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Description**Field of the Invention**

[0001] The present invention relates to anti-TNF α antibodies and their use as therapeutics.

Background of the Invention

[0002] Efficacy of a therapeutic protein can be limited by an unwanted immune reaction to the therapeutic protein. For monoclonal antibodies, a number of techniques have been developed in attempts to reduce the human anti-murine antibody (HAMA) response. In general, these approaches aim to reduce the mouse genetic information in the final antibody construct while increasing the human genetic information. Examples of such approaches are chimeric, humanized and fully human monoclonal antibodies (mAbs).

[0003] Chimeric antibodies contain regions derived from different animal species, such as a murine immunoglobulin (Ig) variable region and a human Ig constant region. Infliximab (sold under the brand name REMICADE®) is a chimeric IgG1 κ monoclonal antibody that specifically binds human tumor necrosis factor- α (TNF α). Infliximab has human constant regions and murine variable regions. The heavy chain variable region (V_H) of infliximab has 119 amino acids; the light chain variable region (V_L) has 107 amino acids. See, U.S. Pat. Nos. 6,277,969, 6,284,471, 6,790,444, and 6,835,823.

[0004] TNF α can be produced by a wide variety of cells, but activated macrophages constitute the most abundant source of this factor (Vassalli, Ann. Rev. Immunol. 10: 411-452 (1992)). TNF α is a soluble homotrimer of 17kD protein subunits (Smith, et al., J. Biol. Chem. 262: 6951-6954 (1987)). A membrane-bound 26kD precursor form of TNF α also exists (Kriegler, et al., Cell 53: 45-53 (1988)).

[0005] TNF α causes pro-inflammatory actions which result in tissue injury, such as inducing procoagulant activity on vascular endothelial cells increasing the adherence of neutrophils and lymphocytes, and stimulating the release of platelet activating factor from macrophages, neutrophils and vascular endothelial cells (Pober, et al., J. Immunol. 136: 1680-1687 (1986); Pober, et al., J. Immunol. 138: 3319-3324 (1987); Camussi, et al., J. Exp. Med. 166: 1390-1404 (1987)).

[0006] The numerous biological effects of TNF α and the closely related cytokine, TNF β (also known as lymphotoxin), are mediated by two TNF transmembrane receptors, the p55 and p75 receptors (Hohmann, et al., J. Biol. Chem. 264: 14927-14934 (1989); Engelmann, et al., J. Biol. Chem. 265: 1531-1536 (1990)). Extracellular domains of TNF receptors derived by proteolytic cleavage inhibit TNF functions (Kohno, et al., Proc. Natl. Acad. Sci. U.S.A. 87: 8331-8335 (1990)). TNF α is associated with infections, immune disorders, neoplastic pathologies, autoimmune pathologies and graft-versus host pathologies (Cerami, et al., Immunol. Today 9: 28-31 (1988); Oliff, et al., Cell 50: 555-563 (1987); Piquet, et al., J. Exp. Med. 166: 1280-1289 (1987)). Dysregulation and, in particular, overproduction of TNF α has been implicated in a variety of human diseases including sepsis, cerebral malaria, and autoimmune diseases such as multiple sclerosis, rheumatoid arthritis (RA), systemic lupus erythematosus, and Crohn's disease, as well as cancer (reviewed in Zhang and Tracey, The Cytokine Handbook, Thomson AW (ed). pp 517-548 (1998)). TNF α can mediate cachexia in cancer, infectious pathology, and other catabolic states (reviewed in Tracey, et al., Ann. N. Y. Acad. Sci. 587: 325-331 (1990)).

[0007] Neutralizing anti-TNF α antibodies that inhibit TNF α activities are useful in treating and/or diagnosing TNF α -mediated diseases. Infliximab has been approved in the United States for treatment of ankylosing spondylitis, Crohn's disease, psoriatic arthritis and rheumatoid arthritis. It can also effectively treat other disorders or symptoms of various immune and autoimmune pathologies as well as inflammatory diseases, such as systemic lupus erythematosus, thyroiditis, graft versus host disease, scleroderma, diabetes mellitus, Grave's disease, sarcoidosis, chronic inflammatory bowel disease, ulcerative colitis, disseminated intravascular coagulation, atherosclerosis and Kawasaki's pathology. See, U.S. Pat. Nos. 5,656,272, 5,698,195, and 5,919,452, all of which are incorporated herein by reference.

[0008] It has been reported that antibodies to infliximab have been observed in some treated patients (Targan et al., N. Engl. J. Med. 337: 1029-1035 (1997); Maini et al., Arthritis Rheum. 41: 1552-1563 (1998)). Accordingly, in order to potentially diminish the incidence of anti-infliximab antibodies in treated patients, it is desirable to reduce the amount of murine amino sequences present in the molecule.

[0009] WO 03/042247 describes the modification of antibodies reactive to TNF alpha to result in anti-TNF alpha antibodies that are less immunogenic than the non-modified parental antibody when used *in vitro*.

Brief Description of the Drawings**[0010]**

Fig. 1 shows the alignment of V_H regions of the TNF α antibody C7 (SEQ ID NO: 3) and infliximab (SEQ ID NO: 1). Identical amino acids are denoted by a "-." Conservative amino acid changes are shown in bold.

Fig. 2 shows the alignment of V_L regions of C7 (SEQ ID NO: 380) and infliximab (SEQ ID NO: 379). Identical amino

acids are denoted by a "-." Conservative amino acid changes are shown in bold.

Fig. 3 shows the ELISA titration curves for C7 and infliximab.

Summary of the Invention

[0011] In one aspect, the invention provides an antibody capable of binding to TNF alpha, wherein the antibody comprises: (a) a polypeptide comprising a polypeptide having the sequence shown in SEQ ID NO: 2; and (b) a polypeptide comprising a polypeptide having the sequence shown in SEQ ID NO: 380, wherein said antibody binds TNF alpha with affinity higher than that of infliximab as determined using a Biacore assay, and wherein the infliximab V_H region has the sequence shown in SEQ ID NO: 1 and the infliximab V_L region has the sequence shown in SEQ ID NO: 379.

[0012] In another aspect, the invention provides a biologically active fragment of an antibody of the invention.

[0013] In another aspect, the invention provides a cell line expressing an antibody of the invention or a biologically active fragment of the invention.

[0014] In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of an antibody of the invention or of at least one biologically active fragment of the invention and a pharmaceutically acceptable carrier or diluent.

[0015] One aspect of the disclosure is a polypeptide comprising a polypeptide having the sequence shown in SEQ ID NO: 2.

[0016] Another aspect of the disclosure is a polypeptide comprising a polypeptide having the sequence shown in SEQ ID NOs: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189 or 190.

[0017] Another aspect of the disclosure is a polynucleotide comprising a polynucleotide having the sequence shown in SEQ ID NOs: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377 or 378 or a complementary sequence.

[0018] Another aspect of the disclosure is a polynucleotide comprising a polynucleotide encoding the amino acid sequence shown in SEQ ID NOs: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189 or 190.

Detailed Description of the Invention

[0019] Single letter amino acid codes are used herein as understood by those skilled in the art.

[0020] The term "immunoglobulin" as used herein refers to a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes. The term "antibody" as used herein refers to a protein of the immunoglobulin family that is capable of interacting or otherwise associating with an antigen, as well as biologically active fragments, regions or derivatives thereof, provided by any known technique, such as, but not limited to enzymatic cleavage (e.g., by papain or pepsin digestion), peptide synthesis or recombinant techniques. Examples of biologically active fragments regions of antibodies include, but are not limited to, Fab, Fab', F(ab')₂ and Fv. These fragments lack the Fc fragment of an intact antibody, clear more rapidly from the circulation, and can have less non-specific tissue binding than an intact antibody. The term "derivatives" includes modified antibodies that functionally resemble immunoglobulin molecules. An exemplary modification can be the addition of a cytotoxic protein such as a bacterial toxin.

The term "antigen" as used herein refers to a substance that is capable of interacting with the antibody and in the context of the present invention is meant to be $\text{TNF}\alpha$. The $\text{TNF}\alpha$ may be soluble $\text{TNF}\alpha$ or membrane associated $\text{TNF}\alpha$. The term " $\text{TNF}\alpha$ antibodies" as used herein includes antibodies capable of binding portions of TNF and inhibiting the binding of $\text{TNF}\alpha$ to TNF receptors.

[0021] The present invention provides $\text{TNF}\alpha$ antibodies that bind to $\text{TNF}\alpha$ and have fewer murine-derived amino acid residues than infliximab. The disclosure also provides nucleic acids encoding the $\text{TNF}\alpha$ antibodies, vectors containing these nucleic acids and methods of making and using the $\text{TNF}\alpha$ antibodies. The invention also provides host cells and compositions.

$\text{TNF}\alpha$ antibody polypeptides and compositions

[0022] The present invention generally relates to a $\text{TNF}\alpha$ antibody as recited in claim 1 comprising a polypeptide having the sequence shown in Formula I (SEQ ID NO: 2):

EVQLX₅ESGGG LVQPGGSLRL SCX₂₃ASX₂₆X₂₇X₂₈FS NHX₃₃MNWVRQA PGKGLEWIGE IRSKSX₅₆X₅₇X₅₈AT
X₆₁YAESVKGRF IISRD₇₆NX₇₈X₇₉X₈₀LX₈₂LEMNSLKT EDTAEYYCAX₁₀₀ NYYGSTX₁₀₇DYW GQGTLTVTS (I)

wherein,

X₅ is V or T; X₂₃ is A or R; X₂₆ is G or Q; X₂₇ is F or S; X₂₈ is I or T; X₃₃ is W or Y; X₅₆ is I or S; X₅₇ is N or Y; X₅₈ is S or G; X₆₁ is H or S; X₇₆ is D or G; X₇₈ is K or G; X₇₉ is N or T; X₈₀ is S or D; X₈₂ is Y or T; X₁₀₀ is R or Q; and X₁₀₇ is Y or P.

[0023] More particularly, the present invention relates to antibodies against $\text{TNF}\alpha$ that are less likely to generate anti-infliximab antibodies in humans.

[0024] The variable regions of the $\text{TNF}\alpha$ antibodies have significant identities with human immunoglobulin sequences or human immunoglobulin germline sequences in the framework regions. Human immunoglobulin sequences can be found in databases such as that of NCBI (<http://ncbi.nlm.nih.gov/>). Human immunoglobulin germline sequences can be found at, for example, <http://vbase.mrc-cpe.cam.ac.uk/>. Exemplary heavy chain variable region amino acid sequences are shown in SEQ ID NOs: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189 or 190. An exemplary light chain variable region sequence is shown in SEQ ID NO: 380.

[0025] The heavy chain constant region can be derived from any of the known classes or isotypes of human heavy chains, including IgA, IgD, IgE, IgG, IgM and subtypes thereof, such as G1, G2, G3 and G4. Since the heavy chain isotype is responsible for the various effector functions of an antibody, the choice of the heavy chain constant region will be guided by the desired effector functions, such as complement fixation, or antibody-dependent cellular cytotoxicity (ADCC). An exemplary heavy chain constant region amino acid sequence is shown in SEQ ID NO: 382. The light chain constant region can be derived from either human light chain isotype kappa or lambda. An exemplary light chain constant region amino acid sequence is shown in SEQ ID NO: 383.

[0026] The $\text{TNF}\alpha$ antibodies of the present invention can bind $\text{TNF}\alpha$ with affinity higher than that of infliximab as determined using a Biacore assay. The affinity of $\text{TNF}\alpha$ antibodies for $\text{TNF}\alpha$ can also be determined experimentally using any other suitable method, e.g., methods using KinExA instrumentation, ELISA and competitive binding assays.

[0027] The $\text{TNF}\alpha$ antibodies of the present invention are capable of blocking or reducing interactions between $\text{TNF}\alpha$ and TNF receptors. These $\text{TNF}\alpha$ antibodies neutralize $\text{TNF}\alpha$ activity in a range of *in vitro* assays, such as cell cytotoxicity, mitogenesis, cytokine induction and induction of adhesion molecules.

[0028] The $\text{TNF}\alpha$ antibodies of the present invention are useful for treating disorders or symptoms of various immune and autoimmune pathologies as well as inflammatory diseases. TNF related pathologies and diseases include, but are not limited to, the following:

(A) acute and chronic immune and autoimmune pathologies, such as systemic lupus erythematosus, rheumatoid arthritis, thyroidosis, graft versus host disease, scleroderma, diabetes mellitus and Graves' disease;

(B) infections, including, but not limited to, sepsis syndrome, cachexia, circulatory collapse and shock resulting from acute or chronic bacterial infection, acute and chronic parasitic and/or bacterial, viral or fungal infectious diseases, such as AIDS (including sequelae such as cachexia, autoimmune disorders, AIDS dementia complex and infections);

(C) inflammatory diseases, such as chronic inflammatory pathologies and vascular inflammatory pathologies, including chronic inflammatory pathologies such as sarcoidosis, chronic inflammatory bowel disease, ulcerative colitis,

and Crohn's pathology and vascular inflammatory pathologies, such as, but not limited to, disseminated intravascular coagulation, atherosclerosis, and Kawasaki's pathology;

(D) neurodegenerative diseases, including, but are not limited to, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo palsy; Cerebellar and Spinocerebellar Disorders, such as astructural lesions of the cerebellum; spinocerebellar degenerations (spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); and systemic disorders (Refsum's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; disorders of the motor unit, such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; subacute sclerosing panencephalitis, Hallerorden-Spatz disease; and Dementia pugilistica, or any subset thereof;

(E) malignant pathologies involving TNF-secreting tumors or other malignancies involving TNF, such as, but not limited to leukemias (acute, chronic myelocytic, chronic lymphocytic and/or myelodysplastic syndrome); lymphomas (Hodgkin's and non-Hodgkin's lymphomas, such as malignant lymphomas (Burkitt's lymphoma or Mycosis fungoides)); and (F) alcohol-induced hepatitis.

[0029] Accordingly, another aspect of the present invention is pharmaceutical compositions as recited in claim 9 comprising at least one TNF α antibody and a pharmaceutically acceptable carrier or diluent known in the art. The carrier or diluent can be a solution, suspension, emulsion, colloid or powder.

[0030] A TNF α antibody of the invention is formulated as a pharmaceutical composition in a therapeutically or prophylactically effective amount. The term "effective amount" generally refers to the quantities of antibody necessary for effective therapy, *i.e.*, the partial or complete alleviation of the symptom or disorder for which treatment was sought. Included within the definition of effective therapy are prophylactic treatments intended to reduce the likelihood of onset of the above-described symptoms or disorders.

[0031] The composition can optionally comprise at least one further compound, protein or composition useful for treating a TNF-related pathology or disease. For example, combination with anti-rheumatic drugs, anti-inflammatory agents, anti-neoplastic agents, radiotherapeutics, immunosuppressives, and cytotoxic drugs to treat various diseases and conditions are contemplated. In this regard, anti-rheumatic drugs can be at least one of auranofin, azathioprine, chloroquine, D-penicillamine, gold sodium thiomalate hydroxychloroquine, Myocrisin and sulfasalazine methotrexate. Anti-inflammatory agents can be at least one of pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

Nucleic acids, vectors and cell lines

[0032] Another aspect of the present disclosure is isolated nucleic acid molecules comprising, complementary to or having significant identity with a polynucleotide encoding at least one TNF α antibody. Other aspects of the present disclosure include recombinant vectors comprising at least one isolated TNF α antibody encoding nucleic acid molecule and cell lines and organisms that are capable of expressing proteins from the nucleic acid molecules. The nucleic acids, expression vectors and cell lines may generally be used to produce the TNF α antibodies of the invention.

[0033] In one embodiment, the nucleic acid compositions of the disclosure comprise polynucleotides encoding polypeptides having amino acid sequences shown in SEQ ID NOs: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189 or 190. Exemplary nucleic acid sequences comprise polynucleotides shown in SEQ ID NOs: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308,

309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377 or 378.

[0034] Typically, the nucleic acids of the present disclosure are used in expression vectors for the preparation of the TNF α antibody polypeptides of the invention. Vectors within the scope of the disclosure provide necessary elements for eukaryotic expression, including viral promoter driven vectors, such as CMV promoter driven vectors, e.g., pcDNA3.1, pCEP4 and their derivatives, Baculovirus expression vectors, Drosophila expression vectors and expression vectors that are driven by mammalian gene promoters, such as human immunoglobulin gene promoters. Other examples include prokaryotic expression vectors, such as T7 promoter driven vectors, e.g., pET41, lactose promoter driven vectors and arabinose gene promoter driven vectors.

[0035] The present invention also relates to cell lines as recited in claim 4 expressing TNF α antibodies. The host cells can be prokaryotic or eukaryotic cells. Exemplary eukaryotic cells are mammalian cells, such as but not limited to, COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, HepG2, 653, SP2/0, NS0, 293, HeLa, myeloma, lymphoma cells, or any derivative thereof. Most preferably, the host cells are HEK293, NS0, SP2/0 or CHO cells. The cell lines of the present invention may stably express at least one TNF α antibody. The cell lines may be generated by stable or transient transfection procedures that are well known in the art.

[0036] The present disclosure further provides methods for expressing at least one TNF α antibody comprising culturing the cell lines under conditions wherein the TNF α antibody is expressed in detectable or recoverable amounts. The present disclosure also provides methods for generating at least one TNF α antibody comprising translating the TNF α antibody encoding nucleic acids under conditions *in vitro* or *in situ*, such that the TNF α antibody is expressed in detectable or recoverable amounts. The present invention also encompasses TNF α antibody produced by the above methods.

[0037] A TNF α antibody can be recovered and purified by well-known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography (HPLC) can also be employed for purification.

Uses

[0038] The TNF α antibodies are useful as, *inter alia*, research reagents and therapeutic agents. In one aspect, the present invention relates to at least one TNF α antibody for use in a method of decreasing or inhibiting the interactions between TNF α and TNF receptors in a mammal in need thereof. The TNF α antibodies neutralize the biological activities of TNF α and therefore function as antagonists of TNF α . The term "antagonist" is used in the broadest sense and includes a molecule that is capable of, directly or indirectly, partially or fully counteracting, reducing or inhibiting one or more biological activities of TNF α .

[0039] The present invention further provides a TNF α antibody for use in reducing the symptoms of, or for use in treating at least one TNF-related condition or disease comprising administering a therapeutically effective amount of at least one TNF α antibody pharmaceutical composition to a patient in need thereof. As described above, such composition comprises an effective amount of at least one TNF α antibody and a pharmaceutically acceptable carrier or diluent. The effective amount for a given therapy, whether curative or preventative, will generally depend upon many different factors, including means of administration, target site and other medicaments administered. Thus, treatment doses will need to be titrated to optimize safety and efficacy.

[0040] The conditions and diseases suitable for treatment using the antibody of the present invention include but are not limited to, various immune disorders, autoimmune pathologies and inflammatory diseases as listed in detail above. These methods can optionally further comprise coadministration or combination therapies with any standard therapy used to treat the diseases.

[0041] The mode of administration can be any suitable route to deliver the pharmaceutically effective amount of TNF α antibody of the present invention to a host. For example, the TNF α antibody can be delivered via parenteral administration, such as subcutaneous, intramuscular, intradermal, intravenous or intranasal administration, or any other means known in the art.

[0042] The present invention is further described with reference to the following examples. These examples are merely to illustrate aspects of the present invention and are not intended as limitations of this invention.

Example 1

Generation of TNF α Antibodies

[0043] Fab libraries were designed based on a combination of infliximab sequence and structure-based criteria. The

design goal was molecules with TNF α binding activity at least equal to that of infliximab with high similarity to human immunoglobulin sequences. For example, one criterion of selection for library members was sequence identity or similarity in framework and complementarity determining regions (CDRs) for both heavy and light chains with homologous human counterparts. The human immunoglobulin database at NCBI (ncbi.nlm.nih.gov) and the human germline immunoglobulin database (vbase.mrc-cpe.cam.ac.uk) were employed. Based on these criteria, V_H polypeptides were designed with substitutions at one or a combination of 17 sites. These V_H combinations were combined with one substituted V_L polypeptide having an amino acid sequence shown in SEQ ID NO: 380 (encoding nucleic acid sequence shown in SEQ ID NO: 381). Synthetic Fab DNA libraries were generated according to the method described in U.S. Pat. No. 6,521,427.

[0044] The Fab libraries were cloned into pTrcHis2A (Cat. No. V365-20, Invitrogen, Carlsbad, CA). Proteins were expressed in *E. coli* and solid-phase ELISA was used to assess Fab binding to human TNF α . Briefly, 96-well plates were coated overnight at 4°C with 1 μ g/ml of rHuTNF-alpha (Biosource, Camarillo, CA) in Carbonate-bicarbonate buffer, pH9.4. After washing in PBS with 0.05% (w/v) Tween-20, the wells were blocked with 1%(w/v) BSA in PBS for 1 hour at room temperature. After washing, plates were incubated with transformed *E. coli* cell lysate diluted in the assay buffer (1% BSA and 0.05% Tween-20 in 10mM PBS) for 2 hours at room temperature. Various concentrations of infliximab (0.5, 1 and 2 ng/ml) were used as positive anti-Human Kappa Light Chain Biotin/anti-penta-His Biotin control. Plates were washed and incubated with ImmunoPure Goat Anti-Human Kappa Chain, Biotin Conjugated (Cat. No. 31780, Pierce Biotechnology, Rockford, IL) and Penta-His Biotin Conjugate (Cat. No. 34440, QIAGEN, Valencia, CA) diluted 1:2000 in the assay buffer for 1 hour at room temperature. Following another washing step, plates were probed for 1 hour at room temperature with 100 μ L/well of Streptavidin POD (Cat. No. 1089153, Roche Applied Science, Indianapolis, IN) diluted 1:4000 in the assay buffer. Plates were further washed and then incubated with 3,3',5,5'-tetramethylbenzidine (TMB, Cat. No. 34028, Pierce Biotechnology) for 30 minutes. Substrate development was stopped by addition of 100 μ L/well TMB Stop Solution (Cat. No. 50-85-05, KPL, Gaithersburg, MD) and the absorbance was measured at 450nm via an automated plate spectrophotometer.

[0045] 188 clones with optical density values of at least twice the background value were further characterized. The V_H amino acid sequences of these clones are shown in SEQ ID NOs: 3 to 190 respectively. The V_L amino acid sequence is shown in SEQ ID NO: 380. Briefly, protein concentration was determined and a titration curve in TNF α ELISA was generated for each clone. A serial dilution curve was generated by eight points titration in duplicate, starting at 50ng/ml. Clones were ranked according to their EC₅₀. The variable regions of selected Fab clones were subcloned into a mammalian construct with infliximab constant region.

Example 2

Sequence Analysis of a TNF α Antibody

[0046] The framework portion of the V_H region of one of the novel TNF α antibodies selected as described in Example 1 (C7) (SEQ ID NO: 3) is identical to human germline sequence (VH3 3-72 and JH4). As shown in Fig. 1, when compared to infliximab, 61 out of the 83 amino acids in the framework regions are identical. Of the 23 positions that are different, 14 of them (shown in bold) are conservative amino acid changes.

[0047] Similarly, the framework portion of C7 V_L region is identical to human germline sequence (VK1 A10 and Jk3). As shown in Fig. 2, when compared to infliximab, 63 out of the 80 amino acids in the framework regions are identical. Of the 17 positions that are different, 13 of them (shown in bold) are conservative amino acid changes.

Example 3

Binding of Antibody C7 to TNF α

[0048] The full-length antibodies were used in a solid-phase ELISA binding assay as described in Example 1 to confirm the TNF α binding. Fig. 3 shows that the ELISA titration curve for C7 is comparable to that of infliximab.

[0049] C7 was also used in a Biacore assay to compare the binding constants of C7 and infliximab to TNF α . The results (not shown) indicated that the binding affinity of C7 to TNF α (K_D = 70 pM) is more than 2-fold higher than that of infliximab (K_D = 170 pM).

[0050] The present invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the scope of the appended claims.

SEQUENCE LISTING

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<151> 2005-08-04

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 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Asp
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<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 29

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 105
 110
 115

<210> 30

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 30

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Ser
 65 70 75 80
 10 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 15 Gly Thr Leu Val Thr Val Ser
 115

<210> 31

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 31

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 20 25 30
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 32

<211> 119

<212> PRT

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 32

55

EP 1 919 951 B1

5 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Thr Phe Ser Asn His
 20 25 30
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Ser
 65 70 75 80
 15 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 33

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 33

30 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 34

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 34

55

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 105
 110
 115

<210> 35

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 35

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 36

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 36

	<210> 37
20	<211> 119
	<212> PRT
	<213> Artificial Sequence
	<220>
25	<223> Infiximab VH variant
	<400> 37

45 <210> 38
<211> 119
<212> PRT
<213> Artificial Sequence

50 <220>
<223> Infliximab VH variant

<400> 38

EP 1 919 951 B1

5 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Ser
 65 70 75 80
 15 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 39

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 39

30 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 40

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 40

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25 <400> 41

<400> 42

25 <400> 43

45 <210> 44
<211> 119
<212> PRT
<213> Artificial Sequence

50 <220>
<223> Infliximab VH variant

<400> 44

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 105
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 115

<210> 45

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 45

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
 50
 55
 60
 65
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 75
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 85
 90
 95
 100
 105
 110
 115

<210> 46

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 46

EP 1 919 951 B1

5 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Thr Phe Ser Asn His
 20 25 30
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 65 70 75 80
 15 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 47

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 47

30 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Ile Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 48

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 48

55

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 15 115

<210> 49

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 49

30 1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr His Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Ser
 35 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 40 115

<210> 50

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 50

55 1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45

EP 1 919 951 B1

Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 65 70 75 80
 5 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 10 Gly Thr Leu Val Thr Val Ser
 115

<210> 51

<211> 119

<212> PRT

15 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

20 <400> 51

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 25 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 30 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 35 Gly Thr Leu Val Thr Val Ser
 115

<210> 52

<211> 119

40 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

45 <400> 52

50

55

EP 1 919 951 B1

5 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Ile Phe Ser Asn His
 20 25 30
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Ser
 15 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110

15 Gly Thr Leu Val Thr Val Ser
 115

<210> 53

<211> 119

20 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

25

<400> 53

30 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 35 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 40 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 54

45 <211> 119

<212> PRT

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 54

55

<210> 55
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Infliximab VH variant

[illegible]

55

25 <400> 57

45 <210> 58
<211> 119
<212> PRT
<213> Artificial Sequence

50 <220>
<223> Infiximab VH variant

<400> 58

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 60
 65
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 90
 95
 100
 105
 110
 115

<210> 59

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 59

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
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 55
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 65
 70
 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 60

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 60

<210> 61
<211> 119
<212> PRT
<213> Artificial Sequence

25 <400> 61

<210> 62
<211> 119
<212> PRT
<213> Artificial Sequence

<400> 62

25 <400> 63

<400> 64

55 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

EP 1 919 951 B1

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 5 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Ser
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 10 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

15 <210> 65
 <211> 119
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> Infliximab VH variant
 <400> 65

25 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 20 25 30
 30 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 65 70 75 80
 35 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

40 <210> 66
 <211> 119
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Infliximab VH variant
 <400> 66

50

55

EP 1 919 951 B1

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 65 70 75 80

Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 67

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 67

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 68

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 68

<210> 69
<211> 119
<212> PRT
<213> Artificial Sequence

25 <400> 69

<210> 70
<211> 119
<212> PRT
<213> Artificial Sequence

<400> 70

<400> 72

<400> 73

<400> 74

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 85
 90
 95
 100
 105
 110
 115

<210> 75

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 75

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 55
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 65
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 85
 90
 95
 100
 105
 110
 115

<210> 76

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 76

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 15

<210> 77

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 77

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 35 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 40

<210> 78

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 78

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 105
 110
 115

<210> 79

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 79

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 80

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 80

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 10 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 15 Gly Thr Leu Val Thr Val Ser
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 25 Gly Thr Leu Val Thr Val Ser
 30 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 45 Gly Thr Leu Val Thr Val Ser
 50 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 55 Gly Thr Leu Val Thr Val Ser

<210> 81

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 81

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Thr Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 40 Gly Thr Leu Val Thr Val Ser
 45 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 50 Gly Thr Leu Val Thr Val Ser
 55 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 60 Gly Thr Leu Val Thr Val Ser

<210> 82

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 82

25 <400> 83

<400> 84

<210> 85
<211> 119
<212> PRT
<213> Artificial Sequence

25 <400> 85

<210> 86
<211> 119
<212> PRT
<213> Artificial Sequence

<400> 86

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 105
 110
 115

<210> 87

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 87

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 85
 90
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<210> 88

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 88

25 <400> 89

<210> 90
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Infliximab VH variant

<400> 90

EP 1 919 951 B1

5 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 20 25 30
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Asp
 65 70 75 80
 15 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 91

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 91

30 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 92

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 92

55

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 65 70 75 80
 10 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 15 Gly Thr Leu Val Thr Val Ser
 115

<210> 93

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 93

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Thr Phe Ser Asn His
 20 25 30
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Asp
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 94

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 94

55

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40

<210> 95

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 95

30 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 35 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Thr Phe Ser Asn His
 40 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 45 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 50 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Ser
 55 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 60 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 65 Gly Thr Leu Val Thr Val Ser
 70

<210> 96

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 96

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 97

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 97

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Asp
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 98

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 98

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 65
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 85
 90
 95
 100
 105
 110
 115

<210> 99

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 99

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
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 70
 75
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 85
 90
 95
 100
 105
 110
 115

<210> 100

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 100

55

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Lys Thr Ser
 65 70 75 80
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 103

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 103

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 104

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 104

15

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EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 10 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 15 Gly Thr Leu Val Thr Val Ser
 115

<210> 107

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 107

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 108

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 108

55

EP 1 919 951 B1

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 109

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 109

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Ile Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 110

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 110

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 105
 110
 115

<210> 111

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 111

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 85
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 95
 100
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<210> 112

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 112

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 55
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 95
 100
 105
 110
 115

<210> 113

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 113

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 55
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 90
 95
 100
 105
 110
 115

<210> 114

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 114

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Ser
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 15 115

<210> 115

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 115

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Ile Phe Ser Asn His
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Ser
 65 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 40 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 115

<210> 116

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 116

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
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 55
 60
 65
 70
 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 117

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 117

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 118

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 118

<210> 119
<211> 119
<212> PRT
<213> Artificial Sequence

25 <400> 119

<210> 120
<211> 119
<212> PRT
<213> Artificial Sequence

 $\langle 400 \rangle$ 120

EP 1 919 951 B1

[illegible]

<210> 121

$\langle 211 \rangle$ 119

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Infliximab VH variant

<400> 121

[illegible]

<210> 122

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 122

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 123

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 123

30 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 35 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Thr Phe Ser Asn His
 40 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 45 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 50 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 55 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 60 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 65 Gly Thr Leu Val Thr Val Ser
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<210> 124

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 124

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 110
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<210> 125

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 125

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 126

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 126

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 127

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 127

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 128

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 128

<400> 129

<400> 130

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 131

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 131

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 132

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 132

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 20 25 30
 5 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 65 70 75 80
 10 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 133

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 133

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Asp
 65 70 75 80
 35 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 134

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 134

EP 1 919 951 B1

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Ser
 65 70 75 80
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 135

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 135

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 20 25 30
 30 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 136

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 136

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40

<210> 137

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 137

30 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 35 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 40 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 45 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr Ser Tyr Ala Glu
 50 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 55 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 60 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 65 Gly Thr Leu Val Thr Val Ser
 70

<210> 138

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 138

<400> 139

<400> 140

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 55
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 65
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 75
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 85
 90
 95
 100
 105
 110
 115

<210> 141

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 141

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
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 55
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 65
 70
 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 142

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 142

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
 50
 55
 60
 65
 70
 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 143

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 143

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
 50
 55
 60
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 70
 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 144

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 144

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Ile Phe Ser Asn His
 20 25 30
 5 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 65 70 75 80
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 145

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 145

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 146

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 146

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 85
 90
 95
 100
 105
 110
 115

<210> 147

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 147

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 100
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 110
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<210> 148

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 148

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 149

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 149

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 150

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 150

	<210> 151
20	<211> 119
	<212> PRT
	<213> Artificial Sequence
	<220>
25	<223> Infliximab VH variant
	<400> 151

45 <210> 152
 <211> 119
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> Infliximab VH variant

 <400> 152

<400> 153

<400> 154

<210> 155
<211> 119
<212> PRT
<213> Artificial Sequence

25 <400> 155

[illegible]

45

<210>	156
<211>	119
<212>	PRT
<213>	Artificial Sequence

<400> 156

<400> 157

<400> 158

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 55
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 65
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 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 159

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 159

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 55
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 65
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 75
 80
 85
 90
 95
 100
 105
 110
 115

<210> 160

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 160

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 95
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 110
 115

<210> 161

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 161

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
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 95
 100
 105
 110
 115

<210> 162

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 162

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 55
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 95
 100
 105
 110
 115

<210> 163

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 163

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 100
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 110
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<210> 164

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 164

	<210> 165
20	<211> 119
	<212> PRT
	<213> Artificial Sequence
	<220>
25	<223> Infiximab VH variant
	<400> 165

45 <210> 166
 <211> 119
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> Infliximab VH variant

 <400> 166

EP 1 919 951 B1

5 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Ile Phe Ser Asn His
 20 25 30
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 15 65 70 75 80
 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 20 Gly Thr Leu Val Thr Val Ser
 115

<210> 167

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 167

30 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 168

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 168

55

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 110
 115

<210> 169

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 169

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 95
 100
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 110
 115

<210> 170

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 170

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 85
 90
 95
 100
 105
 110
 115

<210> 171

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 171

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
 45
 50
 55
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 80
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 90
 95
 100
 105
 110
 115

<210> 172

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 172

EP 1 919 951 B1

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Asn Asp
 65 70 75 80
 10 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 15 115

<210> 173

<211> 119

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

25 <400> 173

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 20 25 30
 30 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 35 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 40 Gly Thr Leu Val Thr Val Ser
 115

<210> 174

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 174

55

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 100
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 110
 115

<210> 175

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 175

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Asn Gly Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 110
 115

<210> 176

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 176

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 100
 105
 110
 115

<210> 177

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 177

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Asp
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 100
 105
 110
 115

<210> 178

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 178

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Asn Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 179

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 179

Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Gly Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 180

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 180

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 20 25 30
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Asn Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Thr Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 181
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Infliximab VH variant

<400> 181

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 20 25 30
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Ser Ala Thr His Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Ser
 65 70 75 80
 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser
 115

<210> 182
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Infliximab VH variant

<400> 182

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
 40
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 55
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 75
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 85
 90
 95
 100
 105
 110
 115

<210> 183

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 183

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Ser
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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<210> 184

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 184

<210> 185
<211> 119
<212> PRT
<213> Artificial Sequence

25 <400> 185

45

<210>	186
<211>	119
<212>	PRT
<213>	Artificial Sequence

<400> 186

EP 1 919 951 B1

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Asn Ser
 25 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 100
 105
 110
 115

<210> 187

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 187

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
 10 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 15 Gly Glu Ile Arg Ser Lys Ser Ser Tyr Gly Ala Thr Ser Tyr Ala Glu
 20 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Gly Thr Asp
 25 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 30 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 35 Gly Thr Leu Val Thr Val Ser
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 75
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 95
 100
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 110
 115

<210> 188

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 188

EP 1 919 951 B1

1 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn His
 Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Gly Ala Thr Ser Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Lys Asn Asp
 10 Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Gln Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 15

<210> 189

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 189

1 Glu Val Gln Leu Thr Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gln Phe Thr Phe Ser Asn His
 30 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 Gly Glu Ile Arg Ser Lys Ser Ile Tyr Ser Ala Thr His Tyr Ala Glu
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Asn Gly Thr Ser
 35 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Pro Asp Tyr Trp Gly Gln
 Gly Thr Leu Val Thr Val Ser
 40

<210> 190

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 190

EP 1 919 951 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Arg Ala Ser Gly Phe Ile Phe Ser Asn His
 20 25 30
 5 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr Ser Tyr Ala Glu
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Gly Asn Lys Thr Asp
 65 70 75 80
 10 Leu Thr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Glu Tyr
 85 90 95
 Tyr Cys Ala Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
 100 105 110
 15 Gly Thr Leu Val Thr Val Ser
 115

<210> 191

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 191

gaggtgcagc tgggtggagag cggaggagga ctggtgcagc ctggaggaag cctgagactg 60
 agctgcgccg ccagcggctt catcttcagc aaccactgga tgaactgggt gagacaggct 120
 30 cctggcaagg gcctggagtg gatcggcgag atccggagca agagcatcaa cagcgccacc 180
 cactacgccg agagcgtgaa gggccggttc atcatcagcc gggacgacaa caagaacagc 240
 ctgtacctgg agatgaacag cctgaagacc gaggacaccg ccgagtacta ctgcgcccgg 300
 aactactacg gcagcaccta cgactactgg ggccaggga ccttggtgac cgtgagc 357

<210> 192

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

<400> 192

gaagtgcagc tgaccgaatc tgggtgggtg ctggttcagc cgggtgggtc tctgcgtctg 60
 45 tcttgccgtg cgtctgggtt catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggttaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaacctct 240
 ctgtacctgg aatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 50 aactactacg gttctaccta cgactactgg ggtcagggta ccttggttac cgtttct 357

<210> 193

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

EP 1 919 951 B1

<400> 193

5 gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgcgcg cgctctcagtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180

10 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 194

<211> 357

15 <212> DNA

<213> Artificial Sequence

<220>

20 <223> Infliximab VH variant

<400> 194

25 gaagttcagt tggttgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

30 <210> 195

<211> 357

<212> DNA

<213> Artificial Sequence

35 <220>

<223> Infliximab VH variant

<400> 195

40 gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgcgcg cgctctcagtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

50 <210> 196

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

55 <400> 196

EP 1 919 951 B1

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 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cgtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaataacta ctgcgcgcag 300
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<210> 197

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

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<400> 197

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25 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaataacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 198

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35

<400> 198

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 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
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<211> 357

<212> DNA

<213> Artificial Sequence

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<223> Infliximab VH variant

<400> 199

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EP 1 919 951 B1

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 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 200

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

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<400> 200

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 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 201

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 201

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 ccgggtaaaag gtctggaatg gatcggtgaa atccggttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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45 <211> 357

<212> DNA

<213> Artificial Sequence

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50 <223> Infliximab VH variant

<400> 202

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EP 1 919 951 B1

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 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgct 300
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<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

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<400> 203

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 204

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 204

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

40

<210> 205

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 205

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgct 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 206
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 206

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtcgcacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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15

<210> 207
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20

<220>
 <223> Infliximab VH variant

25

<400> 207

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaacctct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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30

<210> 208
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 208

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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45

50

<210> 209
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 209

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      tcttgccgcg cgtctcagtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cgggtgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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10 <210> 210

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 210

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      tcttgccgctg cgtctgggttc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
25      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 211

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 211

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      tcttgccgcg cgtctgggttc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cgggtgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaaccgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 212

45 <211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 212

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EP 1 919 951 B1

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 tcttgccggtg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 213

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 213

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 214

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 214

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 tcttgccggtg cgtctcagtt caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 40 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 215

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 215

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 tcttgccggtg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 216
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 216

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tcttgccgcg cgtctgggtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccggttcta aatcttctta cgtgcgacc 180
tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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15

<210> 217
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 217

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tcttgccgtg cgtctcagtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccaggtaaag gtctggaatg gatcggtgaa atccggttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaacctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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30

<210> 218
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

40

<400> 218

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ccgggtaaag gtctggaatg gatcggtgaa atccggttcta aatctatcta ctctgcgacc 180
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ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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50

<210> 219
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 219

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      tcttgccgcg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta cgggtgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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10 <210> 220

<211> 357

<212> DNA

<213> Artificial Sequence

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<223> Infliximab VH variant

<400> 220

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      tcttgccgctg cgtctcagtt caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctaa cgggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
25      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 221

<211> 357

<212> DNA

30 <213> Artificial Sequence

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<223> Infliximab VH variant

35 <400> 221

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      tcttgccgctg cgtctgggttc tatcttctct aaccactaca tgaattgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctaa cgggtgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctacctc cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 222

45 <211> 357

<212> DNA

<213> Artificial Sequence

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50 <223> Infliximab VH variant

<400> 222

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EP 1 919 951 B1

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 ccgggtaaaag gtctggaatg gatcggtgaa atccggttcta aatctatcaa cggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacctc 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
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<210> 223

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 223

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 tcttgccggtg cgtctcagtc taccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccggttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 224

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 224

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 tcttgccgcg cgtctcagtc caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccggttcta aatctatcta cggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacctc 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 40 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 225

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 225

55 gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtttg 60
 tcttgccggtg cgtctcagtc taccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccggttcta aatcttctaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 226
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 226

10

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gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
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ccgggtaaag gtctggaatg gatcggtgaa atccggttcta aatcttctta cggtcgcacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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15

<210> 227
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 227

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ccgggtaaag gtctggaatg gatcggtgaa atccggttcta aatctatcaa ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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30

<210> 228
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 228

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ccgggtaaag gtctggaatg gatcggtgaa atccggttcta aatctatcaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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45

50

<210> 229
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 229

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5      gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
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      ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaaccgac 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctacccc ggactactgg ggtcagggta ccctggttac cgtttct 357

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10 <210> 230

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 230

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      ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
25      aactactacg gttctacccc ggactactgg ggtcagggta ccctggttac cgtttct 357

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<210> 231

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 231

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      ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
      aactactacg gttctacccc ggactactgg ggtcagggta ccctggttac cgtttct 357

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<210> 232

45 <211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 232

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EP 1 919 951 B1

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 233

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 233

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 234

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 234

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 40 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 235

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 235

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa cggtacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 236
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 236

10

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cgggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaccgac 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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15

<210> 237
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 237

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cgggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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30

<210> 238
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 238

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

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45

50

<210> 239
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 239

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      tcttgccgtg cgtctgggtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaaacgac 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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10 <210> 240

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 240

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      tcttgccgtg cgtctgggttc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggttaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
25      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 241

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 241

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      tcttgccgtg cgtctcagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cggtgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaccgac 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 242

45 <211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 242

55

EP 1 919 951 B1

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 tcttgccgcg cgtctgggttc tatcttctct aaccactaca tgaattgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta cgggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 243

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 243

20 gaagttcagc tgaccgaatc tgggtgggtggt ctggttcagc cgggtgggttc tctgcgtctg 60
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 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaaccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 244

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 244

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 tcttgccggtg cgtctcagtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

45 <210> 245

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 245

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 tcttgccgcg cgtctgggttc catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

EP 1 919 951 B1

<210> 246
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 246

10

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tcttgccgctg cgtctcagtc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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15

<210> 247
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 247

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tcttgccgctg cgtctcagtc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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30

35

<210> 248
 <211> 357
 <212> DNA
 <213> Artificial Sequence

40

<220>
 <223> Infliximab VH variant

<400> 248

45

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tcttgccgctg cgtctcagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgccgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300

```

50

```

aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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55

<210> 249
 <211> 357
 <212> DNA
 <213> Artificial Sequence

EP 1 919 951 B1

<220>

<223> Infliximab VH variant

<400> 249

5

10

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tcttgccgtg cgtctggttt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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<210> 250

<211> 357

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<212> DNA

<213> Artificial Sequence

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<223> Infliximab VH variant

20

<400> 250

25

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tcttgccgtg cgtctcagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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30

<210> 251

<211> 357

<212> DNA

<213> Artificial Sequence

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<220>

<223> Infliximab VH variant

<400> 251

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45

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tcttgccgtg cgtctggttt caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaaccgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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<210> 252

<211> 357

<212> DNA

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<213> Artificial Sequence

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<223> Infliximab VH variant

55

<400> 252

EP 1 919 951 B1

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tcttgccgctg cgtctcagtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaacctct 240

```

5

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ctgtacctgg aatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctacccc ggaetactgg ggtcagggta ccctgggttac cgtttct 357

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10

<210> 253
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

 <400> 253

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gaagttcagc tggttgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
ctgtacctgg aatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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25

<210> 254
 <211> 357
 <212> DNA
 <213> Artificial Sequence

30

<220>
 <223> Infliximab VH variant

35

<400> 254

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tcttgccgctg cgtctggttt caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaccgac 240
ctgacctctg aatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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40

<210> 255
 <211> 357
 <212> DNA
 <213> Artificial Sequence

45

<220>
 <223> Infliximab VH variant

50

<400> 255

55

EP 1 919 951 B1

5 gaagttcagc tgaccgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccgtg cgtctgggtt cacccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 256

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 256

20 gaagttcagc tgaccgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccgtg cgtctcagtt catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaacgac 240

25 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 257

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35

<400> 257

40 gaagttcagc tgggtgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccgtg cgtctcagtt cacccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 258

45

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

50

<223> Infliximab VH variant

<400> 258

55

EP 1 919 951 B1

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtcgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 259

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 259

20 gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgtg cgtctggttc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtcgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaacctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 260

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 260

35 gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgtg cgtctggttc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtagctct 240

40 ctgtacctgg aaatgaactc tttgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 261

45 <211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 261

55

EP 1 919 951 B1

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 tcttgccgtg cgtctggttc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cggtcgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 262

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 262

20 gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
 tcttgccggtg cgtctggttc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 263

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 263

35 gaagttcagc tggttgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgtg cgtctggttt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

40

<210> 264

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 264

55 gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
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 ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtcgcgacc 180

EP 1 919 951 B1

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cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaataacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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5

<210> 265

<211> 357

<212> DNA

<213> Artificial Sequence

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<220>

<223> Infliximab VH variant

<400> 265

15

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tcttgccgctg cgtctcagtc taccttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggttaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttt atcatctctc gtgacgacaa cggtaacctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaataacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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20

<210> 266

<211> 357

25

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

30

<400> 266

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ccgggttaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta cgggtgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaataacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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35

<210> 267

<211> 357

40

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

45

<400> 267

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ccgggttaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta cgggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaataacta ctgcgcgcgt 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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50

55

<210> 268

<211> 357

EP 1 919 951 B1

<212> DNA

<213> Artificial Sequence

<220>

5 <223> Infliximab VH variant

<400> 268

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 tcttgccgtg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120

15 ccgggttaaag gtctggaatg gatcggtgaa atccgttcta aatccatcaa cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 269

<211> 357

20 <212> DNA

<213> Artificial Sequence

<220>

25 <223> Infliximab VH variant

<400> 269

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 ccgggttaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaaccgac 240
 ctgacctctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

35 <210> 270

<211> 357

<212> DNA

<213> Artificial Sequence

40 <220>

<223> Infliximab VH variant

<400> 270

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 tcttgccgtg cgtctcagtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggttaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaaccgac 240
 ctgacctctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

50 <210> 271

<211> 357

<212> DNA

55 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

EP 1 919 951 B1

<400> 271

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 tcttgccgtg cgtctgggtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cgggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

10 <210> 272

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 272

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25 tcttgccgcgg cgtcacagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcgt 300
 aactactacg gttctactta cgactactgg ggtcagggta ccctgggttac cgtttct 357

30 <210> 273

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

35 <223> Infliximab VH variant

<400> 273

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 tcttgccgtg cgtctgggtt catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cgggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
 aactactacg gttctacctt cgactactgg ggtcagggta ccctgggttac cgtttct 357

45 <210> 274

<211> 357

<212> DNA

<213> Artificial Sequence

50 <220>

<223> Infliximab VH variant

<400> 274

55

EP 1 919 951 B1

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 tcttgccgcg cgtctcagtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaaccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 275

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 275

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 tcttgccgcg cgtctgggtt cacccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactattacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 276

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 276

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 tcttgccgcg cgtctgggtt cacccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 40 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 277

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 277

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 tcttgccgctg cgtctcagtt cacccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

EP 1 919 951 B1

<210> 278
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 278

10

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tcttgccgtg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtcgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtagccgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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15

<210> 279
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 279

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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30

<210> 280
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 280

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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45

50

<210> 281
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 281

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 tcttgctcgtg cgtctgggttc caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtagcgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

10 <210> 282

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 282

20 gaagttcagc tgggtgaatc tgggtgggtggt ctggttcagc cgggtgggttc tctgcgtcta 60
 tcttgccgtg cgtctgggttc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtagctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

30 <210> 283

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 283

40 gaagttcagc tgaccgaatc tgggtgggtggt ctggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccgtg cgtctgggttc taccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaacctct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aattactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

45 <210> 284

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 284

55

EP 1 919 951 B1

5 gaagttcagc tgggtgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgtg cgtctcagtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgaccctgg aaatgaactc tctaaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 285

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 285

20 gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgtg cgtctgggtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 286

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 286

35 gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgtg cgtctgggtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

40 <210> 287

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 287

55 gaagttcagc tgggtgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgcgg cgtctgggtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

EP 1 919 951 B1

<210> 288
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 288

10

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gaagttcagc tgaccgaatc tggtaggtggc ctggttcagc cgggtgggtc tctgcgtctg 60
tcttgccgtg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtcgcacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaccgac 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtaggggta ccctgggttac cgtttct 357

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15

<210> 289
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 289

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gaagttcagc tgggtgaatc tggtaggtggc ctggttcagc cgggtgggtc tctgcgtctg 60
tcttgccgtg cgtctgggtt cacttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggttaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtaggggta ccctgggttac cgtttct 357

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30

<210> 290
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 290

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gaagttcagc tgggtgaatc tggtaggtggc ctggttcagc cgggtgggtc tctgcgtctg 60
tcttgccgtg cgtctgggtt catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtcgcacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaacctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtaggggta ccctgggttac cgtttct 357

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45

50

<210> 291
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 291

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5      gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
      tcttgccgcg cgtctcagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa cggtaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
      aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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10     <210> 292
        <211> 357
        <212> DNA
        <213> Artificial Sequence

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15     <220>
        <223> Infliximab VH variant

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<400> 292

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20      gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
      tcttgccggtg cgtctcagtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
      cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaacgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
25     aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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30     <210> 293
        <211> 357
        <212> DNA
        <213> Artificial Sequence

```

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        <220>
        <223> Infliximab VH variant

```

<400> 293

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40      gaagttcagc tgaccgaatc tgggtggtggt ctgggttcagc cgggtggttc tctgcgtctg 60
      tcttgccgcg cgtctgggtt catcttctct aaccactaca tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa cggtaactct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
      aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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45     <210> 294
        <211> 357
        <212> DNA
        <213> Artificial Sequence

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50     <220>
        <223> Infliximab VH variant

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<400> 294

55

EP 1 919 951 B1

5 gaagttcagc tgggtgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccgcg cgtctcagtt catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cgtgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaaccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 295

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 295

20 gaagttcagc tgaccgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccggtg cgtctcagtc taccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaaccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 296

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 296

35 gaagttcagc tgaccgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccgcg cgtctcagtt caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactatg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

40

<210> 297

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 297

55 gaagttcagc tgggtgaatc tgggtgggtggt ctgggttcagc cgggtgggttc tctgcgtctg 60
 tcttgccggtg cgtctgggttc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 298
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 298

10

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gaagttcagc  tgggtgaatc  tgggtgggtggt  ctgggttcagc  cgggtgggttc  tctgcgtctg  60
tcttgccgctg  cgtctgggttc  tatcttctct  aaccactgga  tgaactgggt  tcgtcaggcg  120
ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcaa  ctctgcgacc  180
tcttacgcgg  aatctgttaa  aggtcggttc  atcatctctc  gtgacgacaa  caaaaccgac  240
ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcag  300
aactactacg  gttctacccc  ggactactgg  ggtcagggta  ccctgggttac  cgtttct  357

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15

<210> 299
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 299

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gaagttcagc  tgaccgaatc  tgggtgggtggt  ctgggttcagc  cgggtgggttc  tctgcgtctg  60
tcttgccgctg  cgtctgggttc  catcttctct  aaccactaca  tgaactgggt  tcgtcaggcg  120
ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcaa  ctctgcgacc  180
cactacgcgg  aatctgttaa  aggtcggttc  atcatctctc  gtgacgacaa  cggtaactct  240
ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
aactactacg  gttctacccc  ggactactgg  ggtcagggta  ccctgggttac  cgtttct  357

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30

<210> 300
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 300

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gaagttcagc  tgggtgaatc  tgggtgggtggt  ctgggttcagc  cgggtgggttc  tctgcgtctg  60
tcttgctcgtg  cgtctgggttc  caccttctct  aaccactgga  tgaactgggt  tcgtcaggcg  120
ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcta  ctctgcgacc  180
cactacgcgg  aatctgttaa  aggtcggttc  atcatctctc  gtgacgacaa  caaaaccgac  240
ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
aactactacg  gttctacccc  ggactactgg  ggtcagggta  ccctgggttac  cgtttct  357

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45

50

<210> 301
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 301

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5      gaagttcagc  tgggtgaatc  tgggtgggtgg  ctgggttcagc  cgggtgggttc  tctgcgtctg  60
      tcttgccgtg  cgtctcagtt  catcttctct  aaccactaca  tgaactgggt  tcgtcaggcg  120
      ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcta  cggtcgcgacc  180
      cactacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  cggtaaccgac  240
      ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
      aactactacg  gttctaccta  cgactactgg  ggtcagggta  ccctgggttac  cgtttct     357

```

10 <210> 302

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 302

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20      gaagttcagc  tgaccgaatc  tgggtgggtgg  ctgggttcagc  cgggtgggttc  tctgcgtctg  60
      tcttgccgtg  cgtctcagtc  taccttctct  aaccactaca  tgaactgggt  tcgtcaggcg  120
      ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatcttctaa  ctctgcgacc  180
      tcttacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  caaaaactct  240
      ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcag  300
25      aactactacg  gttctacccc  ggactactgg  ggtcagggta  ccctgggttac  cgtttct     357

```

<210> 303

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 303

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40      gaagttcagc  tgggtgaatc  tgggtgggtgg  ctgggttcagc  cgggtgggttc  tctgcgtctg  60
      tcttgccgtg  cgtctgggtc  tatcttctct  aaccactaca  tgaactgggt  tcgtcaggcg  120
      ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcaa  ctctgcgacc  180
      cactacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  cggtaacctct  240
      ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcag  300
      aactactacg  gttctaccta  cgactactgg  ggtcagggta  ccctgggttac  cgtttct     357

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<210> 304

45 <211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 304

55

EP 1 919 951 B1

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 tcttgccgcg cgtctcagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cgtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 305

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

15

<400> 305

20 gaagttcagc tgaccgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
 tcttgccgcg cgtctcagtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaacctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 306

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 306

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 tcttgccgcg cgtctcagtt caccttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gttctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctactcc ggactactgg ggtcagggta ccctgggttac cgttttct 357

40 <210> 307

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 307

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 tcttgccgctg cgtctcagtc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta tgggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

EP 1 919 951 B1

<210> 308
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 308

10

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tcttgccgtg cgtctcagtc taccttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

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15

<210> 309
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 309

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tcttgccgcgg cgtctcagtt caccttctct aaccactaca tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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30

<210> 310
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 310

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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50

<210> 311
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 311

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      ccaggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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10 <210> 312

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 312

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20      gaagttcagc tgggtgaatc tgggtggtggt ctggttcagc cgggtggttc tctgcgtctg 60
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      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cagtgcgacc 180
      cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
25      aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 313

<211> 357

<212> DNA

30 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 313

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      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtacctct 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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<210> 314

45 <211> 357

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Infliximab VH variant

<400> 314

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EP 1 919 951 B1

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 ccgggtaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

<210> 315

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

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<400> 315

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 ccgggtaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta cgggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 316

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 316

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 ccgggtaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaacgac 240
 ctgtacctgg aaatgaactc tttgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

40 <210> 317

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 317

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 ccgggtaaag gtctggaatg gatcgggtgaa atccgttcta aatcttctta cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 318
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

<400> 318

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggtta ccctgggttac cgtttct 357

```

15

<210> 319
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

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<400> 319

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300

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30

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aactactacg gttctaccta cgactactgg ggtcagggtta ccctgggttac cgtttct 357

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35

<210> 320
 <211> 357
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 <213> Artificial Sequence

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<400> 320

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcgt 300
aactactacg gttctacccc ggactactgg ggtcagggtta ccctgggttac cgtttct 357

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<210> 321
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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EP 1 919 951 B1

<220>

<223> Infliximab VH variant

<400> 321

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaacgac 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 322

<211> 357

15

<212> DNA

<213> Artificial Sequence

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20

<400> 322

25

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tcttgcgcg cgctcgggtc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtacctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 323

<211> 357

<212> DNA

<213> Artificial Sequence

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<220>

<223> Infliximab VH variant

<400> 323

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240

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45

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ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 324

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

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<223> Infliximab VH variant

<400> 324

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtagcctct 240
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<211> 357

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<213> Artificial Sequence

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<223> Infliximab VH variant

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<400> 325

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtagccgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 326

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<213> Artificial Sequence

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<223> Infliximab VH variant

<400> 326

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

40 <210> 327

<211> 357

<212> DNA

<213> Artificial Sequence

45 <220>

<223> Infliximab VH variant

50 <400> 327

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 tcttgccggtg cgtctcagtc tatcttctct aaccactaca tgaactgggt tcgtcaggcg 120
 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta cggtagcacc 180

EP 1 919 951 B1

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tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaactct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 328
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

<400> 328

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtagctct 240
ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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<400> 329

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtagcacc 180
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<220>
 <223> Infliximab VH variant

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<400> 330

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ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtagctct 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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55

<210> 331
 <211> 357

EP 1 919 951 B1

<212> DNA

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<220>

5 <223> Infliximab VH variant

<400> 331

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15 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
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<211> 357

20 <212> DNA

<213> Artificial Sequence

<220>

25 <223> Infliximab VH variant

<400> 332

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 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

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<213> Artificial Sequence

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<223> Infliximab VH variant

<400> 333

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<211> 357

<212> DNA

<213> Artificial Sequence

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EP 1 919 951 B1

<400> 334

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      tcttgccgcg cgtctgggtt catcttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggcgcgacc 180
      cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaaacgac 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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<211> 357

<212> DNA

<213> Artificial Sequence

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<223> Infliximab VH variant

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25      tcttgccgcg cgtctcagtc tatcttctct aaccactgga tgaactgggt tcgtcaggcg 120
      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
      cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaaccgac 240
      ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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30 <210> 336

<211> 357

<212> DNA

<213> Artificial Sequence

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35 <223> Infliximab VH variant

<400> 336

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      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
      tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cggtaaccgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
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45 <210> 337

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<212> DNA

<213> Artificial Sequence

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<223> Infliximab VH variant

<400> 337

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EP 1 919 951 B1

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 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
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<213> Artificial Sequence

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<400> 338

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaaccgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 339

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 339

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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<210> 340

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 340

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cggtgcgacc 180
 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

EP 1 919 951 B1

<210> 341
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 341

10

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tcttgccgtg  cgtctcagtt  caccttctct  aaccactaca  tgaactgggt  tcgtcaggcg  120
ccgggtaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatcttctaa  cggtcgcgacc  180
tcttacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  cggtaacgac  240
ctgaccctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaataacta  ctgcgcgcgt  300
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<210> 342
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 342

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tcttgccgtg  cgtctcagtc  taccttctct  aaccactaca  tgaactgggt  tcgtcaggcg  120
ccgggtaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatcttctaa  cggtcgcgacc  180
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ctgaccctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaataacta  ctgcgcgcag  300
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30

<210> 343
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
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<400> 343

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ccgggtaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatcttctta  ctctgcgacc  180
tcttacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacgacaa  caaaaactct  240
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50

<210> 344
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 344

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac tgtttct 357

10 <210> 345

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 345

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 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa cgggtacctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

30 <210> 346

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

35 <400> 346

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cgggtgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa caaaaacgac 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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45 <210> 347

<211> 357

<212> DNA

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50 <223> Infliximab VH variant

<400> 347

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EP 1 919 951 B1

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 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa cgggtacctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

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<400> 348

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 ccgggaaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaaacgac 240
 ctgtacctgg aaatgaattc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

25 <210> 349

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 349

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 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa cggtaacgac 240
 ctgtacctgg aaatgaactc tttgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

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<210> 350

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 350

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctta ctctgcgacc 180
 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacggtaa caaaaacgac 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgtttct 357

EP 1 919 951 B1

<210> 351
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

<400> 351

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ccgggtaaa  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcta  ctctgcgacc  180
cactacgcg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacgacaa  caaaaccgac  240
ctgaccctg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcag  300
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<210> 352
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

25

<400> 352

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ccgggtaaa  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcta  ctctgcgacc  180
cactacgcg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  cggtaaccgac  240
ctgtacctg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
aactactac  gttctaccta  cgactactgg  ggtcagggta  ccctgggttac  cgttttct   357

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<210> 353
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 353

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ccgggtaaa  gtctggaatg  gatcggtgaa  atccgttcta  aatcttctta  cgggtgcgacc  180
cactacgcg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  caaaaccgac  240
ctgtacctg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcag  300
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50

<210> 354
 <211> 357
 <212> DNA
 <213> Artificial Sequence

55

<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 354

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      ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatctatcaa  ctctgcgacc  180
      tcttacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacggtaa  caaaaccgac  240
      ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
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10 <210> 355

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 355

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      ccgggtaaaag  gtctggaatg  gatcggtgaa  atccgttcta  aatcttctta  cgggtgcgacc  180
      cactacgcgg  aatctgttaa  aggtcgtttc  atcatctctc  gtgacgacaa  caaaaccgac  240
      ctgaccctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
25      aactactacg  gttctaccta  cgactactgg  ggtcagggta  ccctgggttac  cgtttct     357

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<210> 356

<211> 357

<212> DNA

30 <213> Artificial Sequence

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<223> Infliximab VH variant

35 <400> 356

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      ctgtacctgg  aaatgaactc  tctgaaaacc  gaagacaccg  cggaatacta  ctgcgcgcgt  300
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<210> 357

45 <211> 357

<212> DNA

<213> Artificial Sequence

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50 <223> Infliximab VH variant

<400> 357

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EP 1 919 951 B1

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 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

<210> 358

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Infliximab VH variant

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<400> 358

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 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

25 <210> 359

<211> 357

<212> DNA

<213> Artificial Sequence

30 <220>

<223> Infliximab VH variant

<400> 359

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 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta ctctgcgacc 180
 tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa cggtaactct 240
 ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

40

<210> 360

<211> 357

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Infliximab VH variant

50 <400> 360

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 ccgggtaaaag gtctggaatg gatcgggtgaa atccgttcta aatctatcta cgggtgcgacc 180
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 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cgggaatacta ctgcgcgcag 300
 aactactacg gttctacccc ggactactgg ggtcagggta ccctgggttac cgttttct 357

EP 1 919 951 B1

<210> 361
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Infliximab VH variant

<400> 361

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa caaaaccgac 240
ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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15

<210> 362
 <211> 357
 <212> DNA
 <213> Artificial Sequence

20

<220>
 <223> Infliximab VH variant

25

<400> 362

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa ctctgcgacc 180
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ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
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30

<210> 363
 <211> 357
 <212> DNA
 <213> Artificial Sequence

35

<220>
 <223> Infliximab VH variant

40

<400> 363

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ccgggtaaag gtctggaatg gatcggtgaa atccgttcta aatctatcaa cgggtgcgacc 180
cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaacctct 240
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aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac cgttttct 357

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 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Infliximab VH variant

EP 1 919 951 B1

<400> 364

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 cactacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacggtaa cggtaacgac 240
 ctgtaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
 aactactatg gttctacccc ggactactgg ggtcagggta ccctgggttac cgtttct 357

10 <210> 365

<211> 357

<212> DNA

<213> Artificial Sequence

15 <220>

<223> Infliximab VH variant

<400> 365

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 ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatcttctaa cggtgcgacc 180
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 aactactacg gttctaccta cgactactgg ggtcagggta ccctgggttac ggtttct 357

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<213> Artificial Sequence

<220>

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EP 1 919 951 B1

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EP 1 919 951 B1

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ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
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      ccgggtaaaag gtctggaatg gatcggtgaa atccgttcta aatctatcta cggtgccgacc 180
      tcttacgcgg aatctgttaa aggtcgtttc atcatctctc gtgacgacaa caaaaacgac 240
      ctgtacctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcag 300
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 cactacgcgg aatctgttaa aggtcggttc atcatctctc gtgacgacaa cggtagctct 240
 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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 ctgaccctgg aaatgaactc tctgaaaacc gaagacaccg cggaatacta ctgcgcgcgt 300
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<210> 379

<211> 107

<212> PRT

<213> Mus musculus

<400> 379

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Glu	Arg	Val	Ser	Phe	Ser	Cys	Arg	Ala	Ser	Gln	Phe	Val	Gly	Ser	Ser
			20					25					30		
Ile	His	Trp	Tyr	Gln	Gln	Arg	Thr	Asn	Gly	Ser	Pro	Arg	Leu	Leu	Ile
			35				40					45			
Lys	Tyr	Ala	Ser	Glu	Ser	Met	Ser	Gly	Ile	Pro	Ser	Arg	Phe	Ser	Gly
	50				55				60						
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Ser	Ile	Asn	Thr	Val	Glu	Ser
	65				70				75					80	
Glu	Asp	Ile	Ala	Asp	Tyr	Tyr	Cys	Gln	Gln	Ser	His	Ser	Trp	Pro	Phe
			85					90						95	
Thr	Phe	Gly	Ser	Gly	Thr	Asn	Leu	Glu	Val	Lys					
			100					105							

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 20 25 30
 5 Ile His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
 35 40 45
 Lys Tyr Ala Ser Glu Ser Met Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
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 10 Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Trp Pro Phe
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

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 cgtttctctg gttctggttc tggtaaccgac ttcaccttca ccatctcttc tctggaagcg 240
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 30 ggtaccaaaag ttgacatcaa a 321

<210> 382
 <211> 112
 <212> PRT
 35 <213> Homo sapiens

<400> 382

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 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 20 25 30
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 35 40 45
 45 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 50 55 60
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 65 70 75 80
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 85 90 95
 50 Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
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<210> 383
 <211> 107
 55 <212> PRT
 <213> Homo sapiens

<400> 383

EP 1 919 951 B1

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 1 5 10 15
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 20 25 30
 5 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 35 40 45
 Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 50 55 60
 Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 65 70 75 80
 10 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 85 90 95
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 100 105

15

Patentkrav

- 1.** Antistof der er i stand til at binde til TNF-alfa, hvor antistoffet omfatter:
- (a) et polypeptid omfattende et polypeptid med sekvensen vist i SEQ ID NO: 2; og
 - (b) et polypeptid omfattende et polypeptid med sekvensen vist i SEQ ID NO: 380,
- 5 hvor antistoffet binder TNF-alfa med affinitet større end den for infliximab som bestemt under anvendelse af et Biacore assay, og hvor infliximab V_H-regionen har sekvensen vist i SEQ ID NO: 1 og infliximab V_L-regionen har sekvensen vist i SEQ ID NO: 379.
- 10 **2.** Antistof ifølge 1, hvor polypeptidet ifølge krav 1(a) med sekvensen vist i SEQ ID NO:2 har sekvensen vist i SEQ ID NO: 3.
- 3.** Biologisk aktivt fragment af antistoffet ifølge krav 1 eller krav 2.
- 15 **4.** Cellelinje der udtrykker antistoffet ifølge krav 1 eller krav 2 eller det biologisk aktive fragment ifølge krav 3.
- 5.** Cellelinje omfattende en vektor omfattende et polynukleotid der koder for polypeptidet angivet i krav 1(a) eller krav 2 og en vektor omfattende et polynukleotid der koder for
- 20 polypeptidet angivet i krav 1(b).
- 6.** Cellelinje ifølge krav 5 hvor polynukleotidet der koder for polypeptidet angivet i krav 1 eller krav 2 har sekvensen vist i SEQ ID NO: 191 eller en komplementær sekvens.
- 25 **7.** Cellelinje ifølge krav 5 eller krav 6, hvor polynukleotidet der koder for polypeptidet angivet i krav 1(b) har sekvensen vist i SEQ ID NO: 381 eller en komplementær sekvens.
- 8.** Cellelinjen ifølge et hvilket som helst af kravene 4 til 7 hvor cellelinjen er en HEK293, NSO, SP2/0 eller CHO cellelinje.
- 30 **9.** Farmaceutisk sammensætning omfattende en effektiv mængde af mindst ét antistof ifølge krav 1 eller krav 2 eller af mindst ét biologisk aktivt fragment ifølge krav 3 og en farmaceutisk acceptabel bærer eller diluent.

1/1

C7 V_H
 EVQLVESGGGLVQPGGSLRLSCAASGFIFSNHWMNWVROAPGKGLEWIGEIRSKSINSAT
 Infliximab V_H --K-E-----MK--V-----S-E-----VA-----

 C7 V_H
 HYAESVKGRFIISRDDNKNSLYLEMNSLKTEDTAEYYCARNYYGSTYDYWGQGTTLVTVS
 Infliximab V_H -----T-----S-SAV--Q-TD-R---GV---S-----
 TL---

Figure 1

C7 V_L
 EIVLTQSPDFQSVPKPKVTTITCRASQFVGSSIHWHYQQKPDQSPKLLIKYASEMSGVPS
 Infliximab V_L D-L-----AIL--S-G-R-SFS-----RTNG--R-----
 I--
 C7 V_L RFSGSGSGTDFTFTISSLEAEDAATYYCQQSHSWPFTFCPGTKVDIK
 Infliximab V_L -----LS-NTV-S--I-D-----S--NLEV--

Figure 2

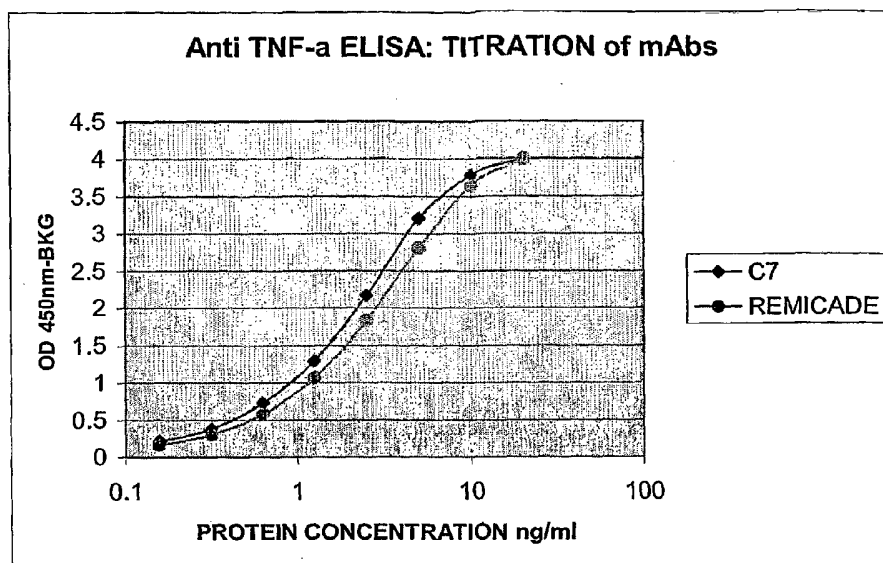


Figure 3