>
<td>0% (0)</td>
<td>11% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Mean Δ DAS28</td>
<td>-1.8</td>
<td>-2.1</td>
<td>-2</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

*p<0.04; †p=0.009

<table>
<thead>
<tr>
<th>Week 16</th>
<th>80mg (n=32)</th>
<th>160mg (n=34)</th>
<th>329mg (n=28)</th>
<th>PBO+MTX (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>75% (24)*</td>
<td>65% (22)*</td>
<td>82% (23)*</td>
<td>36% (12)</td>
</tr>
<tr>
<td>ACR50</td>
<td>41% (13)*</td>
<td>41% (14)*</td>
<td>50% (140)*</td>
<td>15% (5)</td>
</tr>
<tr>
<td>ACR70</td>
<td>22% (7)†</td>
<td>18% (6)†</td>
<td>43% (12)*</td>
<td>6% (2)</td>
</tr>
<tr>
<td>Mean Δ DAS28</td>
<td>-2.7</td>
<td>-2.7</td>
<td>-3.2</td>
<td>-1.1</td>
</tr>
</tbody>
</table>
**Conclusion:** ALD518 or humanized Abl is the first mAb to IL-6, as opposed to an anti-IL-6 receptor mAb, to show a significant, rapid and sustained improvement in disease activity in RA. ALD518 in doses ranging from 80 to 320mg given as 2 IV infusions to pts with active RA was well tolerated with increases in LFTs and total cholesterol and transient neutropenia observed in some patients. There were no infusion reactions associated with administration of ALD518 and no detectible immunogenicity.

**SEQUENCE LISTING**

The biological sequences referenced herein are provided below:

**SEQ ID NO:** 1
VPPGEDSKDVAAHRQPLTSSERIDKQIRYILDGISALRKECNKSNMCESSKEALAENNLNLPMKAEDGCFQSDFNEETCLVHIITGILEEVEYLYLQRNFESSQARAVQMTKVLIQFLQKKAKNLDITTPDPTTNASLTLKIQAQNQWLDMTTHLRISFKEFLQSSLRALRQM

**SEQ ID NO:** 2
MDTRAPTQLLLLLWLPGARCGAYDMTQTPASVSAVGTVTIKCAQSQINNELSWYQQKPGQRPKLLIYRASATGSSRGSGTELFTLTISDLECADAATTYYCQQGYSRLNIDNAFGGGTEVWKRTVAAPSFIFPPSDQQLKGSATASWCLNN

**SEQ ID NO:** 3
METGLRWLLVAVLKGVCQSLEESGRLVTPGTPLTLTCTASGFSLSNYYVTVWRQAPGKLEWIGIIYGSDETAYATWAGRFITSTKTSTTVDLMKMTSLLTAATDWTFCARDDSSDWDAKFNLWGGTLVTVSSASTKGPSVFPLASSKSTSGTAAALGCLVK

**SEQ ID NO:** 4
QASQINNELS

**SEQ ID NO:** 5
RASTLAS

**SEQ ID NO:** 6
QQGYSRLNIDNA

**SEQ ID NO:** 7
NYYVT

**SEQ ID NO:** 8
IIYGSDETAYATWAIG

**SEQ ID NO:** 9
DDSSDWDAAKFNL
SEQ ID NO: 10
ATGGGACAGGGGCCCAACTGAGCTGAGGGGCTCCTGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCAGATGTGCCTAGTATAGCAAGCGCTGCTCGCTGGGGTCTCATCGCGGTTCAAAGGAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTGAGGAATATTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTGTCTTCATCTTCCGCCCATCTGAGAGAGCATTAACAATGAATTATCCTGGTATCAGCAGAAACCAGGGCATCGTCCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGACGATGCAGCGGACGCATCCACTCGTCTGGTGGAATCGTACGTTACGTCGTCTGGTG

SEQ ID NO: 11
ATGGGAGACCTGGGGCTGCGCTGGCTTCTCCTGTCGTGCCTCAAGAGGTGCCATGTCAGTCGCTGGAGTCCGGGGGTGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAACTACTACGTGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAAATTTATGGTAGTGATGAAACGGCCTACGCGACCTGGGCGATAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTCTGTGCCAGAGATGATAGTAGTGACTGGGATGCAAAATTTAACTTGTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGCGCCCTCAACGAGGCCCCATCGGTCTTCCCCCTGGCACCCTCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG

SEQ ID NO: 12
CAGGCCAGTCAGAGCATTACAAATAATGAATTATCC
SEQ ID NO: 13
AGGGCATCCACCTCTGGCATCT
SEQ ID NO: 14
CAACACGGGTATAGTGCTCGAGAATATTGATAATGCT
SEQ ID NO: 15
AACTACTACGTGACC
SEQ ID NO: 16
ATCATTTATTGATGATGAAACGGCCTACGCGACCTGGGCGATAGGC
SEQ ID NO: 17
GATGATAGTAGTGAATGGGATGAAACGGCCTACGCGACCTGGGCGATAGGC
SEQ ID NO: 18
EVQLVESGGGLVQPGGSLRLASCAASGFLSNNYYVTWVRQAPGKGLEVGIIYGSDTAYATWAIGRFTISRDNSNLYLQMNSLRAEDTAVYYCARDDSSWDAAKFNL
SEQ ID NO: 19
EVQLVESGGGLVQPGGSLRLASCAASGFLSNYYVTWVRQAPGKGLEVGIIYGSDTAYATSAIGRFTISRDNSNLYLQMNSLRAEDTAVYYCARDDSSWDAAKFNL
SEQ ID NO: 20
IQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGBKPLLIYRASTLASGVPSRFSGSGGTDLTISSLQPDDFATYYCQQGYSLLNIDNA

SEQ ID NO: 21
MDTRAPTQLLLGLLWLPGARCYADMTQTPASVEVAVGGTVTINQCSETITYWLSWYQQKPQPPKLIIYQAASDLASGVPSRFSGSGAGTETYLTISVQCDDAATYYCQQGGYSGNSSNVNVRGGGTEVWKRVTAAAPS
FIFPPSDEQLKSGTASWCLLLNF YPREAK

SEQ ID NO: 22
METGLRWLLLAVLKVQCEQLKESGGRLVTPTPPLTLTCTASFGSLNDHAMGWVRQAPKGLEYIGFI
NSGGSARYASWAERFTISRTSSTTVDLKMSTLTTEDTATYFCVRGAVWSIHFSDPWGPRLTVVSSASTKGPSVFLAPSSKSTSGGTAALGCLVK

SEQ ID NO: 23
QASETITYWSLS

SEQ ID NO: 24
QASDLAS

SEQ ID NO: 25
QQGYSGSNVNDV

SEQ ID NO: 26
DHAMG

SEQ ID NO: 27
FINSGGSARYASWAEG

SEQ ID NO: 28
GGAWSIHFSDP

SEQ ID NO: 29
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGCTCCTGCTGCTCTGCTCCACAGGATGTGC
CTATGATATGACCCAGACTCCAGCTGCTGAGGTAGCTGCTGGAGCCACACGTCAACCATACTGCC
AGGCAGTGAGACATTACATTTACGTGTTATTCATGCAAGCAGCCAGCGCTGGGATTCAGCGGCAG
CTGATCTACCAGGATCCGATCTGCTGCTGAGGGTGTCAGTCAGGGGTCTGGCAGCTGGGGCAAGGT
AGATCAGTCTCTCACATTACCTACAGGGCTTGCTCGAGTCAGTGCCTGGGACTACCCGTACCTGC
ATAGTGCTAGTAAATGTTGATAATGTTTCGCGAGAGCCAGAGGTGTTGTTAATAGTGCTAGG
GCCTACCTGTTCTACATCTTCGCCAATCTGAGTACAGTCTGCAGTGACATGGAACATCTGGGAG
CTGTGATCTACTCTATCCACAGAGGGCAAG

SEQ ID NO: 30
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGGAGCAGCT
GAAGGAGTCCGGGCTGCTGCTGCTGCTGCTCAAGGRTGGTGCGATGACACCTGCAACCCTGCTGCAAGCT
TCTCCCTAATGAGCCTGGAATGTTGCTGGGAGGCAGGGGGTTGGAAATACATCGGAGTACATCG
TTCAATATAGTTGTTGCTAGCGCACTCGGAGCGCTGGGAGGGGAGGCTTCTGGGAGGGGAGGCT

CTCGACCACGGTGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGTCA
GAGGGGGTGCTGTTTGGAGTATTCATAGTTTTGATCCCTGGGGCCCAGGGACCTGGTCACCGTCTCG
AGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTCGGCACCTCCTCAAGAGACACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCTGGTCAAG
SEQ ID NO: 31
CAGGCCAGTGAGACCATTTACAGTTGGTTATCC
SEQ ID NO: 32
CAGGCATCGATCTGGCATT
SEQ ID NO: 33
CAACAGGGTTATAGTGGTAGTAATGTTGATAATGTT
SEQ ID NO: 34
GACCATGCAATGGGC
SEQ ID NO: 35
TTCATTAATAGTGGTGATTAGCGCAGCTACGCGAGCTGGGCAGAAGGC
SEQ ID NO: 36
GGGGGTGCTGTTTGGAGTATTCATAGTTTTGATCCCTGGGGCCCAGGGAC
SEQ ID NO: 37
MDTRAPTQLLGLLLLWLPAGATFAAVLTQTSPVSAAVGGTVSISCQASQSISVYDNNYLSSWFQQPKQPPKL
LIYGASTLAlSGVGSPFVSGSCTQFTLTITTDVQCDDAATYYCAGVYDSDSDNAFGGGTEVWKRVTAPLS
VFIFPPSDELKLSGTASWCLNNF
SEQ ID NO: 38
METGLRWLTVALKGVQCSLEESGGRVLTPTPLTLCTASGFSSLVYYMNWVRQPAGKGEWIGFIT
MSDNINASWAKGRFTISKSTTVDLKMTSPTTEDTATYFCARSRGWGMGRDLWGPGLTVVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVK
SEQ ID NO: 39
QASQSVYDNNYLS
SEQ ID NO: 40
GASTLAS
SEQ ID NO: 41
AGVYDDDSDNA
SEQ ID NO: 42
VYYMN
SEQ ID NO: 43
FITMSDKNYASWAKG
SEQ ID NO: 44
SRGWGMGRDLW
SEQ ID NO: 45
SEQ ID NO: 55
QASQSVYENNYLS

SEQ ID NO: 56
GASTLDS

SEQ ID NO: 57
AGVYDDSDA

SEQ ID NO: 58
AYYMN

SEQ ID NO: 59
FITLNNVAYANWAKG

SEQ ID NO: 60
SRGWGAMGRLDL

SEQ ID NO: 61
ATGGGACAGCGAGGCCCCACTCAGCTGCTGGGGCTCTGCTGCTGGCTCCCAGGTGCCATATGTG
CCCTGTGCTGACCCAGACTCCATCTCGGTATCTCGACACTGTGGAGGACAGTCAGCATCAGTTG
GGCCAGTCAGGAGATGTTTATGAGAACAACATATTATCTCGGTTCAGCAGAAACCAGGGCAGCGCTCC
AGCTCCTGATCTATAGTGACATCCTGATCTTCTGGGTGGTCCCATCGGCGTTCAAAAGGCAGTGGATCT
GGACACAGTTCACTTCACCATACAGACGTGCGATGTGACGAGTGCCTGCACATTATGTGCGAGG
GTTATGATGATGATGATGATGATGCCGGAGGAGGAGGTGGAGGAAGGTAACGCCTGGAGGAACCCTG
ACTCCAGCATTGACACTGGCGAAAGGCCGATTCACCTTCTCCAAAA
CTTGCAACAGGGTTGAGACTTAAATGACCGTAACCTTGGGAGGCAAGGCCGATTCACCTTCTCCAAAA
TGTCGCACTTTCTCTGGATTCTAGGGTGCATCCACTCTGGATTCTGGGGTCCCATCGCGGTTCAAAGGC
AGTGGATCTG

SEQ ID NO: 62
ATGGGACAGCTGGGGCTGGCTGGCTTCTCCTCTGTTGCTGCTTCAAGTGGTCCAGTGCAGTCAGAGCAGCT
GAAGGAGTCCGGAGGAGGGCTGTAGAACCCTTGAGGAACCCCTGACACTTGACACACTGCTGTACCTC
CTGGGTTCTCTGCTACATGGCAACACCATGAGGCGAGGGAACACGTGGAGCTCCCATCGGTCTTCCCC
CATGTTGCAATTTGTTTATGAGAACAATGACTTGACACTGGCGAAAGGCCGATTCCCTTCTCCAAAA
CTTGCAACAGGGTTGAGACTTAAATGACCGTAACCTTGGGAGGCAAGGCCGATTCACCTTCTCCAAAA
TGTCGCACTTTCTCTGGATTCTAGGGTGCATCCACTCTGGATTCTGGGGTCCCATCGCGGTTCAAAGGC
AGTGGATCTG

SEQ ID NO: 63
CAGGCCAGTCAGAGTGTTATGGAACAACATTATTTATCC

SEQ ID NO: 64
GGTGCACTCCACTCTGGATTCT

SEQ ID NO: 65
GCAGGGCTTTATGATGATGATGATGATGATGCC

SEQ ID NO: 66
CCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGATCGGAAT
CATTGGTGGTTTTGTACCACATACTACGCGACCTGGGCGAAAGGCCGATTCA ... 8 8
QASKLAS
SEQ I D NO: 8 9
LGGYDDDADNA
SEQ I D NO: 9 0
DYAMS
SEQ I D NO: 9 1
IIYAGSGSTWYASWAKG
SEQ I D NO: 9 2
DGYDDYGDFDRLDL
SEQ ID NO: 93
ATGGACAGGGGCCCACACTGCTGCTGGGGCTCCTGCTGCTCTGGCTCCAGGTGCCACATTTGCA
AGCCGTCGTGACCCCCAGCACCCACCTCCCGCCCTGGGTCTTCTACCTGGGAGGCGACAGTCACCATCAAGTGC
AGTCCAGTCCACTCCACCACACGCGCTGACCTGTGGGAGGCACAGTCACCATCAAGTGC
GTTATGATGATGATGATGATGCTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCG
GCCCCATCTGTCTCTTCCCCGCCCATCTGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGCT
CTGCTGAATAACTTC
SEQ ID NO: 94
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCCGGGGGTCGCCCTGGTACGCCTGGGACACCCCTGACGCATCTGGCAAGATCG
ACCTCACTGCTACTGGTGATGGGCTCGCCACGGTCACAGCTGCAAGAGGCTAGAATGGGATGGAAT
CATTTATGCTGGTATGTTGAGCAGCATGGTACCGAGCTGGGCAAGGCGATCCACCATCTCCAAA
CCTGCACCACTGCTGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTG
AGAGATGGGATACGATGAGCAGCATGGGATGCTGACCTGGGCAAGGCGATCCACCATCTCCAAA
CGTCTCGAGGCCTCCACCAAGGGCCCATGGGCTTCCTCCACCTGGCACCCTCCTCCAAGAGCAGCAGCTCCTGG
GGGCACAGCGCCCCCCTGGCCTGGTCAAGGACT
SEQ ID NO: 95
CAGTGCGACGAGGTGTTATAAATAAATTTTCTTATCG
SEQ ID NO: 96
CAGGCATCCAACTGGCATCT
SEQ ID NO: 97
CTAGGCGGGTATGATGATGATGCTGATAATGCT
SEQ ID NO: 98
GACTATGCAATGAGC
SEQ ID NO: 99
ATCATTTATGCTGGTATGTTGAGCAGCATGGTACCGAGCTGGGCAAGGCGATCCACCATCTCCAAA
SEQ ID NO: 100
GATGGATAGATGACTATGGGATGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTGATGCTG
SEQ ID NO: 101
MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQASQSINNELSWYQQKSGQRPKLLI
YRASLTLASGVSRSKFGSGSGETFTLTISDELCAAAAYCQQGYSLRNIDNAFGGTEVWKRTVAAPSVF
FPFSDEQLKSGTASWCLLNF
SEQ ID NO: 102
CAACAGGGTTATAGTCTGAGGAATATTGATAATGCT
AACTACTACATGACC
ATGATTATGGTAGTAGTGAACAGCTACGGAACCTGGCGATAGGC
GATGATAGTAGTGACTGGGATGCAAAATTTAACTTG
EVQLVESGGGLVQPGGLRSLCAASGFSLSNYMTWVRQAPGKGLEWVGMYYGSDEAYANWAIGRTIS
RDNSKNTLYLMNLRADTAYVYCCARDGSDWDKFNLSL
EVQLVESGGGLVQPGGLRSLCAASGFSLSNYMTWVRQAPGKGLEWVGMYYGSDEAYANSAIGRTIS
RDNSKNTLYLMNLRADTAYVYCCARDGSDWDKFNLSL
DIQMTQSPSTLSASVGRVVTACQASQINNLSWYQQPKPGKPKLIIYRASLLASGVPSRFSGSSTTEFTL
TISSLQPPDFATYYCQQGSYLSRNIDNA
MIYGSDEAYANSAIG
MDTRAPTQQLGLLLLWLPATFAAVLTQTPSPVSAAVGGTVITSCQSSQVGNQDLSWFQRPQPKLILLYEISKLESGVPSRFSGSSTTEFTLTISSFGCDDAATYYCLGGYDDDADNA
METGLRWLLLVALRGVQCHSVEEGRGLVTPGTPLTLCTVSFSLSSRTMSWVRQAPGKGLEWIGYIW
SGGSSTYYATWAKGRFTISKSTTVDLKITSPTTEDTATYFCARLGDTGGHAYATRLNL
QSSQVGVNSQDLS
EIISKLES
SRTMS
YIWSSGGSTYYATWAKG
SEQ ID NO: 129
LGDTGGHAYATRLNL

SEQ ID NO: 130
ATGGACACAGGGGCCCCACAGCTGCTGGGCTCCTGCTCCAGGTGCCACATTTGCT
AGCCCGTGCTAGCCAGACACCATCAACCCGTGTGCTGAGCTTGAGGCACAGTCACCACAGTTG
AGTCAGTCAAGTGTGCTATCCCTCTGCTGTTCTCAACGAGGAGGCGGAGGCGAGCCCTCCC
AAGCTCCTGATCTACGAAAATATCCCAAAGTGGGGAATCTGGGTTCCCAGCAGTTGAGATCCG
TGAGACACTTCACCTACACCAAGGCAGTGATGTCGGCTGCAAATTTGC
CGTATTATGATGATGATGCTGATAATGCT

SEQ ID NO: 131
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCACTCGGTGGA
GGAGTCCCGGGGGTCGCCTGTCAGCCTGGGACACCCCGGGGACACCCCTGAGACACTCACAGTCTGTGGATTCT
CCCTCAGTAGTCTGGAATCTGCCTGGGTTCCAGGGGAAAGGGGCTGAGAAGGATCGGATACACAC
ATTGGAATGGGTGGTAGACCATATACAGCGACCTGGGCAGAAAGCCGATTCATTCCACCATCTCAAACCCCT
AACCACCGTGATCCGGAATCTACCAGTGGCAACACCAGACACACGGCAAGGCCACACTTATTTCTGTGCGGAGAT
TGAGCAGTACTGCTGGTCTACGACCTTATAGCTACACTGCCCTAAATCTC

SEQ ID NO: 132
CAGTCCAGTCAAGGTGTTGTTAATAACCAGGACTTATCC

SEQ ID NO: 133
GAAATATCCAAAACCTGGAATCT

SEQ ID NO: 134
CTAGGGCGGTATGATGATGATGCTGATAATGCT

SEQ ID NO: 135
AGTCGTACAATGTCC

SEQ ID NO: 136
TACATTGGAGATGGTGTTAGACCATATACAGCGACCTGGGCAAGGGGC

SEQ ID NO: 137
TTGGGGCATACTGTGTTGTCGACCTGATATGCTACACTTAAATCTC

SEQ ID NO: 138
MDTRAPTQLLGLLLLLWLGATFAAVLQTPSSVAAVGGTVSISCQSSQSYSNKYLAWYQKPGQQPKL
LIFYWSKLSAGAPRSFGSGCTQFTLTISGQCDDAATYCLGAYDDDA

SEQ ID NO: 139
METGLRWTLLLVAVLKVQCSVEESGGRLVKPDEILTLTCTASGFSLEGGYMTWVRQAPGKLEWIGSY
DSGSTYYASWAKGRFTSHTSSTTVDLKMTSLTTEDTATYFCVRSLKYPVTVDSDL

SEQ ID NO: 140
QSSQSVYSNKYL

SEQ ID NO: 141
WTSKLAS
SEQ ID NO: 142
LGAYDDDADNA
SEQ ID NO: 143
GGYMT
SEQ ID NO: 144
ISYDSGSTYASWAKG
SEQ ID NO: 145
SLKYPTVTSDDL
SEQ ID NO: 146
ATGGACACGAGGCCCCACTCACGTGCTGGGGCTCCTGCTCTGGCTCCACCAGGTGCCCACATTTTGCA
GACGATCGCTGCCGCAGTGTTTATAGTATAAATGAGCTACGCAAGAACAGGCGGACTCCTCCAGGGCC
AGCTGCTGACCCAGACACCATCGTCCGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGC
AGTGGACACAAATTCACCTACCATCAGCGCAGTGCAGTGCAAGATGCTGCCACTTACTACTGTCTAG
GGCCTATGATGATGCTGATAATGCT
SEQ ID NO: 147
ATGGGAGACTGGGCCGCTGGCTTCTCCTGGCAGGTGCCTGAAGCCGCTGACACTCACCTGCACAGCCTCG
ATTCTGGACCAAGGGCGCAGTGCAGTGCAAGATGCTGCCACTTACTACTGTCTAG
GGCCTATGATGATGCTGATAATGCT
SEQ ID NO: 148
CAGTCCAGTCAGAGGTCTTTATAGTATAAATGAGCTACGCAAGAACAGGCGGACTCCTCCAGGGCC
AGCTGCTGACCCAGACACCATCGTCCGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGC
AGTGGACACAAATTCACCTACCATCAGCGCAGTGCAGTGCAAGATGCTGCCACTTACTACTGTCTAG
GGCCTATGATGATGCTGATAATGCT
SEQ ID NO: 149
TGGACATCCCAAACGTCATCCT
SEQ ID NO: 150
CTAGGCCTATGATGATGCTGATAATGCT
SEQ ID NO: 151
GGCGGCTACATGACC
SEQ ID NO: 152
ATCAGTTATGATGAGCTAGCACTACTACGCGAGCTGGGCGAAAGGC
SEQ ID NO: 153
TCATCAAAATATCCTACTGTTACTTCTGATGACTTG
SEQ ID NO: 154
MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQSSQSVYNNNDLAWYQQKPGQPPKL
LIYYASTLASGVPSRFKGSGSGTQFTLTISGVQCDDAAAYYCLGGYDDDDADNA

SEQ ID NO: 155
METGLRWLLLAVLKGVQCQSVEESGRLVTPTPLTLTCTVSGLSLSSNTINWVRQAPGKGLEWIGIWS
GGSTYASWVNTRGLFTSIKTSTTVDLKITSPTTEDTATYFCARGGYASGGYPYATRLDL

SEQ ID NO: 156
QSSQSVYNNNDL

SEQ ID NO: 157
YASTLAS

SEQ ID NO: 158
LGGYDDDDADNA

SEQ ID NO: 159
SNTIN

SEQ ID NO: 160
YIWSGGSTYYASWVNG

SEQ ID NO: 161
GGYASGGYPYATRLDL

SEQ ID NO: 162
ATGGGCAAGGGCGCCACCTACGCTGCTGGGGCTCCTGCTGCTCTGGCTCCAGGTGCCACATTTGC
AGCCGTCGTGACCCAGACACCATACACCCCTGTCTGCAGTGGGAGGACAGTCACCACATCGTTGCC
AGTCCAGTCAGTGCGTTATAATAATAAAGCAGTTAGCTGGTATACGAGAAAACCAGGGGACCCCT
AAACTCTGTGATCTATATTGCTCATCCACTCTGGCATTGGGTCCATCGGTTCAAAAGGCAGTGGATCT
GGGACACAGTTCACTCTCCATCAGCGGGTGCAGTGTGACGATGCTGCCGCTTACTACTGTCTAGG
CGTATGATGATGATGCTGATAATGCT

SEQ ID NO: 163
ATGGGAGACTGGGCTGCGCTGGCTTCTCTTGCTGCTGCTCTGGCTCCAGGTGCATCTGGTGGGA
GGAGTCCCGGGGCTCCGCTGTCACGGCTGGGACACACCCCTCAGCACACCTCGTGATTAT
CCTCAGTAGCAATACAAATAAAGTGGGCCCGCCAGGCTCCAGGGAGGGCTGGAGTGGATCAGATA
CATTTGAGTGGTGGTGTTATAGCTACACACAGGCTGGGAGGTGTCTGACACATCGTATCGTATCTC
CGACCACGGGTGGATCTGAAAAATCCACAGTGCCCAACCCGAGACACGGCCACCTATTCTGTGGCCAGA
GGGGATTACGTGCGGTTATCATTTATGCAGTCCCCGCTGATCTC

SEQ ID NO: 164
CAGTCCAGTCCAGTGGTGGTTATAATAAAAGCAGCTTAGCC

SEQ ID NO: 165
TATGCATCCACTCTGGCATCT

SEQ ID NO: 166
CTAGGGCGTTATGATGATGCTGATAATGCT
SEQ ID NO: 167
AGCAATAACAATAAAC
SEQ ID NO: 168
TACATTTGGAGTGGTGGTAGTACATACTACGCGAGCTGGGTGAATGGT
SEQ ID NO: 169
GGGGTTACGCTAGTGGTGGTTATCCTTATGCCACTCGGTTGGATCTC
SEQ ID NO: 170
MDTRAPTQLLLGLLWLPGATFAAVLTQTPSVSAAVGGTVTINCQSSQSVYNNDLWSWYQQRPGQRPKL
LIYGASKLASGVSFKGSGSGBKFTLTISGVQCDDAATYYCLGDYDDADNT
SEQ ID NO: 171
METGLRWLLLVALKGVQCQSLEESGRLVTPGTPLTCTVSGFTLSTNYLSWVRQAPGKGEWIGIYYP
SGNTYCAKWAKGRFTISKSSTTVDLKMSTPTTEDTATYFCARNYGGDES
SEQ ID NO: 172
QSSQSVYNNDYLS
SEQ ID NO: 173
GASKLAS
SEQ ID NO: 174
LGDYDDADNT
SEQ ID NO: 175
TNYYLS
SEQ ID NO: 176
IIYPSGNTYCAKWAKG
SEQ ID NO: 177
NYGGDES
SEQ ID NO: 178
ATGGGACAGAGGGCCCGACTCAGCTGCTGGGGCTCCTGCTGCTCCAGTGCCACATTGCGAGCCGCAGGG
AGCCTGCTGACCAGACACCCTCTCGTCTGCTGCTCTGGCTCCCAGGTGCCACATTTGC
AGCCTGCTGACCAGACACCCTCTCGTCTGCTGCTCTGGCTCCCAGGTGCCACATTTGC
AGTCCAGTCAGAGGTGGTTATAATAAAGCAGACTTTATCTGGTCATCAACAGGGCGGGCGAACGTCCC
AGGCTCTAACATCTATGTGCTTTTCCAACTGGCCATCTGGGCTCCCAGGTGCCACATTTGC
AGGCTCTAACATCTATGTGCTTTTCCAACTGGCCATCTGGGCTCCCAGGTGCCACATTTGC
TGGGGCCACGTGGTTCGGGACGATGTGACGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT
GCGATTATGATGGATGGATGGATGGATGGATGGATGGATGGATGGATGGATGGATGGATGGATGGATGGT
SEQ ID NO: 179
ATGGGACAGAGGGCCCGACTCAGCTGCTGGGGCTCCTGCTGCTCCAGTGCCACATTGCGAGCCGCAGGG
AGCCTGCTGACCAGACACCCTCTCGTCTGCTGCTCTGGCTCCCAGGTGCCACATTTGC
AGGCTCTAACATCTATGTGCTTTTCCAACTGGCCATCTGGGCTCCCAGGTGCCACATTTGC
AGGCTCTAACATCTATGTGCTTTTCCAACTGGCCATCTGGGCTCCCAGGTGCCACATTTGC
CCTGATCGTGAAGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGGCTGGG
ATCATTTATCCTAGTGGTAACACATATTGCGCGAAGTGGGCGAAAGGCCGATTCACCATCTCCAAAAC
CTCGTCGACCACGGTGGATCTGAAAATGACCAGTCCGACAACCGAGGACACAGCCACGTATTTCTGTGCCAGAAATTATGGTGGTGATGAAAGTTTG
SEQ ID NO: 180
CAGTCCAGTCAGAGTGTATTTAATAAACGACTACTTATCC
SEQ ID NO: 181
GGTGCTTCACACTGGCATCT
SEQ ID NO: 182
CTGGGGCGATTATGATGATGATGCTGATAATACT
SEQ ID NO: 183
ACCAACTACTACCTGAGC
SEQ ID NO: 184
ATCATTTATCCTAGTGTAACACATATTGCGCAAGTGCGGCGAAAGGC
SEQ ID NO: 185
AATTATGGTGGTGATGAAAGTTTG
SEQ ID NO: 186
MDTRAPTQLLGLLLLWLPGARGCDWMTQTPASVEAVGGVTIKCQASETIGNALAWYQQKSGQPPKLLIYKASKLASGVPFRKGSGSGTEYTLTISDLECADAAAAYCYQWCYFGD
SEQ ID NO: 187
METGLRWLLLVTLVKGVQCQEQLVESGGGLVQPEGSLTTLTCTASGFDSSGYYMCWVRQAPKKGLEWICIFTITNTYYASWAKGRFTISKSSTTTVLQMTSLTAADTATYLСARGIYSDNNYYAL
SEQ ID NO: 188
QASETIGNALA
SEQ ID NO: 189
KASKLAS
SEQ ID NO: 190
QWCYFGD
SEQ ID NO: 191
SGYYMC
SEQ ID NO: 192
CIFTITTNTYYASWAKG
SEQ ID NO: 193
GIYSDNNYYAL
SEQ ID NO: 194
ATGGACACGAGGGCCCCACTCAGCTGGGGCTTCTCTGCTGTGCTCTGGCTTCAGTGCCAGATGTGA TGTGGTGATGACCCAGACTCCAGCCCTCCGTGGAAGGCGAGCTGGGAGGCGAGACTCACCATACCAGTGCC AGGCCAGTGAGACCATTGGCAATGCATAGCGCTCTGTATCAAGAATACAGGGCAGCTCCTCCAGCTC CTGATCTACAAGGCATCCCCACTGGCATCTGGGCTTCACCGGTCGTTCAAGGCAGTGATCGGAC
AGAGTACACTCTCACCACATCGAGGAGTGTGCGGATGCTGACCTACTACTACTGTCAATGGTGTTATTATGTTT
SEQ ID NO: 195
ATGGGAGACTGGGCTGCGCTGGCTTTCTGTCGCTAAGGTGTCCAGTGTCAGGAGCATGCAGGTGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCAGTAGCGGCTACTACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCGAATTACCATCTCC
AAGACCTCGTGCACCCAGGGTGAACCTGCATCTCGACACGGCCGACACGGCCACCTATCTCTGTGCGAGAGGGATTTATTCTGATAATAATTATTATGCTTG
SEQ ID NO: 196
CAGGCCAGTGAGACCATTGGCAATGCATTAGCC
SEQ ID NO: 197
AAGGCATCCAAAACCTGGCCT
SEQ ID NO: 198
CAATGGTGTTATTTTGGTGATAGTGTT
SEQ ID NO: 199
AGCGGCTACTACATGTGCT
SEQ ID NO: 200
TGTATTTTCCTATTACTACTACTACACTACACTACGCGAGCTGGGCGAAAGGCACTACATCAGGCGACACGGCCACCTATCTCTGTGCGAGAGGGATTTATTCTGATAATAATTATTATGCTTG
SEQ ID NO: 201
GGGATTTATTCTGATAATAATTATTATGCTTG
SEQ ID NO: 202
MDTRAPTQLLGLLLLWLPGARCDWMTQTPASVEAAVGGTTVIKCQASENIALAWYQQKPGQPPKLIYKASTLASSGVSFRFSGSSTGETLTLTISGVQCADAAYCYQWCYFGDSV
SEQ ID NO: 203
METGLRLLLVLAVLKGVQCPQQQLVLZGESGGGLVPGASLTLTCKASGFSFSSGYMCWVRQAPKGCGSIA
CIFTITDNTYANWAQGRFTISKPSPTQVTLQMTSLTAADATYFCARGIYSTDNYYAL
SEQ ID NO: 204
QASENIALA
SEQ ID NO: 205
KASTLAS
SEQ ID NO: 206
QWCYFGDSV
SEQ ID NO: 207
SGYYMC
SEQ ID NO: 208
CIFTITDNTYANWAQ
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
ATGGGACACGGGCGCTCGGGCTCTCTCTGGGCTGCTGCTCGTCCAGGTGCCAGATGTGA
TGTTGTGATGACCCAGACTCCAGCCTCCGTTGAGAGGCAGCTGTGGGAGGCGACAGTCACCATCAAGGCT
AGGCCAGTCAGAGCGTTAGTAGCTACTTTAAACTGGTATACGAAAGGCGACGGCCTCCCAAGCTC
CTGATCTACAGGGCATACACTCTGGAATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGAC
AGAGTTCACTCTCACCACATCGGACCTGGAGTGTGCGATGCTGCCACTTACTACTGTCAATGTACTTATGGTAGTGTCTGCT
SEQ ID NO: 227
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCCGGGGGCTCGCGGTACGCTCCGCCAGGCTCCAGGCAAAGGGCTGGAATGGATCGGAAT
CATTAGTTATAGTGGTACCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCT
CGTCGACCACGGATGGATCTGAAAATCAGTACTCGGACCAACAGGACACGGCACCCTATCTCTGTGCC
AGAGATGACCTAGCTACGAGTTATGGTAGTCTACCTTTTGAGGCCGCGCATGGACCTC
SEQ ID NO: 228
CAGGCCAGTCAGAGCGGTAGTAGCTACTTTAAC
SEQ ID NO: 229
AGGGCATCCACTCTGGAATCT
SEQ ID NO: 230
CAATGTACTTATGGTACTACTAGTAGTATGGTACTCTGCT
SEQ ID NO: 231
AGCAATGCAATAAGC
SEQ ID NO: 232
ATCATTAGTTATAGTGGTACCACATCACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCT
GATGACCTACGACAGTTATGGTATACCTTTTGAGGCCGCGCATGGACCTC
SEQ ID NO: 233
GATGACCTACGACAGTTATGGTATACCTTTTGAGGCCGCGCATGGACCTC
SEQ ID NO: 234
MDTRAPTQLLGLLLLWLPGATFAQVLTQTASPVSAAVGGTVTINCQASQSVYKNNYLSWYQQKPGQPPK
GLIYSASTLDSGVPLRFSGSGSGTQFTLTISDVQCDADATYCLGYSYDCESSGDCYA
SEQ ID NO: 235
METGLRWLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCTASGFSFSYWMCWVRQAPKGLEW1ACIV
TNGNTYYANWAKGRFTISKTSSTTVLQMTSLTAADTATYFCAKAYDL
SEQ ID NO: 236
QASQSVYKNNYLS
SEQ ID NO: 237
SASTLDS
SEQ ID NO: 238
LGSYDCESSGDCYA
SEQ ID NO: 239
SYWMC
SEQ ID NO: 240
CIVTGNGNTYYANWAKG
SEQ ID NO: 241
AYDL
SEQ ID NO: 242
ATGGGACACGAGGGCCCCCCTCGAGTCGCTGGGCTCTCTGCTGTGTGCTCCAGGTGCCACATTTG
CCAAAGTGCTGACCCAGACTGCATCGCCGGCACCTGACGCTACCTGGGTCCACATTGC
AGGCGAGTCGAGGTGTATAAGAAGCAACTACTTATCTGCTGATGCAGAAACCAAGGGCAGGCTCCCA
AAAGGCCTGATCTATTTCTGCACTGACTCTAGATTCTGGGTCCCATTGCGGTTCAGCGGCTGATG
GGGACACAGTTCACTCTCACCATCAGCGACGTGCGAGTGTGACGATGCTGCCACTTACTGTCTAGG
CAGTTATGATTGTAGTGTTGATTGTTATGCT
SEQ ID NO: 243
ATGGGAGACTGGGCTGCGCTGGCTTCTCTGCTGTGCTGGCCTCAGTGTGCTGCTGTTGGA
GGAGTGCGGGGGGAGACCTGTGCAAGGCTGAGGTGATCGCTGCACTCGGCTACTGCTAGATTCT
CCTTCAGTAGCTACTGGATGTGTGCTGGGCGCCAGGCTCAGGGAAGGGGCTGGAGTGGGATCGCATGC
ATTGTATTGGAATACACTACTAGCAGCAGGGGCTGAGGCGGAGACAGCTCAGGCTAGAGG
CTGCTGACGAGGGACACGAGGGGAGACCTGTGCAAGGCTGAGGTGATCGCTGCACTCGGCTACTGCTAGG
CAGTTATGATTGTAGTGTTGATTGTTATGCT
SEQ ID NO: 244
CAGGGCAGTCGAGGTGTTTATAAGAAGCAACTACTTATCC
SEQ ID NO: 245
TCTGCATCGACTCTAGATTCT
SEQ ID NO: 246
CTAGGCAGGTGATTGTAGTGTTGATTGTTATGCT

259
SEQ ID NO: 247

AGCTACTGGATGTGC
SEQ ID NO: 248

TGCATTGTTACTGGTAATGGTAACACTTACTACGCGAACTGGGCGAAAGGC
SEQ ID NO: 249

GCCTATGACTTG
SEQ ID NO: 250

MDTRAPTQLLGLLLLWLPGSTFAAVLTQTPSPVSAAVGGTVSISCQASQSVYDNNYLSWYQQKPGQPPKL
LIYGASTLASGVPSRFKGTGSGTQFTLTITDVQCDDAATYYCAGVFNDDSDDA
SEQ ID NO: 251

METGLRWLLLVAVPKGVQCQSLEESGGRLVTPGTPLTLTCTLSGFSLSAYYMSWVRQAPGKGLEWIGFITL
SDHISYARWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCARSRGWGAMGRLDL
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

ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTTCCACATTTGCC
GCCGTGCTGACCCAGACTCCATCTCCCGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCA
GGCCAGTCAGAGTGTTTATGACAACAACTATTTATCCTGGTATCAGCAGAAACCAGGACAGCCTCCCA
AGCTCCTGATCTATGGTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCACGGGATCT
GGGACACAGTTCACTCTCACCATCACAGACGTGCAGTGTGACGATGCTGCCACTTACTATTGTGCAGG
CGTTTTTAATGATGATAGTGATGATGCC
SEQ ID NO: 259

ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCCCAAAGGTGTCCAGTGTCAGTCGCTGGA

GGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACACTCTCTGGATTCT
CCCTCAGTGCATACTATATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATTC
ATTACTCTGAGTGATCATATATCTTACGCGAGGTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTC


GACCACGGTGATCTGAAATGACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGATGC
SEQ ID NO: 260
CAGGCCAGTCAGAGTTTATGACAAACAACATTTATCC
SEQ ID NO: 261
GCGGTGATCCACTCTTGGCAGC
SEQ ID NO: 262
GCGGTGATCCACTCTTGGCAGC
SEQ ID NO: 263
GCATATATGCAGC
SEQ ID NO: 264
TTCCATTACCTCTGAGTGATCATATATCTTACGCGAGTGGGGCAAGGC
SEQ ID NO: 265
AGCGGTGGCTGGGGTGCAATGGGTCGGTTGGATCTC
SEQ ID NO: 266
MDTRAPTQLLLGLLLGLLLWLPGATFAAVLTQTPSPVSAAVGTVTIASCQASVYNNKNLAWYQQKSGQPPKL
SEQ ID NO: 267
LIYWASTLASVSSRFSGSTQFTLTVSGVQDDAATYYCLGVFDDADNA
SEQ ID NO: 268
QASVYNNKNLAWYQQKSGQPPKL
SEQ ID NO: 269
WASTLAS
SEQ ID NO: 270
LGVFDDADNA
SEQ ID NO: 271
SYSMT
SEQ ID NO: 272
VIGTSGSTYYATWAKG
SEQ ID NO: 273
SLSSITFL
SEQ ID NO: 274
ATGGACACGAGGCCCCCATCTCAGCTGCTGGGGCTCTCGTGCTGTGCCCAGGTGCCACATTGCACG
AGGCCCAGTCAGAGTGTATTTATAAACAAACAAAATTTAGCCTGTGATGCAACAAATCACAGGGCACCTCCC
AGGCCCAGTCAGAGTGTATTTATAAACAAACAAAATTTAGCCTGTGATGCAACAAATCACAGGGCACCTCCC
AAGCTTCCTGATCTACTGGGCAATGGGTCGGTTGGATCTC
SEQ ID NO: 275

GGGACACAGTTCACTCTCACCGTCAGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGG
CGTTTTTGATGATGATGCTGATAATGCT
SEQ ID NO: 275
ATGGGAGCTGGGCTGCGCTGGCTTCTCCTGCTGGCTGCTCAAGGTGTCAATGTCAGTCGGTGGA
GGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACTCAGCACAGGACACAGG
CCACTCTCTGATTCTCCCTCAGTAGCTACTCCATGACCCTGGGTCCGCCAGGCTCCAGGGAAGGG
GCTGGAATATATCGGAGTCATGGTACTAGTGGTAGCACATACTACGCGACCTGGGCGAAAGGCC
ATTCAGTCTCCATGAAAATCACAGTCCGACAACCAGGACACGGCCACCTATTTCTGTGTCAGGAGT
GTTTTCTTCTATTACTTTCTTG
SEQ ID NO: 276
CAGGCCAGTCAGAGTGTTTATAACAACAAAAATTTAGCC
SEQ ID NO: 277
TGGGCATCCACTCTGGCATCT
SEQ ID NO: 278
CTAGGCGTTTTTGATGATGATGCTGATAATGCT
SEQ ID NO: 279
AGCTACTCCATGACC
SEQ ID NO: 280
GTCATTGGTACTAGTGGTAGCACATACTACGCGACCTGGGCGAAAGGCC
SEQ ID NO: 281
AGTCTTTCTTCTATTACTTTCTTG
SEQ ID NO: 282
MDTRAPTQLLGLLLLWLPGARCAFEFQTQPASVEAAVGGTGTINQASQNIYRYLAWYQQPKPGQPPKFLIY
LASTLSGVPSRFKGSQSTRTLISDLECADAAATYYCQSYYSSNSVA
SEQ ID NO: 283
METGLRWLLLLVAKGVQCQEQVLVESGGDLVQPEGSLTTLCTASELDFSSGYWICWVQPGKGLEWIG
CIYTGSSGFTYAWNSWAKGRFTISKTSSSTTQLQMSTLAADTATFYCARGYSFGFYFKL
SEQ ID NO: 284
QASQNIYRYLA
SEQ ID NO: 285
LASTLAS
SEQ ID NO: 286
QSYYSSNSVA
SEQ ID NO: 287
SGYWIC
SEQ ID NO: 288
CIYTGSSGFTYAWNSWAKG
GYSGFGYFKL

ATGGACAGCGAGGGCCACACTCACGTGCTGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCAGATGTGC
ATTCGAATTTGACCCAGACTCCAGCCTCCGTGAGGCACAGCTGACCTCAATTGCC
AGGCCAGTCAGAACACTTTATAGATATTTAGCCCTGTGATAGCAGCCAAACGGCAAGCGACTCCACAT
CTGATCTATCTGGCATCTACTCTGGCATCTGGGGTCCCATCGCGGTTTAAAGGCAGTGGATCTGGGACA
GAGTTCACTCTCACCACAGCGACCTGGAGTGTGCTGCGATGCTGCCACTTACTACTGTCGTCGCT

CAGGCCAGTCAGAACATTTATAGATACTTAGCCTGGTATCAGCAGAAACCAGGGCTGGAGTGGATC
GGTTGCGCATTTATACTGGTAGATGGAAGCTCCGTGAACTGGGGAAGGCCGAAGCTGTGGGAGGCACAG

AGCGGCTACTGGCATCT

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGTTIKCQASEDIYRLLAWYQQKPGQPPKLLI
YDSSDLASGVPSRFKGSATFLASIGVQCDDAATYYCQQAWSYDIDNA

METGLRWLLLAVLKVQVCSVEESGGRLVTPGTLTLTCTASGFSLLSYYMSWVRQPDKGLEDIGI

QASEDIYRLA
DSSDLAS
SEQ ID NO: 302
QQAWSYSDIDNA
SEQ ID NO: 303
SYYMS
SEQ ID NO: 304
IITTSGNTFYASWAKG
SEQ ID NO: 305
TSDIFYYRN
SEQ ID NO: 306
ATGGGACACGAGGCGCCACTCACAGCTGCTGGGGCTCTGCTGGCTCCCAGGGCACAGATGGCC
CTATGATATGGACACGACTCCAGCCTCTGCTGGAGGAGAGCTGGCTAGTCACCACATCAAGTGCCC
AGGCCAGTGAGGACATTTTATAGTTATGGGCTGGTATCACAACAGAACCAGGGGGATCTGCTCATTCA
AGGCAGTGAGGACATTTTATAGGTTATTGGCCTGGTATCAACAGTGGATCTGGGACTA
AGAGTTCTACCTCGCCATCAACGGGGCTGGGCTAGTGCTGCTCCACTTACTACTGTCACACAGGCTTG
GAGTTATAGTGATATGGGATTTTGCTGCAGTCTGCTGCCAGTTGATGGTATGGCTCCTGGATCTGGGC
SEQ ID NO: 307
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAAGGTGTCAGTGCTAGTGGGA
GGAGTCCGGGGGTGCTGGTACGCCGGGGACACCCCTGACACTCACTGCACAGCCTCTGGATTCT
CCCTCAGTAGCTACTACATGAGCTGGGGCTGCCACAGCATCGAGGCAAGGGCTGGAATGGATCGGAATC
ATTACTACTAGTGGTAATACATTTTACGCGAGCTGGGCGAAAGGCCGGCTCACCATCTCCAGAACCTC
GACCAGGTGGATCTGAAAATCACAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAA
CTTCTGATATTTTTATTATCGTAACTTG
SEQ ID NO: 308
CAGGCCAGTGAGGACATTTTATAGGTTATTGGCC
SEQ ID NO: 309
GATTTCATCCGATCTGGCATCT
SEQ ID NO: 310
CAACAGGGCTGGGAGTTATAGTGAATTTGATATGCT
SEQ ID NO: 311
AGCTACTACATGAGC
SEQ ID NO: 312
ATCATTACTAGTGGTAATACATTTTACGCGAGCTGGGCGAAAGGGGACTGAGG
SEQ ID NO: 313
ACTTCTGATATTTTTATTATCGTAACTTG
SEQ ID NO: 314
MDTRAPTQLLGLLLLWLPGATFAAVLTQTASPVSAAVGATVINTQCQSSQSVYNDMDLAWFQQKPGQPPL
LIYASTLASGVPFSGSGTGTEFTLTSGVQCDDAATTYCLGAFFDDADNT
SEQ ID NO: 315
METGLRWLLLAVLKVQCVQSVEGGRLVTGTLPILTCTVSGFSLTRHAIWVRQAPGKGLEWIGCIW
SGGSTYYATWAKGRTISKSTTSTVDRRITSPTTEDTATYFCARVIGDTAGYAYFTGLDL
SEQ ID NO: 316
QSSQSVYNDMDLA
SEQ ID NO: 317
SASTLAS
SEQ ID NO: 318
LGAFFDDADNT
SEQ ID NO: 319
RHAIT
SEQ ID NO: 320
CIWSSGSTYYATWAKG
SEQ ID NO: 321
VIGDTAGYAYFTGLDL
SEQ ID NO: 322
ATGGACACGAGGGCCCCACTCAGCTGCTGGGCTCCTGCTGGCTCCCAAGTGCCACCTTGAC
AGCCGTGCTGACCAACTGCACTGACCTGGCTCCTGCTGGCTGCTCCCAAGTGCCCACTGAC
AGTCCAGTCAGTGGTAAAATGACATGGAGCTTACGCGGCGTCTACGCTGG
AAGCTCCCCATCTACTGTGATCATGCGCTTTGATGATGATGCATGATG
SEQ ID NO: 323
ATGGGAGACTGGGCTGGCCCTGCTGCTGGCCTTCTCTCAGGAGCTGCTGCTGCTGGATG
GGAGTCGAGGGGGCTCCTGCTGACCTGGCTCCTGCTGCTGGCTCCTGCT
CCCTCACTAGGGCATGCAATAACCTTGGGCCCTGCCTCAGGGAGGCTGGGAATGGGACCGATG
CATTGTGGATGATGGGTGATACATCTACGGGGACCTGGCAGAGGACCGACTGATGTCT
CGACCACGCTGGATCTCAGAATCTACGGCCAGCAGGATTAGGATGCTGGAGC
GTCAATTGGGGCATCTGCTGTTATGTTATTTTACGCGGCTGGTGA
SEQ ID NO: 324
CAGTCAGTCAGGACTGGTTTTATAATGACATGGAGCTTACGCGGCGTCTACGCTGG
SEQ ID NO: 325
TCTGCACTGACTGGCATCT
SEQ ID NO: 326
CTAGGGCGCTTTTGATGATGCTGCTAATACT
CGTCGACCACGGTGGATCTGAAAATTACCAGTCCGACAACCGAGGACTCGGCCACATATTTCTGTGCC
AGAGGGGGTGCTGGTAGTGGTGGTGTTTGGCTGCTTGATGGTTTTGATCCC
SEQ ID NO: 340
CAGGCCAGTGAGTAGTTTATAATTTGGTATCC
SEQ ID NO: 341
ACTGCATCCAGTCTGGCATTCT
SEQ ID NO: 342
CAACAGGGTTTACTAGTGTGTTGATAATGTT
SEQ ID NO: 343
AGCTATGCAATGGGC
SEQ ID NO: 344
ATCATTAGTGTAGTGTAGCACACATACTACGCGACTGGGCAGGAGGC
SEQ ID NO: 345
GGGGGTGCTGGTAGTGGTGGTGTTTGGCTGCTTGATGGTTTTGATCCC
SEQ ID NO: 346
MDTRAPTQLGLLLLWLPGAKCADVVMTQTPASVSAVGGTVTINCQASENIYNYLAWYQQKPGQPPKL
LIYTVGDLASGVSSRFKSGSGTEFTLTISDLECADAATYYCQQGYSSSYVDNV
SEQ ID NO: 347
METGLRWLLLVALKGVQCQEQLKESGGRLVTPGTPLTLTCTVSGFSLNDYAVGWFRQAPGKGLEWIGY1
RSGTTAYATWAKGRFTISATSTTVDLKITSPTTEDTATYFCARGGAGSSGVWILDGFAP
SEQ ID NO: 348
QASENIYNYL
SEQ ID NO: 349
TVGDLAS
SEQ ID NO: 350
QQGYSSSYVDNV
SEQ ID NO: 351
DYAVG
SEQ ID NO: 352
YIRSSGTAYATWAKG
SEQ ID NO: 353
GGAGSSGVWILDGFAP
SEQ ID NO: 354
ATGGACACGAGGGCCCCACTCAGCTGCTGGGGCTCTCTGTGCTGGCTCCAGTGCCAAATGTC
CGATGTTGTGATGACCCAGACTCCAGCCTCCGTGCTGGGAGGCACAGTCGCCATCAATT
GCCAGGCCAGTGAAGACATTTATAATTTGGTATGCTCAGCAGAAACCAGGGCAGCCTCCCAAG
CTTCCTGATCTATCTGAGGCGATCTGGCATCTGGGCTCTCATCGCGGTTCAAAGGCAGTGGATCTGG
GACAGAGTTCACTCTACCAGTCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTATTGTCAACAGG
GTTATAGTAGTTATGGTATAATGTT
SEQ ID NO: 355
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGGAGCAGCT
GAAGGAGTCCGGGGTGCGCTCGACGGCCTGGGACACCCCTGACACTCACACTGGCCACAGTCTCTGGAT
CTCCCTCAATGACTATGCAGTGGGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGA
TCTCCCTAACTCTGCTGGGGTCTGGATTGGTCTGGATCTCCAGGCTGCGATAGTGACCGAGGAGGAGG
SEQ ID NO: 356
CAGGCCAGTGAGAACATTTATAATTGGTTAGCC
SEQ ID NO: 357
ACTGTAGGGCACTGGCACATCT
SEQ ID NO: 358
CAACAGGGTTATAGTAGTTATGGTATAATGTT
SEQ ID NO: 359
GACTATGCAGTGGGC
SEQ ID NO: 360
TACATTCTGATAGTGGGTACCACAGCCTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCGCTAC
CTCGACCACGGGATCTGAAATACACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTCGCA
GAGGGGGTGCTGGTAGTAGTGGTGTGTGGATCCTTGATGGTTTTGCTCCC
SEQ ID NO: 361
MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSSVSAAVGGTIVTINCIQSASQSYQNNYLSWFQKPGQPPKL
LIYGAATLASSGVPSRFKSGSGQTFTLTISDCEADAATYYCAGAYRDVDAS
SEQ ID NO: 362
METGLRWLLLAVLKVQCSLESQSGDLVKPGASLTLTCTASGFSFTSTYIYWVRQAPGKLEWIACID
AGSSGTYAATWNGRFITSKSSTTVTLMQSLTAADTATAYFCAKWDYGNVGWGYDL
SEQ ID NO: 363
QASQSYQNNYLS
SEQ ID NO: 364
GAATLAS
SEQ ID NO: 365
AGAYRDVDAS
SEQ ID NO: 366
STYYIY
SEQ ID NO: 367
CIDAGSSGSTYATWNVG
SEQ ID NO: 368
SEQ ID NO: 369
WDYGGNVGWYDL

SEQ ID NO: 370
ATGGACACGAGGGCCCACTCAGCTGCTGGGCTCTCGCCAGGTGCACATTGCT
CAAGTGTCGACCCAGACTCCATCTCTGCTGCTGCGACTGTGGAGGAGGCACAGTCACCACATAATGGCA
GGCCAGTCAAGATTCTTCATGGCAGAAACACACTCACTTGCTGCTTCCAGAGGCCAGCTCCACAA
AGCTCCTGTATCTGTTGCGGCCACCTGTAGCTCTGGGTCTCCATCGCGGTGTTCAAGGGAGTTGGA
CTGAGGTGACGTGACCTGGAGTGGATCT

SEQ ID NO: 371
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCAGTGTCAGTGGTGA
GGAGTCGGCCAGGGGAGCCTGGTCAGCCCTGAACACACTCAGACCCACTGCTGCTGTAGCT
CCTTACTAGTCGACATCTCTACCATCTACTCTGGCTCCAGGGCAAGGGGGGTGAGTGACGGTACGCAG
TGATTTGATGCTGCTGATGAGTGGAGACACTACACTACGCGACCTGGGTGTAATGGCGGATTCACACTCTCC
AAAACCTCGTCAGAGTGTTTATCAGAACAACTACTTATCC

SEQ ID NO: 372
CAGGCCAGTCAGAGTTTATCAGAACAACACTCTTATCC

SEQ ID NO: 373
GGTGCAGCCACTCTCCAGCATCT

SEQ ID NO: 374
GCAGGCGCCTTATAGGGATGTGGATTCT

SEQ ID NO: 375
AGTACCTACTACATCTAC

SEQ ID NO: 376
TGTTATGATGCTGCTAGTAGTGGTACCTACAGCAGCGACTGGGCTGTAATGGC

SEQ ID NO: 377
TGGGATTATGTTGTAATGGTGTTGGTTATGAGTTCTG

SEQ ID NO: 378
MDTRAPTQLLGLLLLWLPARCAFEATQTSPVEAAAVGTTIKCQASQSISSYLAWYQKPGQPPKLIY
RASTLAVPSRFKGSSTFTTLTSDLECAAAATYYQSYSDSN

SEQ ID NO: 379
METGLRLWLLVAVLKGVCQSLEESGGLVKPEGSLTLCASKDGDGTYWFMWVRQPAGKGGLEWIA
CIYTGSSGTFYASWVNGRTISKTSSTTVLQMTSSTATAATYTFCAGYSGYGYFKL

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
ATGGGACACGGGCCCCACTCACTGCTGGGGCTCTCTGCTGCTCTGCTGCTCCCAGGTGCAGATGTGCA
ATTGCCATTTGCCAGCTCTCCCTCGTGGAGGGAGGGCAGTGGGGCAAGGACATGACATAGTCGAC
AGGCCCAGTGCCACTCGATCGATCGATCGAAACGGCCAGCTCAGAGCATTAGTAGTTACTTAGCC
SEQ ID NO: 387
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGTTGGA
GGAGTCCGGGGAGACCTGGTCAAGCTGGAGGTCCTGCATCCCTCCTGCAAGCCTTCTGGGAGTA
ACCTCGGTACCTACTGTTTCATGTGCTGGGCTCCAGCTCAGGGAAGGGCTGGGACAGATGTGCA
TGTTGAGAGATTGTTAGGTTATTTAAGTTG
SEQ ID NO: 388
CAGGCCAGTGCTAGAGCATTAGTAGTTACTTAGGC
SEQ ID NO: 389
AGGGCGTCCACTCTGGCATCT
SEQ ID NO: 390
CAAAGCTATTATGTAGTGGTTTCAAATCCT
SEQ ID NO: 391
ACCTACTGGTTTACTGTC
SEQ ID NO: 392
TGTTTATTACGTTAGTGATTGTTCCACTTTTCTACGCGAGCTGGGTGAATTGCGATTCACCATCTCC
AAAACCTCGTGACCCAGGTGACTCTCCTGCAATAGACTGGGACAGGGCCAGACAGGCGCATTTTT
TTTGTCGAGAGATTGTTAGGTTATTTAAGTTG
SEQ ID NO: 393
GGTTTATTAGTTAGTTATTTAAGTTG
SEQ ID NO: 394
MDTRAPTQLLGLLLLWLPGVTFAIEMTQSPFSVSAAVGTVSISCQASQSVYKNNQLSWYQQKSGQPPKLL
IYGASALASGVPSRFKGSSTGTTFLTDSDVQCDDAATYYCAGAITGSIDTDG
SEQ ID NO: 395
METGLRWLLLVAVLKVQCSLEESGGDLVKGASLTLTCTTSGFSSSYFYICWVRQAPKGGLEWIAICY
GGDGSTYYASWAGRFTISKSSTTSTTVLQMTSLTAADTATYFCAREWAYSQGYFGAFDL
SEQ ID NO: 396
QASQSVYKNNQLS
SEQ ID NO: 397
GASALAS
SEQ ID NO: 398
AGAITGSIDTDG
SEQ ID NO: 399
SSYFIC
SEQ ID NO: 400
CTYGGDGSTYYASWAKG
SEQ ID NO: 401
EWASYOGFYFGAFDL
SEQ ID NO: 402
ATGGGACACGAGGCCCACATCAGCTGCTGGGCTCTCTGCTGGCTCCAGGTGTACACTTTGCC
ATCGAAATGACCCAGAGTCCATTCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCA
GGCCAGTCAGAGTGTTTTATAAGAACAACACAAAAATTATCTCCTGTATCGAGAAATCAAGGGCAGCTCCCA
AGCTCCTGATCTATGTTGTCATCGGCTCTGGCTCTGGCTCCATCGGCGTTCAAAGGCAGTGGATCT
GGGACAGAGTTCACTCCTCAACATGAGCAGTGCAGTGAGGTACGATGCTGCCACTTACTACTGTGCAAGG
CGCTATTACGTGATATTGATACCGGATGG
SEQ ID NO: 403
ATGGGACAGGTGCGCTGCTGGCTTCTTCTCTGCTGCTGCTGCTCAAGGGTGTCAGCTGCTCTGGGA
GGAGTGCCGGGGAGACCTGTCAGCTGCTGGGCTCGACACTCAACTGGFTCGATCTGACTGCA
CTTTCAGTAGCAGCTACTTCTTCTGCTGCTGGTCTGCCAGCCAGGCTCAAGGGAAGGGCTGAACTGATGCA
TGCAATTGATGTCAGACATACATACGAGCTGGGAGGGGAAGGCCGAATCCCATATCTCCAA
AACCTGTCGACCACGGTGACGGGTCAATGACAGTGACGACGCAAGGGCCACCCCATATTTTC
GTGCGAGAGATGGCGATATAGTCAAGGTTATTTTGGTGCTTTTGATCTC
SEQ ID NO: 404
CAGGCCCCATGATGTTTTATAAGAACAACACATTTTCC
SEQ ID NO: 405
GGTGCATCGGCTCTGGCATCT
SEQ ID NO: 406
GCAGGCAGCTATTACTGTTAGTATTGATACCGGATGG

271
SEQ ID NO: 407
AGCAGCTACTTCATTTGC

SEQ ID NO: 408
TGCATTTATGGTGTGATGGCAGCACATACTACGCGAGCTGGGCGAAAGGC

SEQ ID NO: 409
GAATGGGCATATAGTCAAGGTATTTTGGTGTCTTTTGTATCTC

SEQ ID NO: 410
MDTRAPTQLLGLLLWLPGARCDWMTQTPASVEAAVGGTVTKCQASEDISSYLA
YAASNLESGVSSRFKGS SGTEYLTISDLECADAATYYCQCTYGTISIDGNA

SEQ ID NO: 411
METGLRWLLLVAVLKGVQCQSVEESGRLVPDTPPLTLTCVSGFSLSSYFMWV
QAPGEGLEYIGFINP
GGASYAYASWVKGRFTISKSSTTVDLKITSPTTEDTATYFCARVLIVSYGAFTI

SEQ ID NO: 412
QASEDISSYLA

SEQ ID NO: 413
AASNLES

SEQ ID NO: 414
QCTYGTISIDGNA

SEQ ID NO: 415
SYFMT

SEQ ID NO: 416
FINPGGSAYYASWVKG

SEQ ID NO: 417
VLIVSYGAFTI

SEQ ID NO: 418
ATGGACACGAGGCCCACACTCACTGCTGGGGCTCCTGCTTGCTGCTGGCTGCCAGATGTGA
TGGTTGTGATGGACCCCAGACTCAGCTGCTGGGACAGCAGGTGGGAGGCAGCAGCTGCTGTGA
AGGCCCAGTGAGATATTAGCTACTTACCTAGCTGATTCAGCAGAAAAACAGGGGACCTCCCAAGCTC
CTGATCTATGCTTCAATCTGCAAATCTGGGTCTCATTCAATCGCGAGTCCAGTGATCGCGAG
AGAGTACACTCTCCATCACTAGCGACCTGGAGTGGCAGTGGCTGACCCACCTATTACTGTCAATGTA
ATTAATATTCTATTAGTGATGTAATGCT

SEQ ID NO: 419
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTGCTGCTGGGACAGCAGGTGGGAGGCAGCAGCTGCTGTGA
AGGCCCAGTGAGATATTAGCTACTTACCTAGCTGATTCAGCAGAAAAACAGGGGACCTCCCAAGCTC
CTGATCTATGCTTCAATCTGCAAATCTGGGTCTCATTCAATCGCGAGTCCAGTGATCGCGAG
AGAGTACACTCTCCATCACTAGCGACCTGGAGTGGCAGTGGCTGACCCACCTATTACTGTCAATGTA
ATTAATATTCTATTAGTGATGTAATGCT
GACCACGGTAGATCTGAAAATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGG
TTCTGATTGTTTCTTATGGAGCCTTTACCATC
SEQ ID NO: 420
CAGGCCAGTGAGGATATTAGTAGCTACTTAGCC
SEQ ID NO: 421
GCTGCAATCTTGGAATCT
SEQ ID NO: 422
CAATGTACTTATGGTACTATTTCTATTAGTGATGGTAATGCT
SEQ ID NO: 423
AGCTACTTGTTACGTGACC
SEQ ID NO: 424
TTCATTAATCCTGTGTGTCAGCTTTACTAGCGAGCTGGGTAAGGC
SEQ ID NO: 425
GTTCTGATTTCTTATGGGACCTTTACCACATC
SEQ ID NO: 426
MDTRAPTQLLGLLLLWLPGARCDWMQTPTASVAAVGGTVTICKQASEDIESYLAWYYYKPGQPPKLLI
YGASNLESGYSSRFKGSGGTEFTLTISDLECAATYYCQCTYGIISIDGNA
SEQ ID NO: 427
METGLRWLLLVAVLKVLCQSVESGGRLVTGPTLTLTCVSGFSLSSYFMTWVRQPGELEYIGFMN
TGDNYYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFCARVLWAYGAFNI
SEQ ID NO: 428
QASEDIESYLA
SEQ ID NO: 429
GASNLES
SEQ ID NO: 430
QCTYGIISDGN
SEQ ID NO: 431
SYFMT
SEQ ID NO: 432
FMNTGDNAYYASWAKG
SEQ ID NO: 433
VLWAYGAFNI
SEQ ID NO: 434
ATGGACACGAGGGCCCATCTAGCTGCTGGGCTCCTGCTGCTGCCCTCAGTTGCAATGAGATGTGA
TTTGGTGATGACCCAGCTCCAGCCTCCGAGTCTGGGAGGACAGTCACCATCAAGTGGCC
AGGCCAGTGAGGACATTGGAAGCTATCTAGCCTGGTATCAGCAGAAACCAGGCGAGCCTCCCAACGT
CCTGATCTATGGGTACATCAATCTGGGATCTGGGTCTCTGACGTTCAAAAGGCAGTGATCTGGGA

273
CAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTATTGTCAATGCACTT
ATGGTATTATTAGTATTAGTGATGGTAATGCT
SEQ ID NO: 435
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCAGTGTCAGTCGGTGGA
GGAGTCCGGGGGGTCGCTGGTCACGCCTGGGACACCCCTGACACCTACCTGCACAGTGTCTGGATTCT
CCCTCAGTACGCTACTTCATGACCTGGGCTCCGACAGGCTCAGGAGGTGAATACATCGGATTTC
ATGAATATCTGGTGATAAAGGCATATCGCAGTCGAGCTGGGAAAGGGCGATTCACCACATCTCCAAACCTC
GACCACCGTTGATCTGAAATACACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGG
TTCTTGTTGTTGCTTATGGAGCCTTTAACATC
SEQ ID NO: 436
CAGGCCAGTGAGGACATTGAAAGCTATCTAGCC
SEQ ID NO: 437
GGTGCATCCAATCTGGAATCT
SEQ ID NO: 438
CAATGCACTTATGGTATTATTAGTATTAGTGATGGTAATGCT
SEQ ID NO: 439
AGCTACTTCATGACC
SEQ ID NO: 440
TTCATGAATACTGGTGATAAAGGCATATCGCAGTCGAGCTGGGAAAGGGCGATTCACCACATCTCCAAACCTC
GACCACCGTTGATCTGAAATACACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGGG
TTCTTGTTGTTGCTTATGGAGCCTTTAACATC
SEQ ID NO: 442
MDTRAPTQLLGLLLLWLPGATFAAVLQTTPSPVSEPGTVSISCQSSKVSMNNNYLAWSYQQKPGQPPKL
LIYGASNLASGVSPRGSGSHTQFTLTSIDVQCDAAAYYQCGGYYTGYSDDHTG
SEQ ID NO: 443
METGLRWLLLVAVKGVQCSVEESGGRVLKPGDETLTLTCTVSGIDLSSYPMNWVRQAEGKLEWIGFIN
TGGITIVASYWAKGRFTIKSTTSTTVDLKMTSPPTTEDTATYFCARGSYVSSGYAYFFNV
SEQ ID NO: 444
QSSKVSMNNNYLA
SEQ ID NO: 445
GASNLAS
SEQ ID NO: 446
QGGYTGYSDDHTG
SEQ ID NO: 447
SYPMN
SEQ ID NO: 448
FINTGTVYASWAKG
SEQ ID NO: 449
GSYVSSGYAYYFNV

SEQ ID NO: 450
ATGGACACGAGGGCCCACTCAGTGCTGGGCTCTGCTCCTGGCTCCCAGGTGCCACATTTCG
CGCCGTGCTGACCCAGACTCCATCTCCCGTGTCTGAAACCTGTGGGAGGCAAGGTACAGTCAGATGTGGCC
AGTCCAGTAAGAGTTATGAATAAACAAGCTACTTTAGCTGTATACGAAGAAACCCAGGCGAGCTCCC
AAGCTCCTGATCTATGTCATCAAATCTGGGACTGGGTCATACCGGTACAGTCGAGATGTGGAC
GGGACACAGTCACACTCACCATCAAGCAGTTATGACATGCTGCCACTTACTACTGTCAAGG
CGGTTATACTGTTATAGTGAATCATGGGACT

SEQ ID NO: 451
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCCCGGGGCTCGCTGTCAAGCCTGACGAAACCCCTGCACTCACCTGCAAGTCTCTGGAATCG
ACCTCAGTAGCTATCAATGAAACTGGGCTGCCAGCTCCAGGGAAGGGGGCTGAATGGATCGGATTC
ATTAAATCTGTTGACATGCTCTACGCCGAGCTGGGCAAAAGGCAGTTACCCATCTCGCAAAACCTC
GACCCACGTTGAGCTGGAATATGACAGTTCCGACAACCCAGGACACCCGACAAGCTAGTGGCCAGAG
GCGATTATGTCTCAGTTATGCTACTATATTTAATGTC

SEQ ID NO: 452
CAAGTCAGTAAGAGTTATGAAATAACACTTTAGCC

SEQ ID NO: 453
GGTGCAATCCAAATCTGGCAGCT

SEQ ID NO: 454
CAAGGGCAGTTATACTGGTTATAGTGATCATGGGACT

SEQ ID NO: 455
AGCTATCCAATGAAC

SEQ ID NO: 456
TTCATTAATACTGGTTAGTGATCATGGGACT

SEQ ID NO: 457
GCGAGTTATGTTTCTGTTATGCTACTATATTTAATGTC

SEQ ID NO: 458
MDTRAPTQLLGLLLLWLPGATFAAVLQTPSVPVAAVGGTVSISCQSSQSVYNNNWLSWFQKPGPPKL
LIYKASTLASGVPSFKGSGTQFTLTDVQCDVDATYCACGGYLDV

SEQ ID NO: 459
METGLRWLLLVAVLKVQCSVDESQGRVLTPGPLTLTCTVSAPSLSTYSINWVRQAPKGKLEWIGIIAN
SGTTFYANWAKGRFTVSKTTSVDLKITSPTTEDTATYFCARESMYNEYGKFN

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
ATGGGACACGAAGGGCCCCACCTCAGCTGGGGCTCCTGCTGGCTCCACAGGTGCCCATTTTGCC
CGCCGTCTGACAACAGACTCCATCTCCGTGCTGTCAGTGAGGAAGGACACAGTCAGCATCAGTTGC
AGTCCAGTCAGTGGTTTATAATAAAACTGTTATCTCTTGTTTTCAGCAGAACCAGGGAAGGAGCCTCCC
AAGCTCTGATCTAACAAGGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTCTAAAGGCAGTGATCGGAT
TGGGACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGTTGCCACTTACTACCTGTCGGA
GCCTTGATCTGTGATATGTGTTATT
SEQ ID NO: 467
ATGGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCCGGGGTGCGCTGACGCCTGGGACACCCCTGACACTCAGTCTCCATGGAATCGGAATCTC
ATTGCTAATAGTGGTACAGTTGACTACGCGAAGGACTGGGTCCGCCAGGCTCCAGGGGAAGGGCCTGGAA
TGGATCGGAATTGCTAATAGTGGTACCACATTCTACGCGAACTGGGCGAAAGGC
SEQ ID NO: 468
CAGTCCAGTCAGTGGTTTATAATAAACAACCTGGTTATCC
SEQ ID NO: 469
AAGGCATCCACTCTGGCATCT
SEQ ID NO: 470
GGGCGGTTATCTTGATAGTTATT
SEQ ID NO: 471
ACCTATTTAATAAAC
SEQ ID NO: 472
ATCATCGTAAATAGTGGTGACCACATTCTACGCGAAGCAGGGCAGGGAAGGGCGG
SEQ ID NO: 473
GAGAGTGGAATGTACAATGAAATAGTGGTAAAATTTACATC
SEQ ID NO: 474
MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINCQASENIYSFLAWYQQKPGQPPKLLIF
KASTLASGVSSRFKGSGSQTQLTISDLECDADAATYCYQQGATVYIDNN
SEQ ID NO: 475
METGLRWLLLVALKVQCSLESGRLVTPTGLETLTCTVSIGLSAYAMIWVQRAPGEGLEWITIIYP
NGITYYANWAKGRFTVSKTSTAMDALKITSPTTEDTATYFCARDAESSKNAYWGYFN
SEQ ID NO: 476
QASENIYSFLA
SEQ ID NO: 477
KASTLAS
SEQ ID NO: 478
QQGATVYIDNN
SEQ ID NO: 479
AYAMI
SEQ ID NO: 480
IIYPNGITYYANWAKG
SEQ ID NO: 481
DAESSKNAYWGYFN
SEQ ID NO: 482
ATGGACACGAGGGCCCCACTCAAGCTGCTGGGCTCCTGCTCCTGGCTCCAGGGACATGTGC
CTCTGATATGACCCAGACTCCATCCTCCGTGTCGACGTGTGGGAGAAGCAGTCACTCAATG
GCCAGTGGAGACATTATTAGCTTTTTTGCGCTGGATACAGCAACTACGGGAGCCTCCTCCAGCTCC
TGATCTTCAAGGCTTCCACTCGGCGAGTTGCTCATCGCAGTTCAAGGCAATGTGCTCGCTCCG
ACTGTGTATGATATTGATAATAAT
SEQ ID NO: 483
ATGGGACACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGCAGTGTCAGTG
GGAGTGGCTCGGCGAGTCGCTGGCTGCTACTTTGCTGATCAGGTGATGCTGGGACACTG
ACCTCAAGCTGCTGATAGCAGCTGGGCTGCTGCTGGGCTGCTGCTGCTGCTGCTGCTG
ATTTACATTGATACATTACAGGCGAATTGGGCAAGGGCCAGAGGCGAGGTGACCCTCCAAC
ATGGCAGGAAATAGTCTGATTTTGGGTCTCTCTGCGACTTACG
SEQ ID NO: 484
CAGGCGAGTGGAGAATTTATAGCTTTTGCG
SEQ ID NO: 485
AAGGCTTCCACTCTGGCATCT
SEQ ID NO: 486
CAACAGGGGTGCTACTGTGATATAGTATTGATAATAAT
GACCGCGATGGATCTGAAAATCACCAGTCCGACAAACCGAGGACACGGCCACCTATTTCTGTGCCAGAG
ATGCAGAAAGTAGTAAGAATGCTTATTGGGGCTACTTTAACGTC
SEQ ID NO: 500
CAGGCCAGTGAGAACATTTATAGCTTTTTGGCC
SEQ ID NO: 501
AGGGCTTCCACTCTGGCATCT
SEQ ID NO: 502
CAACAGGATGACTAGTAAGATGCTTATTGGGGCTACTTTAACGTC
SEQ ID NO: 503
GCCTATGCAATGATC
SEQ ID NO: 504
ATCATTTATCCTAATGATCAGCAGAAACCAGGGCACTCTCCTAAG
CTCCTGATCTATGATGCATCCGATCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGG
GACCGCGATGGATCTGAAAATCACCAGTCCGACAAACCGAGGACACGGCCACCTATTTCTGTGCCAGAG
ATGCAGAAAGTAGTAAGAATGCTTATTGGGGCTACTTTAACGTC
SEQ ID NO: 506
MDTRAPTQLLGLLLLWLPGATFAIEMTQTPSVSAAVGGTVTINCQASESFSNNMLSWYQQKPGHSPKLLI
YDASDLASGVPSFKGSGSGTQFTLTISGVECDDAATYYCAGYKSDSNDGDNV
SEQ ID NO: 507
METGLRWALLVAVLGCGQSLESSEGGRLVTPTPLTLTCVTSGFSLNRNSITWVRQAPGEGLEWIGIITGS
GRYYANWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCARGHPGLGSGNI
SEQ ID NO: 508
QASESVFNMLNS
SEQ ID NO: 509
DASDLAS
SEQ ID NO: 510
AGYKSDSNDGDNV
SEQ ID NO: 511
RNSIT
SEQ ID NO: 512
IITGSGRYYANWAKG
SEQ ID NO: 513
GHPGLGSGNI
SEQ ID NO: 514
ATGGACACGAGGGCCCTCCACTCAGCTGCTGGGGCTCTCGTCTCTGGCTCCACAGGTGCCACATTTCG
CATTGAAATGACCCAGACTCCATCCCCGCTGCTGCTGGAGGCACTCACATTCGCC
AGGCCCAGTGAGAAGTTTTTTAAAATAATATGTATCTCTGGTATCGAGAAACCAGGGCACTCCTCTTAAG
CTCCTGATCTATGATGCATCCGATCTCGATCGTGGTGTTCAAAAGGCAGTGGAATCTGG
GACACAGTC ACTCTCA CACTGAGTCGCT CAGTGATGC GACACGTG
ATAAAAGTGATAGTAATGATGGCGATAATGTT
SEQ ID NO: 515
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGCTGGAGTCCGGGGGTGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAACAGGAATTCAATAACCCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGGAATGGATCGGAATCATTACTGGTAGTGGTAGAACGTACTACGCGAACTGGGCAAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGATCTCAGAATGACCAGTCCGACAACCGAGGACACGGCCACCTATTCTGTGCCAGAGGCCATCCTGGCTTTGGTAGTGGTAACATC
SEQ ID NO: 516
CAGGCCAGTGAGAGTGTTTTTAATAATATGTTATCC
SEQ ID NO: 517
GATGCATCCGATCTGGCATCT
SEQ ID NO: 518
GCAGGGTATAAAAGTGATAGTAATGATGGCGATAATGTT
SEQ ID NO: 519
AGGAATTCAATAACC
SEQ ID NO: 520
ATCATTACTGGTAGTGGTAGAAGCGACTACGCAGCTACTTTGGATTCTCCCTCAACAGGAATTCAATAACCCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGGAATGGATCGGAATCATTACTGGTAGTGGTAGAACGTACTACGCGAACTGGGCAAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTGATCTCAGAATGACCAGTCCGACAACCGAGGACACGGCCACCTATTCTGTGCCAGAGGCCATCCTGGCTTTGGTAGTGGTAACATC
SEQ ID NO: 521
MDTRAPTQLLGLLLLWLPGATFAQVLTQTASSVSAAVGGTVTINCQSSQSVYNYLWSYYWQKPGQPKL
IYTASSLASGVPSPFKGSQSTQFTLTISEVQCDDAATYYCQGYSY
SEQ ID NO: 522
METGLRWLLLAVLVKGVQCSLEESGRLVTPGPLTLTCTASGFSLNNYYIQWVRQAPGEGLEWIGIIYA
GGSAYYATWANGRFTIATKSTTVDLKMTSLLTTEDTATYFCARGTFDGYEL
SEQ ID NO: 523
QSSQSVYNYL
SEQ ID NO: 524
QSSQSVYNYL
SEQ ID NO: 525
TASSLAS
SEQ ID NO: 526
QGYSYSPIIT
SEQ ID NO: 527
NYYYQ
SEQ ID NO: 528
IIYAGGSAYYATWANG
SEQ ID NO: 529
GTFDGYEL

SEQ ID NO: 530
ATGGACACAGGGCCCATCAGCTGCTGCTTGCTGGCTCCAGGTGCCACATTTGCC
GCAAGTGCTGACCCAGACTGCTCGCTGCTGCTGCTGGAGGGCACAGTCACCACAAATTGCC
AGTCCAGTTGCTGGTTATAATAATAACTACCTATCCTGCTATACGAGAAACCAGGACGCTCCCAAAG
CTCCTGATCTATACTGCAATCCAGCTGCTGCTGGAGGGGTCAAAGGCAGTGGATCTGGG
GACAGTTGACAGCAGATGCGAGTGTACGTGACGTCACCTACTACTGTCGACAGGCT
ATTATAGTGGTCCCTATAATTAC

SEQ ID NO: 531
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGCCAGTGCAGTCGGACGAGCTGACAGGGAGG
GGAGTCCGGGGGCGCCTGGTCAGCCTAGCTGGATTCTTCTGGAATGGATCGGGATC
ATTATGCTGGGTAGCGCATACTACGCGACCTGGGAACACCGGCGATTCACCATCGCCAAAACCTC
GTCGACACGGTGAGATCTGACAGTCTGACAAACCGAGAGACCGCCACCTATTTCTGTGCC
GACAGCATTGATGGATGAGTTG

SEQ ID NO: 532
CAGTCCAGTGAGTGTATGATACTATACCTATCC

SEQ ID NO: 533
ACTGCAAACATCGCAGG

SEQ ID NO: 534
CAAGGCTATTATAAGTGGTCCCTATAATTACT

SEQ ID NO: 535
AACTAATACATACAA

SEQ ID NO: 536
ATCATTTATGCTGGTATCAGGCACTACAGCGACCTGGGAAACCGG

SEQ ID NO: 537
GGGACATTTGATGGATGAGTTG

SEQ ID NO: 538
MDTRAPTLQALLGLLLLWLPATFAQVLQTTPSVVSVPVGDTVTISCSQSESVYSSNNLLSWYQQKPGQQPKL
YRASLNAGVPVPSFKGSGTQFTLTSQAQCCDAATYYCQGYSGVINS

SEQ ID NO: 539
METGLRLLLLVAVLKGVCQSVSVEESGGRVTPGTPLTLTCTSVGFSLSYIFMSWVRQAPGEGLEYIGFNP
GGSAYYASWASGRLTISKSTTVDLKITSPTTEDTATYFCARILIVSYIAGFI

SEQ ID NO: 540
QSESVESVYSSNNLLS

SEQ ID NO: 541
RASNLAS
SEQ ID NO: 542
QGYYSQVINS
SEQ ID NO: 543
SYFMS
SEQ ID NO: 544
FINPQGAYYASWASG
SEQ ID NO: 545
ILIVSYGAFTI
SEQ ID NO: 546
ATGGGACACGGGAGGGCCCCAATCGGTGCTGCGGCTCTGCTGCTGCTGCTGGCTCCAGGTCACCACATTTGC
CCAGGTGCTGACCCAGACCCATCCAGCTGGCTCTGCTGGGAGACACAGTCCATCAATGGGAGATCGTCTG
GGGACACAGTTCACTCTCACTCATCGACGGGCACAGGTGACGATGCTGCTGACCTTACTACTGTCAAGG
CTTATAGTGTTGTCATATATAGT
SEQ ID NO: 547
ATGGGAGACTGGGCTGGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCGCGGGGGTGCGGGCTGCTGGCTGACACGGGACACGGGAGACACAGTCCATCAGGTGACGATGCT
GCTGCTGACCTTACTACTGTCAAGGCTTATAGTGTTGTCATATATAGT
SEQ ID NO: 548
CAGTCAGCTGAGACGCTTTATAGTAATGTAATACCTCTTATCC
SEQ ID NO: 549
AGGGCATCCAATCTGGCATCT
SEQ ID NO: 550
CAAGGCATTATTAGTGTTGTCATATAGT
SEQ ID NO: 551
AGCTACTTCATGAGC
SEQ ID NO: 552
TTCATTAATCTGGTGAGGCTACATCGAGCTCTGGCGATCGCTGGCAGGTGCTGCTGACCTTACTACTGTCA
SEQ ID NO: 553
ATTCTTATGGGGTTCTATGAGGCCTTACCATC
SEQ ID NO: 554
MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGTVTIKQATESINGELESWYYQKPGQAPKLL
YSASTLASGVPSRFKGSGSGTQFTLTITGVECDDAATYYCQQGYSANIDNA

SEQ ID NO: 555
METGLRWILLLAVAVLKGVQCQSLEESGGRLVTPGTLTLTCTVSGFSLSKYYMSWVRQAPEKGLKYIGYID
STTVNTYYATWARGRFTISKTSTTVDLKITSPTSETDATYFARGSTYFTDGGHRLDL

SEQ ID NO: 556
QATESINGELES

SEQ ID NO: 557
SASTLAS

SEQ ID NO: 558
QQGYSANIDNA

SEQ ID NO: 559
KYYMS

SEQ ID NO: 560
YIDSTTVNTYYATWARG

SEQ ID NO: 561
GSTYFTDGGHRLDL

SEQ ID NO: 562
ATGGACACGAGGGCCCCCCTACGCTGCTGGGGCTCCTGCTCTGGCTCCCAGGTGCCAGATGTGC
CTATGATATGACCCAGACTCCAGCCTCTGTTGAGTGTAAGTCTGTGGAGGGCACAAGTCACCATCAAGTGCC
AGGCCACTGAGACATTGGCAAATGATTATCACCTGTTGATCGAAGGAAACCGAGGCTGCCCAAGCTC
CTGATCTATTTCTGCATCCACTCTGCGATCTGGGTTCCCATCGGGTTCAAAAGGAGATGATCTGGGACA
CAGTTACATCTCAACCACCGGGGCTGAGTGTGATGATGCTGCACTTACCTACTGCTCAACAGGGTTAT
AGTAGTGCTAATATTGATAATGCT

SEQ ID NO: 563
ATGGAGACTGGGCTGCGCTGGCTTCTCTGCTGCTGGCTCTGGCTCCAAGGTGTCATGTCAGTCCTGCGA
GGAGTCGCGGAGGGCTGCTGCCAGCAGCAGAAGGGGCTGAAATACATCGGATAC
ATTGATAGTACTACTATAATACATACTACGCGAATGGCGAGGCGCAATACATCTCCCAAAC
CTGACACTCCCGATCTGACATCGACAGCTCGGCAACGAGCGCCCATCAATTCTGTGCA
GAGGAGATGTACTTTATTTGATGATGGCCATCGGTGATTGATCTC

SEQ ID NO: 564
CAGGCCACCTGAGAGCATTGGCAATGAGTTATCC

SEQ ID NO: 565
TCTGCAATCCACTCTGGCATCT

SEQ ID NO: 566
CAACAGGGTTATAGTAGTGCTAAATATTGATAATGCT
SEQ ID NO:  567
AAGTACTACATGAGC
SEQ ID NO:  568
TACATTGATAGTACTACTGTTAATACATACTACGCGAGCTGGGCGAGAGGC
SEQ ID NO:  569
GGAAGTACTTATTTTACTGATGGAGGACATCGGTTGGATCTC
SEQ ID NO:  570
MDTRAPTQLLLGLLLLWPAGARCRYMTQPSVEAVAVGTVIKCIQATESIGNELSWYQQKPGQAPKLLI
YSASTLASGVPFSKGSHTQFTLTITVECDDAAATYCYCQGGYSSANIDNA
SEQ ID NO:  571
METGLRWLLLVAVLGVQCSLESVGRILLTPTPLTLTCTVSGFSTYNMGWVRQAGPGKLESWGSITI
DGRTYASWAKRGFTVSKSSTTVDLKMTSTTGDATAYFCARILIVSAYGAFII
SEQ ID NO:  572
QATESIGNELS
SEQ ID NO:  573
SASTLAS
SEQ ID NO:  574
QQGYS SANIDNA
SEQ ID NO:  575
TYNMG
SEQ ID NO:  576
SITIDGRYYASWAKG
SEQ ID NO:  577
ILIVSAYGAFII
SEQ ID NO:  578
ATGGGACACGAGGGCCCACTAGCTGCTGGGCTCTGCTCTGGCTCTCCAGGTGCAAGATGTGCT
CTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCC
AGGCCACTGAGAGCATTGGAATAGGTATATCTCTGGTATCGAAGAACGGGCAGCTCCTCAGAGCTC
CTGATCTAATCTTCACTCAGCTGGTCTGGGTTCTGGGCTACATCAGGACAGCTATCCAGACCTTCTG
AGTATGTGCTAATATTGATAATGC
SEQ ID NO:  579
ATGGGACACGAGGGCCTGCTGCTTCTGCTCCTGCTCTGGCTCTCCAGGTGCAAGATGTGCT
CTATGATATGACCCAGACTCCAGCCTCTGTGGAGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCC
AGGCCACTGAGAGCATTGGAATAGGTATATCTCTGGTATCGAAGAACGGGCAGCTCCTCAGAGCTC
CTGATCTAATCTTCACTCAGCTGGTCTGGGTTCTGGGCTACATCAGGACAGCTATCCAGACCTTCTG
AGTATGTGCTAATATTGATAATGC
CGACCACGGTGATCTGACAAAATGACCAGTCTGACAACCGGGGACACGGCCACCTATTTCTGTGCCAGG
ATTCTTATTGTTTCTTATGGGGCCTTTACCATC
SEQ ID NO: 580
CAGGCCACCTGAGACAGCATGGAATTCTTATTGTTTCTTATGGGGCCTTTACCATC
SEQ ID NO: 581
TCTGCACTCCACTCTGGCATCT
SEQ ID NO: 582
CAACAGGGGTATAGTAGTGCTAATATTGATAATGCT
SEQ ID NO: 583
ACCTACACACATGGGC
SEQ ID NO: 584
AGTATTACTATTGATGGTCGCACATACTACGCGAGCTGGGCGAAAGGC
SEQ ID NO: 585
ATTCTTATTGTTTCTTATGGGGCCTTTACCATC
SEQ ID NO: 586
VAAPSVFIFPSDEQLKGSATSVCLNNFYPREAKVQWKVDNALQSGNSQESVETQDSKSTYSLSSLTL
SKADYEKHKYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 587
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTT
GTGTGCCCTGTAATAACCTCTATCCCAAGAGAGGCGCAAGAGAAGCTGGAAGGTGGATAACGCCCTCCA
ATCGGGTAACCTCAGAGAGCTGTCACAGACAGCAAGGAACAGCACCTACAGCAGACGC
ACCCCTACGCTGAGAAAGCAGACTACCAAGAAACACAAAGATCTACCGCTGAGAAGTGCAAGTTCTAC
GCTGAGCTGAGCCGTCCACAAAGAGCCTCAACAGAGGGAGAGGAGGAGGTG
SEQ ID NO: 588
ASTKGPSVFPLAPSSKSTSGTAALGCLVKDYFEPVTVSWNSGALTSGVHFTPVAVLQSSGLYSLSSWTVP
SSSLGTQTICYNHVNASPTKVDKRVEPKSCPDKHCPTCPAPELLEGGPSVFLFPPKPDTLVQISRTPEVTV
WDVSHEDPEVFNWYVDVEVHNKATKPREQYASTYRWSVLTQLHDWNGKEYKCKVSNKALPA
PIEKTSKAKGQPREFPQVYTLPSREEMTKQVSLATLKVGFYPSDIAVEWESNGQPENNYKTTNPVLDSG
SFFLYSKLTVKSRWQQGNFVSCSMHEALHNHYTQKLSLSPGK
SEQ ID NO: 589
GCCTCCACCAAGGGCCCATCGTGCTTCCCTCCCTGGCACCCTTCCCTCAAGAGACCTCCTCTGGGGGCAGACG
GCCTCCTGGCTGCTTGCTAAGGACTCTCCCTCCGAACCCGGTGACGGTGCTGGAACTCACGGCGC
TGACACACGCCGCTACACCTTCCGGCTGGCTTCACATCAGCTACCTCCACTCCACAGACCTG
TGACCCTGCCCCTCAGCAGCTTGGGCAACCAAGACCTACATCTGCAACGTGAACTCAACACACACAG
ACCAAAGGTGACAAAGAGGTGGAGCCAAAATTTGGACAAAAACTCAACATGGCCACAGTGGCCAG
CACCTGAACTCCTGAGGGGACCCGTAGCTCGTCTCTCTCTCTCCCCCCAACAAAAGCAGACACCCCTC
ATGATCT
CCCCGACCACCTGAGCTGCTATGGAAGAGCATGGA

285
TGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGC ... I D NO: 601
GISALRKETCNKSNM
SEQ ID NO: 602
ALRKETCNKSNMCES
SEQ ID NO: 603
KETCNKSNMCE S SKE
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
ENNLNLPKMAEKDGDC
SEQ ID NO: 610
LNLPMAEKDGCFQRS
SEQ ID NO: 611
PKMAEKDGCFQSGF
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
LEYLQNRFESSEEEQA
SEQ ID NO: 623
LQNRFES SEEQARAV
SEQ ID NO: 624
RFES SEEQARAVQM
SEQ ID NO: 625
SSEEQARAVQMSTKV
SEQ ID NO: 626
EQARAVQMSTKVLIQ
SEQ ID NO: 627
RAVQMSTKVLIQFLQ
SEQ ID NO: 628
QMSTKVLQFLQKKA
SEQ ID NO: 629
TKVLQFLQKKA
SEQ ID NO: 630
LQFLQKKAKNLD
SEQ ID NO: 631
FKKAKNLD
SEQ ID NO: 632
DAITTPPDPT
SEQ ID NO: 633
KNLDAITTPPDPT
SEQ ID NO: 634
DAITTPPDPTTNA
SEQ ID NO: 635
TTPPDPTTNASLL
SEQ ID NO: 636
DPTNASLLTKLQAQ
SEQ ID NO: 637
TNASLLTKLQAQNQW
SEQ ID NO: 638
SLLTKLQAQNQW
SEQ ID NO: 639
TKLQAQNQW
SEQ ID NO: 640
QAQNQW
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
FKEFLQS SLRALRQM
SEQ ID NO: 647
AYDMTQTQPASVAAVGGTVTIKCQASQSINNELSWYQQKPGQRPKLIIYRASTLASGVSSRFKGSSTFET
LTISDLCEADAATYYCQQGYSLRNIDNAFGGGEVWK
SEQ ID NO: 648
AIQMTQSPSSLSAVGDRVTITCRASQGIRNDLGWYQQKPKGKPKLIIYAASSLQSGVPSRFSGSGSTDF
LTISSLQPEDFATYYC
SEQ ID NO: 649
DIQMTQSPSSLAVGDRVTITCRASQGISNYLAWYQQKPKGKVPKLIIYAASSLQSGVPSRFSGSGSTDF
LTISSLQPEDVATYYC
SEQ ID NO: 650
DIQMTQSPSTLSAVGDRVTITCRASQISSWLAWYQQKPKGKPKLIIYKASSLESVPSRFSGSGSTEFTL
TISLQPDDFATYYC
SEQ ID NO: 651
AIQMTQSPSSLSAVGDRVTITCQASQSINNELSWYQQKPKGKPKLIIYRASTLASGVPSRFSGSGSTDF
LTISSLQPEDFATYYCQQGYSLRNIDNAFGGTKEIK
SEQ ID NO: 652
QSLEESGGRLETPGTPLTCTASGFSLSNNYYVTWRQAPKGKLEGWIIYGSDETAYATWAIGRFTISKTST
TVDLKMTSLTAADTATYFCARDGSDWDAKFNWGGQLTVSS
SEQ ID NO: 653
EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPKGKLEGWVSIYSGSTYYADSVKGRFTIS
DNSKNTLQLMNSLRAEDTAVYYCAR
SEQ ID NO: 654
EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPKGKLEGWVSIYSGSTYYADSVKGRFTIS
DNSKNTLQLMNSLRAEDTAVYYCAR
SEQ ID NO: 655
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSWTVPSSLGTQTYICNVNHKPSNTK
VDKRVEPKSCDKTHCTCPPCPAPELGGPSVFLFPPKDTLMLSRVETVCCDWEDPEVKFSNLYFVTQG
VEVHAKTPREEQYASTYRVSVLTVHDDWLENGKEYKCKVSNKAPAPIEKTIKASQAGQPREPQVYTL
PPSRDELTKQVSLTCLVKGFYPSDSIAEVHESWNGQPENNYKTTPPLLDGSFFLYSKLTQVEKSRWQG
FSCSVMHEALHNHYTYQKSLSPK

SEQ ID NO: 665
EVQLVESGGGLVQPGGLRSLSAISAGFSLSNYVTWVRQAPGKLEGWVIGYIGDEATAYATSAIGRFTISR
DNSKNTLYQMNLRAEDTAVYCARDDSSDWDAEKFLWGGGTQTVVSAKPSVFPPLAPSSKTSGG
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSWTVPSSLGTQTYICNVNHKPSNTK
VDKRVEPKSCDKTHCTCPPCPAPELGGPSVFLFPPKDTLMLSRVETVCCDWEDPEVKFSNLYFVTQG
VEVHAKTPREEQYASTYRVSVLTVHDDWLENGKEYKCKVSNKAPAPIEKTIKASQAGQPREPQVYTL
PPSRDELTKQVSLTCLVKGFYPSDSIAEVHESWNGQPENNYKTTPPLLDGSFFLYSKLTQVEKSRWQG
FSCSVMHEALHNHYTYQKSLSPK

SEQ ID NO: 666
IQMTQSPSSLASAVGDRVTITCQASQINSLWSNYQVQPKGAPKLLIIYRASLSFVPSRFSGSGSTDFDLTI
SSLQPDFATYYCQQQYGSLRNDNIAAFGGGTVKVEIKRTVAAPSVFIFPSDEQLKSGTASWCLLNNFYPREA
KLVWQVDNASLQSGNSQESVETQDSKSTDYLSSTLASKYDEKHYKAVEVTHQCLSSVPKSFNRECG

SEQ ID NO: 667
MDTRAPTQLPLLILLWLPGARCYAMDQTQPASVEAVAGGTGVTINCQASETITYSWLSWYQQPKPGQPPKLLI
YQASDLASGVPISRFSGSAGTEYTLTISVGVQCDAAATYYCQQQYGSGSNV

SEQ ID NO: 668
METGLRWLLLVAVLKGVQCEQLKESGGLVTPGTPLLTCTASGFSLNDHAMGWVRQAPGKLEYIGFI
NSGGSARYASWAERFTISRSTTTVDKMTSLTTEDTATYFCVRGGAVWSIHSFD

SEQ ID NO: 669
ATGGACACGAGGGCCCCCACCCTAGCTGCTGGGCTCCTGCTGCTCTGCTCCCAGGTCCAGAATGTC
CTATGATTAGCACCAGACTCCAGCTCTTGAGAGGTAGCTGTGGGAGGGCAAGCTACCACTCATTAATTGC
AGGCCGATGACTGACATTATATTGTTATCTGATATCAACAGAACGGCCAGGCTCTCTCAGAGTCT
CTGATCTACAGGGATCCAGCATCAGCTCAGCTGGGATCCACACAGGCTGGGACGGCAGTGAGGAC
AGGATCACCTCCACCATCGCGGCTGAGTGACATGTCGCACTCAGTCAGAAGCAGTAGTCTCAGAGGT
ATAGTGTAATGTGTAATGTG

SEQ ID NO: 670
ATGGAGACTGGGCTGCTGCTGGTCTCCTCCTCTGTGCTGCTCTGCTCCCAGGTCCAGAATGTC
CTATGATTAGCACCAGACTCCAGCTCTTGAGAGGTAGCTGTGGGAGGGCAAGCTACCACTCATTAATTGC
AGGCCGATGACTGACATTATATTGTTATCTGATATCAACAGAACGGCCAGGCTCTCTCAGAGTCT
CTGATCTACAGGGATCCAGCATCAGCTCAGCTGGGATCCACACAGGCTGGGACGGCAGTGAGGAC
AGGATCACCTCCACCATCGCGGCTGAGTGACATGTCGCACTCAGTCAGAAGCAGTAGTCTCAGAGGT
ATAGTGTAATGTGTAATGTG
SEQ ID NO: 671
MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSVAAVGGTVSISCQASQSVDNYLNLSWFAQKPGQPPKL
LIYGASTLASVPSRFVGSFGSTQFRTLTDVQCDAAATYYCAGVYDDDSDNA

SEQ ID NO: 672
METGLRWLLLVALKVQVCSLESSESGGLVTPGTPLTLTCTASGSFSLSVYMNWVRQAPKGLEWIGFIT
MSDNINASWAKGRTFTISKSTTVDLKMTSSPTTEDTATYFACRSGWGMGRDLDL

SEQ ID NO: 673
ATGGACACGAGGCCCCACTCACTCAGTCTGCTGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCACATTTGC
CGCCGTGCTGACCACTCCATCTCCCCTCTGCTGCTGCAGTGCTGCCAGTTCA
AGGGCACTGAATGTTTATGACACAAACTAATCTCTGTCAGCGAAGACGGCAGCTCC
AAACCTGCTGCTGCTGCTGTTTG

SEQ ID NO: 674
MDTRAPTQLLGLLLLWLPGATFADDPVLTVQTPSVAAVGGTVSISCQASQSVDNYLNLSWFAQKPGQPPKL
LIYGASTLASVPSRFVGSFGSTQFRTLTDVQCDAAATYYCAGVYDDDSDNA

SEQ ID NO: 675
ATGGACACGAGGCCCCACTCACTCAGTCTGCTGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCACATTTGC
CGCCGTGCTGACCACTCCATCTCCCCTCTGCTGCTGCAGTGCTGCCAGTTCA
AGGGCACTGAATGTTTATGACACAAACTAATCTCTGTCAGCGAAGACGGCAGCTCC
AAACCTGCTGCTGCTGCTGTTTG

SEQ ID NO: 676
METGLRWLLLVALKVQVCSLESSESGGLVTPGTPLTLTCTASGSFSLSVYMNWVRQAPKGLEWIGFIT
MSDNINASWAKGRTFTISKSTTVDLKMTSSPTTEDTATYFACRSGWGMGRDLDL

SEQ ID NO: 677
ATGGACACGAGGCCCCACTCACTCAGTCTGCTGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCACATTTGC
CGCCGTGCTGACCACTCCATCTCCCCTCTGCTGCTGCAGTGCTGCCAGTTCA
AGGGCACTGAATGTTTATGACACAAACTAATCTCTGTCAGCGAAGACGGCAGCTCC
AAACCTGCTGCTGCTGCTGTTTG

SEQ ID NO: 678
MDTRAPTQLLGLLLLWLPGATFADDPVLTVQTPSVAAVGGTVSISCQASQSVDNYLNLSWFAQKPGQPPKL
LIYGASTLASVPSRFVGSFGSTQFRTLTDVQCDAAATYYCAGVYDDDSDNA

292
ATTCATTACTCTGAATAATAATGTAGCTTACGCGAACTGGGCGAAAGGCCGATTCACCTTCTCCAAAA
CCTCGACCACGGTGATCTGAAAATGACCAGTCCGACACCCGAGGACACGGCCACCTATTTCTGTGCC
AGGAGTCGTGGCTGGGTGAATGATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCA
GAGTCGTGGCTGGGTGAATGATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCA

SEQ ID NO: 679
MDTRAPTLSLGLLLLWLPAGTAFQVLTQTPSPSSAVAAVGVTVPINCCASQSVDWNLLGWYWQQKRGQP
YGLYAS6LASGVPSRFGSGSTQFTL6TISDL6EADDAATTTYCAGG65GNIFA

SEQ ID NO: 680
METGLRLWLLLVAVLKGVQCSVEESGRLVTTPGTPLTTCTVSGFSLLSSYAMS6WVRQAPK6GLEWIGII
FGTYYATWAKGRFTISKSTTTVDLR6ITS7T6DTAT6F6CARGGGPGNGGDI

SEQ ID NO: 681
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGC6TCCAGTGTC6TCAGTCG6
GGAGTCGGGGGGTGCTGACCGCTGGGACACCCCTAACTC6ACTGCACAGTCTCTGTGGTCTCT
CCCTCA6TACTATGCAAT6AGCTGGT6GGGTC6CCAG6CG6GCTCAAGG6AAGGGCTGGAGTGATCG6
GTC6ATCGGAAT

SEQ ID NO: 682
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGC6TCCAGTGTC6TCAGTCG6
GGAGTCGGGGGGTGCTGACCGCTGGGACACCCCTAACTC6ACTGCACAGTCTCTGTGGTCTCT
CCCTCA6TACTATGCAAT6AGCTGGT6GGGTC6CCAG6CG6GCTCAAGG6AAGGGCTGGAGTGATCG6
GTC6ATCGGAAT

SEQ ID NO: 683
MDTRAPTLSLGLLLLWLPAGTAFQVLTQTPSPSSAVAAVGVTVPINCCASQSVDWNLLGWYWQQKRGQP
YGLYAS6LASGVPSRFGSGSTQFTL6TISDL6EADDAATTTYCAGG65GNIFA

SEQ ID NO: 684
METGLRLWLLLVAVLKGVQCSVEESGRLVTTPGTPLTTCTVSGFSLLSSYAMS6WVRQAPK6GLEWIGII
FGTYYATWAKGRFTISKSTTTVDLR6ITS7T6DTAT6F6CARGGGPGNGGDI

SEQ ID NO: 685
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGC6TCCAGTGTC6TCAGTCG6
GGAGTCGGGGGGTGCTGACCGCTGGGACACCCCTAACTC6ACTGCACAGTCTCTGTGGTCTCT
CCCTCA6TACTATGCAAT6AGCTGGT6GGGTC6CCAG6CG6GCTCAAGG6AAGGGCTGGAGTGATCG6
GTC6ATCGGAAT

SEQ ID NO: 686
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACGCTCACCTGCACAGTCTCTGGAATCG
ACCTCAGTCACTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATG
ATTTATGCTGGTAGTGGTAGCACATGGTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAA
CCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCC
AGAGATGGATACGATGACTATGGTGATTTCGATCGATTGGATCTC
SEQ ID NO: 687
MDTRAPTQLLGLLLLWLPGARCAAYMTQTPASVSAAVGGTVTIKCQASQSINNELSWYQQKSGQRPKLLI
YRASTLASGVSSRFKSGSGTEFTLTISDLECADAATYYCQQGYSLRNIDNA
SEQ ID NO: 688
METGLRWLLLVAVLGSVGCQSLESSEGGLVTPGPTPLTCTATASGFSLSNYYMTWVRQAPGKGLEWIGMIY
GSDETAAYANWAIGRFTISKTTTVD1KMTS1TAADTATYF1CARDDDSDWDAKFN1
SEQ ID NO: 689
ATGGACACGAGGGCCCCCACTCAGCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCAGATGTGC
CTATGATATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAATGCC
AGGCCAGTCAAGCATTAAACATGAATTATCCTGGTATCAGCAGAAATCAGGGCAGCGTCCCAAGCTC
CTGATCTATAGGGCATCCACTCTGCGATCTGGGACACCCCTGACGCTCACCTGCACAGCCTCTGGATTCTC
CCTCAGTAACTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATG
ATTTATGGTAGTGATGAAACAGCCTACGCGAACTGGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
ATGATAGTAGTGACTGGGATGCAAAATTTAACTTG
SEQ ID NO: 690
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCTCAGGTGTCCAGTGTCAGTCGGTGGA
GGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGATTCTC
CCTCAGTAACTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATG
ATTTATGGTAGTGATGAAACAGCCTACGCGAACTGGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
GACCAACGTGGTACGTGAAAAATGACAGCTGACAGCGGCGATAGGCCGATTCACCATCTCCAAAAACCTC
ATGATAGTAGTGACTGGGATGCAAAATTTAACTTG
SEQ ID NO: 691
EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYMTWVRQAPGKGLEWIGMIYGSDETAAYANWAIGRFTIS
RDNSKNTLYQMNSLRAEDTAVYVYCARDDDSDWDAKFN1LWQGTLVTVSASTKGPVSFPFLAPSSKSTSG
GTAALGCLVKDYFPEPVTVSWSNGALTSGVHTFPAVLQSSGLYLSWWTSPSSLG1GTQTYICN1YNHKSNT
KVDKVRPKEKDRKTCPTCPAPELLGGPSVLBPFPKDRLMSRTPEVTCWVDSHEDPEVFNYWYV
GVEVHNAKTTPREEQYASTYRWSVLT1HQDWNGLNGKEYCKVSNKALPAPIEKTI5SAKAGQPRPQVYTV
LPSPRDLET1QNOVSLTC1VKGFPSPDA1VEWESNGQPENNYYKTTTPVLSDSGFLYSLKTLVDSKRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 692
EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYMTWVRQAPGKGLEWIGMIYGSDETAAYANSAIGRTIS
RDNSKNTLYQMNSLRAEDTAVYVYCARDDDSDWDAKFN1LWQGTLVTVSASTKGPVSFPFLAPSSKSTSG
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSWVTVPSSSLGTQTYICNVNHKPSNTK
VDKRVEKQSDKTHTCPPCPAPELLGGPSVFPLPVPDKDDTPPTLSVVDVLNYKDVEVPFNWYVDG
VEVHNAKTPREEQYASTYRVMVSTTVLHQLDWNGLKEYKCKVSNKALPAPIETISKAKGQPREPQVYTL
PPSREEMTKQNSLQLVLKGYFGYPSDIAVEWESNGQPENNYKTTTPVLSDDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLPGK

SEQ ID NO: 705
ATGAAGTGGGTAACCTTTATTTCCCTCTGGTTTCTCTTTAGCAGCGCTTATTCCGCTATCCAGATGACCC
AGTCTCCTTCCCTCGATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCAGTCAGAGCA
TTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCTGTATTCATAGGGCA
TCCACGTGCGATCCTGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCAC
CATCAGCAGGCTGACGTGATGATGATTTTGCAACTTATTACTGCAACAGGGTTATATTAGTCTAGGAAACA
TTGATAATGCTTTTCGCGGAGAGGCAACAGGAAAGCTAGACGTTGAGGCTGAAATCTGAGCTG

SEQ ID NO: 706
MKWVTISLLFLFSAYSAIQMTPSLSASVGDRVTITCQASQSINNESLYWQQKPGKAPKLLIYRASL
SGVPSRFSGSGTDFTLTISSLQPDFATYYCQQGYSLRNIDNAFFGGTKEIKRTVAAAPVESFFPSDEQL
KSGTASWCLLNFFPREAKVQWKVDNALSGNSQESVTEQDSKLYSTSLLTLSKADYEKHKVACE
VTHQGLSSPVTSFNRGEC

SEQ ID NO: 707
ATGAAGTGGGTAACCTTTATTTCCCTCTGGTTTCTCTTTAGCAGCGCTTATTCCGCTATCCAGATGACCC
AGTCTCCTTCCCTCGATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCAGTCAGAGCA
TTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCTGTATTCATAGGGCA
TCCACGTGCGATCCTGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCAC
CATCAGCAGGCTGACGTGATGATGATTTTGCAACTTATTACTGCAACAGGGTTATATTAGTCTAGGAAACA
TTGATAATGCTTTTCGCGGAGAGGCAACAGGAAAGCTAGACGTTGAGGCTGAAATCTGAGCTG

TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSWVTVPSSSLGTQTYICNVNHKPSNTK
VDKRVEKQSDKTHTCPPCPAPELLGGPSVFPLPVPDKDDTPPTLSVVDVLNYKDVEVPFNWYVDG
VEVHNAKTPREEQYASTYRVMVSTTVLHQLDWNGLKEYKCKVSNKALPAPIETISKAKGQPREPQVYTL
PPSREEMTKQNSLQLVLKGYFGYPSDIAVEWESNGQPENNYKTTTPVLSDDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLPGK

SEQ ID NO: 705
ATGAAGTGGGTAACCTTTATTTCCCTCTGGTTTCTCTTTAGCAGCGCTTATTCCGCTATCCAGATGACCC
AGTCTCCTTCCCTCGATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCAGTCAGAGCA
TTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCTGTATTCATAGGGCA
TCCACGTGCGATCCTGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCAC
CATCAGCAGGCTGACGTGATGATGATTTTGCAACTTATTACTGCAACAGGGTTATATTAGTCTAGGAAACA
TTGATAATGCTTTTCGCGGAGAGGCAACAGGAAAGCTAGACGTTGAGGCTGAAATCTGAGCTG

SEQ ID NO: 706
MKWVTISLLFLFSAYSAIQMTPSLSASVGDRVTITCQASQSINNESLYWQQKPGKAPKLLIYRASL
SGVPSRFSGSGTDFTLTISSLQPDFATYYCQQGYSLRNIDNAFFGGTKEIKRTVAAAPVESFFPSDEQL
KSGTASWCLLNFFPREAKVQWKVDNALSGNSQESVTEQDSKLYSTSLLTLSKADYEKHKVACE
VTHQGLSSPVTSFNRGEC

SEQ ID NO: 707
ATGAAGTGGGTAACCTTTATTTCCCTCTGGTTTCTCTTTAGCAGCGCTTATTCCGCTATCCAGATGACCC
AGTCTCCTTCCCTCGATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCAGTCAGAGCA
TTAACAATGAGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCTGTATTCATAGGGCA
TCCACGTGCGATCCTGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCTCAC
CATCAGCAGGCTGACGTGATGATGATTTTGCAACTTATTACTGCAACAGGGTTATATTAGTCTAGGAAACA
TTGATAATGCTTTTCGCGGAGAGGCAACAGGAAAGCTAGACGTTGAGGCTGAAATCTGAGCTG

297
CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGGCAAGCC
GCCCGAGAACCACAGGTGTACACCCCGGAGAGATGACCAAGAACCAGGTCAGC
CTCCGTGCAAGACCCAGGCTCCGACTCCACGCAGCCACGTTGCGGAGTGGAGAGCAATGGCGCC
GGAGAACAACACTACAGGACACGGCCTCCGCTTCGACCTGACGCTCCGGAGAACCAGGAC
TCACCGTGAGCAAGGACGGCTGACCGAGGAGAGGAACGTCTTCTCATTCTTGAGCAGGCTCTG
CACAACCCACTACACGCAGAGAGGCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 708
MKWVTISLLFLFSSAYSEVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGEWVGIYG
SDETAYATSAGRFTISRDNSKNTLYQMNLRRAEDTAVYCYADSSDDWDAKFNWLWGQTLVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSNSGALTSGVHTFPAVLQSSGLYLYLSSWT
VGPSVS

SEQ ID NO: 709
AIQMTQPSSSLASVGDRVITCQASQINNELSWYQQPKPGKAPKLIYRASTLASHPSWRFSGGSATDFTL
TISLQPDIFATYYQCGGYSRNNNAAFGGGTVEIKR

SEQ ID NO: 710
RASQGIRNDLG

SEQ ID NO: 711
RASQGISNYLA

SEQ ID NO: 712
RASQSISSWLA

SEQ ID NO: 713
AAASSLQS

SEQ ID NO: 714
AASTLQS

SEQ ID NO: 715
KASSLES

SEQ ID NO: 716
SNCYMS

SEQ ID NO: 717
VIYSGGSTYAADSVKG

SEQ ID NO: 718
VIYSGGSTRYADSVKG

SEQ ID NO: 719
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWSNGALTSGVHTFPAVLQSSGLYSLSWTWTV
SSSLTQTYICNVHKPSNTKVDKVEPKSCDKTHTCPPCPAPELGGPSVFLLSPKKDQITLMISRTPEVTCV
WDVSHEDPEVKFNWYVDGEVHNAAKTMPREEQYASTYRWSVTLVHQDWLNGKEYKCKVSNKALPA
PIEKTISAKGQPREPQVYTLPSREDLTKNOVSLTCLVKGYPFDIATVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLPGK

SEQ ID NO: 720
ATCCAGATGACCCAGTCTTCCTTCTCTCTGTCTGCACTCTGATGGAGACAGAGTCACCATCACTTGCCAG
GCCAGTCAGCATTAACAACTAGTATCTCTGTATCAAGCAAACCCGACGCTCAAGTGC
GCTCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG
ACTTCACTCTCACATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCACACAGGGTTATA
GTTATAGTCTGAGGAATATTGATAATGCT

SEQ ID NO: 721
GCCTATGATATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAGTG
CCAGCCGACGATCATAAACAAATGATTATCTCTGTATCAAGCAAACCCGACGCTCAAGTGC
GCTCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG
ACTTCACTCTCACATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCACACAGGGTTATA
GTTATAGTCTGAGGAATATTGATAATGCT

SEQ ID NO: 722
ATCCAGATGACCCAGTCTTCCTTCTCTCTGTCTGCACTCTGATGGAGACAGAGTCACCATCACTTGCCAG
GCCAGTCAGCATTAACAACTAGTATCTCTGTATCAAGCAAACCCGACGCTCAAGTGC
GCTCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG
ACTTCACTCTCACATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCACACAGGGTTATA
GTTATAGTCTGAGGAATATTGATAATGCT

SEQ ID NO: 723
GCTATCCAGATGACCCAGTCTTCTCTTCTCTCTGTCTGCACTCTGATGGAGACAGAGTCACCATCACTTGCCAG
GCCAGTCAGCATTAACAACTAGTATCTCTGTATCAAGCAAACCCGACGCTCAAGTGC
GCTCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG
ACTTCACTCTCACATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCACACAGGGTTATA
GTTATAGTCTGAGGAATATTGATAATGCT

SEQ ID NO: 724
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 725
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 726
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 727
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 728
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 729
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 730
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT

SEQ ID NO: 731
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTG
AGCCTCTGAGGAATATTGATAATGCT
What is claimed is:

1. A method of preventing, treating, or diagnosing a disease or condition associated with IL-6, comprising administration of an Ab1 antibody or antibody fragment to a subject in need thereof, wherein the Ab1 antibody or antibody fragment comprises:

   a light chain polypeptide comprising: a polypeptide having at least 75% identity to SEQ ID NO: 709, a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 723, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723; and

   a heavy chain polypeptide comprising: a polypeptide having at least 75% identity to SEQ ID NO: 657, a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 700, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700;

   wherein the Ab1 antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6.

2. The method of claim 1, wherein the light chain polypeptide includes one or more substitutions within the light chain framework region(s) relative to the light chain framework region sequences of SEQ ID NO: 709.

3. The method of claim 2 wherein one or more of the substitutions within the light chain framework region(s) is substitution with the sequence of a corresponding position of a donor sequence, wherein the donor sequence is comprising: SEQ ID NO: 2; a human, rabbit, or a non-human primate light chain sequence; and a light chain of any of Ab2, Ab3, Ab4, Ab5, Ab6, Ab7,
wherein the substitution results in replacement, insertion, and/or deletion of one or more amino acids, and

wherein the corresponding position is determined by sequence alignment between the framework region of SEQ ID NO: 709 and the donor sequence.

4. The method of claim 1, wherein the heavy chain polypeptide includes one or more substitutions within the heavy chain framework region(s) relative to the heavy chain framework region sequences of SEQ ID NO: 657.

5. The method of claim 4 wherein one or more of the substitutions within the heavy chain framework region(s) is substitution with the sequence of a corresponding position of a donor sequence, wherein the donor sequence is comprising: SEQ ID NO: 3; a human, rabbit, or a non-human primate heavy chain sequence; and a heavy chain of any of Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab1O, Ab11, AM2, AM3, AM4, AM5, AM6, AM7, AM8, AM9, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, or Ab36,

wherein the substitution results in replacement, insertion, and/or deletion of one or more amino acids, and

wherein the corresponding position is determined by sequence alignment between the framework region of SEQ ID NO: 657 and the donor sequence.

6. The method of any of claims 1-5, wherein the light chain polypeptide comprises one or more Abl light chain CDR polypeptide comprising:

a light chain CDR1 having at least 72.7% identity (identical to at least 8 out of 11 residues) to SEQ ID NO: 4;
a light chain CDR2 having at least 85.7% identity (identical to at least 6 out of 7 residues) to SEQ ID NO: 5;

a light chain CDR3 having at least 50% identity (identical to at least 6 out of 12 residues) to SEQ ID NO: 6;

a light chain CDR1 having at least 90.9% similarity (similar to at least 10 out of 11 residues) to SEQ ID NO: 4;

a light chain CDR2 having at least 100% similarity (similar to at least 7 out of 7 residues) to SEQ ID NO: 5; or

a light chain CDR3 having at least 66.6% similarity (similar to at least 8 out of 12 residues) to SEQ ID NO: 6;

and wherein the heavy chain polypeptide comprises one or more Abl heavy chain CDR polypeptide comprising:

a heavy chain CDR1 having at least 80% identity (identical to at least 4 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 50% identity (identical to at least 8 out of 16 residues) to SEQ ID NO: 120;

a heavy chain CDR3 having at least 33.3% identity (identical to at least 4 out of 12 residues) to SEQ ID NO: 9;

a heavy chain CDR1 having at least 100% similarity (similar to at least 5 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 56.2% similarity (similar to at least 9 out of 16 residues) to SEQ ID NO: 120; or

a heavy chain CDR3 having at least 50% similarity (similar to at least 6 out of 12 residues) to SEQ ID NO: 9.
7. The method of any of claims 1-5, wherein the light chain polypeptide comprises one or more Abl light chain CDR polypeptide comprising:

- a light chain CDR1 having at least 81.8% identity (identical to at least 9 out of 11 residues) to SEQ ID NO: 4;
- a light chain CDR2 having at least 71.4% identity (identical to at least 5 out of 7 residues) to SEQ ID NO: 5; or
- a light chain CDR3 having at least 83.3% identity (identical to at least 10 out of 12 residues) to SEQ ID NO: 6;

and wherein the heavy chain polypeptide comprises one or more Abl heavy chain CDR polypeptide comprising:

- a heavy chain CDR1 having at least 60% identity (identical to at least 3 out of 5 residues) to SEQ ID NO: 7;
- a heavy chain CDR2 having at least 87.5% identity (identical to at least 14 out of 16 residues) to SEQ ID NO: 120; or
- a heavy chain CDR3 having at least 83.3% identity (identical to at least 10 out of 12 residues) to SEQ ID NO: 9.

8. The method of any of claims 6-7, wherein the Abl antibody or antibody fragment comprises at least two of said light chain CDR polypeptides and at least two of said heavy chain CDR polypeptides.

9. A method of preventing or treating a disease or condition associated with IL-6, comprising administration of an Abl antibody or antibody fragment to a subject in need thereof, wherein the Abl antibody or antibody fragment comprises:

- two or more Abl light chain CDR polypeptides comprising:
  - a light chain CDR1 having at least 72.7% identity (identical to at least 8 out of 11 residues) to SEQ ID NO: 4;
a light chain CDR2 having at least 85.7% identity (identical to at least 6 out of 7 residues) to SEQ ID NO: 5; or

a light chain CDR3 having at least 50% identity (identical to at least 6 out of 12 residues) to SEQ ID NO: 6;

and two or more Abl heavy chain CDR polypeptide comprising:

- a heavy chain CDR1 having at least 80% identity (identical to at least 4 out of 5 residues) to SEQ ID NO: 7;

- a heavy chain CDR2 having at least 50% identity (identical to at least 8 out of 16 residues) to SEQ ID NO: 120; or

- a heavy chain CDR3 having at least 33.3% identity (identical to at least 4 out of 12 residues) to SEQ ID NO: 9;

wherein the Abl antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6.

10. A method of preventing or treating a disease or condition associated with IL-6, comprising administration of an Abl antibody or antibody fragment to a subject in need thereof, wherein the Abl antibody or antibody fragment comprises:

- two or more Abl light chain CDR polypeptides comprising:

  - a light chain CDR1 having at least 90.9% similarity (similar to at least 10 out of 11 residues) to SEQ ID NO: 4;

  - a light chain CDR2 having at least 100% similarity (similar to at least 7 out of 7 residues) to SEQ ID NO: 5; or

  - a light chain CDR3 having at least 66.6% similarity (similar to at least 8 out of 12 residues) to SEQ ID NO: 6;

and two or more Abl heavy chain CDR polypeptide comprising:
a heavy chain CDR1 having at least 100% similarity (similar to at least 5 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 56.2% similarity (similar to at least 9 out of 16 residues) to SEQ ID NO: 120; or

a heavy chain CDR3 having at least 50% similarity (similar to at least 6 out of 12 residues) to SEQ ID NO: 9;

wherein the Abl antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6.

11. The method of any of claims 9-10 wherein said Abl antibody or antibody fragment comprises said light chain CDR1, said light chain CDR3, said heavy chain CDR2, and said heavy chain CDR3.

12. The method of any of claims 9-10 wherein said Abl antibody or antibody fragment comprises said light chain CDR1, said light chain CDR2, said light chain CDR3, said heavy chain CDR1, said heavy chain CDR2, and said heavy chain CDR3.

13. The method of any of claims 9-12 wherein said light and heavy chain CDR polypeptides are comprised in an antibody or antibody fragment comprising Fab, Fab', F(\(\text{ab}'\))\(_2\), Fv, scFv, IgNAR, SMIP, camelbody, or nanobody.

14. The method of any of claims 9-12 wherein the framework regions (FRs) 1, 2, 3 and 4 in the variable light and heavy regions of said Abl antibody or antibody fragment, respectively, are human FRs which are unmodified or which have each been modified by the substitution of at most 2 or 3 human FR residues with the corresponding FR residues of the parent rabbit antibody light or heavy chain of SEQ ID NO: 2 and SEQ ID NO: 3, respectively,

wherein said human light chain FRs 1, 2 and 3 have been derived from a human variable light chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the subsequence of the
parent rabbit antibody light chain of SEQ ID NO: 2 extending from the beginning of FR1 to the end of FR3; and

wherein said human light chain FR4 has been derived from a human variable light chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the parent rabbit antibody light chain FR4 contained in SEQ ID NO: 2; and

wherein said human heavy chain FRs 1, 2 and 3 have been derived from a human variable heavy chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the subsequence of the parent rabbit antibody heavy chain of SEQ ID NO: 3 extending from the beginning of FR1 to the end of FR3; and

wherein said human heavy chain FR4 has been derived from a human variable heavy chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the parent rabbit antibody heavy chain FR4 contained in SEQ ID NO: 3.

15. The method of any of claims 1-14, wherein the Abl antibody or antibody fragment has an \textit{in vivo} half-life of at least about 22 days in a healthy human subject.

16. The method of any of claims 1-14, wherein the Abl antibody or antibody fragment has an \textit{in vivo} half-life of at least about 25 days in a healthy human subject.

17. The method of any of claims 1-14, wherein the Abl antibody or antibody fragment has an \textit{in vivo} half-life of at least about 30 days in a healthy human subject.

18. The method of any of claims 1-17, wherein the Abl antibody or antibody fragment has a binding affinity (Kd) for IL-6 of less than about 50 picomolar, or a rate of dissociation (K_{off}) from IL-6 of less than or equal to $10^{-4}$ S$^{-1}$. 
19. The method of any of claims 1-18, wherein the Abl 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 consisting essentially of the polypeptides of SEQ ID NO: 702 and SEQ ID NO: 704 or the polypeptides of SEQ ID NO: 2 and SEQ ID NO: 3.

20. The method of claim 19, wherein said binding to the same linear or conformational epitope(s) and/or competition for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof is ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide and includes 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 of SEQ ID NO: 1.

21. The method of any of claims 1-20, wherein the Abl antibody or antibody fragment is aglycosylated.

22. The method of any of claims 1-21, wherein the Abl antibody or antibody fragment contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation.

23. The method of any of claims 1-22, wherein the Abl antibody or antibody fragment is a human, humanized, single chain, or chimeric antibody.

24. The method of any of claims 1-23, wherein the Abl antibody or antibody fragment is comprising Fab, Fab', F(ab')2, Fv, or scFv.

25. The method of any of claims 1-24, wherein said Abl antibody or antibody fragment further comprises a human Fc.

26. The method of claim 25, wherein said human Fc is derived from IgGl, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgGlO, IgGl 1, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19.
27. The method of any of claims 1-26, wherein the one or more activity associated with IL-6 is an in vivo activity comprising:

- decreased serum albumin;
- elevated C-reactive protein ("CRP");
- fatigue;
- fever;
- anorexia (loss of appetite);
- weight loss;
- cachexia;
- weakness;
- decreased Glasgow Prognostic Score ("GPS");
- elevated serum D-dimer;
- abnormal coagulation profile;
- or any combination thereof.

28. The method of any of claims 1-26, wherein one or more of the one or more activity associated with IL-6 is an in vitro activity comprising:

- stimulation of proliferation of T1165 cells;
- binding of IL-6 to IL-6R;
- activation (dimerization) of the gpl30 signal-transducing glycoprotein;
- formation of IL-6/IL-6R/gpl30 multimers;
- stimulation of haptoglobin production by HepG2 cells modified to express human IL-6 receptor;
- or any combination thereof.

29. The method of any of claims 1-28 wherein the Abl antibody or antibody fragment is expressed from a recombinant cell.

30. The method of claim 29 wherein the cell is selected from a mammalian, yeast, bacterial, and insect cell.

31. The method of claim 30 wherein the cell is a yeast cell.

32. The method of claim 31 wherein the cell is a diploidal yeast cell.

33. The method of claim 31 wherein the yeast cell is a Pichia yeast.

34. The method of any of claims 1-33 wherein the disease or condition associated with IL-6 is comprising:
- cancer;
- a disease or condition associated with hypercoagulation;
- a disease or condition associated with elevated serum CRP;
- a disease or condition associated with hypoalbuminemia;
- an inflammatory disorder;
- a viral disorder;
- a wasting syndrome;
- an autoimmune disorder;
- or any combination thereof.
35. The method of any of claims 1-33 wherein the disease or condition associated with IL-6 is comprising: general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), cytokine storm, avian influenza, H1N1 influenza, porcine influenza, H5N1 influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, or systemic inflammatory response syndrome (SIRS).

36. The method of claim 34 wherein the disease or condition associated with hypercoagulation is comprising: cancer, 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.

37. The method of claim 34 wherein the disease or condition associated with elevated serum CRP is comprising: chronic inflammatory diseases, 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, 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, hepatitis B, hepatitis C, other organ specific autoimmune diseases, burns, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, allergic asthma, other allergic conditions or any combination thereof.

38. The method of claim 34 wherein the disease or condition associated with hypoalbuminemia is comprising: cancer, advanced cancer, rheumatoid arthritis, AIDS, heart disease, liver 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), inflammatory bowel disease, celiac's disease, trauma, burns, or any combination thereof.

39. The method of any of claims 34-38, wherein the cancer is comprising: Acanthoma, Acinic cell carcinoma, Acoustic neuroma, Acral lentiginous melanoma, Acrospiroma, Acute

40. The method of claim 39, wherein the cancer is comprising: Colorectal Cancer, Non-Small Cell Lung Cancer, Cholangiocarcinoma, Mesothelioma, Castleman's disease, Renal Cell Carcinoma, or any combination thereof.

41. The method of any of claims 1-40 wherein prior to administration of the Abl antibody or antibody fragment the subject has exhibited or is at risk for developing one or more of the following symptoms:
decreased serum albumin; elevated serum C-reactive protein ("CRP"); fatigue; fever; anorexia (loss of appetite); weight loss; cachexia; weakness; decreased Glasgow Prognostic Score ("GPS"); elevated serum D-dimer; abnormal coagulation profile; and any combination thereof.

42. The method of **claim 41** wherein said symptom is a side-effect of another therapeutic agent administered to the subject prior to, concurrent with, or subsequent to administration of the Abl antibody or antibody fragment.

43. The method of any of **claims 1-40** wherein the Abl antibody or antibody fragment is administered in a therapeutically effective amount for prevention or treatment of one or more symptom associated with elevated IL-6.

44. The method of **claim 43** wherein the therapeutically effective amount is between about 0.1 and 20 mg/kg of body weight of recipient subject.

45. The method of **claim 41** further comprising monitoring the subject to assess said symptom subsequent to administration of the Abl antibody.

46. The method of **claim 41** wherein said symptom is exhibited prior to Abl antibody or antibody fragment administration.

47. The method of **claim 46** wherein said symptom is improved or restored to a normal condition within approximately 1-5 weeks of Abl antibody administration.

48. The method of **claim 47** wherein said symptom thereafter remains improved for an entire period intervening two consecutive Abl antibody administrations.

49. The method of **claim 41**, wherein the subject's coagulation profile is assessed by measurement of the subject'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.

50. The method of **claim 41**, wherein the subject's coagulation profile is assessed by a functional measurement of clotting ability.
51. The method of claim 50, wherein the functional measurement of clotting ability is selected from prothrombin time (PT), prothrombin ratio (PR), international normalized ratio (INR), or any combination thereof.

52. The method of claim 41, further comprising: measuring the subject's international normalized ratio (INR) prior to administration of the Abl antibody or antibody fragment, and administering to the subject the Abl antibody or antibody fragment if the subject's INR is less than about 0.9.

53. The method of claim 41, further comprising: measuring the subject's international normalized ratio (INR) prior to administration of the Abl antibody or antibody fragment, and administering to the subject the Abl antibody or antibody fragment if the subject's INR is less than about 0.5.

54. The method of any of claims 52-53, wherein the subject's INR is raised to greater than approximately 0.9 within 4 weeks of administering to the subject the Abl antibody or antibody fragment.

55. The method of claim 41, further comprising: measuring the subject's serum D-dimer level prior to administration of the Abl antibody or antibody fragment, and administering the Abl antibody or antibody fragment if the subject's serum D-dimer level is above the normal reference range.

56. The method of claim 55, wherein the subject'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 subject the Abl antibody or antibody fragment.

57. The method of claim 41 that results in a prolonged improvement in the subject's coagulation profile.

58. The method of claim 41, wherein the subject's coagulation profile is measurably improved within about 2 weeks of administration of the Abl antibody or antibody fragment.
59. The method of claim 58, wherein the subject's coagulation profile remains measurably improved approximately 12 weeks after administering to the subject the Abl antibody or antibody fragment.

60. The method of claim 41, further comprising: measuring the subject's body temperature prior to administration of the Abl antibody or antibody fragment, and administering the Abl antibody or antibody fragment if the subject's body temperature higher than about 38 °C.

61. The method of claim 41, further comprising: measuring the subject's body weight prior to administration of the Abl antibody or antibody fragment, and administering the Abl antibody or antibody fragment if the subject's weight has declined by approximately 5% or more within approximately 30 days, or if the subject's lean body mass index is less than about 17 kg/m² (male subject) or less than about 14 kg/m² (female subject).

62. The method of claim 41, further comprising: measuring the subject's muscular strength prior to administration of the Abl antibody or antibody fragment, and administering the Abl antibody or antibody fragment if the subject's muscular strength has declined by greater than approximately 20% within approximately 30 days.

63. The method of claim 41, that results in a prolonged improvement in cachexia, weakness, fatigue, and/or fever in the subject.

64. The method of claim 41, wherein the subject's body mass is raised by approximately 1 kilogram within approximately 4 weeks of administration of the Abl antibody or antibody fragment.

65. The method of claim 41, wherein the subject's cachexia is measurably improved within about 4 weeks of Abl antibody or antibody fragment administration.

66. The method of claim 65, wherein the subject's cachexia is assessed by measurement of the subject's total body mass, lean body mass, lean body mass index, and/or appendicular lean body mass.
67. The method of claim 66, wherein the measurement of the subject's body mass discounts (subtracts) the estimated weight of the subject's tumor(s) and/or extravascular fluid collection(s).

68. The method of claim 66, wherein the subject's cachexia remains measurably improved approximately 8 weeks after Abl antibody or antibody fragment administration.

69. The method of claim 41, wherein the subject's weakness is measurably improved within about 2 weeks of Abl antibody or antibody fragment administration.

70. The method of claim 69, wherein the subject's weakness remains measurably improved approximately 12 weeks after Abl antibody or antibody fragment administration.

71. The method of claim 41, wherein the subject's fatigue is measurably improved within about 1 week of Abl antibody or antibody fragment administration.

72. The method of claim 71, wherein the subject's fatigue is measured by the FACIT-F FS test.

73. The method of claim 72, wherein the subject's FACIT-F FS score is improved by at least about 10 points.

74. The method of claim 71, wherein the subject's fatigue remains measurably improved approximately 12 weeks after anti-IL-6 antibody administration.

75. The method of claim 41, wherein the subject's fever is measurably improved within about 1 week of Abl antibody or antibody fragment administration.

76. The method of claim 75, wherein the subject's fever remains measurably improved approximately 12 weeks after Abl antibody or antibody fragment administration.

77. The method of claim 41, wherein said subject exhibits an elevated serum CRP level prior to administration of the Abl antibody or antibody fragment.

78. The method of claim 41 wherein said subject exhibits a reduced serum albumin level prior to administration of the Abl antibody or antibody fragment.
79. The method of claim 41, whereby the subject's Glasgow Prognostic Score (GPS) is improved.

80. The method of claim 41, further comprising: measuring the subject's serum CRP level prior to administration of the Abl antibody or antibody fragment, and administering the Abl antibody or antibody fragment if the subject's serum CRP level is at least approximately 5 mg/L.

81. The method of claim 41, wherein the subject's serum CRP level is reduced to less than approximately 10 mg/L within 1 week of administration of the Abl antibody or antibody fragment.

82. The method of claim 41, wherein the subject's serum CRP level is reduced to less than approximately 5 mg/L within 1 week of administration of the Abl antibody or antibody fragment.

83. The method of claim 41, wherein the subject's serum CRP level is reduced to less than approximately 1 mg/L within 1 week of administration of the Abl antibody or antibody fragment.

84. The method of claim 41 that results in a prolonged reduction in serum CRP level of the subject.

85. The method of claim 81, wherein 14 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.

86. The method of claim 81, wherein 21 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.

87. The method of claim 81, wherein 28 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.

88. The method of claim 81, wherein 35 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.
89. The method of claim 81, wherein 42 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.

90. The method of claim 81, wherein 49 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.

91. The method of claim 81, wherein 56 days after Abl antibody or antibody fragment administration the subject's serum CRP level remains less than approximately 10 mg/L.

92. The method of claim 41, further comprising: measuring the subject's serum albumin level prior to administration of the Abl antibody or antibody fragment, and administering the Abl antibody or antibody fragment if the subject's serum albumin level is less than approximately 35 g/L.

93. The method of claim 92, wherein the subject's serum albumin level is increased to greater than approximately 35 g/L within about 5 weeks of administration of the Abl antibody or antibody fragment.

94. The method of claim 41 that results in a prolonged increase in serum albumin level of the subject.

95. The method of claim 94, wherein 42 days after Abl antibody or antibody fragment administration the subject's serum albumin level remains above 35 g/L.

96. The method of claim 94, wherein 49 days after Abl antibody or antibody fragment administration the subject's serum albumin level remains above 35 g/L.

97. The method of claim 94, wherein 56 days after Abl antibody or antibody fragment administration the subject's serum albumin level remains above 35 g/L.

98. The method of claim 41, wherein the subject's serum albumin level is increased by about 5 g/L within approximately 5 weeks of administering the Abl antibody or antibody fragment.
99. The method of **claim 41** further comprising monitoring the subject to assess coagulation profile.

100. The method of **claim 41** wherein the subject has exhibited an elevated serum D-dimer level prior to treatment.

101. The method of **claim 41** wherein the subject has exhibited an elevated serum C-reactive protein (CRP) level prior to treatment.

102. The method of any of **claims 1-101** wherein the anti-IL-6 antibody or antibody fragment is administered to the subject with a frequency at most once per period of approximately four weeks.

103. The method of **claim 102**, wherein the anti-IL-6 antibody or antibody fragment is administered to the subject with a frequency at most once per period of approximately eight weeks.

104. The method of **claim 103**, wherein the anti-IL-6 antibody or antibody fragment is administered to the subject with a frequency at most once per period of approximately twelve weeks.

105. The method of **claim 104**, wherein the anti-IL-6 antibody or antibody fragment is administered to the subject with a frequency at most once per period of approximately sixteen weeks.

106. The method of any of **claims 1-40**, wherein the Abl antibody or antibody fragment is administered in a diagnostically effective amount for detection of IL-6 expressing disease sites.

107. The method of **claim 106**, wherein the Abl antibody or antibody fragment is directly or indirectly coupled to a radionuclide, fluorophore, or other detectable label that facilitates detection of the antibody at IL-6 expressing disease sites.

108. The method of **claim 106**, which is used to detect IL-6 expressing tumors or metastases.
109. The method of claim 106, which is used to detect the presence of sites of inflammation associated with IL-6 expressing cells.

110. The method of claim 106, wherein the results are used to facilitate design of an appropriate therapeutic regimen.

111. The method of claim 106, wherein said therapeutic regimen includes radiotherapy, chemotherapy or a combination thereof.

112. The method of any of claims 1-101, wherein the Abl antibody or antibody fragment is co-administered with another therapeutic agent comprising: chemotherapy agents, statins, cytokines, immunosuppressive agents, gene therapy agents, anti-coagulants, anti-cachexia agents, anti-weakness agent, anti-fatigue agent, anti-fever agent, anti-nausea agents, antiemetic agents, IL-6 antagonists, cytotoxic agents, analgesics, antipyretics, anti-inflammatory agents, antibiotics, antiviral agents, anti-cytokine agents, other therapeutic agents, or any combination thereof.

113. The method of claim 112, wherein the chemotherapy agent is comprising: VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids, vinblastine, vincristine, vindesine, vinorelbine, mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1 antagonists, interleukins, IL-12, IL-2, IL-12R antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

114. The method of claim 112, wherein the anti-coagulant is comprising: 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.

115. The method of claim 112, wherein the statin is comprising: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

116. The method of claim 112, wherein the another therapeutic agent is an antagonist of a factor comprising tumor necrosis factor-alpha, Interferon gamma, Interleukin 1 alpha, Interleukin 1 beta, Interleukin 6, proteolysis inducing factor, leukemia-inhibitory factor, or any combination thereof.

117. The method of claim 112, wherein the anti-cachexia agent is comprising: cannabis, dronabinol (Marinol™), nabilone (Cesamet), cannabidiol, cannabichromene, tetrahydrocannabinol, Sativex, megestrol acetate, or any combination thereof.

118. The method of claim 112, wherein the anti-nausea agent or antiemetic agent is comprising: 5-HT3 receptor antagonists, ajwain, alizapride, anticholinergics, antihistamines, aprepitant, benzodiazepines, cannabichromene, cannabidiol, cannabinoids, cannabis, casopitant, chlorpromazine, cyclizine, dexamethasone, dexamethasone, dimenhydrinate (Gravol™), diphenhydramine, dolasetron, domperidone, dopamine antagonists, doxylamine, dronabinol (Marinol™), droperidol, emetrol, ginger, granisetron, haloperidol, hydroxyzine, hyoscine, lorazepam, meclizine, metoclopramide, midazolam, muscimol, nabilone (Cesamet), nkl receptor antagonists, ondansetron, palonosetron, peppermint, Phenergan, prochlorperazine, Promacot, promethazine, Pentazine, propofol, sativex, tetrahydrocannabinol, trimethobenzamide, tropisetron, nandrolone, stilbestrol, thalidomide, lenalidomide, ghrelin agonists, myostatin antagonists, anti-myostatin antibodies, selective androgen receptor modulators, selective estrogen receptor modulators, angiotensin All antagonists, beta two adenergic receptor agonists, beta three adenergic receptor agonists, or any combination thereof.

119. The method of claim 112, wherein the another therapeutic agent is comprising tamoxifen, BCL-2 antagonists, estrogen, bisphosphonates, teriparatide, strontium ranelate, sodium alendronate (Fosamax), risedronate (Actonel), raloxifene, ibandronate (Boniva), sodium alendronate (Fosamax), risedronate (Actonel), raloxifene, ibandronate (Boniva),
Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulfacetamide, Sulfamethizole, Sulfanilamide, 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, 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, famiclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, fusion inhibitor, ganciclovir, gardasil, ibicabine, idoxuridine, imiquimod, imunovir, indinavir, inosine, integrase inhibitor, interferon, interferon type I, interferon type II, interferon type III, lamivudine, lopinavir, loviride, maraviroc, MK-0518, moroxydine, nelfimavir, 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, zidovudine, or any combination thereof.

120. The method of **claim 112**, wherein the cytotoxic agent, chemotherapeutic agent, or immunosuppressive agent is comprising: 1-dehydrotestosterone, 1-methylnitrosourea, 5-fluorouracil, 6-mercaptopurine, 6-mercaptopurine, 6-thioguanine, Abatacept, abraxane, acitretin, aclorubicin, Actinium-225 ($^{225}$Ac), actinomycin, Adalimumab, adenosine deaminase inhibitors, Afelimomab, Aflibercept, Aflutzumab, Alefacect, altretamin, alvocidib, aminolevulinic acid/methyl aminolevulinate, aminopterin, aminopterin, amrubicin, amsacrine, amsacrine, anagrelide, Anakinra, anthracyclines, antifolates, Anti-lymphocyte globulin, Antimetabolites, Antithymocyte globulin, arsenic trioxide, Aselizumab, asparaginase, asparagine depleters, Astatine-211 ($^{211}$At), Atlizumab, Atorolimumab, atrasentan, Avastin™, azacitidine, Azathioprine,
azelastine, aziridines, Basiliximab, BAYX antibodies, Belatacept, Belimumab, belotecan, bendamustine, Bertilimumab, bexarotene, bisantrene, Bismuth-213 \(^{213}\text{Bi}\), Bismuth-212 \(^{212}\text{Bi}\), bleomycin, bleomycin, bleomycin, BLyS antibodies, bortezomib, busulfan, busulfan, Calcineurin inhibitors, calicheamicin, camptotheacin, camptotheecins, capecitabine, carboplatin (paraplatin), carboquone, carminomycin, carmustine, carmustine (BSNU), CAT antibodies, CD1a antibodies, CD147/Basigin antibodies, CD154 antibodies, CD18 antibodies, CD20 antibodies, CD23 antibodies, CD3 antibodies, CD4 antibodies, CD40 antibodies, CD62L/L-selectin antibodies, CD80 antibodies, CDK inhibitors, Cedelizumab, celecoxib, Certolizumab pegol, chlorambucil, chlorambucils, Ciclosporin, cis-dichlorodiamine platinum (II) (DDP) cisplatin, cladribine, Clenoliximab, clofarabine, colchicine, complement component 5 antibodies, Copper-67 \(^{67}\text{Cu}\), corticosteroids, CTLA-4 antibodies, CTLA-4 fusion proteins, Cyclophilin inhibitors, cyclophosphamides, cyclophosphamide, cytarabine, cytarabine, cytochalasin B, cytoplasmin ribonucleases, dacarbazine, Daclizumab, dactinomycin, dactinomycin (actinomycin D), daunorubicin, daunorubicin, daunorubicin (formerly daunomycin), decitabine, Deforolimus, demecolcine, detorubicin, dibromomannitol, diethylcarbamazine, dihydrofolate reductase inhibitors, dihydroxy anthracin dione, diphertheria toxin, DNA polymerase inhibitors, docetaxel, Dorlimomab aritox, Dorlixizumab, doxorubicin (adriamycin), DXL625, Eculizumab, Efalizumab, efaproxiral, EGFR antagonists, elesclomol, elsamitracin, Elsilimomab, emetine, endothelin receptor antagonists, epipodophyllotoxins, epirubicin, epothilones, Erbitux™, Erlizumab, estramustine, Etanercept, ethidium bromide, etoglucid, etoposide, etoposide phosphate, Everolimus, Faralimomab, farnesyltransferase inhibitors, FKBP inhibitors, floxuridine, fludarabine, fluorouracil, Fontolizumab, fotemustine, Galiximab, Gallium-67 \(^{67}\text{Ga}\), Gantenerumab, Gavilimomab, gemcitabine, glucocorticoids, Golimumab, Gomiliximab, gramicidin D, Gusperimus, Herceptin®, hydrazines, hydroxyurea, hypomethylating agents, idarubicin, Idarubicine, ifosfamide, IL-1 antagonists, IL-1 receptor antagonists, IL-12, IL-12 antibodies, IL-12R antagonists, IL-13 antibodies, IL-2, IL-2 inhibitors, IL-2 receptor/CD25 antibodies, IL-6 antibodies, imatinib mesylate, Immunoglobulin E antibodies, IMP dehydrogenase inhibitors, Infliximab, Inolimomab, Integrin antibodies, Interferon antibodies, interferons, Interleukin 5 antibodies, Interleukin-6 receptor antibodies, interleukins, Iodine-125 \(^{125}\text{I}\), Iodine-131 \(^{131}\text{I}\), Ipilimumab, irinotecan, ixabepilone, Keliximab, larotaxel, Lead-212 \(^{212}\text{Pb}\), Lebrilizumab, Leflunomide, Lenalidomide, Lerdelimumab, leucovorine, LFA-1
antibodies, lidocaine, lipoxygenase inhibitors, lomustine (CCNU), lonidamine, lucanthone, Lumiliximab, Lutetium-177 (¹⁷⁷Lu), Macrolides, mannosulfan, Maslimomab, masoprocol, mechlorethamine, melphalan, Mepolizumab, mercaptopurine, Metelimumab, Methotrexate, microtubule assembly inhibitors, microtubule stability enhancers, mithramycin, mitobronitol, mitoguazone, mitomycin, mitomycin C, mitotane, mitoxantrone, Morolimumab, mTOR inhibitors, Muromonab-CD3, mustines, Mycophenolic acid, myototane (0,P'(DDD)), Natalizumab, nedaplatin, Nerelimomab, nimustine, nitrogen mustards, nitrosoureas, nordihydroguaiaretic acid, oblimersen, ocrelizumab, Ocrelimomab, Odulimomab, ofatumumab, olaparib, Omalizumab, ortataxel, Otelixizumab, oxaliplatin, oxaliplatin, paclitaxel (taxol), Pascolizumab, PDGF antagonists, pegaspargase, pemetrexed, Pentostatin, Pertuzumab, Pexelizumab, phosphodiesterase inhibitors, Phosphorus-32 (³²P), Pimecrolimus Abetimus, pirarubicin, pixontrone, platins, plicamycin, poly ADP ribose polymerase inhibitors, porfimer sodium, porphyrin derivatives, prednimustine, procaine, procarbazine, procarbazine, propranolol, proteasome inhibitors, pseudomonas exotoxin, Pseudomonas toxin, purine synthesis inhibitors, puromycin, pyrimidine synthesis inhibitors, radionuclides, radiotherapy, raltitrexed, ranimustine, Reslizumab, retinoid X receptor agonists, retinoids, Rhenium-186 (¹⁸⁶Re), Rhenium-188 (¹⁸⁸Re), ribonucleotide reductase inhibitors, ricin, Riloncept, Rituxan®, Rovelizumab, rubitecan, Ruplizumab, Samarium-153 (¹⁵³Sm), satraplatin, Scandium-47 (⁴⁷Sc), selective androgen receptor modulators, selective estrogen receptor modulators, seliciclib, semustine, sex hormone antagonists, Siplizumab, Sirolimus, steroid aromatase inhibitors, steroids, streptozocin, streptozotocin, Tacrolimus, talaporfin, Talizumab, taxanes, taxols, tegafur, Telimomab aritox, temoporfm, temozolomide, temsirolimus, Temsirolimus, Teneliximab, teniposide, Teplizumab, Teriflunomide, tesetaxel, testolactone, tetracaine, Thalidomide, thioepa chlorambucil, thiopurines thioguanine, ThioTEPA, thymidylate synthase inhibitors, tiazofurin, tipifarnib, Topoisomerase inhibitors, TNF antagonists, TNF antibodies, TNF fusion proteins, TNF receptor fusion proteins, TNF-alpha inhibitors, Tocilizumab, topoisomerase inhibitors, topotecan, Toralizumab, trabectedin, Tremelimumab, treosulfan, tretonoin, triazenes, triaziquone, triethylenemelamine, triplatin tetrani trate, trofosfamide, tumor antigen specific monoclonal antibodies, tyrosine kinase inhibitors, uramustine, Ustekinumab, valrubicin, Valrubicine, Vapaliximab, VEGF antagonists, Vepalimomab, verteporfin, vinblastine, vinca alkaloids, vincristine, vindesine, vinflunine, vinorelbine, Visilizumab, vorinostat, Yttrium-88 (⁸⁸Y),
Yttrium-90 (\(^{90}\text{Y}\)), Zanolimumab, zileuton, Ziralimumab, Zolimomab aritox, zorubicin, Zotarolimus, or any combination thereof.

121. The method of claim 112, wherein the another active agent is one or more agonist, antagonist, or modulator of a factor comprising: \(\gamma\text{NF-alpha}\), IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-alpha, IFN-gamma, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, or any combination thereof.

122. The method of claim 112, wherein the IL-6 antagonist is comprising: anti-IL-6 antibodies or fragments thereof, antisense nucleic acids, polypeptides, small molecules, or any combination thereof.

123. The method of claim 122, wherein the antisense nucleic acid comprises at least approximately 10 nucleotides of a sequence encoding IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.

124. The method of Claim 122 wherein the IL-6 antagonist is an anti-IL-6 antibody.

125. The method of claim 122, wherein the antisense nucleic acid comprises DNA, RNA, peptide nucleic acid, locked nucleic acid, morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, threose nucleic acid, or any combination thereof. The method of claim 122, wherein the anti-IL-6 antibody or fragment thereof is comprising: Abl, 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, Ab36, an IL-6 binding fragment of any of the foregoing, a variant of any of the foregoing, or any combination thereof.

126. The method of claim 122, wherein the IL-6 antagonist polypeptide comprises a fragment of a polypeptide having a sequence selected from the group consisting IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, and SYK.

127. The method of claim 126, wherein the fragment is at least 40 amino acids in length.

128. The method of claim 122, wherein the IL-6 antagonist comprises a soluble IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.
129. The method of claim 112, wherein the IL-6 antagonist is coupled to a half-life increasing moiety.

130. The method of any of claims 112-129, wherein the Abl antibody or antibody fragment is directly or indirectly coupled to one or more of said another therapeutic agent.

131. The method of any of claims 1-101, wherein the Abl antibody or antibody fragment is directly or indirectly coupled to a detectable label.

132. The method of claim 131 wherein the detectable label is comprising: fluorescent dyes, bioluminescent materials, radioactive materials, chemiluminescent moieties, streptavidin, avidin, biotin, radioactive materials, enzymes, substrates, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, 3\text{alpha}-galactosidase, luciferase, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin, dansyl chloride, luminol, luciferin, aequorin, Iodine 125 (\(^{125}\)I), Carbon 14 (\(^{14}\)C), Sulfur 35 (\(^{35}\)S), Tritium (\(^{3}\)H), Phosphorus 32 (\(^{32}\)P), or any combination thereof.

133. The method of any of claims 1-30 or claims 34-128, wherein the Abl antibody is administered to the subject in the form of one or more nucleic acids that encode the Abl antibody.

134. The method of claim 133 wherein the one or more nucleic acids are introduced into the recipient as a virus, liposome, cationic lipid complex, cationic polymer complex, or nanoparticle complex.

135. The method of claim 133 wherein the one or more nucleic acids are comprised of yeast or human preferred codons.

136. The method of claim 133 wherein the one or more nucleic acids are comprised in a vector.

137. The method of claim 136 wherein the vector is a plasmid or recombinant viral vector.

138. The method of claim 133 wherein the one or more nucleic acids comprise the heavy and light chain polynucleotide sequences of SEQ ID NO: 723 and SEQ ID NO: 700; SEQ ID
NO: 701 and SEQ ID NO: 703; SEQ ID NO: 705 and SEQ ID NO: 707; SEQ ID NO: 720 and SEQ ID NO: 724; and SEQ ID NO: 10 and SEQ ID NO: 11.

139. The method of any of the foregoing claims, wherein the Abl antibody comprises:

(a) light and heavy chain polypeptides comprising: SEQ ID NO: 709 and SEQ ID NO: 657; SEQ ID NO: 702 and SEQ ID NO: 704; SEQ ID NO: 706 and SEQ ID NO: 708; SEQ ID NO: 20 and SEQ ID NO: 19; or SEQ ID NO: 2 and SEQ ID NO: 3;

(b) a polypeptide having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any of the polypeptides of (a);

(c) a polynucleotide that hybridizes under moderately or highly stringent hybridization conditions to any of the heavy and light chain polynucleotide sequences of SEQ ID NO: 723 and SEQ ID NO: 700; SEQ ID NO: 701 and SEQ ID NO: 703; SEQ ID NO: 705 and SEQ ID NO: 707; SEQ ID NO: 720 and SEQ ID NO: 724; and SEQ ID NO: 10 and SEQ ID NO: 11;

(d) a polynucleotide having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any of the heavy and light chain polynucleotide sequences of SEQ ID NO: 723 and SEQ ID NO: 700; SEQ ID NO: 701 and SEQ ID NO: 703; SEQ ID NO: 705 and SEQ ID NO: 707; SEQ ID NO: 720 and SEQ ID NO: 724; and SEQ ID NO: 10 and SEQ ID NO: 11;

(e) a polypeptide encoded by any of the polynucleotides of (c) or (d).

140. A therapeutic composition comprising an Abl antibody and another therapeutic compound,

wherein the Abl antibody comprises:

a light chain polypeptide comprising: a polypeptide having at least 75% identity to SEQ ID NO: 709, a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 723, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723, or a polypeptide encoded by a polynucleotide that hybridizes
under high stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723; and

a heavy chain polypeptide comprising: a polypeptide having at least 75% identity to SEQ ID NO: 657, a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 700, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700;

wherein the Abl antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6;

and wherein the another therapeutic compound comprising: chemotherapy agents, statins, cytokines, gene therapy agents, anti-coagulants, anti-cachexia agents, anti-weakeness agent, anti-fatigue agent, anti-fever agent, anti-nausea agents, antiemetic agents, IL-6 antagonist, a cytotoxic agent, another therapeutic compound, or any combination thereof.

141. The composition of claim 140, wherein the light chain polypeptide includes one or more substitutions within the light chain framework region(s) relative to the light chain framework region sequences of SEQ ID NO: 709.

142. The composition of claim 141, wherein one or more of the substitutions within the light chain framework region(s) is substitution with the sequence of a corresponding position of a donor sequence, wherein the donor sequence is comprising: SEQ ID NO: 2; a human, rabbit, or a non-human primate light chain sequence; and a light chain of any of 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,

wherein the substitution results in replacement, insertion, and/or deletion of one or more amino acids, and
wherein the corresponding position is determined by sequence alignment between the framework region of SEQ ID NO: 709 and the donor sequence.

143. The composition of claim 142, wherein the heavy chain polypeptide includes one or more substitutions within the heavy chain framework region(s) relative to the heavy chain framework region sequences of SEQ ID NO: 657.

144. The composition of claim 143, wherein one or more of the substitutions within the heavy chain framework region(s) is substitution with the sequence of a corresponding position of a donor sequence, wherein the donor sequence is comprising: SEQ ID NO: 3; a human, rabbit, or a non-human primate heavy chain sequence; and a heavy chain of any of 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,

wherein the substitution results in replacement, insertion, and/or deletion of one or more amino acids, and

wherein the corresponding position is determined by sequence alignment between the framework region of SEQ ID NO: 657 and the donor sequence.

145. The composition of any of claims 140-144, wherein the light chain polypeptide comprises one or more Abl light chain CDR polypeptide comprising:

a light chain CDR1 having at least 72.7% identity (identical to at least 8 out of 11 residues) to SEQ ID NO: 4;

a light chain CDR2 having at least 85.7% identity (identical to at least 6 out of 7 residues) to SEQ ID NO: 5;

a light chain CDR3 having at least 50% identity (identical to at least 6 out of 12 residues) to SEQ ID NO: 6;

a light chain CDR1 having at least 90.9% similarity (similar to at least 10 out of 11 residues) to SEQ ID NO: 4;
a light chain CDR2 having at least 100% similarity (similar to at least 7 out of 7 residues) to SEQ ID NO: 5; or

a light chain CDR3 having at least 66.6% similarity (similar to at least 8 out of 12 residues) to SEQ ID NO: 6;

and wherein the heavy chain polypeptide comprises one or more Abl heavy chain CDR polypeptide comprising:

a heavy chain CDR1 having at least 80% identity (identical to at least 4 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 50% identity (identical to at least 8 out of 16 residues) to SEQ ID NO: 120;

a heavy chain CDR3 having at least 33.3% identity (identical to at least 4 out of 12 residues) to SEQ ID NO: 9;

a heavy chain CDR1 having at least 100% similarity (similar to at least 5 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 56.2% similarity (similar to at least 9 out of 16 residues) to SEQ ID NO: 120; or

a heavy chain CDR3 having at least 50% similarity (similar to at least 6 out of 12 residues) to SEQ ID NO: 9.

146. The composition of any of claims 140-144, wherein the light chain polypeptide comprises one or more Abl light chain CDR polypeptide comprising:

a light chain CDR1 having at least 81.8% identity (identical to at least 9 out of 11 residues) to SEQ ID NO: 4;

a light chain CDR2 having at least 71.4% identity (identical to at least 5 out of 7 residues) to SEQ ID NO: 5; or
a light chain CDR3 having at least 83.3% identity (identical to at least 10 out of 12 residues) to SEQ ID NO: 6;

and wherein the heavy chain polypeptide comprises one or more Abl heavy chain CDR polypeptide comprising:

a heavy chain CDR1 having at least 60% identity (identical to at least 3 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 87.5% identity (identical to at least 14 out of 16 residues) to SEQ ID NO: 120; or

a heavy chain CDR3 having at least 83.3% identity (identical to at least 10 out of 12 residues) to SEQ ID NO: 9.

147. The composition of any of claims 145-146, wherein the Abl antibody or antibody fragment comprises at least two of said light chain CDR polypeptides and at least two of said heavy chain CDR polypeptides.

148. A therapeutic composition comprising an Abl antibody and another therapeutic compound,

wherein the Abl antibody comprises:

two or more Abl light chain CDR polypeptides comprising:

a light chain CDR1 having at least 72.7% identity (identical to at least 8 out of 11 residues) to SEQ ID NO: 4;

a light chain CDR2 having at least 85.7% identity (identical to at least 6 out of 7 residues) to SEQ ID NO: 5; or

a light chain CDR3 having at least 50% identity (identical to at least 6 out of 12 residues) to SEQ ID NO: 6;

and two or more Abl heavy chain CDR polypeptide comprising:
a heavy chain CDR1 having at least 80% identity (identical to at least 4 out of 5 residues) to SEQ ID NO: 7;

a heavy chain CDR2 having at least 50% identity (identical to at least 8 out of 16 residues) to SEQ ID NO: 120; or

a heavy chain CDR3 having at least 33.3% identity (identical to at least 4 out of 12 residues) to SEQ ID NO: 9;

wherein the Abl antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6;

and wherein the another therapeutic compound comprising: chemotherapy agents, statins, cytokines, gene therapy agents, anti-coagulants, anti-cachexia agents, anti-weakness agent, anti-fatigue agent, anti-fever agent, anti-nausea agents, antiemetic agents, IL-6 antagonist, a cytotoxic agent, another therapeutic compound, or any combination thereof.

149. A therapeutic composition comprising an Abl antibody and another therapeutic compound,

wherein the Abl antibody comprises:

a light chain CDR1 having at least 90.9% similarity (similar to at least 10 out of 11 residues) to SEQ ID NO: 4;

a light chain CDR2 having at least 100% similarity (similar to at least 7 out of 7 residues) to SEQ ID NO: 5; and

a light chain CDR3 having at least 66.6% similarity (similar to at least 8 out of 12 residues) to SEQ ID NO: 6;

and two or more Abl heavy chain CDR polypeptide comprising:

a heavy chain CDR1 having at least 100% similarity (similar to at least 5 out of 5 residues) to SEQ ID NO: 7;
a heavy chain CDR2 having at least 56.2% similarity (similar to at least 9 out of 16 residues) to SEQ ID NO: 120; or

a heavy chain CDR3 having at least 50% similarity (similar to at least 6 out of 12 residues) to SEQ ID NO: 9;

wherein the Abl antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6;

and wherein the another therapeutic compound comprising: chemotherapy agents, statins, cytokines, gene therapy agents, anti-coagulants, anti-cachexia agents, anti-weakness agent, anti-fatigue agent, anti-fever agent, anti-nausea agents, antiemetic agents, IL-6 antagonist, a cytotoxic agent, another therapeutic compound, or any combination thereof.

150. The composition of any of claims 148-149, wherein said Abl antibody or antibody fragment comprises said light chain CDR1, said light chain CDR3, said heavy chain CDR2, and said heavy chain CDR3.

151. The composition of any of claims 148-149, wherein said Abl antibody or antibody fragment comprises said light chain CDR1, said light chain CDR2, said light chain CDR3, said heavy chain CDR1, said heavy chain CDR2, and said heavy chain CDR3.

152. The composition of any of claims 144-147, wherein said light and heavy chain CDR polypeptides are comprised in an antibody or antibody fragment comprising Fab, Fab', F(ab')2, Fv, scFv, IgNAR, SMIP, camelbodies, or nanobodies.

153. The composition of any of claims 148-151, wherein the framework regions (FRs) 1, 2, 3 and 4 in the variable light and heavy regions of said Abl antibody or antibody fragment, respectively, are human FRs which are unmodified or which have each been modified by the substitution of at most 2 or 3 human FR residues with the corresponding FR residues of the parent rabbit antibody light or heavy chain of SEQ ID NO: 2 and SEQ ID NO: 3, respectively,

wherein said human light chain FRs 1, 2 and 3 have been derived from a human variable light chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human
germline antibody sequences contained in the library or database) to the subsequence of the parent rabbit antibody light chain of SEQ ID NO: 2 extending from the beginning of FR1 to the end of FR3; and

wherein said human light chain FR4 has been derived from a human variable light chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the parent rabbit antibody light chain FR4 contained in SEQ ID NO: 2; and

wherein said human heavy chain FRs 1, 2 and 3 have been derived from a human variable heavy chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the subsequence of the parent rabbit antibody heavy chain of SEQ ID NO: 3 extending from the beginning of FR1 to the end of FR3; and

wherein said human heavy chain FR4 has been derived from a human variable heavy chain antibody sequence that has been selected from a library or database of human germline antibody sequences based on its high level of homology (relative to other human germline antibody sequences contained in the library or database) to the parent rabbit antibody heavy chain FR4 contained in SEQ ID NO: 3.

154. The composition of any of claims 140-153, wherein the Abl antibody or antibody fragment has an in vivo half-life of at least about 22 days in a healthy human subject.

155. The composition of any of claims 140-153, wherein the Abl antibody or antibody fragment has an in vivo half-life of at least about 25 days in a healthy human subject.

156. The composition of any of claims 140-153, wherein the Abl antibody or antibody fragment has an in vivo half-life of at least about 30 days in a healthy human subject.
157. The composition of any of claims 140-156, wherein the Abl antibody or antibody fragment has a binding affinity (Kd) for IL-6 of less than about 50 picomolar, or a rate of dissociation (Kd) from IL-6 of less than or equal to 10⁻³ S⁻¹.

158. The composition of any of claims 140-157, wherein the Abl 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 consisting essentially of the polypeptides of SEQ ID NO: 702 and SEQ ID NO: 704 or the polypeptides of SEQ ID NO: 2 and SEQ ID NO: 3.

159. The composition of claim 158, wherein said binding to the same linear or conformational epitope(s) and/or competition for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof is ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide and includes 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 of SEQ ID NO: 1.

160. The composition of any of claims 140-159, wherein the Abl antibody or antibody fragment is aglycosylated.

161. The composition of any of claims 140-160, wherein the Abl antibody or antibody fragment contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation.

162. The composition of any of claims 140-161, wherein the Abl antibody or antibody fragment is a human, humanized, single chain, or chimeric antibody.

163. The composition of any of claims 140-162, wherein the Abl antibody or antibody fragment is comprising Fab, Fab', F(ab')₂, Fv, or scFv.

164. The composition of any of claims 140-163, wherein said Abl antibody or antibody fragment further comprises a human Fc.
165. The composition of claim 164, wherein said human Fc is derived from IgGl, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgGlo, IgGl1, IgGl2, IgGl3, IgGl4, IgGl5, IgGl6, IgGl7, IgGl8 or IgGl9.

166. The composition of any of claims 140-165, wherein the one or more activity associated with IL-6 is an in vivo activity comprising:

- decreased serum albumin;
- elevated C-reactive protein ("CRP");
- fatigue;
- fever;
- anorexia (loss of appetite);
- weight loss;
- cachexia;
- weakness;
- decreased Glasgow Prognostic Score ("GPS");
- elevated serum D-dimer;
- abnormal coagulation profile;
- or any combination thereof.

167. The composition of any of claims 140-165, wherein one or more of the one or more activity associated with IL-6 is an in vitro activity comprising:

- stimulation of proliferation of T1165 cells;
- binding of IL-6 to IL-6R;
- activation (dimerization) of the gpl30 signal-transducing glycoprotein;
- formation of IL-6/IL-6R/gpl30 multimers;
- stimulation of haptoglobin production by HepG2 cells modified to express human IL-6 receptor;
- or any combination thereof.

168. The composition of any of claims 140-167, wherein the Abl antibody or antibody fragment is expressed from a recombinant cell.

169. The composition of claim 168, wherein the cell is selected from a mammalian, yeast, bacterial, and insect cell.

170. The composition of claim 169, wherein the cell is a yeast cell.

171. The composition of claim 170, wherein the cell is a diploidal yeast cell.

172. The composition of claim 171, wherein the yeast cell is a Pichia yeast.

173. The composition of any of claims 140-172, wherein the Abl antibody or antibody fragment is co-administered with another therapeutic agent comprising: chemotherapy agents, statins, cytokines, immunosuppressive agents, gene therapy agents, anti-coagulants, anti-
cachexia agents, anti-weakness agent, anti-fatigue agent, anti-fever agent, anti-nausea agents, antiemetic agents, IL-6 antagonists, cytotoxic agents, analgesics, antipyretics, anti-inflammatory agents, antibiotics, antiviral agents, anti-cytokine agents, other therapeutic agents, or any combination thereof.

174. The composition of **claim 173**, wherein the chemotherapy agent is comprising: VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids, vinblastine, vincristine, vindesine, vinorelbine, mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1 antagonists, interleukins, IL-12, IL-2, IL-12R antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux™, Avastin™, Pertuzumab, anti-CD20 antibodies, Rituxan®, ocrelizumab, ofatumumab, DXL625, Herceptin®, or any combination thereof.

175. The composition of **claim 173**, wherein the anti-coagulant is comprising: 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.

176. The composition of **claim 173**, wherein the statin is comprising: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or any combination thereof.

177. The composition of **claim 173**, wherein the another therapeutic agent is an antagonist of a factor comprising tumor necrosis factor-alpha, Interferon gamma, Interleukin 1 alpha, Interleukin 1 beta, Interleukin 6, proteolysis inducing factor, leukemia-inhibitory factor, or any combination thereof.
178. The composition of claim 173, wherein the anti-cachexia agent is comprising: cannabis, dronabinol (Marinol™), nabilone (Cesamet), cannabidiol, cannabichromene, tetrahydrocannabinol, Sativex, megestrol acetate, or any combination thereof.

179. The composition of claim 173, wherein the anti-nausea agent or antiemetic agent is comprising: 5-HT3 receptor antagonists, ajwain, alizapride, anticholinergics, antihistamines, aprepitant, benzodiazepines, cannabichromene, cannabidiol, cannabinoids, cannabis, casopitant, chlorpromazine, cyclizine, dexamethasone, dexamethasone, dimenhydrinate (Gravol™), diphenhydramine, dolasetron, domperidone, dopamine antagonists, doxylamine, dronabinol (Marinol™), droperidol, emetrol, ginger, granisetron, haloperidol, hydroxyzine, hyoscine, lorazepam, meclizine, metoclopramide, midazolam, muscimol, nabilone (Cesamet), nkl receptor antagonists, ondansetron, palonosetron, peppermint, Phenergan, prochlorperazine, Promacot, promethazine, Pentazine, propofol, sativex, tetrahydrocannabinol, trimethobenzamide, tropisetron, nandrolone, stilbestrol, thalidomide, lenalidomide, ghrelin agonists, myostatin antagonists, anti-myostatin antibodies, selective androgen receptor modulators, selective estrogen receptor modulators, angiotensin II antagonists, beta two adenergic receptor agonists, beta three adenergic receptor agonists, or any combination thereof.

180. The composition of claim 173, wherein the another therapeutic agent is comprising tamoxifen, BCL-2 antagonists, estrogen, bisphosphonates, teriparatide, strontium ranelate, sodium alendronate (Fosamax), risedronate (Actonel), raloxifene, ibandronate (Boniva), Obatoclax, ABT-263, gossypol, gefitinib, epidermal growth factor receptor tyrosine kinase inhibitors, erlotinib, epidermal growth factor receptor inhibitors, psoralens, trioxysalen, methoxsalen, bergapten, retinoids, etretinate, acitretin, infliximab (Remicade®), adalimumab, infliximab, etanercept, Zenapax™, Cyclosporine, Methotrexate, granulocyte-colony stimulating factor, filgrastim, lenograstim, Neupogen, Neulasta, 2-Arylpropionic acids, Aceclofenac, Acemetacin, Acetylsalicylic acid (Aspirin), Alclofenac, Alminopofen, Amoxiprin, Ampyron, Auyrlalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxaprofen, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofewzone, COX-2 inhibitors, Dexibuprofen, Dextroprofen, Diclofenac, Diflunisal, Doxicam, 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, Piroxicam, Pirprofen, profens, Proglumetac, Pyrazolidine derivatives, Rofecoxib, Salicyl salicylate, Salicylamide, Salicylates, Sulfinpyrazone, Sulindac, Suprofen, Tenoxicam, Tiaprofenic acid, Tolmetin, and Valdecoxib. Antibiotics include Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ansamycins, Arsenophenamine, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenems, Carbenicillin, Cefaclor, Cefadroxil, Cefalexin, 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, Oxacin, Oxytetracycline, Paromomycin, Penicillin, Penicillins, Pipercillin, Platensimycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulfaetamide, 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, adeovir, amantadine, amprenavir, an antiretroviral fixed dose combination, an antiretroviral synergistic enhancer, arbidol, atazanavir, atripla, brivudine, didofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine,
efavirenz, emtricitabine, enfuvirtide, entecavir, entry inhibitors, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, fusion inhibitor, ganciclovir, gartasil, ibicatabine, 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, nexcavir, 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, zidovudine, or any combination thereof.

181. The composition of claim 173, wherein the cytotoxic agent, chemotherapeutic agent, or immunosuppressive agent is comprising: 1-dehydrotestosterone, 1-methylnitrosourea, 5-fluorouracil, 6-mercaptopurine, 6-thioguanine, Abatacept, abraxane, acitretin, aclarubicin, Actinium-225 (²²⁵Ac), actinomycin, Adalimumab, adenosine deaminase inhibitors, Afelimomab, Aflibercept, Aflutuzumab, Alefacept, alitretinoin, alkyl sulfonates, alkylating agents, altretamine, alvocidib, aminolevulinic acid/methyl aminolevulinate, aminopterin, amrubicin, amisacrine, anagrelide, Anakinra, anthracenediones, anthracyclines, anthracyclines, anthracyclines, anthracycline (AMC); antimyotic agents, antibiotics, anti-CD20 antibodies, antifolates, Anti-lymphocyte globulin, Antimetabolites, Antithymocyte globulin, arsenic trioxide, Aselizumab, asparaginase, asparagine depleters, Astatine-211 (²¹¹At), Atlizumab, Atorolimumab, atrasentan, Avastin™, azacitidine, Azathioprine, azelastine, aziridines, Basiliximab, BAYX antibodies, Belatacept, Belimumab, belotecan, bendamustine, Bertilimumab, bexarotene, bisantrene, Bismuth -213 (²¹³Bi), Bismuth-212 (²¹²Bi), bleomycin, bleomycin, bleomycin, BLyS antibodies, bortezomib, busulfan, busulfan, Calcineurin inhibitors, calicheamicin, camptothecin, camptothecins, capcetabine, carboplatin (paraplatin), carboquone, carmofur, carmustine, carbustine (BSNU), CAT antibodies, CD1 la antibodies, CD147/Basigin antibodies, CD154 antibodies, CD18 antibodies, CD20 antibodies, CD23 antibodies, CD3 antibodies, CD4 antibodies, CD40 antibodies, CD62L/L-selectin antibodies, CD80 antibodies, CDK inhibitors, Cedelizumab, celecoxib, Certolizumab pegol, chlorambucil, chlorambucils, Ciclosporin, cis-dichlorodiamine platinum (II) (DDP) cisplatin, cladribine, Clenoliximab, clofarabine, colchicine, Complement component 5 antibodies, Copper-67 (⁶⁷Cu), corticosteroids, CTLA-4 antibodies, CTLA-4 fusion proteins, Cyclophilin inhibitors,
cyclophosphamides, cyclothosphamide, cytarabine, cytarabine, cytochalasin B, cytotoxic ribonucleases, dacarbazine, Daclizumab, dactinomycin, dactinomycin (actinomycin D), daunorubicin, daunorubicin, daunorubicin (formerly daunomycin), decitabine, Deforolimus, demecolcine, detorubicin, dibromomannitol, diethlylcarbamazine, dihydrofolate reductase inhibitors, dihydroxy anthracin dione, diphtheria toxin, DNA polymerase inhibitors, docetaxel, Dorlimomab aritox, Dorlixizumab, doxorubicin (adriamycin), DXL625, Eculizumab, Efalizumab, efaproxiral, EGFR antagonists, elesclomol, elsamitrucin, Elsilimomab, emetine, endothelin receptor antagonists, epipodophyllotoxins, epirubicin, epothilones, Erbitux™, Erlizumab, estramustine, Etanercept, ethidium bromide, etoglucid, etoposide, etoposide phosphate, Everolimus, Faralimomab, farnesyltransferase inhibitors, FKBP inhibitors, floxuridine, fludarabine, fluorouracil, Fontolizumab, fotemustine, Galiximab, Gallium-67 (Ga), Gantenerumab, Gavilimomab, gemcitabine, glucocorticoids, Golimumab, Gomiliximab, gramicidin D, Gusperimus, Herceptin®, hydrazines, hydroxyurea, hypomethylating agents, idarubicin, IdaRubicine, ifosfamide, IL-1 antagonists, IL-1 receptor antagonists, IL-12, IL-12 antibodies, IL-12R antagonists, IL-13 antibodies, IL-2, IL-2 inhibitors, IL-2 receptor/CD25 antibodies, IL-6 antibodies, imatinib mesylate, Immunoglobin E antibodies, IMP dehydrogenase inhibitors, Infliximab, Inolimomab, Integrin antibodies, Interferon antibodies, interferons, Interleukin 5 antibodies, Interleukin-6 receptor antibodies, interleukins, Iodine-125 (125I), Iodine-131 (131I), Ipihumumab, irinotecan, ixabeplione, Keliximab, larotaxel, Lead-212 (212Pb), Lebritilizumab, Lefunomide, Lenalidomide, Lerdelimumab, leucovorine, LFA-1 antibodies, lidocaine, lipoxygenase inhibitors, limustine (CCNU), Liodamine, luncanthone, Lumiliximab, Lutetium-177 (177Lu), Macrolides, mannosulfan, Maskimomab, masprocol, mechlorethamine, melphalan, Mepolizumab, mercaptopurine, Metelimumab, Methotrexate, microtubule assembly inhibitors, microtubule stability enhancers, mithramycin, mitobronitol, mitoguazone, mitomycin, mitomycin C, mitotane, mitoxantrone, Morolimumab, mTOR inhibitors, Muromonab-CD3, mustines, Mycophenolic acid, mytotane (0.P′-(DDD)), Natalizumab, nedaplatin, Nerelimumab, nimustine, nitrogen mustards, nitrosoarases, nordihydroguaiaretic acid, oblimersen, ocrelizumab, Ocrelizumab, Odulimomab, ofatumumab, olaparib, Omalizumab, ortaxel, Otelixizumab, oxaliplatin, oxaliplatin, paclitaxel (taxol), Pascolizumab, PDGF antagonists, pegaspargase, pemetrexed, Pentostatin, Pertuzumab, Pexelizumab, phosphodiesterase inhibitors, Phosphorus-32 (32P), Pimecrolimus Abetimus,
pirarubicin, pixantrone, platins, plicamycin, poly ADP ribose polymerase inhibitors, porfimer sodium, porphyrin derivatives, prednimustine, procaine, procarbazine, procarbazine, propranolol, proteasome inhibitors, pseudomonas exotoxin, Pseudomonas toxin, purine synthesis inhibitors, puromycin, pyrimidine synthesis inhibitors, radionuclides, radiotherapy, raltitrexed, ranimustine, Reslizumab, retinoid X receptor agonists, retinoids, Rhenium-186 ($^{186}$Re), Rhenium-188 ($^{188}$Re), ribonucleotide reductase inhibitors, ricin, Rilonacept, Rituxan®, Rovelizumab, rubitecan, Ruplizumab, Samarium-153 ($^{153}$Sm), satraplatin, Scandium-47 ($^{47}$Sc), selective androgen receptor modulators, selective estrogen receptor modulators, seliciclib, semustine, sex hormone antagonists, Siplizumab, Sirolimus, steroid aromatase inhibitors, steroids, streptozocin, streptozotocin, Tacrolimus, talaporfm, Talizumab, taxanes, taxols, tegafur, Telimomab aritox, temoporfm, temozolomide, temsirolimus, Temsirolimus, Teneliximab, teniposide, Teplizumab, Teriflunomide, tesetaxel, testolactone, tetracaine, Thalidomide, throepa chlorambucil, thiopurines thioguanine, ThioTEPA, thymidylate synthase inhibitors, tiazofurin, tipifarnib, T-lymphocyte antibodies, TNF antagonists, TNF antibodies, TNF fusion proteins, TNF receptor fusion proteins, TNF-alpha inhibitors, Tocilizumab, topoisomerase inhibitors, topotecan, Toralizumab, trabectedin, Tremelimimab, treosulfan, tretinoin, triazenes, triaziquone, triethylenemelamine, triplatin tetranitrate, trofosfamide, tumor antigen specific monoclonal antibodies, tyrosine kinase inhibitors, uramustine, Ustekinumab, valrubicin, Valrubicine, Vapaliximab, VEGF antagonists, Vepalimobab, verteporfin, vinblastine, vinca alkaloids, vincristine, vindesine, vinflunine, vinorelbine, Visilizumab, vorinostat, Yttrium-88 ($^{88}$Y), Yttrium-90 ($^{90}$Y), Zanolimumab, zileuton, Ziralimumab, Zolimomab aritox, zorubicin, Zotarolimus, or any combination thereof.

182. The composition of claim 173, wherein the another active agent is one or more agonist, antagonist, or modulator of a factor comprising: TNF-alpha, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-alpha, IFN-gamma, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, or any combination thereof.

183. The composition of claim 173, wherein the IL-6 antagonist is comprising: anti-IL-6 antibodies or fragments thereof, antisense nucleic acids, polypeptides, small molecules, or any combination thereof.
184. The composition of claim 183, wherein the antisense nucleic acid comprises at least approximately 10 nucleotides of a sequence encoding IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.

185. The composition of claim 183, wherein the antisense nucleic acid comprises DNA, RNA, peptide nucleic acid, locked nucleic acid, morpholino (phosphorodiamidate morpholino oligo), glycerol nucleic acid, threose nucleic acid, or any combination thereof.

186. The composition of claim 183, wherein the anti-IL-6 antibody or fragment thereof is comprising: Abl, 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, Ab36, an IL-6 binding fragment of any of the foregoing, a variant of any of the foregoing, or any combination thereof.

187. The composition of claim 183, wherein the IL-6 antagonist polypeptide comprises a fragment of a polypeptide having a sequence selected from the group consisting IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, or SYK.

188. The composition of claim 187, wherein the fragment is at least 40 amino acids in length.

189. The composition of claim 183, wherein the IL-6 antagonist comprises a soluble IL-6, IL-6 receptor alpha, gpl30, p38 MAP kinase, JAK1, JAK2, JAK3, SYK, or any combination thereof.

190. The composition of claim 173, wherein the IL-6 antagonist is coupled to a half-life increasing moiety.

191. The composition of any of claims 170-190, wherein the Abl antibody or antibody fragment is directly or indirectly coupled to one or more of said another therapeutic agent.

192. The composition of any of claims 140-167, wherein the Abl antibody or antibody fragment is directly or indirectly coupled to a detectable label.
193. The composition of claim 192 wherein the detectable label is comprising: fluorescent dyes, bioluminescent materials, radioactive materials, chemiluminescent moieties, streptavidin, avidin, biotin, radioactive materials, enzymes, substrates, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, 34eto-galactosidase, luciferase, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin, dansyl chloride, luminol, luciferin, aequorin, Iodine 125 (125I), Carbon 14 (14C), Sulfur 35 (35S), Tritium (3H), Phosphorus 32 (32P), or any combination thereof.

194. The composition of any of claims 140-193, wherein the Abl antibody is administered to the subject in the form of one or more nucleic acids that encode the Abl antibody.

195. The composition of claim 194, wherein the one or more nucleic acids are introduced into the recipient as a virus, liposome, cationic lipid complex, cationic polymer complex, or nanoparticle complex.

196. The composition of claim 194, wherein the one or more nucleic acids are comprised of yeast or human preferred codons.

197. The composition of claim 194, wherein the one or more nucleic acids are comprised in a vector.

198. The composition of claim 194, wherein the vector is a plasmid or recombinant viral vector.

199. The composition of claim 194, wherein the one or more nucleic acids comprise the heavy and light chain polynucleotide sequences of SEQ ID NO: 723 and SEQ ID NO: 700; SEQ ID NO: 701 and SEQ ID NO: 703; SEQ ID NO: 705 and SEQ ID NO: 707; SEQ ID NO: 720 and SEQ ID NO: 724; and SEQ ID NO: 10 and SEQ ID NO: 11.

200. The composition of any of claims 140-193, wherein the Abl antibody comprises:

(a) light and heavy chain polypeptides comprising: SEQ ID NO: 709 and SEQ ID NO: 657; SEQ ID NO: 702 and SEQ ID NO: 704; SEQ ID NO: 706 and SEQ ID NO: 708; SEQ ID NO: 20 and SEQ ID NO: 19; or SEQ ID NO: 2 and SEQ ID NO: 3.
(b) a polypeptide having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any of the polypeptides of (a);

(c) a polynucleotide that hybridizes under moderately or highly stringent hybridization conditions to any of the heavy and light chain polynucleotide sequences of SEQ ID NO: 723 and SEQ ID NO: 700; SEQ ID NO: 701 and SEQ ID NO: 703; SEQ ID NO: 705 and SEQ ID NO: 707; SEQ ID NO: 720 and SEQ ID NO: 724; and SEQ ID NO: 10 and SEQ ID NO: 11;

(d) a polynucleotide having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any of the heavy and light chain polynucleotide sequences of SEQ ID NO: 723 and SEQ ID NO: 700; SEQ ID NO: 701 and SEQ ID NO: 703; SEQ ID NO: 705 and SEQ ID NO: 707; SEQ ID NO: 720 and SEQ ID NO: 724; and SEQ ID NO: 10 and SEQ ID NO: 11;

(e) a polypeptide encoded by any of the polynucleotides of (c) or (d).

201. A method of treating rheumatoid arthritis by subcutaneously administering an effective dosage of an anti-IL-6 antibody having the same epitopic specificity as Abl or an antibody that competes with Abl for binding to IL-6 to a patient in need thereof.

202. The method of claim 201 wherein said antibody or antibody fragment comprises a light chain polypeptide comprising: a polypeptide having at least 75% identity to SEQ ID NO: 709, a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 723, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 723; and a heavy chain polypeptide comprising: a polypeptide having at least 75% identity to SEQ ID NO: 657, a polypeptide encoded by a polynucleotide that has at least 75% identity to the polynucleotide of SEQ ID NO: 700, a polypeptide encoded by a polynucleotide that hybridizes under medium stringency conditions to a polynucleotide having the sequence of the reverse complement of SEQ ID NO: 700, or a polypeptide encoded by a polynucleotide that hybridizes under high stringency conditions to a polynucleotide having the
sequence of the reverse complement of SEQ ID NO: 700; wherein the Abl antibody or antibody fragment specifically binds to IL-6 and antagonizes one or more activity associated with IL-6.

203. The method of claim 201 wherein the subcutaneous dosage is at least about 50 or 100 mg.

204. The method of claim 201 wherein the efficacy of said subcutaneous administration is determined by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

205. The method of claim 201 wherein said subcutaneous administration results in an improvement in disease as manifested by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

206. The method of claim 205 wherein said subcutaneous administration results in a prolonged improvement in disease (observed at least 4, 6, 8, 10, 12, 14 or 16 weeks after antibody administration) as manifested by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

207. The method of any one of claims 201-206 wherein said patient has previously received or is still receiving methotrexate.

208. The method of any one of claims 201-207 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 90% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.
209. The method of any one of claims 201-207 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 95% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

210. The method of any one of claims 201-207 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 98% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

211. The method of any one of claims 201-207 wherein said anti-IL-6 antibody contains the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

212. A method of treating rheumatoid arthritis by intravenously or subcutaneously administering an anti-IL-6 antibody having the same epitopic specificity as Ab 1 by intravenously administering a dosage of about ( +/- 20%) 80, 160 or 320 mg of said antibody to a patient in need thereof.

213. The method of claim 212 wherein the patient is administered said dosage every 8 weeks or 2 months.

214. The method of claim 212 wherein said dosage is administered at least twice.

215. The method of claim 212 wherein the first dosage is on day one and the second dosage during week 8 (8th week after day 0.)

216. The method of claim 212 which improves at least one of the following(i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control intravenous formulation.

217. The method of claim 212 wherein said intravenous administration results in an improvement in disease as manifested by at least one of the following(i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control intravenous formulation.
218. The method of claim 217 wherein said subcutaneous administration results in a prolonged improvement in disease (observed at least 4, 6, 8, 10, 12, 14 or 16 weeks after antibody administration) as manifested by at least one of the following (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

219. The method of any one of claims 212-218 wherein said patient has previously received or is still receiving methotrexate.

220. The method of any one of claims 212-218 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 90% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

221. The method of any one of claims 212-218 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 95% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20 of the applications incorporated by reference herein.

222. The method of any one of claims 212-218 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 98% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

223. The method of any one of claims 212-218 wherein said anti-IL-6 antibody contains the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

224. The method of any foregoing claim, wherein said anti-IL-6 antibody is comprised in a composition formulated for subcutaneous or intravenous injection.

225. A composition for treatment comprising an effective subcutaneous dosage of an anti-IL-6 antibody having the same epitopic specificity as Abl or an antibody that competes with Abl for binding to IL-6 to a patient in need thereof.

226. The composition according to claim 225 wherein the subcutaneous dosage is at least about 50 or 100 mg.
227. The composition according to claim 225 wherein the efficacy of said subcutaneous administration is determined by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

228. The composition according to claim 225 wherein subcutaneous administration results in an improvement in disease as manifested by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

229. The composition according to claim 225 wherein said subcutaneous administration results in a prolonged improvement in disease (observed at least 4, 6, 8, 10, 12, 14 or 16 weeks after antibody administration) as manifested by at least one of the following: (i) improved DAS-28 scores, (ii) improved EULAR scores, (iii) improved LDAS scores (iv) improved ACR scores, (v) an increase in serum albumin, (vi) a decrease in CRP relative to patients not treated with said antibody or patients receiving a placebo or control subcutaneous formulation.

230. The composition of any one of claims 225-229 further comprising methotrexate.

231. The composition of any one of claims 225-230 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 90% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20 of the applications incorporated by reference herein.

232. The composition of any one of claims 225-230 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 95% identical has the variable heavy and light sequences contained in SEQ ID NO: 18 or 19 and SEQ ID NO: 20.

233. The composition of any one of claims 225-230 wherein said anti-IL-6 antibody contains variable heavy and light sequences which are at least 98% identical has the variable heavy and light sequences contained in SEQ ID NO: 19 or 20 of the applications incorporated by reference herein.
234. The composition of any one of claims 225-230 wherein said anti-IL-6 antibody contains the variable heavy and light sequences contained in SEQ ID NO: 19 or 20.

235. A method of preventing or treating a disease or disorder associated with IL-6 or a disease or disorder that can be treated by administering an antagonist of IL-6, comprising administering a composition according to any one of claims 225-230.

236. The method of claim 235, wherein said disease is rheumatoid arthritis.

237. The method of claim 235, wherein said disease or disorder is selected from the group consisting of: fever, cachexia, weakness, cancer, thrombosis, and hypoalbuminemia.

238. The method of claim 235, wherein said disease or disorder is selected from the group consisting of: general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosi (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).
239. A method of using an anti-IL-6 antibody or antibody fragments according to the invention for preventing or alleviating the onset of graft-versus-host disease (GVHD), or leukemia relapse in a subject receiving transplanted cells, tissues or organs.

240. The method of claim 239 wherein the subject has or is to receive a hematopoietic stem cell transplant (HCT), bone marrow transplantation (BMT).

241. The method of claim 239 wherein the subject has or is to receive transplanted cells, tissues or organs potentially containing dendritic cells.

242. The method of claim 239 wherein the subject has or is to receive transplanted cells, tissues or organs potentially containing BDCAA4+ plasmacytoid dendritic cells.

243. The method of claim 242 wherein the transplanted cells, tissues or organ comprise pancreatic, liver or skin cells.

244. A method of pre-treating cells, tissues or organ which are to be used for transplant to reduce the risk of GVHD or leukemia comprising contacting said cells, tissue or organ in vitro with an IL-6 antagonist in order to reduce IL-6 expression.

245. The method of claim 244 wherein the cells, tissues or organ are also contacted with an IL-10 antagonist.

246. A method of reducing the risk of leukemia relapse in a leukemia subject who has or is to receive transplanted cells, tissues or organs, especially those potentially containing dendritic cells by administering prior, concurrent or after transplant an amount of at least one anti-IL-6 antibody or antibody fragment according to the invention sufficient to prevent or reduce the risk of leukemia relapse.

247. The method of claim 246 wherein said leukemia includes Chronic Leukemias and Acute Leukemias.

248. The method of claim 246 wherein said leukemia includes chronic myelogenous leukemia(CML), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL),
acute lymphocytic leukemia (ALL), hairy cell leukemia, T cell prolymphcytic leukemia, (T-PLL) and large granular lymphocytic leukemia.

249. A cancer treatment regimen that includes the administration of at least one chemotherapeutic agent and/or radiation, wherein the efficacy of said chemotherapeutic or radiation against the cancer is enhanced by further administering an anti-IL-6 antibody or antibody fragment tumor that is selected from Abl, 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, Ab36, and chimeric or humanized variants thereof and IL-6 binding fragment of any of the foregoing.

250. A method of treating or preventing mucositis in a patient at risk of developing mucositis as a result of chemotherapy or radiotherapy, by administering an amount of an anti-IL-6 antibody according to the invention in an amount effective to treat or prevent the onset of mucositis.

251. The method of claim 250 wherein the mucositis is oral or gastrointestinal mucositis.

252. The method of claim 250 wherein the patient treated has one or more symptoms of oral mucositis.

253. The method of claim 250 wherein the patient treated has one or more symptoms of gastrointestinal mucositis.

254. The method of claim 250 wherein the patient has a cancer selected from head and neck cancer, esophageal cancer, throat cancer, lung cancer, gastrointestinal cancers such as stomach cancer, colorectal cancer, pancreatic cancer, as well as hematological cancers such as multiple myeloma, leukemia, and lymphoma.

255. The method of claim 250 wherein the patient has or is to receive autologous stem cell or bone marrow transplant.

256. The method of claim 250 wherein the patient has multiple myeloma.
257. A method of potentiating the effect of a chemotherapeutic agent or radiation against a treated cancer in a patient comprising administering an anti-IL-6 antibody or antibody fragment according to the invention in an amount effective to enhance the effect of said chemotherapeutic agent or radiation which is further administered to treat said cancer.

258. The method of Claim 257 wherein said anti-IL-6 antibody or antibody fragment is administered prior, concurrent or after administration of said chemotherapeutic or radiation.

259. The method of Claim 257 wherein the chemotherapeutic is an EGFR inhibitor.

260. The method of Claim 259 wherein said EGFR inhibitor is selected from the group consisting of Cetuximab (Erbitux) available from ImClone, Erlotinib (Tarceva) available from OSI Pharmaceuticals, Gefitinib (Iressa) available from AstraZeneca, Lapatinib (Tykerb) available from Glaxo, Panitumumab (Vectibix) available from Amgen, Sunitinib or Sutent (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-lH-indol-3-ylidene)methyl]-2,4-dimethyl-lH-pyrrole-3-carboxamide) marketed by Pfizer, Gefitinib or N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine marketed by AstraZeneca, and Zalutumumab in clinical development by GenMab.

261. The method of Claim 259 wherein the patient has a cancer that has exhibited resistance to said chemotherapeutic or radiation after at least one round of chemotherapy or radiation.

262. The method of claim 259 which reduces or prevents the treated cancer from invading or metastasizing to other sites in the body.

263. The method of claim 259 which results in increased apoptosis of the treated cancer cells.

264. The method of claim 259 wherein the treated cancer is selected from advanced and non-advanced cancers including metastasized cancers such as metastatic and non-metastatic lung cancer, breast cancer, head and neck cancer, (FiNSCC), pharyngeal cancer, pancreatic cancer, colorectal cancer, anal cancer, glioblastoma multiforme, epithelial cancers, renal cell carcinomas, acute or chronic myelogenous leukemia and other leukemias.
265. The method of Claim 264 wherein the cancer is non-small cell lung cancer (NSCLC) or acute myelogenous leukemia (AML).

266. The method of claim 264 or 265 wherein the chemotherapeutic is erlotinib or sunitinib.

267. The method of claim 265 wherein the subject's cancer has developed a resistance to said chemotherapeutic prior to administration of said anti-IL-6 antibody or antibody fragment.

268. The method of claim 259 wherein a biopsy is effected prior to anti-IL-6 antibody therapy which indicates that the treated cancer comprises cells which are expressing IL-6 at elevated levels.

269. The method of Claim 259 wherein in vivo imaging is effected using an anti-IL-6 antibody or antibody fragment prior to said treatment which reveals increased IL-6 levels at the site(s) of the treated cancer.

270. The method of claim 257 wherein said patient is determined to express elevated IL-6 levels prior to treatment.

271. A method of identifying cancers that are potentially resistant to the effects of a chemotherapeutic or radiation by assaying for IL-6 using an antibody according to the invention in order to detect whether elevated IL-6 levels are present at the site of the treated cancer.
FIG. 3
Ab4 Blocks GP130 Binding

FIG. 10A
Ab3 Blocks GP130 Binding

FIG. 10B
Ab8 Blocks GP130 Binding

\[ \text{Binding (nm)} \]

\[ \text{Time (Seconds)} \]

FIG. 10C

*Control Antibody*  
*GP130*  
*IL6R1*  
*IL6*  
*Ab8*
Ab2 Inhibits GP130 Binding

![Graph showing the binding of antibodies to IL6R1 and GP130 over time.]

FIG. 10D
Ab1, Ab6, and Ab7 Blocks IL6R1 and GP130 Binding

FIG. 10E
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Ab1</th>
<th>Ab2</th>
<th>Ab3</th>
<th>Ab4</th>
<th>Ab6</th>
<th>Ab7</th>
<th>Ab8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks IL6 Binding to R1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blocks IL6 Binding to GP130</td>
<td>Yes</td>
<td>Partial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

FIG. 11
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 VPGEDSKDVDAPHR (SEQ ID NO: 590)</td>
<td>20 ENNLNLPHMAEKDGSC (SEQ ID NO: 609)</td>
<td>30 QMSTKVLIQFLQKKA (SEQ ID NO: 628)</td>
<td></td>
</tr>
<tr>
<td>2 GEDSKDVDAPHRQFL (SEQ ID NO: 591)</td>
<td>21 LNLKMAEKDGCFQFQS</td>
<td>40 TTVLQFLQKXAKKLNL (SEQ ID NO: 629)</td>
<td></td>
</tr>
<tr>
<td>3 SKDVAPHRQPLTSSE (SEQ ID NO: 592)</td>
<td>22 PKMAEKDGCFQFQSGFEN</td>
<td>41 LIQFLQKKAKNLDAI (SEQ ID NO: 630)</td>
<td></td>
</tr>
<tr>
<td>4 VAPHRQPLTSSERI (SEQ ID NO: 593)</td>
<td>23 AEKGDCFQFQSGFNEET</td>
<td>42 FLQKAKNLDATTP (SEQ ID NO: 631)</td>
<td></td>
</tr>
<tr>
<td>5 PHQPLTSSERIDRQ (SEQ ID NO: 594)</td>
<td>24 DGCQFQSGFNEETCLV</td>
<td>43 KKAQNLDATTPDOPT (SEQ ID NO: 632)</td>
<td></td>
</tr>
<tr>
<td>6 QPLTSSERIDQIY (SEQ ID NO: 595)</td>
<td>25 FQSGFNEETCLV (SEQ ID NO: 614)</td>
<td>44 KNKTDATTPDPTTNA (SEQ ID NO: 633)</td>
<td></td>
</tr>
<tr>
<td>7 TSSERIDQIYILD (SEQ ID NO: 596)</td>
<td>26 GFQNEETCLV (SEQ ID NO: 615)</td>
<td>45 DATTPDPTTNASLL (SEQ ID NO: 634)</td>
<td></td>
</tr>
<tr>
<td>8 ERIDQIYILDGI (SEQ ID NO: 597)</td>
<td>27 EETCLV (SEQ ID NO: 616)</td>
<td>46 TTDPTTNASLLTKL (SEQ ID NO: 635)</td>
<td></td>
</tr>
<tr>
<td>9 DKQIYILDGLISALR (SEQ ID NO: 598)</td>
<td>28 CLVKIITGLLEFEVY</td>
<td>47 DPTTNASLLTKLQA (SEQ ID NO: 636)</td>
<td></td>
</tr>
<tr>
<td>10 IRYILDGLISALR (SEQ ID NO: 599)</td>
<td>29 KIITGLLEFEVLYE</td>
<td>48 TNSLTKLQAQNQW (SEQ ID NO: 637)</td>
<td></td>
</tr>
<tr>
<td>11 ILDELGALKNTCKN (SEQ ID NO: 600)</td>
<td>30 TGLLEFEVLEYLQ R (SEQ ID NO: 619)</td>
<td>49 SLITLQAOQNQWQQ (SEQ ID NO: 638)</td>
<td></td>
</tr>
<tr>
<td>12 GIALRKTNCNSM (SEQ ID NO: 601)</td>
<td>31 LBFEVLEYLQNRFE</td>
<td>50 TKLQAQNQWQQKMTT (SEQ ID NO: 639)</td>
<td></td>
</tr>
<tr>
<td>13 ALRKTNCNSM (SEQ ID NO: 602)</td>
<td>32 ELYFLEYLQNRFFSE</td>
<td>51 QACNQLQDMTTHIL (SEQ ID NO: 640)</td>
<td></td>
</tr>
<tr>
<td>14 KETCNKSNMCCSSE (SEQ ID NO: 603)</td>
<td>33 LEYLFNRFESSQEQ</td>
<td>52 NWLQDMTTHLILRS (SEQ ID NO: 641)</td>
<td></td>
</tr>
<tr>
<td>15 CNKSNMCCSSE (SEQ ID NO: 604)</td>
<td>34 LQTNRFESSQEQARAV</td>
<td>53 LQCMTHLILRSFKE (SEQ ID NO: 642)</td>
<td></td>
</tr>
<tr>
<td>16 SNNMCCSSEAKLA (SEQ ID NO: 605)</td>
<td>35 RFESSEEQEQARAVQMS</td>
<td>54 MTHLILRSFKEFLQ (SEQ ID NO: 643)</td>
<td></td>
</tr>
<tr>
<td>17 CESSKEALEKL (SEQ ID NO: 606)</td>
<td>36 SSEQARAVQMSSTKV</td>
<td>55 HLARFKEFLQSSL (SEQ ID NO: 644)</td>
<td></td>
</tr>
<tr>
<td>18 SKEALANKLNLPKM (SEQ ID NO: 607)</td>
<td>37 EQARAVQMSSTKVLIQ</td>
<td>56 LRSFKEFLQSSLRAL (SEQ ID NO: 645)</td>
<td></td>
</tr>
<tr>
<td>19 ALAENNLNLPHMAEK (SEQ ID NO: 608)</td>
<td>38 RAVQMSSTKVLIQFLQ</td>
<td>57 PKEFLQSSLRALQRQ (SEQ ID NO: 646)</td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 12**
A. Surface Plasmon Resonance: Averaged Binding Constants Determined at 25° C for Ab1 to IL-6

<table>
<thead>
<tr>
<th>Species (IL-6)</th>
<th>$K_a$ (M$^{-1}$ s$^{-1}$)</th>
<th>$K_d$ (s$^{-1}$)</th>
<th>$K_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1.6e6</td>
<td>2.2e-3</td>
<td>1.4 nM</td>
</tr>
<tr>
<td>Mouse</td>
<td>1.1e6</td>
<td>4.0e-4</td>
<td>0.4 nM</td>
</tr>
<tr>
<td>Dog</td>
<td>Below LOQ$^a$</td>
<td>Below LOQ$^a$</td>
<td>Below LOQ$^a$</td>
</tr>
<tr>
<td>Human</td>
<td>1.6e5</td>
<td>5e-7</td>
<td>4 pM</td>
</tr>
<tr>
<td>Cynomolgus monkey</td>
<td>9.6e4</td>
<td>3e-6</td>
<td>31 pM</td>
</tr>
</tbody>
</table>

a. Below Limit of Quantitation

B. IC50 Values for Ab1 Against Human, Cynomolgus Monkey, Mouse, Rat and Dog IL-6 in the T1165 Assay.

<table>
<thead>
<tr>
<th>IL-6 Species</th>
<th>IC50 (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>13</td>
</tr>
<tr>
<td>Cynomolgus monkey</td>
<td>12</td>
</tr>
<tr>
<td>Mouse</td>
<td>1840</td>
</tr>
<tr>
<td>Rat</td>
<td>2060</td>
</tr>
<tr>
<td>Dog</td>
<td>No Inhibition of Cell Proliferation</td>
</tr>
</tbody>
</table>

FIG. 15
<table>
<thead>
<tr>
<th>Dose of Ab1</th>
<th>T1/2 (days)</th>
<th>AUC (µg·h/ml)</th>
<th>Cmax (µg/ml)</th>
<th>Tmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg</td>
<td>10.3</td>
<td>35</td>
<td>0.1</td>
<td>8</td>
</tr>
<tr>
<td>3mg</td>
<td>11.6</td>
<td>229</td>
<td>0.7</td>
<td>4</td>
</tr>
<tr>
<td>10mg</td>
<td>22.4</td>
<td>1473</td>
<td>4.0</td>
<td>4</td>
</tr>
<tr>
<td>30mg</td>
<td>25.1</td>
<td>9076</td>
<td>19.4</td>
<td>4</td>
</tr>
<tr>
<td>100mg</td>
<td>30.3</td>
<td>26128</td>
<td>48.0</td>
<td>12</td>
</tr>
<tr>
<td>300mg</td>
<td>30.2</td>
<td>92891</td>
<td>188.0</td>
<td>12</td>
</tr>
<tr>
<td>640mg</td>
<td>30.3</td>
<td>175684</td>
<td>306.0</td>
<td>12</td>
</tr>
</tbody>
</table>
Pharmacokinetics of Ab1 in Patients with Advanced Cancer

Elimination half-life: 31d

Mean Plasma Concentration of Ab1 given as a Single IV Infusion of 80 mg (n=2) or 160 mg (n=3) (Mean +/- SEM)

**FIG. 20**
### Unprecedented Elimination Half-life of Ab1

<table>
<thead>
<tr>
<th>Ab1</th>
<th>Cynomolgus Monkey (days)</th>
<th>Human (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab1</td>
<td>15-21</td>
<td>~31</td>
</tr>
<tr>
<td>Actemra (Tocilizumab)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Remicade</td>
<td>5</td>
<td>8 to 9.5</td>
</tr>
<tr>
<td>Synagis</td>
<td>8.6</td>
<td>20</td>
</tr>
<tr>
<td>Erbitux</td>
<td>3 to 7</td>
<td>5</td>
</tr>
<tr>
<td>Zenapax</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Avastin</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>10</td>
<td>18 to 22</td>
</tr>
</tbody>
</table>

**FIG. 21**
Ab1 Increases Hemoglobin Concentration in Patients with Advanced Cancer

Single IV infusion of 80 mg, 160 mg, or 320 mg Ab1 (n=8) (Mean +/− SEM)

Time (weeks)

Hemoglobin Concentration (g/dL)
Mean Plasma Lipid Concentration After Ab1 Infusion in Patients with Advanced Cancer

Plasma Lipid Concentration (mmol/l)

Time (weeks)

Single IV infusion of 80 mg, 160 mg, or 320 mg Ab1 (n=8) (Mean +/- SEM)

FIG. 23
Mean Neutrophil Counts After Ab1 Infusion in Patients with Advanced Cancer

Single IV infusion of 80 mg, 160 mg, or 320 mg Ab1 (n=8) (Mean +/- SEM)

FIG. 24
Ab1 Suppresses Serum CRP in Patients with Advanced Cancer

Mean % Baseline CRP vs Time (weeks)

Single IV Infusion of 80mg or 160mg Ab1 (n=5) (Mean +/- SEM)

FIG. 26A
Ab1 Suppresses Serum CRP in Patients with Advanced Cancer

**FIG. 26B**

80mg, as a Single IV Infusion
Ab1 Prevents Weight Loss in a Mouse Cancer Cachexia Model

Control (PBS)

Ab1 Treated (30 mg/kg)

FIG. 28
FIG. 29

Ab1 Promotes Weight Gain in Patients with Advanced Cancer

Time (weeks)

Single IV Infusion of 80mg or 160mg Ab1 (n=5)

Weight (kg)
Ab1 Reduces Fatigue in Patients with Advanced Cancer

FIG. 30

Single IV infusion of 80mg or 160mg Ab1 (n=5) Mean Score for U.S. General Population = 40.1

Mean FACIT-FS Subscale Score

Time (weeks)
Ab1 Increase Plasma Albumin Concentration in Patients with Advanced Cancer

Plasma Albumin Concentration (g/L)

Time (weeks)

Single IV Infusion of 80 mg or 160 mg Ab1 (n=5)

FIG. 33
PREFERRED ANTI-IL-6 ANTIBODY HUMANIZATION

FR1
SEQ ID NO: 6478AYDMTZTPASVSAVGTVTICG QASOQINNELS WYQQKPGQRKLLIY RASTLA GVVSRFGSGSKTEFTLITSLDLECAADAATYYC
SEQ ID NO: 6481AOMTSPPSLSASVGPRVTVTC GAGRGINNLDG WYQCOGSKAPKKLLIY AASSLOS GYVSRESGSGSTGFETILITSLQDPEDFATYYC
SEQ ID NO: 649D1OMTSPPSLSASVNLDDRIVTIC GAGRGINNLDG WYQCOGSKAPKKLLIY AASSLOS GYVSRESGSGSTGFETILITSLQDPEDFATYYC
SEQ ID NO: 650D1OMTSPPSLSASVNLDDRIVTIC GAGRGINNLDG WYQCOGSKAPKKLLIY AASSLOS GYVSRESGSGSTGFETILITSLQDPEDFATYYC
SEQ ID NO: 651AOMTSPPSLSASVGPRVTVTC GAGRGINNLDG WYQCOGSKAPKKLLIY AASSLOS GYVSRESGSGSTGFETILITSLQDPEDFATYYC
SEQ ID NO: 651AOMTSPPSLSASVGPRVTVTC GAGRGINNLDG WYQCOGSKAPKKLLIY AASSLOS GYVSRESGSGSTGFETILITSLQDPEDFATYYC

CDR3
SEQ ID NO: 6478QGXSILRHNIDNA FGGSTEVVVKR
SEQ ID NO: 648
SEQ ID NO: 649 FGGSTKVEIKR
SEQ ID NO: 650
SEQ ID NO: 651QGXSILRHNIDNA FGGSTKVEIKR
SEQ ID NO: 651QGXSILRHNIDNA FGGSTKVEIKR

FR4
FIG. 34
<table>
<thead>
<tr>
<th>SEQ ID NO:</th>
<th>FR1</th>
<th>CDR1</th>
<th>FR2</th>
<th>CDR2</th>
<th>FR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>652-QSLEESGSLVTFTPLTCTASGFLS</td>
<td>NYYVT</td>
<td>WVQAPGKGLDEGIG</td>
<td>LIYG-SDETAYATWAIG</td>
<td>RFTISKTST-...TVLKLMTSLTAADTATYFCAR</td>
<td></td>
</tr>
<tr>
<td>653BVQLVEESGGLVSQGSLRSLCAAGGTVS</td>
<td>SNYMS</td>
<td>WVQAPGKGLDEGIG</td>
<td>VIYS-GSSTYYADSVKG</td>
<td>RFTISRDNSKNTLYLQMNLSRRAEDTAVYVYCAR</td>
<td></td>
</tr>
<tr>
<td>654BVQLVEESGGLVSQGSLRSLCAAGGTVS</td>
<td>SNYMS</td>
<td>WVQAPGKGLDEGIG</td>
<td>VIYS-GSSTYYADSVKG</td>
<td>RFTISRDNSKNTLYLQMNLSRRAEDTAVYVYCAR</td>
<td></td>
</tr>
<tr>
<td>655EVQLQGSGGLVSQGSLRSLCAAGGTVS</td>
<td>SYAMS</td>
<td>WVQAPGKGLDEGIG</td>
<td>VIYS-GSSTYYADSVKG</td>
<td>RFTISRDNSKNTLYLQMNLSRRAEDTAVYVYCAK</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEQ ID NO:</th>
<th>CDR3</th>
<th>FR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>652DDSITMDAKFNLL</td>
<td>WSGGTLVTVSS</td>
<td></td>
</tr>
<tr>
<td>653</td>
<td>WSGGTLVTVSS</td>
<td></td>
</tr>
<tr>
<td>654</td>
<td>WSGGTLVTVSS</td>
<td></td>
</tr>
<tr>
<td>655</td>
<td>WSGGTLVTVSS</td>
<td></td>
</tr>
<tr>
<td>656DDSITMDAKFNLL</td>
<td>WSGGTLVTVSS</td>
<td></td>
</tr>
<tr>
<td>657DDSITMDAKFNLL</td>
<td>WSGGTLVTVSS</td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 34**

(Continued)
<table>
<thead>
<tr>
<th>CDR1</th>
<th>FR1</th>
<th>CDR2</th>
<th>FR2</th>
<th>CDR3</th>
<th>FR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>QASGSLNENLQ WYQKPGQRPKLL</td>
<td>RASTLAS</td>
<td>GYSRFGSGSGGTFLLTISLDEADAAYY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASGQSRNLGL WYQKGPQAPKLL</td>
<td>AASLGS</td>
<td>GVSRFSGSGSGGTFLLTISLQFDDFATYYC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASGQSLYNLA WYQKGPQAPKLL</td>
<td>AASTLS</td>
<td>GVSRFSGSGSGGTFLLTISLQFDDFATYYC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASGQSLNSW</td>
<td>WYQKGPQAPKLL</td>
<td>KASSLS</td>
<td>GVSRFSGSGSGGTFLLTISLQFDDFATYYC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QASGSLNENLQ WYQKPGQRPKLL</td>
<td>RASTLAS</td>
<td>GYSGSTEVWVKR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASGQSLNENLQ WYQKPGQRPKLL</td>
<td>RASTLAS</td>
<td>GYSGSTEVWVKR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASGQSLNENLQ WYQKPGQRPKLL</td>
<td>RASTLAS</td>
<td>GYSGSTEVWVKR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 35**
## PREFERRED ANTI-IL-6 ANTIBODY HUMANIZATION

<table>
<thead>
<tr>
<th>FR1</th>
<th>CDR1</th>
<th>FR2</th>
<th>CDR2</th>
<th>FR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEQ ID No: 662-QSLEEGGRLVTPGTLTGLCTASGFLS</td>
<td>NYYVT</td>
<td>WVRQAPGKGLEWIG</td>
<td>LIYG-SDTAYATWAIG</td>
<td>RFTISKTGRT--TVLKLMTSLCAADTATYFCAR</td>
</tr>
<tr>
<td>SEQ ID No: 652-EVLVVEGGGLQPGGSLRLSLSAGGETVS</td>
<td>SNYMS</td>
<td>WVRQAPGKGLEWIG</td>
<td>VLYG-SDTAYATWAIG</td>
<td>RFTISRDNSKNTLYLQMSLRAEDTAVYCAR</td>
</tr>
<tr>
<td>SEQ ID No: 654-EVQLVSEGGGLQPGGSLRLSLSAGGETVS</td>
<td>SNYMS</td>
<td>WVRQAPGKGLEWIG</td>
<td>VLYG-SDTAYATWAIG</td>
<td>RFTISRDNSKNTLYLQMSLRAEDTAVYCAR</td>
</tr>
<tr>
<td>SEQ ID No: 655-EVQLVSEGGGLQPGGSLRLSLSAGGETVS</td>
<td>SAMS</td>
<td>WVRQAPGKGLEWIG</td>
<td>VLYG-SDTAYATWAIG</td>
<td>RFTISRDNSKNTLYLQMSLRAEDTAVYCAR</td>
</tr>
<tr>
<td>SEQ ID No: 656-EVQLVSEGGGLQPGGSLRLSLSAGGETVS</td>
<td>NYYVT</td>
<td>WVRQAPGKGLEWIG</td>
<td>LIYG-SDTAYATWAIG</td>
<td>RFTISRDNSKNTLYLQMSLRAEDTAVYCAR</td>
</tr>
<tr>
<td>SEQ ID No: 657-EVQLVSEGGGLQPGGSLRLSLSAGGETVS</td>
<td>NYYVT</td>
<td>WVRQAPGKGLEWIG</td>
<td>LIYG-SDTAYATWAIG</td>
<td>RFTISRDNSKNTLYLQMSLRAEDTAVYCAR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDR3</th>
<th>FR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEQ ID No: 662-EGSDDWDAKFN</td>
<td>WQGTLTVVSS</td>
</tr>
<tr>
<td>SEQ ID No: 653</td>
<td></td>
</tr>
<tr>
<td>SEQ ID No: 654</td>
<td>WQGTLTVVSS</td>
</tr>
<tr>
<td>SEQ ID No: 655</td>
<td></td>
</tr>
<tr>
<td>SEQ ID No: 656-EGSDDWDAKFN</td>
<td>WQGTLTVVSS</td>
</tr>
<tr>
<td>SEQ ID No: 657-EGSDDWDAKFN</td>
<td>WQGTLTVVSS</td>
</tr>
</tbody>
</table>

**FIG. 35**

(Continued)
## Alignment of Ab1 light chains

<table>
<thead>
<tr>
<th>SEQ ID NO:</th>
<th>AAR</th>
<th>CDR1</th>
<th>FR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>MDTRAFTQLLGLLMLWLPGAR</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
</tr>
<tr>
<td>20</td>
<td>IOMTQSPSSLSASVGRVITTIC</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
<tr>
<td>647</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
<tr>
<td>651</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
<tr>
<td>660</td>
<td>MDTRAFTQLLGLLMLWLPGAR</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
</tr>
<tr>
<td>666</td>
<td>IOMTQSPSSLSASVGRVITTIC</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
<tr>
<td>699</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
<tr>
<td>702</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
<tr>
<td>706</td>
<td>MKWVTFISLLFLFSSAYS</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
</tr>
<tr>
<td>709</td>
<td>AYDMTQPASVSAAVGGTVTIK</td>
<td>QASQ5INNELS WYQQKPGQRPKLLIY</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDR2</th>
<th>FR3</th>
<th>CDR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RASTLAS</td>
<td>GVSSRFKGSWSGTEFTLSIDLECAATAYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVPSRFSYSGSGTDFLTLSLQPDDFATYYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVSSRFKGSWSGTEFTLSIDLECAATAYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVPSRFSYSGSGTDFLTLSLQPDDFATYYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVSSRFKGSWSGTEFTLSIDLECAATAYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVPSRFSYSGSGTDFLTLSLQPDDFATYYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVSSRFKGSWSGTEFTLSIDLECAATAYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVPSRFSYSGSGTDFLTLSLQPDDFATYYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVSSRFKGSWSGTEFTLSIDLECAATAYC</td>
<td>QGYSLRNIDNA</td>
</tr>
<tr>
<td>RASTLAS</td>
<td>GVPSRFSYSGSGTDFLTLSLQPDDFATYYC</td>
<td>QGYSLRNIDNA</td>
</tr>
</tbody>
</table>

**FIG. 36A**
Alignment of Ab1 light chains (continued)

FR4

kappa constant light chain

SEQ ID NO: 2  FGGGETVVVR T VAAPSVFIFPPDEQLKSGTASVVCLLN
SEQ ID NO: 20
SEQ ID NO: 647  FGGGETVVVR
SEQ ID NO: 651  FGGGKTVEIKR
SEQ ID NO: 660
SEQ ID NO: 666  FGGGKTVEIKR T VAAPSVFIFPPDEQLKSGTASVVCLLNNFYPREAKV0KVDNALQSGN
SEQ ID NO: 699  FGGGKTVEIKR T
SEQ ID NO: 702  FGGGKTVEIKR T VAAPSVFIFPPDEQLKSGTASVVCLLNNFYPREAKV0KVDNALQSGN
SEQ ID NO: 706  FGGGKTVEIKR T VAAPSVFIFPPDEQLKSGTASVVCLLNNFYPREAKV0KVDNALQSGN
SEQ ID NO: 709  FGGGKTVEIKR

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  SQESVTEQDSKDTYSLSSTLTLSKADYEHKVACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 699
SEQ ID NO: 702  SQESVTEQDSKDTYSLSSTLTLSKADYEHKVACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 706  SQESVTEQDSKDTYSLSSTLTLSKADYEHKVACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 709

FIG. 36B
Alignment of Ab1 heavy chains

<table>
<thead>
<tr>
<th>SEQ ID</th>
<th>NO: 3</th>
<th>METGLRWLLLLVAVLKGVQC</th>
<th>FR1</th>
<th>CDR1</th>
<th>FR2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-QSLGEGGRLVTPGTPLTLTCASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 18</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 19</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 652</td>
<td>-QSLGEGGRLVTPGTPLTLTCASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 656</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 657</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 658</td>
<td>METGLRWLLLLVAVLKGVQC</td>
<td>-QSLGEGGRLVTPGTPLTLTCASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 661</td>
<td>METGLRWLLLLVAVLKGVQC</td>
<td>-QSLGEGGRLVTPGTPLTLTCASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 664</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 665</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 704</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 708</td>
<td>MKWVTFISLLFLFSSAYS</td>
<td>EVLQVESEQGGLVQPGGSLRLGCAASFGSL</td>
<td>NYYVT</td>
<td>WWFQQAPKGGLEWIG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEQ ID</th>
<th>NO: 3</th>
<th>IIGGSGTAYATAWG</th>
<th>FR3</th>
<th>CDR3</th>
<th>FR4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RFTISKTST--TVDLMKMTSLTAADTATYFCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
<td></td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 18</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 19</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 652</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 656</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 657</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 658</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 661</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 664</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 665</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 704</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
<tr>
<td>SEQ ID</td>
<td>NO: 708</td>
<td>IIGGSGTAYATAWG</td>
<td>RFTISRDNKNTLYLQMN5LRADTAVYCAR</td>
<td>DSSSDWDAKFN</td>
<td>WGGQLTVTSS</td>
</tr>
</tbody>
</table>

FIG. 37A
Alignment of Ab1 heavy chains (continued)

gamma-1 constant heavy chain polypeptide
SEQ ID NO: 3  ASTKGPVSVPFPAPSSKSTSGTALGCLVK
SEQ ID NO: 658  ASTKGPVSVPFPAPSSKSTSGTALGCLVK
SEQ ID NO: 664  ASTKGPVSVPFPAPSSKSTSGTALGCLVKDYPFEPVTSWNHSGLTSGVHTFPAVLQSGLYSSLVSVTVPS
SEQ ID NO: 665  ASTKGPVSVPFPAPSSKSTSGTALGCLVKDYPFEPVTSWNHSGLTSGVHTFPAVLQSGLYSSLVSVTVPS
SEQ ID NO: 704  ASTKGPVSVPFPAPSSKSTSGTALGCLVKDYPFEPVTSWNHSGLTSGVHTFPAVLQSGLYSSLVSVTVPS
SEQ ID NO: 708  ASTKGPVSVPFPAPSSKSTSGTALGCLVKDYPFEPVTSWNHSGLTSGVHTFPAVLQSGLYSSLVSVTVPS

gamma-1 constant heavy chain polypeptide, continued
SEQ ID NO: 664  LGTQTYICNVNHKPSNTKVDKREVPSKDCTHTCPAPELLEGGPVSFLFFPKPDKTMISRTPEVTCVVV
SEQ ID NO: 665  LGTQTYICNVNHKPSNTKVDKREVPSKDCTHTCPAPELLEGGPVSFLFFPKPDKTMISRTPEVTCVVV
SEQ ID NO: 704  LGTQTYICNVNHKPSNTKVDKREVPSKDCTHTCPAPELLEGGPVSFLFFPKPDKTMISRTPEVTCVVV
SEQ ID NO: 708  LGTQTYICNVNHKPSNTKVDKREVPSKDCTHTCPAPELLEGGPVSFLFFPKPDKTMISRTPEVTCVVV

gamma-1 constant heavy chain polypeptide, continued
SEQ ID NO: 664  HEDPEVKFPNWYDGVHNAKTLPREEQYASTYRVVSVLTVLHQRDLNGKEYKCKVSNKALPAPIETISAKGQ
SEQ ID NO: 665  HEDPEVKFPNWYDGVHNAKTLPREEQYASTYRVVSVLTVLHQRDLNGKEYKCKVSNKALPAPIETISAKGQ
SEQ ID NO: 704  HEDPEVKFPNWYDGVHNAKTLPREEQYASTYRVVSVLTVLHQRDLNGKEYKCKVSNKALPAPIETISAKGQ
SEQ ID NO: 708  HEDPEVKFPNWYDGVHNAKTLPREEQYASTYRVVSVLTVLHQRDLNGKEYKCKVSNKALPAPIETISAKGQ

gamma-1 constant heavy chain polypeptide, continued
SEQ ID NO: 664  PREPQVYTLPPSRDELTKVQVSLTCLVKGFPYPSDIAVEWEQSNQKENNYKTTPVLDSDGSFFLYSKLVDTKSRW
SEQ ID NO: 665  PREPQVYTLPPSRDELTKVQVSLTCLVKGFPYPSDIAVEWEQSNQKENNYKTTPVLDSDGSFFLYSKLVDTKSRW
SEQ ID NO: 704  PREPQVYTLPPSRDELTKVQVSLTCLVKGFPYPSDIAVEWEQSNQKENNYKTTPVLDSDGSFFLYSKLVDTKSRW
SEQ ID NO: 708  PREPQVYTLPPSRDELTKVQVSLTCLVKGFPYPSDIAVEWEQSNQKENNYKTTPVLDSDGSFFLYSKLVDTKSRW

gamma-1 constant heavy chain polypeptide, continued
SEQ ID NO: 664  QQGNVFVSCSVMHEALHNYTQKSLSLSGK
SEQ ID NO: 665  QQGNVFVSCSVMHEALHNYTQKSLSLSGK
SEQ ID NO: 704  QQGNVFVSCSVMHEALHNYTQKSLSLSGK
SEQ ID NO: 708  QQGNVFVSCSVMHEALHNYTQKSLSLSGK
Mean (± SEM) C-Reactive Protein Concentration Versus Time:
Ab1 Versus Placebo in NSCLC Patients

- Ab1 80mg (n=29)
- Ab1 160mg (n=32)
- Ab1 320mg (n=32)
- Placebo (n=31)

**FIG. 38**
Mean (±SD) Plasma C-Reactive Protein Concentration ALD518 80mg, 160mg, and 320mg as a Single i.v. Infusion in Patients with Advanced Cancer (n=8)

FIG. 40

Time (weeks)

Mean CRP Plasma Concentration (mg/l)
Mean (±SD) C-Reactive Protein Concentration Versus Time: Ab1 Versus Placebo in Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate

FIG. 41
FIG. 44

Mean (±SEM) Hemoglobin Concentration (g/dl) in NSCLC Patients with a Baseline Hemoglobin Below 11g/l at baseline Versus Time:

- □ Ab 320mg (n=11)
- △ Ab 160mg (n=10)
- ○ Ab 80mg (n=8)
- ◊ Placebo (n=8)
Mean (± SEM) Hemoglobin Concentration: Ab1 Versus Placebo in Patients with Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate

- Ab1 80mg (n=32)
- Ab1 160mg (n=33)
- Ab1 320mg (n=29)
- Placebo (n=33)

Normal Range = 11.5-15.5 g/dl

FIG. 45
Mean (±SEM) Albumin Concentration in NSCLC Patients with a Baseline Albumin ≤35 g/l at baseline Versus Time: Ab1 Versus Placebo

Ab1 320mg (n=7)
Ab1 160mg (n=8)
Ab1 80mg (n=10)
Placebo (n=10)

FIG. 48
Mean (±SD) Change from Baseline in Body Weight (kg) Versus Time: Ab1 Versus Placebo in NSCLC Patients

Ab1 320mg (n=32)
Ab1 160mg (n=32)
Ab1 80mg (n=29)
Placebo (n=31)

Mean Change from Baseline in Body Weight (kg)

Time (weeks)

FIG. 49
Percentage Change in Mean ± SEM Lean Body Mass (kg) Over Time Using DEXA:

- Ab1 80mg (n=8)
- Ab1 160mg (n=15)
- Ab1 320mg (n=12)
- Placebo (n=20)

Change in Mean Lean Body Mass (kg)

Time (weeks)

FIG. 51
Mean (± SD) Change from Baseline FACIT-F Fatigue Subscale Score Versus Time: Ab1 Versus Placebo in NSCLC Patients

- ▲ Ab1 320mg (n=32)
- □ Ab1 160mg (n=32)
- ◆ Ab1 80mg (n=29)
- ▼ Placebo (n=31)

**FIG. 53**
<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=33)</th>
<th>Ab1 80mg (n=32)</th>
<th>Ab1 160mg (n=34)</th>
<th>Ab1 320mg (n=28)</th>
<th>Ab1 Pooled (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>75% (p=0.0026)</td>
<td>65% (p=0.0283)</td>
<td>82% (p=0.0005)</td>
<td>73% (p=0.0002)</td>
</tr>
<tr>
<td>ACR 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>41% (p=0.0281)</td>
<td>41% (p=0.0291)</td>
<td>50% (p=0.0052)</td>
<td>44% (p=0.0032)</td>
</tr>
<tr>
<td>ACR 70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>22% (p=0.0824)</td>
<td>18% (p=0.2585)</td>
<td>43% (p=0.0015)</td>
<td>27% (p=0.0130)</td>
</tr>
</tbody>
</table>

**FIG. 56**
Percentage Patients Achieving an ACR50 Score Versus Time: Ab1 Versus Placebo MITT in Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate

FIG. 58
Mean (± SEM) Change from Baseline HAQ-DI Score Versus Time: Ab1 Versus Placebo in Patients with Rheumatoid Arthritis with an Inadequate Response to Methotrexate.

Placebo (n=33)
Ab1 80mg (n=32)
Ab1 160mg (n=34)
Ab1 320mg (n=28)

Mean Change from Baseline HAQ-DI Score

Time (weeks)
Mean ± SD DAS28-CRP Score Versus Time: Ab1 Versus Placebo in Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate

Time (weeks)

Mean DAS28 Score

FIG. 62
Percentage Patients Achieving a Good/Moderate EULAR Response Versus Time: Ab1 Versus Placebo in Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate

FIG. 63
Ab1 SC 100 mg (n=6)
Ab1 SC 50 mg (n=6)
Placebo SC (n=3)
Ab1 IV 100 mg (n=6)
Placebo IV (n=3)

Healthy Male Subjects, 18-65 Years Old (n=27)

Screening Day -21

Day 1 Randomized And Single Dose Administered

Study Unblinded At Week 12:
Ab1 Subjects Monitored To Week 24

Week 24

Week 12 Primary Outcome: Safety Over 12 Weeks

Subjects Randomized to Placebo were Followed up for 12 Weeks after which they Discontinued from the Study.

SC = Subcutaneous. IV = Intravenous

FIG. 64
Plasma Concentrations of Ab1

Ab1 Plasma Concentration (μg/ml)

Time Post - Dose (days)

Ab1 SC 50 mg
SC Ab1 100 mg
IV Ab1 50 mg

Data are Mean: Error Bars Represent Standard Deviation. IV = Intravenous; SC = Subcutaneous

FIG. 65
### Adverse Events

<table>
<thead>
<tr>
<th>MedRA Preferred Term</th>
<th>Up to Week 12</th>
<th>Week 12 - Week 24*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SC 50 mg n=6</td>
<td>SC 100 mg n=6</td>
</tr>
<tr>
<td>Subjects With an AE</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>AE Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuations Due to AEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**FIG. 67**
<table>
<thead>
<tr>
<th>Condition</th>
<th>AE Reported in ≥2 Subjects in any Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site</td>
<td>1</td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
</tr>
<tr>
<td>Injection Site</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
</tr>
<tr>
<td>URTI</td>
<td>0</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>0</td>
</tr>
</tbody>
</table>

FIG. 67 (Continued)

Patients Randomized to Placebo (IV or SC) Discontinued at Week 12 and are Not Included in Week 24 Analyses; AE = Adverse Event; SC = Subcutaneous; IV = Intravenous; URTI = Upper Respiratory Tract Infection.
### Ab1 Injection Site Reactions to Week 12*

<table>
<thead>
<tr>
<th></th>
<th>50 mg n=6</th>
<th>100 mg n=6</th>
<th>100 mg n=6</th>
<th>Placebo SC n=6</th>
<th>Placebo IV n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Subjects With Injection Site Reaction</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injection Site Pruritis</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Injection Site Rash</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All Injection Site Reactions were Reported in the First 12 Weeks of the Study, SC = Subcutaneous; IV = Intravenous
### Clinical Laboratory Evaluations Over 24 Weeks (Ab1)

<table>
<thead>
<tr>
<th></th>
<th>SC 50 mg n=6</th>
<th>SC 100 mg n=6</th>
<th>IV 100 mg n=6</th>
<th>Placebo* n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ALT</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Elevated Total Bilirubin</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elevated Direct Bilirubin</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low Neutrophil Count†</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Low Platelet Count†</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*SC and IV Groups Combined Up to Week 12 Only, After Which Placebo-Treated Patients Discontinued: †Below the Lower Limit of Normal; SC = Subcutaneous; IV = Intravenous; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase

**FIG. 69**
**Ab1 Plasma Pharmacokinetic Parameters to Week 24**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SC 50 mg n=6</th>
<th>SC 100 mg n=6</th>
<th>IV 100 mg n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/mL) (CV)*</td>
<td>5.57 (24%)</td>
<td>9.19 (34%)</td>
<td>33.6 (30%)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (days) (min, max)†</td>
<td>6 (6, 14)</td>
<td>5.5 (2, 28)</td>
<td>0.17 (0.17, 0.34)</td>
</tr>
<tr>
<td>$AUC_{0-24\text{ wk}}$ (day·μg/mL) (CV)*</td>
<td>218 (34%)</td>
<td>435 (19%)</td>
<td>732 (22%)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (day·μg/mL) (CV)*</td>
<td>224 (39%)</td>
<td>444 (20%)</td>
<td>746 (22%)</td>
</tr>
<tr>
<td>$t_{1/2}$ (days ± SD)‡</td>
<td>33.6 ± 21.7</td>
<td>31.1 ± 9.0</td>
<td>30.7 ± 5.9</td>
</tr>
<tr>
<td>$CL$ (mL/day) (CV)*</td>
<td>223 (32%)</td>
<td>225 (21%)</td>
<td>134 (27%)</td>
</tr>
</tbody>
</table>

*Data are Geometric Mean (Coefficient of Variation %, CV%). †Data are Median (Minimum, Maximum)
‡Data are Mean (± SD). CV = Coefficient of Variation; $C_{\text{max}}$ = Maximum Plasma Concentration;
$AUC$ = Area Under Curve; SD = Standard Deviation; CL = Apparent Total Body Clearance for IV and
Apparent Total Body Clearance Divided by Bioavailability for SC; IV = Intravenous;
SC = Subcutaneous; $T_{\text{max}}$ = Time to Maximum Plasma Concentration; $t_{1/2}$ = Terminal Plasma Half-Life

*FIG. 70*