



(11) **EP 1 603 949 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 2 (W2 B1)
Corrections, see
Claims DE 1-4
Claims EN 1-4

(51) Int Cl.:
C07K 16/28 ^(2006.01) **A61K 39/395** ^(2006.01)
A61P 37/00 ^(2006.01) **A61P 37/06** ^(2006.01)

(86) International application number:
PCT/US2004/007444

(48) Corrigendum issued on:
02.02.2011 Bulletin 2011/05

(87) International publication number:
WO 2004/083249 (30.09.2004 Gazette 2004/40)

(45) Date of publication and mention
of the grant of the patent:
27.01.2010 Bulletin 2010/04

(21) Application number: **04720349.2**

(22) Date of filing: **12.03.2004**

(54) **ANTIBODIES AGAINST HUMAN IL-21 RECEPTOR AND USES THEREFOR**

ANTIKÖRPER GEGEN IL21-REZEPTOR UND DEREN VERWENDUNG

ANTICORPS DIRIGES CONTRE LE RECEPTEUR HUMAIN DE L'IL-21 ET UTILISATIONS
CORRESPONDANTES

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IT LI LU MC NL PL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

- **VALGE-ARCHER, Viia**
Cambridge CB1 6BE (GB)
- **COLLINS, Mary**
Natick, MA 01760 (US)
- **WILLIAMS, Andrew James**
Herts, SG8 7TG (GB)
- **WITEK, Joanne**
Acton, MA 01720 (US)

(30) Priority: **14.03.2003 US 454336 P**

(43) Date of publication of application:
14.12.2005 Bulletin 2005/50

(60) Divisional application:
09178337.3 / 2 184 298

(73) Proprietors:

- **Wyeth LLC**
Madison, NJ 07940 (US)
- **MedImmune Limited**
Cambridge
CB21 6GH (GB)

(74) Representative: **Körfer, Thomas**
Mitscherlich & Partner
Patent- und Rechtsanwälte
Postfach 33 06 09
80066 München (DE)

(72) Inventors:

- **YOUNG, Deborah, A.**
Melrose, MA 02176 (US)
- **WHITTERS, Matthew, J.**
Hudson, MA 01749 (US)

(56) References cited:
WO-A-01/77171 WO-A-01/85792
WO-A-03/028630 US-A1- 2002 128 446
US-A1- 2003 148 447

- **COLLINS MARY ET AL: "IL-21 and IL-21 receptor:
A new cytokine pathway modulates innate and
adaptive immunity." IMMUNOLOGIC
RESEARCH, vol. 28, no. 2, 2003, pages 131-140,
XP009036147 ISSN: 0257-277X**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 603 949 B9

Description**TECHNICAL FIELD**

[0001] This invention relates to antibodies, e.g., human antibodies, and antigen-binding fragments thereof that bind the interleukin-21 (IL-21) receptor, in particular, the human IL-21 receptor, and their use in regulating immune responses mediated by the IL-21 receptor. The antibodies disclosed herein are useful in diagnosing, preventing, and/or treating immune disorders, e.g., autoimmune disorders.

BACKGROUND OF THE INVENTION

[0002] Antigens initiate immune responses and activate the two largest populations of lymphocytes: T cells and B cells. After encountering antigen, T cells proliferate and differentiate into effector cells, while B cells proliferate and differentiate into antibody-secreting plasma cells. Proliferation and differentiation of lymphocytes are regulated by extracellular proteins. Some of these proteins are called cytokines, which are small proteins (<30 kDa) secreted by lymphocytes and other cell types.

[0003] Interleukin-21 (IL-21) is a recently discovered cytokine, which is closely related to IL-2, IL-4 and IL-15 (Parrish-Novak et al. (2000) Nature 408:57-63). Human IL-21 has a molecular weight of about 15 kDa, consists of 131 amino acids, and shares about 57% identity with mouse IL-21. IL-21 is produced primarily by activated CD4⁺ T cells.

[0004] IL-21 receptor (IL-21 R) is a transmembrane, IL-21-binding protein that belongs to the class I cytokine receptor family. Both human and mouse IL-21 R have been described in WO 01/85792, herein incorporated by reference. The predicted size of human IL-21 R is about 529 amino acids. IL-21R shows high sequence homology to IL-2 receptor β chain and IL-4 receptor α chain (Ozaki et al. (2000) Proc. Natl. Acad. Sci. USA 97:11439-11444). The human and mouse IL-21R amino acid sequences share about 62% identity. Upon ligand binding, IL-21R associates with the common gamma cytokine receptor chain (γ_c) that is shared by receptors for IL-2, IL-3, IL-4, IL-7, IL-9, IL-13 and IL-15 (Ozaki et al. (2000) *supra*; Asao et al. (2001) J. Immunol. 167:1-5).

[0005] IL-21 R. is expressed primarily in lymphoid tissues, such as B cells, T cells, and natural killer (NK) cells. The widespread lymphoid distribution of IL-21 R suggests that IL-21 may play a role in immune regulation. Indeed, *in vitro* studies have shown that IL-21 significantly modulates the function of B cells, CD4⁺ and CD8⁺ T cells, and NK cells (Parrish-Novak et al. (2000) *supra*; Kasaian, M.T. et al. (2002) Immunity. 16:559-569). IL-21 and IL-21 R have also been shown to be important for modulating the activity of macrophages, and synovial cells. For example, IL-21 augments the proliferation of B cells stimulated with anti-CD40 antibody, and suppresses the proliferation of B cells stimulated with anti-IgM and IL-4. IL-21 augments the proliferation and cytolytic activity of T cells and human NK cells. IL-21 also mediates the expression of cytokines, chemokines, or combination thereof, secreted by T cells, NK cells, macrophages, and synovial cells. Because of the dependence of B cells, T cells, NK cells, macrophages, and synovial cells on IL-21, altering IL-21 binding to IL-21 R may affect certain immune responses. Such a manipulation provides a means for treating immune system disorders, such as autoimmune disease disorders, inflammatory disorders, allergies, transplant rejection, cancer, immune deficiency, and other disorders.

WO 01/77171 A1 describes anti-zalpa 11 antibodies having uiluitiming activity (zalpa 11 antagonists). Said antibodies are used for the detertion of the zalpa receptor distribution or various cells.

US 200210128446 A1) disclosed anti-zalpa 11 antibodies used within methods for stimulating the proliferation and/or development of hematoporedic cells.

SUMMARY OF THE INVENTION

[0006] The present application provides antibodies that antagonizes IL-21R activity as defined in claim 1 with high affinity and specificity. The antibody reduces, inhibits or antagonizes IL-21 R activity. Such antibodies can be used to regulate immune responses or immune cell-associated disorders by antagonizing IL-21R activity. In other embodiments, an anti-IL-21R antibody can be used diagnostically, or as a targeting antibody to deliver a therapeutic or a cytotoxic agent to an IL-21 R-expressing cell. Thus, anti-IL-21 R antibodies of the invention are useful in diagnosing and treating immune cell-associated pathologies (e.g., pathologies associated with activity of at least one of: T cells (CD8⁺, CD4⁺ T cells), NK cells, B cells, macrophages and megakaryocytes, including transplant rejection and autoimmune disorders).

[0007] Accordingly, in one aspect, the invention features an isolated antibody that binds to IL-21R as set out in claim 1. An anti-IL-21R antibody may have at least one of the following characteristics: (1) it is a monoclonal or single specificity antibody; (2) it is a human or *in vitro* generated antibody; (3) it binds to IL-21 R, in particular, the extracellular domain of human IL-21R, with an affinity constant (K_a) of at least 10^6 M⁻¹; and (4) it inhibits binding of IL-21 to IL-21R with an IC₅₀ of 10 nM or less as an IgG, for example, as measured by a cell-based assay described in Example 9, or it inhibits the binding of an antibody to IL-21 R with an IC₅₀ of 10 nM or less, for example, as measured by an epitope binding

assay described in Example 11.

[0008] Nonlimiting illustrative embodiments of the antibodies of the invention are referred to herein as "MUF", "MUF-germline", "MU11", "18G4", "18A5", "19F5", "CP5G2" and "R18." The antibodies of the invention specifically bind to the extracellular domain of an IL-21 R, e.g., about amino acid 20 to 235 of SEQ ID NO:43 (human IL-21 R), or a sequence that is at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto. The antibodies specifically bind to a fragment of an IL-21 R, e.g., a fragment of at least 10, 20, 50, 75, 100, 150, or 200 amino acids contiguous to the amino acid sequence set forth in SEQ ID NO:43, or a sequence that is at least 95%, 96%, 97%, 98%, 99% or more identical thereto. The antibody binds to the extracellular domain of an IL-21 R and competitively inhibits binding of "MUF", "MUF-germline", "MU11", "18G4", "18A5", "19F5", "CP5G2" or "R18" to its target epitope. In yet other embodiments, an antibody binds to the extracellular domain of an IL-21 R and competitively inhibits binding of IL-21 to IL-21 R. Such an inhibition of binding of IL-21 to its receptor by an antibody of the invention can be measured by one or more assays provided herein.

[0009] In one embodiment, an antibody of the present invention includes a V_H domain, and a V_L domain, or the scFv fragment of "MUF", "MUF-germline", "MU11", "18G4", "18A5", "19F5", "CP5G2" or "R18". For example, an antibody includes a V_H and/or a V_L domain having amino acid sequence as set forth in Tables 1A and 1B (SEQ ID NO:1, 19, 47, 65, 83, 101, 119 or 137 for V_H and SEQ ID NO:2, 20, 48, 66, 84, 102, 120 or 138 for V_L), or a sequence substantially identical thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10 or 15 amino acid residues from SEQ ID NO:1, 2, 19, 20, 47, 48, 65, 66, 83, 84, 101, 102, 119, 120, 137 or 138). In another embodiment, the antibody includes a V_H and V_L domain encoded by a nucleic acid having a nucleotide sequence as set forth in Tables 1A and 1B (SEQ ID NO:10, 28, 56, 74, 92, 110, 128, or 146 for V_H and SEQ ID NO:11, 29, 57, 75, 93, 111, 129, or 147 for V_L), or a sequence substantially identical thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30 or 45 nucleotides from SEQ ID NO:10, 11, 28, 29, 56, 57, 74, 75, 92, 93, 110, 111, 128, 129, 146 or 147). Typically, the V_H and V_L domains in a scFv fragment are linked by a linker sequence.

[0010] In other embodiments, the antibody includes an scFv domain having an amino acid sequence as set forth in Tables 1A and 1B (SEQ ID NO:3, 21, 49, 67, 85, 103, 121, or 139) or a sequence substantially identical thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, 15, 20, 30 or 35 amino acid residues from SEQ ID NO:3, 21, 49, 67, 85, 103, 121, or 139). In another embodiment, the antibody includes an scFv domain encoded by a nucleic acid having a nucleotide sequence as set forth in Tables 1A and 1B (SEQ ID NO:12, 30, 58, 76, 94, 112, 130, or 148), or a sequence substantially identical thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, 45, 60, 90 or 105 nucleotides from SEQ ID NO:12, 30, 58, 76, 94, 112, 130, or 148). Disclosed is also an antibody comprising at least one complementarity determining region (CDR) of these V_H and V_L domains. For example, the antibody can include one, two, or three CDR's of the V_H domain (i.e., H1, H2, and H3) having an amino acid sequence as set forth in Tables 1A and 1B (SEQ ID NO:4, 5, 6, 22, 23, 24, 50, 51, 52, 68, 69, 70, 86, 87, 88, 104, 105, 106, 122, 123, 124, 140, 141, or 142), or a sequence substantially homologous thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto). Disclosed is also, a sequence that is substantially homologous to the H1, H2, or H3 amino acid sequences set forth in SEQ ID NO:4, 5, 6, 22, 23, 24, 50, 51, 52, 68, 69, 70, 86, 87, 88, 104, 105, 106, 122, 123, 124, 140, 141, or 142 includes one or more amino acid substitutions, for example, one or more conservative amino acid substitutions. The antibody can include one, two, or three CDR's of the V_L domain (i.e., L1, L2 and L3) having an amino acid sequence as set forth in Tables 1A and 1B (SEQ ID NO:7, 8, 9, 25, 26, 27, 53, 54, 55, 71, 72, 73, 89, 90, 91, 107, 108, 109, 125, 126, 127, 143, 144, or 145), or a sequence substantially identical thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto). Disclosed is also, a sequence that is substantially homologous to the L1, L2, or L3 amino acid sequences set forth in SEQ ID NO:7, 8, 9, 25, 26, 27, 53, 54, 55, 71, 72, 73, 89, 90, 91, 107, 108, 109, 125, 126, 127, 143, 144 or 145 includes one or more amino acid substitutions, for example, one or more conservative amino acid substitutions.

[0011] Disclosed is also, an antibody comprises a CDR of the V_H domain of MUF, MU11, MUF-germline, 18G4, 18A5, 19F5, CP5G2, or R18, having the amino acid sequence set forth in Tables 1A and 1B (SEQ ID NO:6, 24, 52, 70, 88, 106, 124, or 142), or a sequence substantially identical thereto (e.g., a sequence at least about 95%, 96%, 97%, 98%, 99% or more identical thereto), which includes one or more amino acid substitutions, for example, one or more conservative amino acid substitutions. The antibody may either comprise a heavy chain variable region including a single CDR, such as H3, or any combinations of H1, H2 and H3. For example, an antibody may include CDR (H3) in combination with CDR2 (H2). An antibody may include a CDR3 (H3) in combination with a CDR1 (H1), or a combination of H1 and H2 CDRs. However, preferably, an antibody includes a heavy chain variable region comprising a CDR3 (H3), as set forth in any of SEQ ID NO:6, 24, 52, 70, 88, 106, 124, 142, and amino acid substitutions thereof, for example, one or more conservative amino acid substitutions, either alone or in combination with one or both of H1 and H2.

[0012] Similarly, disclosed is also, an antibody comprising a CDR of the V_L domain of MUF, MU11, MUF-germline, 18G4, 18A5, 19F5, CP5G2, or R18, e.g., an L3 CDR having the amino acid sequence as set forth in Tables 1A and 1B (SEQ. ID NO:9, 27, 55, 73, 91, 109, 127, or 145), or a sequence substantially identical thereto (e.g., a sequence at least

about 95%, 96%, 97%, 98%, 99% or more identical thereto), which includes one or more amino acid substitutions, for example, one or more conservative amino acid substitutions. An antibody may either comprise a light chain variable region including a single CDR, such as L3, or any combinations of L1, L2 and L3. For example, an antibody may include an L3 in combination with an L2. An antibody may include an L3 in combination with an L1. In yet, an antibody may include a combination of L1 and L2 CDRs. However, preferably, an antibody includes a light chain variable region comprising an L3, as set forth in any of SEQ ID NO:9, 27, 55, 73, 91, 109, 127, 145 and amino acid substitutions thereof, for example, one or more conservative amino acid substitutions thereof, either alone or in combination with one or both of L1 and L2.

[0013] An antibody competes for IL-21 R binding with an antibody which includes a V_H domain which is at least 95%, 96%, 97%, 98%, 99%, or more than 99% identical to an amino acid sequence set forth in SEQ ID NO:1, 19, 47, 65, 83, 101, 119 or 137, and a V_L domain which is at least 95%, 96%, 97%, 98%, 99%, or more than 99% identical to an amino acid sequence set forth in SEQ ID NO:2, 20, 48, 66, 84, 102, 120 or 138. An antibody competes for IL-21 R binding with an antibody that includes a heavy chain variable region comprising at least one heavy chain CDR chosen from SEQ ID NO:6, 24, 52, 70, 88, 106, 124, 142 and amino acid substitutions thereof, for example, one or more conservative amino acid substitutions thereof. An antibody competes for IL-21 R binding, for example, human IL-21 R binding, with an antibody that includes a light chain variable region comprising at least one light chain CDR chosen from SEQ ID NO:9, 27, 55, 73, 91, 109, 127, 145 and amino acid substitutions thereof, for example, one or more conservative amino acid substitutions thereof. An antibody with which an antibody of the invention competes for binding to IL-21 R, for example, human IL-21 R, may include both a heavy chain CDR chosen from SEQ ID NO:6, 24, 52, 70, 88, 106, 124, and 142, and a light chain CDR chosen from SEQ ID NO:9, 27, 55, 73, 91, 109, 127, and 145. An antibody includes more than one heavy chain CDR chosen from SEQ ID NO:4, 5, 6 for MUF; SEQ ID NO:22, 23, 24 for MU11; SEQ ID NO:50, 51, 52 for 18G4; SEQ ID NO:68, 69, 70 for 18A5; SEQ ID NO:86, 87, 88 for MUF-germline; SEQ ID NO:104, 105, 106 for 19F5; SEQ ID NO:122,123,124 for CP5G2; and SEQ ID NO:140, 141, 142 for R18, and/or one or more light chain variable region CDR chosen from SEQ ID NO:7, 8, 9 for MUF; SEQ ID NO:25, 26, 27 for MU11; SEQ ID NO:53, 54, 55 for 18G4; SEQ ID NO:71, 72, 73 for 18A5; SEQ ID NO:89, 90, 91 for MUF-germline; SEQ ID NO:107, 108, 109 for 19F5; SEQ ID NO:125, 126, 127 for CP5G2; and SEQ ID NO:143, 144, 145 for R18.

[0014] In yet other embodiments, an antibody according to the invention competes with IL-21, for example, human IL-21, for binding to IL-21R, for example, human IL-21 R.

[0015] An antibody of the invention can be full-length (e.g., include at least one complete heavy chain and at least one complete light chain) or can include only an antigen-binding fragment (e.g., a Fab, $F(ab')_2$, Fv or a single chain Fv fragment (scFv)). An antibody can include a constant region, or a portion thereof, chosen from any of: the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes. For example, heavy chain constant regions of the various isotypes can be used, including: IgG₁, IgG₂, IgG₃, IgG₄, IgM, IgA₁, IgA₂, IgD, and IgE. The light chain constant region can be chosen from kappa or lambda. An antibody may be an IgG, or it may also be IgG_{1κ} or IgG_{1λ}.

[0016] An anti-IL-21 R antibody described herein can be derivatized or linked to another functional molecule (such as another peptide or protein (e.g., a Fab fragment)). For example, an antibody of the invention can be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to at least one other molecular entity, such as another antibody (e.g., a bispecific or a multispecific antibody), toxin, radioisotope, cytotoxic or cytostatic agent, among others.

[0017] in another aspect, the invention features a pharmaceutical composition containing at least one anti-IL-21 R antibody and a pharmaceutically acceptable carrier. The pharmaceutical composition can further include a combination of at least one anti-IL-21R antibody and at least one therapeutic agent (e.g., cytokine and growth factor inhibitors, immunosuppressants, anti-inflammatory agents, metabolic inhibitors, enzyme inhibitors, cytotoxic agents, cytostatic agents, or combinations thereof, as described in more detail herein). Combinations of the anti-IL-21 R antibody and a therapeutic agent are also within the scope of the invention. The compositions and combinations of the invention can be used to regulate IL-21-dependent immune cells, such as B cells, T cells, NK cells, macrophages, and synovial cells.

[0018] In another aspect, the invention features an antibody according to the invention for manufacture of a medicament for treating an immune cell-associated disease as defined in claim 21. The use includes administering to the subject an anti-IL-21 R antibody in an amount sufficient to inhibit at least one IL-21 R activity of immune cells, thereby treating the immune cell-associated disease.

[0019] The anti-IL-21 R antibody can be administered to the subject, alone or in combination, with other therapeutic agents as described herein. The subject may be a mammal suffering from an immune cell-associated pathology (e.g., pathology associated with the aberrant activity of at least one of: T cells, NK cells, B cells, macrophages and megakaryocytes). The subject may be human. For example, the antibody can be used to treat a subject with an immune cell-associated disorder such as transplant rejection and autoimmune disease. Autoimmune diseases may include diabetes mellitus (type I), arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and ankylosing spondylitis), multiple sclerosis, myasthenia gravis, vasculitis, systemic lupus erythematosus, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, scleroderma, asthma, allergy,

inflammatory bowel disease (IBD), and Crohn's disease. Treatment of an arthritic disorder (e.g., a disorder chosen from at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and ankylosing spondylitis) using the anti-IL-21 R antibodies of the present invention is an embodiment of the invention.

[0020] The antibodies of the invention may be used for detecting the presence of IL-21R in a sample, *in vitro*. Samples may include biological samples such as serum, plasma, tissue and biopsy. The antibodies can be used to diagnose a disorder, such as an immune cell-associated disorder as described herein by (1) contacting the sample with an anti-IL-21 R antibody, and (2) detecting formation of a complex between the anti-IL-21 R antibody and the sample or the control sample, wherein a statistically significant change in the formation of the complex in the sample relative to a control sample, is indicative of the presence of the IL-21 R in the sample.

[0021] The antibodies of the invention may be used for detecting the presence of IL-21R *in vivo* (e.g., *in vivo* imaging in a subject) to diagnose a disorder, e.g., an immune cell-associated disorder as described herein by (1) administering an anti-IL-21R antibody to a subject or a control subject under conditions that allow binding of the antibody to IL-21 R, and (2) detecting formation of a complex between the antibody and IL-21 R, wherein a statistically significant change in the formation of the complex in the subject relative to a control, e.g., a control subject, is indicative of the presence of IL-21R.

[0022] An antibody according to the invention may be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials.

[0023] The antibodies of the invention may be used for delivering or targeting an agent, e.g., a therapeutic or a cytotoxic agent, to an IL-21 R-expressing cell *in vivo* by administering an anti-IL-21 R antibody to a subject under conditions that allow binding of the antibody to IL-21 R. The antibody may be coupled to a second therapeutic moiety, such as a toxin.

[0024] The disclosure provides nucleic acid sequences from the V_H and V_L domains of MUF, MUF-germline, MU11, 18G4, 18A5, 19F5, CP5G2 and R18. Also provided are nucleic acid sequences that comprise at least one CDR from MUF, MUF-germline, MU11, 18G4, 18A5, 19F5, CP5G2 and R18. The disclosure also provides vectors and host cells comprising such nucleic acids.

[0025] The disclosure further provides methods of producing new V_H and V_L domains and functional antibodies comprising all or a portion of such domains derived from the V_H or V_L domains of MUF, MUF-germline, MU11, 18G4, 18A5, 19F5, CP5G2 or R18.

[0026] Additional aspects of the disclosure will be set forth in part in the description, and in part will be obvious from the description, or may be learned by practicing the invention. The invention is set forth and particularly pointed out in the claims, and the disclosure should not be construed as limiting the scope of the claims. The following detailed description includes exemplary representations of various embodiments of the invention, which are not restrictive of the invention as claimed. The accompanying figures constitute a part of this specification and, together with the description, serve only to illustrate embodiments and not limit the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0027] Figure 1A depicts the result of an ELISA which shows that MU11 specifically bind to human IL-21 R.

[0028] Figure 1B depicts the result of a binding assay analyzed by FACS which shows that both MUF and MU11 bind on the surface of human IL-21 R.

[0029] Figure 1C depicts the result of a binding assay analyzed by FACS which shows that MUF binds IL-21 R on mouse B cells.

[0030] Figure 2 depicts the result of an ELISA which shows that MUF inhibits the binding of human IL-21 to human IL-21 R.

[0031] Figure 3A depicts the result of a cell-proliferation assay which shows that addition of MUF blocked the ability of IL-21 to increase the proliferation of human CD4+ T cells.

[0032] Figure 3B depicts the result of a cell-proliferation assay which shows that MU11 blocked the ability of IL-21 in COS cell culture media to increase the proliferation of mouse CD4+ T cells.

[0033] Figure 3C depicts the result of a cell-proliferation assay which shows that MU11 blocked the ability of IL-21 in COS cell culture media to increase the proliferation of mouse CD8+ T cells, in a dose-dependent manner.

[0034] Figure 4 depicts the result of a cell-proliferation assay which shows that both MUF scFv and MUF IgG blocked the ability of IL-21 to increase the proliferation of Baf3Mu-1 cells which express an IL-21 R.

[0035] Figures 5A depicts that addition of IL-21 to human fibroblast-like synoviocytes isolated from arthritis patients leads to an increase in the secretion of chemokines MCP-1 and GRO.

[0036] Figure 5B depicts that addition of IL-21 to human fibroblast-like synoviocytes isolated from arthritis patients leads to an increase in the secretion of chemokines 1-309, TARC, Eotaxin, MDC, Lymph, SDF1B, IP-10, I-TAC, MG and MP3B.

[0037] Figures 5C and 5D depict that addition of IL-21 to human fibroblast-like synoviocytes isolated from arthritis

patients leads to an increase in the secretion of cytokines IFN-alpha and TNF-alpha (FIG. 5C) and IL-6 and IL8 (FIG. 5D).

[0038] Figure 5E shows that IL-21 exacerbates collagen induced arthritis (CIA) in a mouse model for arthritis, as measured by the indicia for CIA.

[0039] Figure 6 shows that IL-21 increases the proliferation of C57BU6J cells in a mixed lymphocyte reaction, an *in vitro* model for transplant rejection.

DETAILED DESCRIPTION

Definitions

[0040] In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

[0041] The **"antibody"** refers to an immunoglobulin or fragment thereof, and encompasses any polypeptide comprising an antigen-binding site. The term is not limited to polyclonal, monoclonal, monospecific, polyspecific, non-specific, humanized, human, single-chain, chimeric, synthetic, recombinant, hybrid, mutated, grafted, and *in vitro* generated antibodies. Unless preceded by the word "intact," the term "antibody" includes antibody fragments such as Fab, F(ab')₂, Fv, scFv, Fd, dAb, and other antibody fragments that retain antigen-binding function. Typically, such fragments would comprise an antigen-binding domain.

[0042] The terms **"antigen-binding domain"** and **"antigen-binding fragment"** refer to a part of an antibody molecule that comprises amino acids responsible for the specific binding between antibody and antigen. The part of the antigen that is specifically recognized and bound by the antibody is referred to as the "epitope." An antigen-binding domain may comprise an antibody light chain variable region (V_L) and an antibody heavy chain variable region (V_H); however, it does not have to comprise both. Fd fragments, for example, have two V_H regions and often retain some antigen-binding function of the intact antigen-binding domain. Examples of antigen-binding fragments of an antibody include (1) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_H1 domains; (2) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (3) a Fd fragment consisting of the two V_H and C_H1 domains; (4) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (5) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (6) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0043] The term **"effective amount"** refers to a dosage or amount that is sufficient to regulate IL-21 R activity to ameliorate clinical symptoms or achieve a desired biological outcome, e.g., decreased T cell and/or B cell activity, suppression of autoimmunity, suppression of transplant rejection, etc.

[0044] The term **"human antibody"** includes antibodies having variable and constant regions corresponding substantially to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat, et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs, and in particular, CDR3. The human antibody can have at least one, two, three, four, five, or more positions replaced with an amino acid residue that is not encoded by the human germline immunoglobulin sequence.

[0045] The term **"IL-21R activity"** refers to at least one cellular process initiated or interrupted as a result of IL-21 binding to IL-21 R on the cell. IL-21 R activities include at least one of, but are not limited to: (1) binding IL-21 (e.g., human IL-21); (2) associating with signal transduction molecules (e.g., γ c and/or JAK-1); (3) stimulating phosphorylation of STAT proteins (e.g., STAT5, STAT3, or combination thereof); (4) activating STAT proteins; and (5) modulating (e.g., increasing or decreasing) proliferation, differentiation, effector cell function, cytolytic activity, cytokine secretion, survival, or combinations thereof, of immune cells. Immune cells may include CD8+ and CD4+ T cells, NK cells, B cells, macrophages, and megakaryocytes. IL-21 R activity can be determined *in vitro*, for example, using T cell proliferation assays as described in Examples 8 and 9. IL-21R activity can also be determined *in vivo*, for example, by scoring progression of an immune response or disorder as described in Example 12.

[0046] The phrase **"inhibit"** or **"antagonize"** IL-21R activity and its cognates refer to a reduction, inhibition, or otherwise diminution of at least one activity of IL-21 R due to binding an anti-IL-21 R antibody, wherein the reduction is relative to the activity of IL-21 R in the absence of the same antibody. The activity can be measured as described in Examples 7, 8, 9 and 11. Inhibition or antagonism does not necessarily indicate a total elimination of the IL-21 R polypeptide biological

activity. A reduction in activity may be about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more.

[0047] The term "**interleukin-21 receptor**" or "**IL-21R**" refers to a class I cytokine receptor, also known as NILR (WO 01/85792; Parrish-Novak et al. (2000) Nature 408:57-63; Ozaki et al. (2000) Proc. Natl. Acad. Sci. USA 97:11439-11444). Upon ligand binding, IL-21 R interacts with a common γ cytokine receptor chain (γ_c) (Asao et al. (2001) J. Immunol. 167: 1-5), and induces the phosphorylation of STAT1 and STAT3 (Asao et al. (2001) *supra* or STAT5 (Ozaki et al. (2000) *supra*). IL-21 R shows widespread lymphoid tissue distribution. The term "IL-21R" refers to a receptor (which may be mammalian) which is capable of binding to IL-21, and has at least one of the following features: (1) an amino acid sequence of a naturally occurring mammalian IL-21 R polypeptide or a fragment thereof, e.g., an amino acid sequence shown as SEQ ID NO:43 (human) or SEQ ID NO:45 (murine) or a fragment thereof; (2) an amino acid sequence substantially identical to, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to, an amino acid sequence shown as SEQ ID NO:43 (human) or SEQ ID NO:45 (murine) or a fragment thereof; (3) an amino acid sequence which is encoded by a naturally occurring mammalian IL-21 R nucleotide sequence or a fragment thereof (e.g., SEQ ID NO: 44 (human) or SEQ ID NO:46 (murine) or a fragment thereof); (4) an amino acid sequence encoded by a nucleotide sequence which is substantially identical to, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to, a nucleotide sequence shown as SEQ ID NO:44 (human) or SEQ ID NO:46 (murine) or a fragment thereof; (5) an amino acid sequence encoded by a nucleotide sequence degenerate to a naturally occurring IL-21 R nucleotide sequence or a fragment thereof, e.g., SEQ ID NO:44 (human) or SEQ ID NO:46 (murine) or a fragment thereof; or (6) a nucleotide sequence that hybridizes to one of the foregoing nucleotide sequences under stringent conditions, e.g., highly stringent conditions. The IL-21R may bind to IL-21 of mammalian origin, e.g., human or mouse. (Parrish-Novak et al. (2000) *supra*).

[0048] As used herein, "**in vitro generated antibody**" refers to an antibody where all or part of the variable region (e.g., at least one CDR) is generated in a non-immune cell selection (e.g., an *in vitro* phage display, protein chip or any other method in which candidate sequences can be tested for their ability to bind to an antigen). This term excludes sequences generated by genomic rearrangement in an immune cell.

[0049] The term "**isolated**" refers to a molecule that is substantially free of its natural environment. For instance, an isolated protein is substantially free of cellular material or other proteins from the cell or tissue source from which it was derived. The term also refers to preparations where the isolated protein is sufficiently pure for pharmaceutical compositions; or at least 70-80% (w/w) pure; or at least 80-90% (w/w) pure; or at least 90-95% pure; or at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

[0050] The nucleotide sequence and the predicted amino acid sequence of human IL-21R are shown in SEQ ID NO: 44 and SEQ ID NO:43, respectively. Analysis of the human IL-21R amino acid sequence (SEQ ID NO:43) revealed the following structural features: a leader sequence (about amino acids 1-19 of SEQ ID NO:43); a WSXWS motif (about amino acids 213-217 of SEQ ID NO:43); a transmembrane domain (about amino acids 236-252 of SEQ ID NO:43); an extracellular domain (about amino acids 1-235 of SEQ ID NO:43 and about 20-235 of the mature IL-21R sequence); and an intracellular domain from about amino acids 253-538 of SEQ ID NO:43. The mature human IL-21R is believed to have the sequence of amino acids 20-538 of SEQ ID NO:43.

[0051] The term "**repertoire**" refers to a genetically diverse collection of nucleotide sequences derived wholly or partially from sequences encoding immunoglobulins. The sequences may be generated by rearrangement *in vivo* of the V, D, and J segments of heavy chains, and the V and J segments of light chains. Alternatively, the sequences can be generated from a cell in response to which rearrangement occurs, e.g., *in vitro* stimulation. Alternatively, part or all of the sequences may be obtained by DNA splicing, nucleotide synthesis, mutagenesis, and other methods, see, e.g., U.S. Patent 5,565,332.

[0052] The terms "**specific binding**", "**selective binding**" and "**selectively binds**" refer to two molecules forming a complex that is relatively stable under physiologic conditions. Selective binding is characterized by a high affinity and a low to moderate capacity as distinguished from nonspecific binding which usually has a low affinity with a moderate to high capacity. Typically, binding is considered specific or selective when the affinity constant K_a is higher than $10^6 \cdot M^{-1}$. If necessary, nonspecific binding can be reduced without substantially affecting selective binding by varying the binding conditions. The appropriate binding conditions, such as concentration of antibodies, ionic strength of the solution, temperature, time allowed for binding, concentration of a blocking agent (e.g., serum albumin, milk casein), etc., may be optimized by a skilled artisan using routine techniques. Illustrative conditions are set forth in Examples 1-11, but other conditions known to the person of ordinary skill in the art fall within the scope of this invention.

[0053] As used herein, the term "**stringent**" describes conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in that reference and either can be used. One example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by at least one wash in 0.2X SSC, 0.1 % SDS at 50°C. A second example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1 % SDS at 55°C. Another example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1 % SDS at 60°C. A further example of stringent hybridization conditions is hybridization in 6X

SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1 % SDS at 65°C. High stringent conditions include hybridization in 0.5 M sodium phosphate, 7% SDS at 65°C, followed by at least one wash at 0.2X SSC, 1 % SDS at 65°C.

[0054] The phrase **"substantially as set out," "substantially identical"** or **"substantially homologous"** means that the relevant amino acid or nucleotide sequence. (e.g., CDR(s), V_H, or V_L domain) will be identical to or have insubstantial differences (through conserved amino acid substitutions) in comparison to the sequences which are set out. Insubstantial differences include minor amino acid changes, such as 1 or 2 substitutions in a 5 amino acid sequence of a specified region. In the case of antibodies, the second antibody has the same specificity and has at least 50% of the affinity of the same.

[0055] Sequences substantially identical or homologous (e.g., at least about 85% sequence identity) to the sequences disclosed herein are also part of this application. The sequence identity can be about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher. Alternatively, substantial identity or homology exists when the nucleic acid segments will hybridize under selective hybridization conditions (e.g., highly stringent hybridization conditions), to the complement of the strand. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form.

[0056] The percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Tool (BLAST) described by Altschul et al. ((1990) J. Mol. Biol., 215: 403-410); the algorithm of Needleman et al. ((1970) J. Mol. Biol., 48: 444-453); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci., 4: 11-17). A set of parameters may be the Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[0057] The term **"therapeutic agent"** is a substance that treats or assists in treating a medical disorder. As used herein, a therapeutic agent refers to a substance, when administered to a subject with anti-IL-21R antibody, provides a better treatment compared to administration of the therapeutic agent or anti-IL-21R antibody alone. These therapeutic agents may include, but are not limited to, substances that modulate immune cells or immune responses in a manner that complements the IL-21R activity of anti-IL-21R antibodies. Non-limiting examples and uses of therapeutic agents are described herein.

[0058] As used herein, a **"therapeutically effective amount"** of an anti-IL-21R antibody refers to an amount of an antibody which is effective, upon single or multiple dose administration to a subject (such as a human patient) at treating, preventing, curing, delaying, reducing the severity of, ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the subject beyond that expected in the absence of such treatment.

[0059] The term **"treatment"** refers to a therapeutic or preventative measure. The treatment may be administered to a subject having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

Anti-IL-21R Antibodies

[0060] The disclosure provides novel anti-IL-21R antibodies that comprise novel antigen-binding fragments.

[0061] In general, antibodies can be made, for example, using traditional hybridoma techniques (Kohler and Milstein (1975) Nature, 256: 495-499), recombinant DNA methods (U.S. Patent 4,816,567), or phage display using antibody libraries (Clackson et al. (1991) Nature, 352: 624-628; Marks et al. (1991) J. Mol. Biol., 222: 581-597). For additional antibody production techniques, see Antibodies: A Laboratory Manual, eds. Harlow et al., Cold Spring Harbor Laboratory, 1988. The present invention is not limited to any particular source, method of production, or other special characteristics of an antibody.

[0062] Intact antibodies are immunoglobulins (Ig), and they typically are tetrameric glycosylated proteins composed of two light chains (~25 kDa each) and two heavy chains (~50 kDa each). Light chains are classified into two isotypes (λ and κ), and heavy chains are classified into five isotypes (A, D, E, G, and M). Some heavy chain isotypes are further divided into isotype subclasses, e.g., IgG₁, IgG₂, IgG₃, and IgG₄.

[0063] The domain and three dimensional structures of different antibodies are known in the art (Harlow et al., supra). In brief, the light chain is composed of a constant domain (C_L) and an N-terminal variable domain (V_L). The heavy chain is composed of three or four constant domains (C_H), a hinge region, and a N-terminal variable domain (V_H). The C_H adjacent to the V_H domain is designated C_H1. The V_H and V_L domains contain four regions of conserved sequence called framework (FR) regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequence called complementarity determining regions (CDR). The CDRs (CDR1, CDR2, and CDR3) contain most of the antibody amino acids that specifically binds antigen. Heavy chain CDRs are denoted H1, H2, and H3, while light chain CDRs are denoted L1, L2, and L3.

[0064] The Fab fragment (Fragment antigen-binding) consists of V_H-C_H1 and V_L-C_L domains covalently linked by a

disulfide bond between the constant regions. The F_v fragment is smaller and consists of V_H and V_L domains non-covalently linked. To overcome the tendency of non-covalently domains to dissociate, a single chain F_v fragment (scF_v) can be constructed. The scF_v contains a flexible polypeptide that links the (1) C-terminus of V_H to the N-terminus of V_L , or the (2) C-terminus of V_L to the N-terminus of V_H . A 15-mer $(Gly_4Ser)_3$ peptide may be used as a linker, but other linkers are known in the art.

[0065] Antibody diversity is created by use of multiple germline genes encoding variable regions and a variety of somatic events. The somatic events include recombination of variable gene segments and diversity (D) and joining (J) gene segments to make a complete V_H region and the recombination of variable and joining gene segments to make a complete V_L region. CDR3 (H3) is the greatest source of molecular diversity within an antibody sequence. H3, for example, can be as short as two amino acid residues or greater than 26. The smallest antigen-binding fragment is the F_v , which consists of the V_H and the V_L domains.

[0066] Antibodies and compositions having identical or similar CDR sequence to those disclosed herein are not likely to have been independently generated. The sequence of antibody genes after assembly and somatic mutation is highly varied, and these varied genes are estimated to encode 10^{10} different antibody molecules (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, CA, 1995).

[0067] The present disclosure provides novel CDRs derived from human immunoglobulin gene libraries. The structure for carrying a CDR is generally an antibody heavy or light chain or portion thereof, where the CDR is located to a naturally occurring CDR region. The structures and locations of variable domains may be determined as described in Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, MD (1991).

[0068] DNA and amino acid (AA) sequences of illustrative embodiments of the anti-IL-21R antibodies of this invention, including their scF_v fragments, V_H and V_L domains, and CDRs, are set forth in the Sequence Listing and enumerated in Tables 1A and 1B. Specific embodiments of the antibodies are identified as MUF, MUF-germline, MU11, 18G4, 18A5, 19F5, CP5G2 and R18. The CDR positions in the V_H and V_L domains of the antibodies are listed in Table 2.

Table 1A: AA and DNA Sequences of V_H and V_L Domains, F_v , and CDRs

REGION	TYPE	MUF	MU11	18G4	18A5
V_H	AA	SEQ ID NO:1	SEQ ID NO:19	SEQ ID NO:47	SEQ D NO:65
V_L	AA	SEQ ID NO:2	SEQ ID NO:20	SEQ ID NO:48	SEQ ID NO:66
scF_v	AA	SEQ ID NO:3	SEQ ID NO:21	SEQ ID NO:49	SEQ ID NO:67
H1	AA	SEQ ID NO:4	SEQ ID NO:22	SEQ ID NO:50	SEQ ID NO:68
H2	AA	SEQ ID NO:5	SEQ ID NO:23	SEQ ID NO:51	SEQ ID NO:69
H3	AA	SEQ ID NO:6	SEQ ID NO:24	SEQ ID NO:52	SEQ ID NO:70
L1	AA	SEQ ID NO:7	SEQ ID NO:25	SEQ ID NO:53	SEQ ID NO:71
L2	AA	SEQ ID NO:8	SEQ ID NO:26	SEQ ID NO:54	SEQ ID NO:72
L3	AA	SEQ ID NO:9	SEQ ID NO:27	SEQ ID NO:55	SEQ ID NO:73
V_H	DNA	SEQ ID NO:10	SEQ ID NO:28	SEQ ID NO:56	SEQ ID NO:74
V_L	DNA	SEQ ID NO:11	SEQ ID NO:29	SEQ ID NO:57	SEQ ID NO:75
scF_v	DNA	SEQ ID NO:12	SEQ ID NO:30	SEQ ID NO:58	SEQ ID NO:76
H1	DNA	SEQ ID NO:13	SEQ ID NO:31	SEQ ID NO:59	SEQ ID NO:77
H2	DNA	SEQ ID NO:14	SEQ ID No	SEQ ID NO:60	SEQ ID NO:78
H3	DNA	SEQ ID NO:15	SEQ ID NO:33	SEQ ID NO:61	SEQ ID NO:79
L1	DNA	SEQ ID NO:16	SEQ ID NO:34	SEQ ID NO:62	SEQ ID NO:80
L2	DNA	SEQ ID NO:17	SEQ ID NO:35	SEQ ID NO:63	SEQ ID NO:81
L3	DNA	SEQ ID NO:18	SEQ ID NO:36	SEQ ID NO:64	SEQ ID NO:82

EP 1 603 949 B9

Table 1B: AA and DNA Sequences of V_H and V_L Domains, F_v, and CDRs

REGION	TYPE	MUF GERMLINE	19F5	CP5G2	R18
V _H	AA	SEQ ID NO:83	SEQ ID NO:101	SEQ ID NO:119	SEQ D NO:137
V _L	AA	SEQ ID NO:84	SEQ ID NO:102	SEQ ID NO:120	SEQ ID NO:138
scF _v	AA	SEQ ID NO:85	SEQ ID NO:103	SEQ ID NO:121	SEQ ID NO:139
H1	AA	SEQ ID NO:86	SEQ ID NO:104	SEQ ID NO:122	SEQ ID NO:140
H2	AA	SEQ ID NO:87	SEQ ID NO:105	SEQ ID NO:123	SEQ ID NO:141
H3	AA	SEQ ID NO:88	SEQ ID NO:106	SEQ ID NO:124	SEQ ID NO:142
L1	AA	SEQ ID NO:89	SEQ ID NO:107	SEQ ID NO:125	SEP ID NO:143
L2	AA	SEQ ID NO:90	SEQ ID NO:108	SEQ ID NO:126	SEQ ID NO:144
L3	AA	SEQ ID NO:91	SEQ ID NO:109	SEQ ID NO:127	SEQ ID NO:145
V _H	DNA	SEQ ID NO:92	SEQ ID NO:110	SEQ ID NO:128	SEQ ID NO:146
V _L	DNA	SEQ ID NO:93	SEQ ID NO:111	SEQ ID NO:129	SEQ ID NO:147
scF _v	DNA	SEQ ID NO:94	SEQ ID NO:112	SEQ ID NO:130	SEQ ID NO:148
H1	DNA	SEQ ID NO:95	SEQ ID NO:113	SEQ ID NO:131	SEQ ID NO:149
H2	DNA	SEQ ID NO:96	SEQ ID NO:114	SEQ ID NO:132	SEQ ID NO:150
H3	DNA	SEQ ID NO:97	SEQ ID NO:115	SEQ ID NO:133	SEQ ID NO:151
L1	DNA	SEQ ID NO:98	SEQ ID NO:116	SEQ ID NO:134	SEQ ID NO:152
L2	DNA	SEQ ID NO:99	SEQ ID NO:117	SEQ ID NO:135.	SEQ ID NO:153
L3	DNA	SEQ ID NO:100	SEQ ID NO:118	SEQ ID NO:136	SEQ ID NO:154

Table 2: Positions of CDRs within AA Sequences

CDR	MUF (SEQ ID NO:1)	MUF (SEQ ID NO:2)	MU11 (SEQ ID NO:21)	18G4 (SEQ ID NO:49)
H1	31-35		31-35	31-35
H2	50-66		50-66	50-66
H3	99-105		99-106	99-105
L1		23-33	156-166	156-166
L2		49-55	182-188	182-188
L3		88-100	221-229	221-231

CDR	18A5 (SEQ ID NO:67)	19F5 (SEQ ID NO:103)	CP5G2 (SEQ ID NO:121)	R18 (SEQ ID NO:139)
H1	31-36	31-35	31-35	31-35
H2	51-66	50-66	50-66	50-66
H3	99-107	99-109	99-107	99-110
L1	158-168	160-170	158-168	161-171
L2	184-190	186-192	184-190	187-193
L3	223-234	225-236	223-234	226-236

CDR	MUF GERMLINE (SEQ ID NO:85)
H1	31-35
H2	50-66
H3	99-105
L1	156-166
L2	182-188
L3	221-233

[0069] Anti-IL-21R antibodies of this invention may optionally comprise antibody constant regions or parts thereof. For example, a V_L domain may be attached at its C-terminal end to a light chain constant domain like C_κ or C_λ . Similarly, a V_H domain or portion thereof may be attached to all or part of a heavy chain like IgA, IgD, IgE, IgG, and IgM, and any isotype subclass. Constant regions are known in the art (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, MD (1991)).

[0070] In exemplary embodiments, MUF comprises heavy and light chain constant domains human IgG_{1 λ} , and MU11 comprises the heavy and light chain constant domains of human IgG_{1 κ} . In these antibodies, the sequences of the heavy chains outside of the V_H domain are identical. The DNA and amino acid sequences for the C-terminal fragment of the λ light chain are set forth in SEQ ID NO:40 and SEQ ID NO:39, respectively. The DNA and amino acid sequences for the C-terminal fragment of the κ chain are set forth in SEQ ID NO:42 and SEQ ID NO:41, respectively. The DNA and amino acid sequences for the C-terminal fragment of IgG₁ heavy chain are set forth in SEQ ID NO:38 and SEQ ID NO:37, respectively.

[0071] Certain embodiments comprise a V_H domain and a V_L domain, or the scF_v fragment of the F_v fragment from MUF, MUF-germline, MU11, 18G4, 18A5, 19F5, CP5G2, or R18. Also disclosed are antibodies comprising one, two, three, four, five or six complementarity determining regions (CDRs) from the V_H and V_L domains. Antibodies whose CDR sequences are set out in SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 19, 20, 21, 22, 23, 24, 25, 26, 27, 47, 48, 49, 50, 51, 52, 53, 54, 55, 65, 66, 67, 68, 69, 70, 71, 72, 73, 83, 84, 85, 86, 87, 88, 89, 90, 91, 101, 102, 103, 104, 105, 106, 107,

108, 109, 119, 120, 121, 122, 123, 124, 125, 126, 127, 137, 138, 139, 140, 141, 142, 143, 144, or 145 are encompassed within the scope of this invention. For example, an antibody comprises a CDR3 (H3) fragment of the V_H domain of MUF, MUF-germline, MU11, 18G4, 18A5, 19F5, CP5G2, or R18.

[0072] The V_H and/or V_L domains may be germlined, i.e., the framework regions (FR) of these domains are mutated using conventional molecular biology techniques to match those produced by the germline cells. The FR sequences remain diverged from the consensus germline sequences.

[0073] Amino acid and nucleic acid sequences for the germlined MUF are provided. Amino acid sequence for the V_H domain of the germlined MUF is depicted in SEQ ID NO:83 and 85. Amino acid sequence for the V_L domain of the germlined MUF is depicted in SEQ ID NO:84 and 85. Nucleic acid sequence for the germlined MUF V_H domain is depicted in SEQ ID NO:92 and 94 and that for the germlined V_L domain is depicted in SEQ ID NO:93 and 94. Germline sequences for the V_H and V_L domains can be identified by performing amino acid and nucleic acid sequence alignments against the VBASE database (MRC Center for Protein Engineering, UK). The FR regions of the scFvs are mutated in conformity with the closest matches in the VBASE database and the CDR portions are kept intact.

[0074] Antibodies specifically react with an epitope in the extracellular domain of human IL-21R. The predicted extracellular domain consists of a sequence from about amino acid 20 to about amino acid 235 of SEQ ID NO:43. Anti-IL-21R antibodies block the binding of IL-21 to IL-21R. The anti-IL-21R antibodies specifically react with an epitope in the extracellular domain of mouse IL-21R. The extracellular domain of murine IL-21R consists of a sequence from about amino acid 20 to about amino acid 236 of SEQ ID NO:45. The extracellular domain of mouse IL-21R is about 65% identical to the human counterpart.

[0075] It is contemplated that antibodies of this invention may bind other proteins, such as, for example, recombinant proteins comprising all or portion of the IL-21R extracellular domain.

[0076] One of ordinary skill in the art will recognize that the disclosed antibodies may be used to detect, measure, and/or inhibit proteins that differ somewhat from IL-21R. For example, these proteins may be homologs of IL-21R. Anti-IL-21R antibodies are expected to bind proteins that comprise a sequence which is at least about 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to any sequence of at least 100, 80, 60, 40, or 20 contiguous amino acids in the sequence set forth SEQ ID NO:43.

[0077] In addition to sequence homology analyses, epitope mapping (see, e.g., Epitope Mapping Protocols, ed. Morris, Humana Press, 1996), and secondary and tertiary structure analyses can be carried out to identified specific 3D structures assumed by the presently disclosed antibodies and their complexes with antigens. Such methods include, but are not limited to, X-ray crystallography (Engstrom (1974) Biochem. Exp. Biol., 11:7-13) and computer modeling of virtual representations of the present antibodies (Fletterick et al. (1986) Computer Graphics and Molecular Modeling, in Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

[0078] Anti-IL-21R antibodies produced by creating antibodies with altered Tables 1A and 1B V_H and/or V_L sequence (s) may be obtained. Such antibodies may be derived by a skilled artisan using techniques known in the art. For example, amino acid substitutions, deletions, or additions can be introduced in FR and/or CDR regions. FR changes are usually designed to improve the stability and immunogenicity of the antibody, while CDR changes are typically designed to increase antibody affinity for its antigen. The changes that increase affinity may be tested by altering CDR sequence and measuring antibody affinity for its target (see Antibody Engineering, 2nd ed., Oxford University Press, ed. Borrebaeck, 1995).

[0079] Antibodies whose CDR sequences differ insubstantially from those set out in SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 19, 20, 21, 22, 23, 24, 25, 26, 27, 47, 48, 49, 50, 51, 52, 53, 54, 55, 65, 66, 67, 68, 69, 70, 71, 72, 73, 83, 84, 85, 86, 87, 88, 89, 90, 91, 101, 102, 103, 104, 105, 106, 107, 108, 109, 119, 120, 121, 122, 123, 124, 125, 126, 127, 137, 138, 139, 140, 141, 142, 143, 144, or 145 are described within the scope of this invention. Typically, this involves substitution of an amino acid with an amino acid having similar charge, hydrophobic, or stereochemical characteristics. More drastic substitutions in FR regions, in contrast to CDR regions, may also be made as long as they do not adversely affect the binding properties of the antibody. Substitutions may also be made to germline the antibody or stabilize the antigen binding site.

[0080] Conservative modifications will produce molecules having functional and chemical characteristics similar to those of the molecule from which such modifications are made. In contrast, substantial modifications in the functional and/or chemical characteristics of the molecules may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (1) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (2) the charge or hydrophobicity of the molecule at the target site, or (3) the size of the molecule.

[0081] For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for "alanine scanning mutagenesis" (see, for example, MacLennan et al., 1998, Acta Physiol. Scand. Suppl. 643:55-67; Sasaki et al., 1998, Adv. Biophys. 35:1-24).

[0082] Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the molecule sequence, or to increase or decrease the affinity of the molecules described herein. Exemplary amino acid substitutions are set forth in Table 3.

Table 3: Amino Acid Substitutions

Original Residues	Exemplary Substitutions	More Conservative Substitutions
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn	Asn
Gly (G)	Pro, Ala	Ala
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, 1, 4 Diamino-butyric Acid, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Leu
Pro (P)	Ala	Gly
Ser (S)	Thr, Ala, Cys	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0083] In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

[0084] A method for making a variant V_H domain may comprise adding, deleting, or substituting at least one amino acid in the disclosed V_H domains, or combining the disclosed V_H domains with at least one V_L domain, and testing the variant V_H domain for IL-21R binding or modulation of IL-21R activity.

[0085] An analogous method for making a variant V_L domain may comprise adding, deleting, or substituting at least one amino acid in the disclosed V_L domains, or combining the disclosed V_L domains with at least one V_H domain, and testing the variant V_L domain for IL-21R binding or modulation of IL-21R activity.

[0086] A method for preparing antigen-binding fragments that bind IL-21R may comprise:

- providing a starting repertoire of nucleic acids encoding a V_H domain which lacks one or more of CDR1, 2 or 3 or contains a CDR1, 2 or 3 to be replaced;
- inserting into or replacing the CDR1, 2 or 3 region of the starting repertoire with a nucleic acid encoding an amino acid sequence as substantially as set out herein for a V_H CDR 1, 2 or 3, yielding a product repertoire;
- expressing the nucleic acids of the product repertoire;
- selecting a specific antigen-binding fragment that binds to IL-21R; and
- recovering the specific antigen-binding fragment or nucleic acid encoding it.

[0087] An analogous method in which the V_L CDR1, 2 or 3 is combined with a repertoire of nucleic acids encoding a V_L domain which lacks a CDR1, 2 or 3 or contains a CDR1, 2 or 3 to be replaced.

[0088] Using recombinant DNA methodology, a disclosed CDR sequence may be introduced into a repertoire of V_H or V_L domains lacking the respective CDR (Marks et al. (BioTechnology (1992) 10: 779-783). For example, a primer adjacent to the 5' end of the variable domain and a primer to the third FR can be used to generate a repertoire of variable domain sequences lacking CDR3. This repertoire can be combined with a CDR3 of a disclosed antibody. Using analogous techniques, portions of a disclosed CDR sequence may be shuffled with portions of CDR sequences from other antibodies to provide a repertoire of antigen-binding fragments that bind IL-21R. Either repertoire can be expressed in a host system such as phage display (described in WO 92/01047) so suitable antigen-binding fragments that bind to IL-21R can be selected.

[0089] A further alternative uses random mutagenesis of the disclosed V_H or V_L sequences to generate variant V_H or V_L domains still capable of binding IL-21R. A technique using error-prone PCR is described by Gram et al. (Proc. Nat. Acad. Sci. U.S.A. (1992) 89: 3576-3580).

[0090] Another method uses direct mutagenesis of the disclosed V_H or V_L sequences. Such techniques are disclosed by Barbas et al. (Proc. Nat. Acad. Sci. U.S.A. (1994) 91: 3809-3813) and Schier et al. (J. Mol. Biol. (1996) 263: 551-567).

[0091] A portion of a variable domain will comprise at least one CDR region substantially as set out herein and, optionally, intervening framework regions from the V_H or V_L domains as set out herein. The portion may include the C-terminal half of FR1 and/or the N-terminal half of FR4. Additional residues at the N-terminal or C-terminal end of the variable domain may not be same residues found in naturally occurring antibodies. For example, construction of antibodies by recombinant DNA techniques often introduces N- or C-terminal residues from its use of linkers. Some linkers may be used to join variable domains to other variable domains (e.g., diabodies), constant domains, or proteinaceous labels.

[0092] Although the embodiments illustrated in the Examples comprise a "matching" pair of V_H and V_L domains, a skilled artisan will recognize that alternative embodiments may comprise antigen-binding fragments containing only a single CDR from either V_L or V_H domain. Either one of the single chain specific antigen-binding domains can be used to screen for complementary domains capable of forming a two-domain specific antigen-binding fragment capable of, for example, binding to IL-21R. The screening may be accomplished by phage display screening methods using the so-called hierarchical dual combinatorial approach disclosed in WO 92/01047. In this approach, an individual colony containing either a H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques as described.

[0093] In some alternative embodiments, the anti-IL-21R antibodies can be linked to a protein (e.g., albumin) by chemical cross-linking or recombinant methods. The disclosed antibodies may also be linked to a variety of nonproteinaceous polymers (e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes) in manners set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337. The antibodies can be chemically modified by covalent conjugation to a polymer, for example, to increase their half-life in blood circulation. Exemplary polymers and attachment methods are shown in U.S. Pat. Nos. 4,766,106; 4,179,337; 4,495,285; and 4,609,546.

[0094] The disclosed antibodies can be modified to alter their glycosylation; that is, at least one carbohydrate moiety can be deleted or added to the antibody. Deletion or addition of glycosylation sites can be accomplished by changing amino acid sequence to delete or create glycosylation consensus sites, which are well known in the art. Another means of adding carbohydrate moieties is the chemical or enzymatic coupling of glycosides to amino acid residues of the antibody (see WO 87/05330 and Aplin et al. (1981) CRC Crit. Rev. Biochem., 22: 259-306). Removal of carbohydrate moieties can also be accomplished chemically or enzymatically (see Hakimuddin et al. (1987) Arch. Biochem. Biophys., 259: 52; Edge et al. (1981) Anal. Biochem., 118: 131; Thotakura et al. (1987) Meth. Enzymol., 138: 350).

[0095] Methods for altering an antibody constant region are known in the art. Antibodies with altered function (e.g., altered affinity for an effector ligand such as FcR on a cell or the C1 component of complement) can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see e.g., EP 388,151 A1, US 5,624,821 and US 5,648,260). Similar types of alterations could be described which if applied to a murine or other species antibody would reduce or eliminate similar functions.

[0096] For example, it is possible to alter the affinity of an Fc region of an antibody (e.g., an IgG, such as a human IgG) for FcR (e.g., Fc gamma R1) or C1q. The affinity may be altered by replacing at least one specified residue with at least one residue having an appropriate functionality on its side chain, or by introducing a charged functional group, such as glutamate or aspartate, or perhaps an aromatic non-polar residue such as phenylalanine, tyrosine, tryptophan or alanine (see e.g., US 5,624,821).

[0097] For example, replacing residue 297 (asparagine) with alanine in the IgG constant region significantly inhibits recruitment of effector cells, while only slightly reducing (about three fold weaker) affinity for C1q (see e.g., US 5,624,821). The numbering of the residues in the heavy chain is that of the EU index (see Kabat et al., 1991 *supra*). This alteration destroys the glycosylation site and it is believed that the presence of carbohydrate is required for Fc receptor binding. Any other substitution at this site that destroys the glycosylation site is believed cause a similar decrease in lytic activity.

Other amino acid substitutions, e.g., changing any one of residues 318 (Glu), 320 (Lys) and 322 (Lys), to Ala, are also known to abolish Clq binding to the Fc region of IgG antibodies (see e.g., US 5,624,821).

[0098] Modified antibodies can be produced which have a reduced interaction with an Fc receptor. For example, it has been shown that in human IgG₃, which binds to the human Fc gamma R1 receptor, changing Leu 235 to Glu destroys its interaction with the receptor. Mutations on adjacent or close sites in the hinge link region of an antibody (e.g., replacing residues 234, 236 or 237 with Ala) can also be used to affect antibody affinity for the Fc gamma R1 receptor. The numbering of the residues in the heavy chain is based in the EU index (see Kabat et al., 1991 *supra*).

[0099] Additional methods for altering the lytic activity of an antibody, for example, by altering at least one amino acid in the N-terminal region of the CH2 domain, are described in WO 94/29351 by Morgan et al. and US 5,624,821.

[0100] The antibodies of this invention may be tagged with a detectable or functional label. These labels include radiolabels (e.g., ¹³¹I or ⁹⁹Tc), enzymatic labels (e.g., horseradish peroxidase or alkaline phosphatase), and other chemical moieties (e.g., biotin).

[0101] One of skill in the art will appreciate that the modifications described above are not all-exhaustive, and that many other modifications are obvious to a skilled artisan in light of the teachings of the present disclosure.

Nucleic Acids, Cloning and Expression Systems.

[0102] The disclosure provides isolated nucleic acids encoding the disclosed antibodies. The nucleic acids may comprise DNA or RNA, and they may be synthetic (completely or partially) or recombinant (completely or partially). Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T.

[0103] Also provided are nucleic acids that comprise a coding sequence for one, two, or three CDR's, a V_H domain, a V_L domain, or combinations thereof, as disclosed herein, or a sequence substantially identical thereto (e.g., a sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher identical thereto, or which is capable of hybridizing under stringent conditions to the sequences disclosed).

[0104] The isolated nucleic acids have nucleotide sequences encoding heavy chain and light chain variable regions of an anti-IL-21R antibody having at least one CDR chosen from the amino acid sequences of SEQ ID NO:4, 5, 6, 7, 8, 9, 22, 23, 24, 25, 26, 27, 50, 51, 52, 53, 54, 55, 68, 69, 70, 71, 72, 73, 86, 87, 88, 89, 90, 91, 104, 105, 106, 107, 108, 109, 122, 123, 124, 125, 126, 127, 140, 141, 142, 143, 144 and 145 or sequence encoding a CDR which differs by one or two amino acids from the sequences described herein. The amino acid sequence of a CDR includes conservative amino acid substitutions of one or more amino acids in sequences shown in SEQ ID NO:4, 5, 6, 7, 8, 9, 22, 23, 24, 25, 26, 27, 50, 51, 52, 53, 54, 55, 68, 69, 70, 71, 72, 73, 86, 87, 88, 89, 90, 91, 104,- 105, 106, 107, 108, 109, 122, 123, 124, 125, 126, 127, 140, 141, 142, 143, 144 and 145.

[0105] A nucleic acid may encode only the light chain or the heavy chain variable region, or may also encode an antibody light or heavy chain constant region, operatively linked to the corresponding variable region. A light chain variable region (V_L) is linked to a constant region chosen from a kappa or a lambda constant region. The light chain constant region may also be a human kappa or lambda type. A heavy chain variable region (V_H) is linked to a heavy chain constant region of an antibody isotype chosen from IgG (e.g., IgG₁, IgG₂, IgG₃, IgG₄), IgM, IgA₁, IgA₂, IgD, and IgE. The heavy chain constant region may be an IgG (e.g., an IgG₁) isotype.

[0106] Nucleic acid compositions while often in the native sequence (of cDNA or genomic DNA or mixtures thereof) except for modified restriction sites and the like, may be mutated in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, nucleotide sequences substantially identical to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

[0107] In one embodiment, a nucleic acid differs (e.g., differs by substitution, insertion, or deletion) from that of the sequences provided (e.g., as follows: by at least one but less than 10, 20, 30, or 40 nucleotides; at least one but less than 1%, 5%, 10% or 20% of the nucleotides in the subject nucleic acid). If necessary for this analysis the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences. The difference may be at a nucleotide(s) encoding a non-essential residue(s), or the difference may be a conservative substitution(s). The disclosure also provides nucleic acid constructs in the form of plasmids, vectors, transcription or expression cassettes, which comprise at least one nucleic acid as described herein.

[0108] The disclosure further provides a host cell that comprises at least one nucleic acid construct described herein. Also provided are the methods of making the encoded protein(s) from the nucleic acid(s) comprising sequence described herein. The method comprises culturing host cells under appropriate conditions so they express the protein from the nucleic acid. Following expression and production, the V_H or V_L domain, or specific binding member may be isolated and/or purified using any suitable technique, then used as appropriate.

[0109] Antigen-binding fragments, V_H and/or V_L domains, and encoding nucleic acid molecules and vectors may be

isolated and/or purified from their natural environment, in substantially pure or homogenous form, or, in the case of nucleic acid, free or substantially free of nucleic acid or genes of origin other than the sequence encoding a polypeptide with the require function.

[0110] Systems for cloning and expressing polypeptides in a variety of host cells are known in the art. Cells suitable for producing antibodies are described in, for example, Fernandez et al. (1999) *Gene Expression Systems*, Academic Press, eds. In brief, suitable host cells include mammalian cells, insect cells, plant cells, yeast cells, or prokaryotic cells, e.g., *E. coli*. Mammalian cells available in the art for heterologous polypeptide expression include lymphocytic cell lines (e.g., NSO), HEK293 cells, Chinese hamster ovary (CHQ) cells, COS cells, HeLa cells, baby hamster kidney cells, oocyte cells, and cells from a transgenic animal, e.g., mammary epithelial cell. The MUF and MU11 antibodies are expressed in HEK293 or CHO cells. Nucleic acids encoding the antibodies of the invention are placed under the control of a tissue-specific promoter (e.g., a mammary specific promoter) and the antibodies are produced in transgenic animals. For example, antibodies are secreted into the milk of the transgenic animal, such as a transgenic cow, pig, horse, sheep, goat or rodent. Suitable vectors may be chosen or constructed to contain appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes, and other sequences. The vectors may also contain a plasmid or viral backbone. For details, see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press (1989). Many established techniques used with vectors, including the manipulation, preparation, mutagenesis, sequencing, and transfection of DNA, are described in *Current Protocols in Molecular Biology*, Second Edition, Ausubel et al. eds., John Wiley & Sons (1992).

[0111] A further aspect of the disclosure provides a method of introducing the nucleic acid into a host cell. For eukaryotic cells, suitable transfection techniques may include calcium phosphate, DEAE-Dextran, electroporation, liposome-mediated transfection, and transduction using retrovirus or other viruses, e.g., vaccinia or baculovirus. For bacterial cells, suitable techniques may include calcium chloride transformation, electroporation, and transfection using bacteriophage. DNA introduction may be followed by a selection method (e.g., drug resistance) to select cells that contain the nucleic acid.

Biological Deposits

[0112] CHO cells transformed with vectors containing MUF heavy chain and light chain, and CHO cells transformed with vectors containing MU11 heavy and light chain, were deposited on March 5, 2003, at American Tissue Culture Collection (ATCC) under respective Deposit Designation Numbers PTA-5031 and PTA-5030. The address of the depository is 10801 University Blvd, Manassas, VA 20110, U.S.A.

Uses of Anti-IL-21R Antibodies

[0113] Anti-IL-21R antibodies that act as antagonists to IL-21R are used to regulate at least one IL-21R-mediated immune response, wherein the immune response comprises cell proliferation, cytokine secretion, chemokine secretion, and cytolytic activity, of T cells, B cells, NK cells, macrophages, or synovial cells. Accordingly, the antibodies of the invention can be used to inhibit the activity (e.g., proliferation, differentiation, and/or survival) of an immune or hematopoietic cell (e.g., a cell of myeloid, lymphoid, or erythroid lineage, or precursor cells thereof), and, thus, can be used to treat a variety of immune disorders and hyperproliferative disorders. Non-limiting examples of immune disorders that can be treated include, but are not limited to, transplant rejection, graft-versus-host disease, allergies (for example, atopic allergy) and autoimmune diseases. Autoimmune diseases may include diabetes mellitus, arthritic disorders (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and ankylosing spondylitis), spondyloarthropathy, multiple sclerosis, encephalomyelitis, myasthenia gravis, systemic lupus erythematosus, cutaneous lupus erythematosus, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjögren's Syndrome, IBD (including Crohn's disease and ulcerative colitis), asthma (including intrinsic asthma and allergic asthma), scleroderma and vasculitis.

[0114] Multiple sclerosis is a central nervous system disease that is characterized by inflammation and loss of myelin sheaths - the fatty material that insulates nerves and is needed for proper nerve function. Inflammation that results from an immune response that is dependent on IL-21 can be treated with the antibodies and compositions of this invention. In the experimental autoimmune encephalitis (EAE) mouse model for multiple sclerosis (Tuohy et al. (*J. Immunol.* (1988) 141: 1126-1130), Sobel et al. (*J. Immunol.* (1984) 132: 2393-2401), and Traugott (*Cell Immunol.* (1989) 119: 114-129), treatment of mice with MU11 injections prior (and continuously) to EAE induction profoundly delays the onset of the disease. The antibodies of this invention may similarly be used to treat multiple sclerosis in humans.

[0115] Arthritis is a disease characterized by inflammation in the joints. Rheumatoid Arthritis (RA) is the most frequent form of arthritis, involving inflammation of connective tissue and the synovial membrane, a membrane that lines the joint. The inflamed synovial membrane often infiltrates the joint and damages joint cartilage and bone. Studies show that treatment of synovial cells and macrophages with IL-21 induces these cells to secrete cytokines and chemokines associated with inflammation. In the collagen induced arthritis (CIA) mouse model for rheumatoid arthritis (Courtenay et al.

(Nature (1980) 283: 666-628) and Williams et al. (Immunol. (1995) 84: 433-439)), treatment of mice with IL-21 subsequently (and continuously) to CIA induction exacerbates the disease. Increased secretion of inflammatory cytokines and chemokines, and more importantly, increased disease resulting from immune responses that are dependent on IL-21 may be treated with the antibodies of this invention. Similarly, the antibodies and compositions of this invention may be

used to treat RA or other arthritic diseases in humans.

[0116] Transplant rejection is the immunological phenomenon where tissues from a donor are specifically "attacked" by immune cells of the host. The principle "attacking" cells are T cells, whose T cell receptors recognize the donor's MHC molecules as "foreign." This recognition activates the T cell, which proliferates and secretes a variety of cytokines and cytolytic proteins that ultimately destroy the transplant. T cells in a mixed lymphocyte reaction (MLR), an *in vitro* assay of transplant rejection, proliferate more strongly when supplemented with IL-21. MLR and transplantation models have been described by Current Protocols in Immunology, Second Edition, Coligan et al. eds., John Wiley & Sons, 1994; Kasaian et al. (Immunity (2002) 16: 559-569); Fulmer et al. (Am. J. Anat. (1963) 113: 273-285), and Lenschow et al. (Science (1992) 257: 789-792). The antibodies and compositions of this invention may be used to reduce the MLR and treat transplant rejection and related diseases (e.g., graft versus host disease) in humans that are dependent on IL-21.

[0117] Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies, including antibodies to DNA, nuclear antigens, and ribonucleoproteins. These autoantibodies are associated with tissue and organ damage. The cause of SLE is unknown, but the occurrence of autoantibodies suggests inadequate inhibition of autoreactive T cells or B cells. The antibodies and compositions of this invention can be used to inhibit the IL-21 mediated activities of autoreactive T cells and B cells, and treat SLE or related diseases in NZB X NZW mice (the mouse model for SLE) (Immunologic Defects in Laboratory Animals, Gershwin et al. eds., Plenum Press, 1981) or in humans.

[0118] Antibodies of this invention can also be used to treat hyperproliferative disorders associated with aberrant activity of IL-21-responsive cells and IL-21R-responsive cells. Examples of such cells include neoplastic cells of hematopoietic origin, e.g., cells arising from myeloid, lymphoid or erythroid lineages, or precursor cells thereof. Examples of such neoplastic disorders include leukemic cancers, and tumors of the blood, bone marrow (e.g., myeloma), and lymph tissue (e.g., lymphomas). In certain embodiments, the present invention is directed to the treatment of various leukemic cancers including, but not limited to, acute promyeloid leukemia (APML), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) (reviewed in Vaickus, L. (1991) Crit. Rev. in Oncol./Hematol. 11:267-97). Examples of lymphoid malignancies that may be treated by the subject methods include, but are not limited to, acute lymphoblastic leukemia (ALL, which includes B-lineage ALL and T-lineage ALL), chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL), and Waldenstrom's macroglobulinemia (WM). Additional forms of malignant lymphomas that can be treated by the present invention include, but not limited to, non-Hodgkin's lymphoma, peripheral T cell lymphomas, adult T cell leukemia/lymphoma (ATL), cutaneous T cell lymphoma (CTCL), large granular lymphocytic leukemia (LGL), Hodgkin's lymphoma, and variants thereof.

Combination Therapy

[0119] In one embodiment, a pharmaceutical composition comprising at least one, anti-IL-21R antibody of the invention and at least one therapeutic agent is administered in combination therapy. The therapy is useful for treating pathological conditions or disorders, such as immune and inflammatory disorders. The term "in combination" in this context means that the antibody composition and the therapeutic agent are given substantially contemporaneously, either simultaneously or sequentially. If given sequentially, at the onset of administration of the second compound, the first of the two compounds may still be detectable at effective concentrations at the site of treatment.

[0120] For example, the combination therapy can include at least one anti-IL-21R antibody co-formulated with, and/or co-administered with, at least one additional therapeutic agent. The additional agents may include at least one cytokine inhibitor, growth factor inhibitor, immunosuppressant, anti-inflammatory agent, metabolic inhibitor, enzyme inhibitor, cytotoxic agent, and cytostatic agent, as described in more detail below. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies. Moreover, the therapeutic agents disclosed herein act on pathways that differ from the IL-21/IL-21R pathway, and thus are expected to enhance and/or synergize with the effects of the anti-IL-21R antibodies.

[0121] Therapeutic agents used in combination with anti-IL-21R antibodies may be those agents that interfere at different stages in the autoimmune and subsequent inflammatory response. In one embodiment, at least one anti-IL-21R antibody described herein may be co-formulated with, and/or co-administered with, at least one cytokine and/or growth factor antagonist. The antagonists may include soluble receptors, peptide inhibitors, small molecules, ligand fusions, antibodies (that bind cytokines or growth factors or their receptors or other cell surface molecules), and "anti-inflammatory cytokines" and agonists thereof.

[0122] Non-limiting examples of the agents that can be used in combination with the anti-IL-21R antibodies described herein, include, but are not limited to, antagonists of at least one interleukin (e.g., IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-

13, IL-15, IL-16, IL-17, IL-18, and IL-22); cytokine (e.g., $\text{TNF}\alpha$, LT, EMAP-II, and GM-CSF); and growth factor (e.g., FGF and PDGF). The agents may also include, but not limited to, antagonists of at least one receptor for an interleukin, cytokine, and growth factor. Anti-IL-21R antibodies can also be combined with inhibitors (e.g., antibodies) to cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, or their ligands (e.g., CD154 (gp39, CD40L)), or LFA-1/ICAM-1 and VLA-4/VCAM-1 (Yusuf-Makagiansar et al. (2002) Med Res Rev 22(2):146-67)). Antagonists that can be used in combination with anti-IL-21R antibodies described herein may include antagonists of IL-1, IL-12, $\text{TNF}\alpha$, IL-15, IL-17, IL-18, IL-22, and their receptors.

[0123] Examples of those agents include IL-12 antagonists (such as antibodies that bind IL-12 (see e.g., WO 00/56772, Genetics Institute/BASF)); IL-12 receptor inhibitors (such as antibodies to the IL-12 receptor); and soluble IL-12 receptor and fragments thereof. Examples of IL-15 antagonists include antibodies against IL-15 or its receptor, soluble fragments of the IL-15 receptor, and IL-15-binding proteins. Examples of IL-18 antagonists include antibodies to IL-18, soluble fragments of the IL-18 receptor, and IL-18 binding proteins (IL-18BP, Mallet et al. (2001) Circ. Res. 28). Examples of IL-1 antagonists include Interleukin-1-Converting Enzyme (ICE) inhibitors (such as Vx740), IL-1 antagonists (e.g., IL-1 RA (ANIKINRA, AMGEN)), sIL-1RII (Immunex), and anti-IL-1 receptor antibodies.

[0124] Examples of TNF antagonists include antibodies to TNF (e.g., human $\text{TNF}\alpha$), such as D2E7 (human anti- $\text{TNF}\alpha$ antibody, U.S. 6,258,562, Humira™, BASF); CDP-571/CDP-870/BAY-10-3356 (humanized anti- $\text{TNF}\alpha$ antibodies, Celltech/Pharmacia); cA2 (chimeric anti- $\text{TNF}\alpha$ antibody, Remicade™, Centocor); and anti-TNF antibody fragments (e.g., CPD870). Other examples include soluble TNF receptor (e.g., human p55 or p75) fragments and derivatives, such as p55 kDTNFR-IgG (55 kD TNF receptor-IgG fusion protein, Lenercept™) and 75 kDTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™, Immunex, see, e.g., Arthritis & Rheumatism (1994) Vol. 37, S295; J. Invest. Med. (1996) Vol. 44, 235A). Further examples include enzyme antagonists (e.g., $\text{TNF}\alpha$ converting enzyme inhibitors (TACE) such as alpha-sulfonyl hydroxamic acid derivative (WO 01/55112) or N-hydroxyformamide inhibitor (GW 3333, -005, or-022)) and TNF-bp/s-TNFR (soluble TNF binding protein, see e.g., Arthritis & Rheumatism (1996) Vol. 39, No. 9 (supplement), S284; and Am. J. Physiol. Heart Circ. Physiol. (1995) Vol. 268, pp. 37-42). TNF antagonists may be soluble TNF receptor (e.g., human p55 or p75) fragments and derivatives, such as 75 kDTNFR-IgG; and $\text{TNF}\alpha$ converting enzyme (TACE) inhibitors.

[0125] The anti-IL-21R antibodies described herein can be administered in combination with at least one of the following: IL-13 antagonists, such as soluble IL-13 receptors and/or anti-IL-13 antibodies; and IL-2 antagonists, such as IL-2 fusion proteins (e.g., DAB 486-IL-2 and/or DAB 389-IL-2, Seragen, see e.g., Arthritis & Rheumatism (1993) Vol. 36, 1223) and anti-IL-2R antibodies (e.g., anti-Tac (humanized antibody, Protein Design Labs, see Cancer Res. 1990 Mar 1;50(5): 1495-502)). Another combination includes anti-IL-21R antibodies in combination with non-depleting anti-CD4 inhibitors such as IDEC-CE9.1/SB 210396 (anti-CD4 antibody, IDEC/SmithKline). Yet other combinations include anti-IL-21R antibodies with CD80 (B7.1) and CD86 (B7.2) co-stimulatory pathway antagonists (such as antibodies, soluble receptors, or antagonistic ligands); P-selectin glycoprotein ligand (PSGL); and anti-inflammatory cytokines and agonists thereof (e.g., antibodies). The anti-inflammatory cytokines may include IL-4 (DNAX/Schering); IL-10 (SCH 52000, recombinant IL-10, DNAX/Schering); IL-13; and TGF.

[0126] At least one anti-IL-21R antibody can be co-formulated with, and/or co-administered with, at least one anti-inflammatory drug, immunosuppressant, metabolic inhibitor, and enzymatic inhibitor. Non-limiting examples of the drugs or inhibitors that can be used in combination with the IL-21 antagonists described herein, include, but are not limited to, at least one of: non-steroidal anti-inflammatory drug (NSAID) (such as ibuprofen, Tenidap (see e.g., Arthritis & Rheumatism (1996) Vol. 39, No. 9 (supplement), S280)), Naproxen (see e.g., Neuro Report (1996) Vol. 7, pp. 1209-1213), Meloxicam, Piroxicam, Diclofenac, and Indomethacin); Sulfasalazine (see e.g., Arthritis & Rheumatism (1996) Vol. 39, No. 9 (supplement), S281); corticosteroid (such as prednisolone); cytokine suppressive anti-inflammatory drug (CSAID); and an inhibitor of nucleotide biosynthesis (such as an inhibitor of purine biosynthesis (e.g., folate antagonist such as methotrexate) and an inhibitor of pyrimidine biosynthesis (e.g., a dihydroorotate dehydrogenase (DHODH) inhibitor such as leflunomide (see e.g., Arthritis & Rheumatism (1996) Vol. 39, No. 9 (supplement), S131; Inflammation Research (1996) Vol. 45, pp. 103-107)). Therapeutic agents for use in combination with IL-21/IL-21R antagonists may include NSAIDs, CSAIDs, DHODH inhibitors (such as leflunomide), and folate antagonists (such as methotrexate).

[0127] Examples of additional inhibitors include at least one of: corticosteroid (oral, inhaled and local injection); immunosuppressant (such as cyclosporin and tacrolimus (FK-506)); a mTOR inhibitor (such as sirolimus (rapamycin) or a rapamycin derivative (e.g., ester rapamycin derivative such as CCI-779 (Elit. L. (2002) Current Opinion Investig. Drugs 3(8):1249-53; Huang, S. et al. (2002) Current Opinion Investig. Drugs 3(2):295-304)); an agent which interferes with the signaling of proinflammatory cytokines such as $\text{TNF}\alpha$ and IL-1 (e.g., IRAK, NIK, IKK, p38 or a MAP kinase inhibitor); a COX2 inhibitor (e.g., celecoxib and variants thereof (MK-966), see e.g., Arthritis & Rheumatism (1996) Vol. 39, No. 9 (supplement), S81); a phosphodiesterase inhibitor (such as R973401, see e.g., Arthritis & Rheumatism (1996) Vol. 39, No. 9 (supplement), S282); a phospholipase inhibitor (e.g., an inhibitor of cytosolic phospholipase 2 (cPLA2) such as trifluoromethyl ketone analogs (U.S. 6,350,892)); an inhibitor of vascular endothelial cell growth factor (VEGF); an inhibitor of the VEGF receptor; and an inhibitor of angiogenesis. Therapeutic agents for use in combination with anti-IL-21R

antibodies may include immunosuppressants (such as cyclosporine and tacrolimus (FK-506)); and mTOR inhibitors (such as sirolimus (rapamycin) or rapamycin derivatives (e.g., ester rapamycin derivatives such as CCI-779)); COX2 inhibitors (such as celecoxib and variants thereof); and phospholipase inhibitors (such as inhibitors of cytosolic phospholipase 2 (cPLA2) (e.g., trifluoromethyl ketone analogs)).

[0128] Examples of therapeutic agents that can be co-administered and/or co-formulated with at least one anti-IL-21R antibody, include, but are not limited to, at least one of: TNF antagonists (such as anti-TNF antibodies); soluble fragments of TNF receptors (e.g., human p55 and p75) and derivatives thereof (such as p55 kDTNFR-IgG (55 kD TNF receptor-IgG fusion protein, Lenercept™) and 75 kDTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™)); TNF enzyme antagonists (such as TACE inhibitors); antagonists of IL-12, IL-15, IL-17, IL-18, and IL-22; T cell and B cell depleting agents (such as anti-CD4 or anti-CD22 antibodies); small molecule inhibitors (such as methotrexate and leflunomide); sirolimus (rapamycin) and analogs thereof (such as CCI-779); Cox-2 and cPLA2 inhibitors; p38, TPL-2, Mk-2 and NFκB inhibitors; RAGE and soluble RAGE; P-selectin and PSGL-1 inhibitors (such as antibodies to and small molecule inhibitors); and estrogen receptor beta (ERB) agonists, and ERB-NFκB antagonists. Therapeutic agents that can be co-administered and/or co-formulated with at least one anti-IL-21R antibody may include at least one of: a soluble fragment of a TNF receptor (e.g., human p55 or p75) such as 75 kDTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™); methotrexate; leflunomide; and sirolimus (rapamycin) and analogs thereof (such as CCI-779).

[0129] The anti-IL-21R antibodies disclosed herein can be used in combination with other therapeutic agents to treat specific immune disorders as discussed in further detail below.

[0130] Non-limiting examples of agents for treating arthritic disorders (e.g., rheumatoid arthritis, inflammatory arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and psoriatic arthritis), with which an anti-IL-21R antibody can be combined include at least one of the following: TNF antagonists (such as anti-TNF antibodies); soluble fragments of TNF receptors (e.g., human p55 and p75) and derivatives thereof (such as p55 kDTNFR-IgG (55 kD TNF receptor-IgG fusion protein, Lenercept™) and 75 kDTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™)); TNF enzyme antagonists (such as TACE inhibitors); antagonists of IL-12, IL-15, IL-17, IL-18, and IL-22; T cell and B cell depleting agents (such as anti-CD4 or anti-CD22 antibodies); small molecule inhibitors (such as methotrexate and leflunomide); sirolimus (rapamycin) and analogs thereof (e.g., CCI-779); Cox-2 and cPLA2 inhibitors; NSAIDs; p38, TPL-2, Mk-2, and NFκB inhibitors; RAGE or soluble RAGE; P-selectin or PSGL-1 inhibitors (such as small molecule inhibitors and antibodies to); estrogen receptor beta (ERB) agonists, and ERB-NFκB antagonists. Therapeutic agents that can be co-administered and/or co-formulated with at least one IL-21/IL-21R antagonist may include at least one of: a soluble fragment of a TNF receptor (e.g., human p55 or p75) such as 75 kDTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™); methotrexate; leflunomide; and sirolimus (rapamycin) or an analog thereof (e.g., CCI-779).

[0131] Non-limiting examples of agents for treating multiple sclerosis with which anti-IL-21R antibody can be combined include interferon-β (for example, IFNβ-1a and IFNβ-1b), copaxone, corticosteroids, IL-1 inhibitors, TNF inhibitors, antibodies to CD40 ligand, antibodies to CD80, and IL-12 antagonists.

[0132] Non-limiting examples of agents for treating inflammatory bowel disease or Crohn's disease with which an anti-IL-21R antibody can be combined include budenoside; epidermal growth factor; corticosteroids; cyclosporine; sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1 monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; TNF antagonists as described herein; IL-4, IL-10, IL-13, and/or TNFβ or agonists thereof (e.g., agonist antibodies); IL-11; glucuronide- or dextran-conjugated prodrugs of prednisolone, dexamethasone or budesonide; ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); slow-release mesalazine; methotrexate; antagonists of Platelet Activating Factor (PAF); ciprofloxacin; and lignocaine.

[0133] An anti-IL-21R antibody can be used in combination with at least one antibody directed at other targets involved in regulating immune responses, e.g., transplant rejection or graft versus host disease. Non-limiting examples of agents for treating immune responses with which an IL-21/IL-21R antagonist can be combined include the following: antibodies against cell surface molecules, including but not limited to CD25 (IL-2 receptor α), CD11a (LFA-1), CD54 (ICAM-1), CD4, CD45, CD28/CTLA4, CD80 (B7-1), CD86 (B7-2), or combinations thereof. An anti-IL-21R antibody is used in combination with at least one general immunosuppressive agent, such as cyclosporin A or FK506.

[0134] Another aspect of the present disclosure accordingly relates to kits for carrying out the combined administration of anti-IL-21R antibodies with other therapeutic agents. The kit comprises at least one anti-IL-21R antibody formulated in a pharmaceutical carrier, and at least one therapeutic agent, formulated as appropriate in one or more separate pharmaceutical preparations.

Diagnostic Uses

[0135] Antibodies according to this invention may also be used to detect the presence of IL-21R in biological samples. By correlating the presence or level of these proteins with a medical condition, one of skill in the art can diagnose the

associated medical condition. For example, stimulated T cells increase their expression of IL-21R, and an unusually high concentration of IL-21R expressing T cells in joints may indicate joint inflammation and possible arthritis. Illustrative medical conditions that may be diagnosed by the antibodies of this invention include multiple sclerosis, rheumatoid arthritis, and transplant rejection.

[0136] Antibody-based detection methods are well known in the art, and include ELISA, radioimmunoassays, immunoblots, Western blots; flow cytometry, immunofluorescence, immunoprecipitation, and other related techniques. The antibodies may be provided in a diagnostic kit that incorporates at least one of these procedures to detect IL-21R. The kit may contain other components, packaging, instructions, or other material to aid the detection of the protein and use of the kit.

[0137] Antibodies may be modified with detectable markers, including ligand groups (e.g., biotin), fluorophores and chromophores, radioisotopes, electron-dense reagents, or enzymes. Enzymes are detected by their activity. For example, horseradish peroxidase is detected by its ability to convert tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a spectrophotometer. Other suitable binding partners include biotin and avidin, IgG and protein A, and other receptor-ligand pairs known in the art.

[0138] Antibodies can also be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to at least one other molecular entity, such as another antibody (e.g., a bispecific or a multispecific antibody), toxins, radioisotopes, cytotoxic or cytostatic agents, among others. Other permutations and possibilities are apparent to those of ordinary skill in the art, and they are considered equivalents within the scope of this invention.

Pharmaceutical Compositions and Methods of Administration

[0139] Certain embodiments of the invention include compositions comprising the disclosed antibodies. The compositions may be suitable for pharmaceutical use and administration to patients. The compositions comprise an antibody of the present invention and a pharmaceutical excipient. As used herein, "pharmaceutical excipient" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, etc., that are compatible with pharmaceutical administration. Use of these agents for pharmaceutically active substances is well known in the art. Compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions. The pharmaceutical compositions may also be included in a container, pack, or dispenser together with instructions for administration.

[0140] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Methods to accomplish the administration are known to those of ordinary skill in the art. It may also be possible to create compositions which may be topically or orally administered, or which may be capable of transmission across mucous membranes. For example, the administration may be intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal.

[0141] Solutions or suspensions used for intradermal or subcutaneous application typically include at least one of the following components: a sterile diluent such as water, saline solution, fixed oils, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetate, citrate, or phosphate; and tonicity agents such as sodium chloride or dextrose. The pH can be adjusted with acids or bases. Such preparations may be enclosed in ampoules, disposable syringes, or multiple dose vials.

[0142] Solutions or suspensions used for intravenous administration include a carrier such as physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ), ethanol, or polyol. In all cases, the composition must be sterile and fluid for easy syringability. Proper fluidity can often be obtained using lecithin or surfactants. The composition must also be stable under the conditions of manufacture and storage. Prevention of microorganisms can be achieved with antibacterial and antifungal agents, e.g., parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, etc. In many cases, isotonic agents (sugar), polyalcohols (mannitol and sorbitol), or sodium chloride may be included in the composition. Prolonged absorption of the composition can be accomplished by adding an agent which delays absorption, e.g., aluminum monostearate and gelatin.

[0143] Oral compositions include an inert diluent or edible carrier. The composition can be enclosed in gelatin or compressed into tablets. For the purpose of oral administration, the antibodies can be incorporated with excipients and placed in tablets, troches, or capsules. Pharmaceutically compatible binding agents or adjuvant materials can be included in the composition. The tablets, troches, and capsules, may contain (1) a binder such as microcrystalline cellulose, gum tragacanth or gelatin; (2) an excipient such as starch or lactose, (3) a disintegrating agent such as alginic acid, Primogel, or corn starch; (4) a lubricant such as magnesium stearate; (5) a glidant such as colloidal silicon dioxide; or (6) a sweetening agent or a flavoring agent.

[0144] Compositions may also be administered by a transmucosal or transdermal route. For example, antibodies that comprise a Fc portion may be capable of crossing mucous membranes in the intestine, mouth, or lungs (via Fc receptors). Transmucosal administration can be accomplished through the use of lozenges, nasal sprays, inhalers, or suppositories.

Transdermal administration can also be accomplished through the use of composition containing ointments, salves, gels, or creams known in the art. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used. For administration by inhalation, antibodies are delivered in an aerosol spray from a pressured container or dispenser, which contains a propellant (e.g., liquid or gas) or a nebulizer.

[0145] In certain embodiments, antibodies of this invention are prepared with carriers to protect the antibodies against rapid elimination from the body. Biodegradable polymers (e.g., ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid) are often used. Methods for the preparation of such formulations are known by those skilled in the art. Liposomal suspensions can be used as pharmaceutically acceptable carriers too. The liposomes can be prepared according to established methods known in the art (U.S. Patent No. 4,522,811).

[0146] Antibodies or antibody compositions of the invention are administered in therapeutically effective amounts as described. Therapeutically effective amounts may vary with the subject's age, condition, sex, and severity of medical condition. Appropriate dosage may be determined by a physician based on clinical indications. Antibodies or compositions may be given as a bolus dose to maximize the circulating levels of antibodies for the greatest length of time. Continuous infusion may also be used after the bolus dose.

[0147] As used herein, the term "subject" is intended to include human and non-human animals. Subjects may include a human patient having a disorder characterized by cells that express IL-21R, e.g., a cancer cell or an immune cell. The term "non-human animals" of the invention includes all vertebrates, such as non-human primates, sheep, dogs, cows, chickens, amphibians, reptiles, etc.

[0148] Examples of dosage ranges that can be administered to a subject can be chosen from: 1 μ g/kg to 20 mg/kg, 1 μ g/kg to 10 mg/kg, 1 μ g/kg to 1 mg/kg, 10 μ g/kg to 1 mg/kg, 10 μ g/kg to 100 μ g/kg, 100 μ g to 1 mg/kg, 500 μ g/kg to 1 mg/kg.

[0149] It may be advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited for the patient. Each dosage unit contains a predetermined quantity of antibody calculated to produce a therapeutic effect in association with the carrier.

The dosage unit depends on the characteristics of the antibodies and the particular therapeutic effect to be achieved.

[0150] Toxicity and therapeutic efficacy of the composition can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Antibodies that exhibit large therapeutic indices may be less toxic and/or more therapeutically effective.

[0151] The data obtained from the cell culture assays and animal studies can be used to formulate a dosage range in humans. The dosage of these compounds may lie within the range of circulating antibody concentrations in the blood, that includes an ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage composition form employed and the route of administration. For any antibody used in the present invention, the therapeutically effective dose can be estimated initially using cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of antibody which achieves a half-maximal inhibition of symptoms). The effects of any particular dosage can be monitored by a suitable bioassay. Examples of suitable bioassays include DNA replication assays, transcription-based assays, IL-21R/IL-21 binding assays, and other immunological assays.

[0152] The following examples do not in any way limit the scope of the invention. One of ordinary skill in the art will recognize the numerous modifications and variations that may be performed without altering the spirit or scope of the present invention. Such modifications and variations are encompassed within the scope of the invention.

EXAMPLES

Example 1: Selection of MUF and MU11 Anti-IL-21R scF_v's

[0153] An scF_v phagemid library, which is an expanded version of the 1.38x10¹⁰ library described by Vaughan et al. ((1996) Nature Biotech., 14: 309-314), was used to select antibodies specific for human IL-21R. Wells of microtiter plates were coated with soluble IL-21R fusion protein or control fusion protein (5-20 μ g/ml in phosphate buffered saline (PBS)) and incubated overnight at 4°C. Wells were washed in PBS, then blocked for 1 hour at 37°C in MPBS (3% milk powder in PBS). Purified phage (10¹² transducing units), blocked for 1 hour in MPBS, were added to the control fusion protein coated wells and incubated for 1 hour. The unbound phage was then transferred to IL-21R fusion protein wells and incubated for one hour. Wells were washed 5 times with PBST (0.1 % v/v Tween 20 in PBS), then 5 times with PBS. Bound phage were eluted and used to infect exponentially growing *E. coli* TG1. Infected cells were grown in 2TY broth for 1 hour at 37°C, then streaked onto 2TYAG plates and incubated overnight at 30°C. The next day, colonies were transferred into 10 ml of 2TY broth plus 15% glycerol and stored at -70°C. Later, colonies from this first round of selection were thawed and superinfected with helper phage to rescue (generate) scF_v antibody-expressing phage for a second

round of selection.

Example 2: Selection of R18 and 19F5 Anti-IL-21R scFvs

[0154] Anti-IL21R scFv (R18) was isolated using 200 nM of biotinylated human IL-21R fusion protein (bio.hIL21R) (Wyeth, Giralda Farms, NJ) in solution. Purified scFv phage (10^{12} tu) was blocked with MPBS and 125 μ g/ml control fusion protein, as described above in Example 1. Biotinylated IL-21R fusion protein was added to the blocked phage to a final concentration of 200 nM and incubated for 1 hour at room temperature. Phage/antigen was added to 75 μ l of Dynal M280 Streptavidin magnetic beads (Dynal Biotech Inc., Lake Success, NY) that had been blocked for 90 minutes at room temperature in 1 ml of 3% MPBS. The mixture was incubated for 15 minutes at room temperature with mixing. Beads were captured using a magnetic rack and washed 5 times in 1 ml PBST followed by three washes in PBS. Bound phage were eluted with 500 μ l of 10 μ g/ml trypsin in 0.2 M sodium phosphate buffer, pH 7.0 and incubated at 37°C for 30 minutes. Eluted phage were used to infect 10 ml exponentially growing *E. coli* TG-1 cells as described above. ScFv clones were isolated after three rounds of selection.

[0155] ScFv production was induced by addition of 1 mM IPTG to exponentially growing cultures and incubation overnight at 30°C. Crude scFv-containing periplasmic extracts (Griffiths et al. (1993) EMBO J., 12:725-734) were screened for the ability to inhibit the binding of human IL-21R fusion protein to human IL-21-FLAG tagged protein. Briefly, anti-FLAG antibody was immobilized onto plastic and used to capture FLAG-tagged human IL-21 protein. Binding of human IL-21R fusion protein was detected with a Europium-labelled antibody to the IL-21R fusion protein, and time resolved fluorescence was detected with the DELFIA reagent kit (PerkinElmer, Boston, MA). Purified scFv R18 clone exhibited an IC_{50} value of 770 nM for inhibition of IL-21R fusion protein binding to IL-21-FLAG tagged protein.

[0156] Anti-IL21R clone 19F5 was isolated by selection method as used for R18, except that 50 nM of human IL-21R fusion protein was used in the third round of selection.

Example 3: Selection of 18A5 and 18G4 Anti-IL-21R scFvs

[0157] Anti-IL21R scFvs, 18A5 and 18G4, were isolated by selecting on IL-21R expressing cell lines and IL-21R fusion protein in solution. Transfected hBaf3Mu-1 cells (Wyeth, Giralda Farms, NJ) expressing the human IL-21R on the cell surface were cultured using standard tissue culture methods. Purified scFv phage (10^{12} tu) were blocked with 1×10^8 un-transfected Baf3 cells for 1 hour at room temperature in MPBS.

[0158] Blocked phage were added to 1×10^7 hBaf3Mu-1 cells, which had been pre-incubated in MPBS for 1 hour. This was followed by incubation for one hour at room temperature with mixing. The hBaf3Mu-1 cells were subsequently washed 6 times in PBST. Specifically bound phage were eluted from the cells using 10 μ g/ml of trypsin in 0.2 M sodium phosphate buffer, pH 7.0, and incubated at 37°C for 30 minutes with shaking. The eluted phage supernatant was used to infect *E. coli* TG-1 cells as described above.

[0159] ScFv-expressing phage for the second round of selection were produced as described above. Phage were blocked with MPBS and 125 μ g/ml control fusion protein. Selection was carried out in solution with biotinylated human IL-21R fusion protein (Wyeth) following selection method described for R18, except that beads were washed 5 times in 1 ml of MPBS / 0.1 % (v/v) Tween 20 followed by three washes in PBS.

[0160] ScFv antibody-expressing phage particles were then further selected using selection method using hBaf3Mu-1 cells, as described above.

Example 4: Selection of CP5G2 Anti-IL-21R scFv

[0161] Clone CP5G2 was isolated by selection on murine IL-21R tagged with hexahistidine and a Flag affinity tag (hIL21R.His.Flag) (Wyeth, Giralda Farms, NJ). Purified scFv phage (10^{12} tu) were blocked with MPBS plus 30 μ l anti-Flag agarose beads for 1 hour at room temperature. hIL-21R.His.Flag, at a final concentration of 25 nM in MPBS, was added to blocked phage and incubated at room temperature for 1 hour. The library/antigen mixture was then added to 100 μ l of anti-Flag agarose beads that had been blocked in MPBS for 2 hours at room temperature, washed 3 times in PBS, and incubated a further 30 minutes with mixing. The beads were washed 4 times with PBST, followed by 4 times with PBS and the phage were eluted from the beads with 0.5 μ g/ml trypsin in 50 mM Tris, pH 8.0, 1 mM $CaCl_2$, as described above. Beads were collected using centrifugation. Eluted phage were used to infect 10 ml *E. coli* TG-1 cells, as described above. A second round of soluble selection was carried out, also as described above.

[0162] Colonies were picked into 96 well plates containing 100 μ l of 2TYAG. Crude scFv-containing periplasmic extracts were produced as described above, except the buffer used was 20% (w/v) sucrose, 50mM Tris-HCl, pH 7.5, 1 mM EDTA. Crude scFv-containing extracts were screened for the ability to inhibit the binding of 16 ng/ml biotinylated murine IL-21 (bio.mIL21) to murine IL-21R protein immobilized on plastic in a 96 well microtitre plate assay. Binding of bio.mIL21 was detected with Europium-labelled streptavidin and TRF detected using the DELFIA reagent kit (PerkinElmer,

Boston, MA).

[0163] Purified CP5G2 scFv exhibited an IC₅₀ value of 590 nM in the above assay for inhibition of binding of IL-21 to IL-21R.

Example 5: Identification of scF_v's from MUF and MU11 phage clones

[0164] To establish the specificity of the scF_v's for IL-21R, a phage ELISA was performed against the IL-21R fusion protein. Individual TG1 cell colonies from the second selection were transferred to microtiter wells containing 100 µl of 2TYAG medium. M13K07 helper phage (10 moi) was added to the exponentially growing TG1 culture, and the samples were incubated for one hour at 37°C. Plates were centrifuged and supernatant was removed, then the remaining pellets were suspended in 100 µl of 2TYAG and incubated overnight at 30°C with shaking. The next day, plates were centrifuged and phage supernatant was transferred to new microtiter plate wells. Phage was blocked in MPBS prior to ELISA.

[0165] Wells of microtiter plates were coated with IL-21R fusion protein or control fusion protein (0.5-2.5 µg/ml) and incubated overnight at 4°C. The next day, fusion protein solution was removed and wells were blocked for 1 hour in MPBS. Wells were washed with PBS, then 50 µl of blocked phage was added. Plates were incubated for 1 hour, then washed 3 times with PBST and 3 times with PBS. Anti-M13-HRP conjugate (Pharmacia, Peapack, NJ) was added to wells, and the samples were incubated for one hour. Wells were washed 3 times with PBST and 3 times with PBS. TMB was added to wells, and the samples were incubated until color developed. The reaction was stopped with 25 µl of 0.5 M H₂SO₄. The color signal was measured by reading absorbance at 450 nm using a microtiter plate reader. Two phage clones showed specific binding to the IL-21R fusion protein and not the control fusion protein, and these clones are referred to in this application as MUF and MU11 phage clones.

[0166] Individual TG-1 colonies containing MUF and MU11 phage clones were streaked onto 2TYAG plates and incubated overnight at 30°C. Using pCANTAB6 vector specific oligos, the V_H and V_L regions of the phage were amplified by PCR and sequenced. Database searches revealed that the V_L region of the MUF phage clone originated from lambda chain, and the V_L region of the MU11 phage clone originated from kappa chain.

Example 6: Conversion of scF_v to IgG

[0167] The V_H and V_L regions from the MUF and MU11 phage clones were amplified by PCR using clone-specific primers. The PCR products were digested with restriction enzymes and subcloned into appropriate vectors (see Example 2) containing the human IgG₁ heavy chain constant domain (Takahashi et al. (1982) Cell 29, 671) or the human lambda light chain constant domain or the human kappa light chain constant domain (Hieter et al. (1982) Nature 294: 536). The four constructs encode polypeptides referred to in this application as MUF heavy chain, MUF light chain, MU11 heavy chain, and MU11 light chain.

[0168] Vectors containing MUF heavy chain, MUF light chain, MU11 heavy chain, and MU11 light chain, were prepared, sequenced, and used to transfect HEK293 or CHO cells using standard techniques. Cells expressing MUF heavy and light chains produced MUF antibody, which is referred to in this application as "MUF", and cells expressing MU11 heavy and light chains produced MU11 antibody, which is referred to in this application as "MU11." Secreted antibodies were purified using protein A Sepharose (Pharmacia), then dialyzed with PBS.

[0169] Binding specificity of antibodies were determined as follows: ELISA plates were coated overnight with 2.5 µg/ml of IL-21R fusion protein. Plates were washed with PBSB (PBS + 1 % bovine serum albumin), then incubated with various concentrations of MUF or MU11 for 2 hours at 25°C. The plates were washed, then a saturating amount of HRP-conjugated goat anti-human antibody was added. The plates were incubated for 1 hour at 25°C, then washed with PBSB, and developed with using TMB. An example of the results obtained by the ELISA is presented in Figure 1A.

[0170] Binding specificity of the antibodies was further confirmed by cell surface staining. Human IL-21R transduced TF-1 cells were bound with purified or biotinylated MUF or MU11 (1 mg/ml). Cells were incubated on ice for 30 minutes, washed with PBSB, then suspended in a solution containing PE-conjugated anti-human IgG antibody or PE-conjugated avidin. Cells were incubated on ice for 30 minutes, washed, then analyzed on a FACScan. The results are presented in Figure 1B. Purified mouse B cells were similarly stained with MUF, and the results are presented in Figure 1C.

Example 7: MUF Blocks Binding of IL-21 to IL-21R

[0171] Inhibition assays were performed to assess the ability of the antibodies to block binding of IL-21 to IL-21R. The ELISA was performed as described in Example 3 with the following modifications. After incubation with MUF or MU11 for 2 hours at 25°C, biotin-conjugated IL-21 (1 µg/ml) was added, and the samples were incubated for 1 hour at 25°C. After washing, saturating amount of avidin-HRP was added, and the samples were further incubated for 1 hour at 25°C. The wells were washed with PBSB, and the samples were developed using TMB. Results are presented in Figure 2. Under these conditions, MUF blocked the binding of IL-21 to IL-21R, whereas MU11 did not. These data suggest that

MUF and MU11 recognize different epitopes of IL-21R.

Example 8: MUF and MU11 Decrease T Cell Responses

[0172] Proliferation assays were performed to assess the antibody's ability to block the IL-21 mediated T cell proliferation. Human CD4⁺ T cells (5×10^4 cells/well) were stimulated with PHA (phytohemagglutinin) and human IL-21. IL-21 in COS cell culture media (COS CM) was added to different samples at various concentrations. In indicated samples, MUF, MU11, or human IgG₁ isotype control were added. After 72 hours, ³H-thymidine was added, and cell proliferation was measured by incorporated radioactivity using a LKB 1205 liquid scintillation counter. As shown in Figure 3A, IL-21 increased the proliferation of PHA-stimulated T cells. Addition of MUF blocked the ability of IL-21 to increase proliferation in the range between about 1:500 and 1:10,000. MUF blockage was overcome at higher doses of IL-21. Addition of MU11 or isotype control antibody did not significantly affect IL-21 augmented proliferation of human T cells.

[0173] In Figure 3B, a PLP-specific mouse CD4⁺ T cell line was stimulated with PLP peptide (1 μ g/ml) and SJL mouse spleen cells. IL-21 in COS cell culture media (COS IL-21) was titrated as shown on the X-axis. "Cos Mock" is COS culture medium without IL-21. In indicated samples, MU11 (1 μ g/ml) was added. After 72 hours, ³H-thymidine was added, and proliferation was measured by incorporated radioactivity. As shown in Figure 3B, IL-21 increased the proliferation of stimulated mouse T cells. Addition MU11 blocked the ability of IL-21 to increase proliferation of mouse CD4⁺ T cells. These data suggest that MU11 acts as a non-competitive inhibitor: it blocks IL-21's ability to increase proliferation even though it does not block IL-21 binding to the receptor.

[0174] In Figure 3C, purified CD8⁺ mouse T cells were stimulated with tosyl-beads (Dynal, Great Neck, NY) coated with anti-CD3 antibody. IL-21 in COS cell culture media (COS s/n) was titrated as indicated in the X-axis. The sample labeled "no antibody" was used as a control. In indicated samples, MU11 was added at the marked concentration. After 72 hours, ³H-thymidine was added, and proliferation was measured by incorporated radioactivity. As shown in Figure 3C, the addition of MU11 blocked, in a dose dependent manner, the ability of IL-21 to increase the proliferation of CD8⁺ T cells.

Example 9: Inhibition of Cell Proliferation by scFvs and IgGs

[0175] Antibodies of the invention were tested in a cell-based assay for IL-21R antagonism. In one such experiment, various scFv phage clones that were isolated as described in Examples 1-3, were tested in a cell-based assay for their potency to inhibit cell-proliferation by blocking IL-21 binding to IL-21R. A hBaf3Mu-1 cell suspension expressing human IL21R was used for such an assay. hBaf3Mu-1 cells (Wyeth) were washed to remove traces of murine IL-3 from their growth medium and incubated for 2 hours in growth RPMI Glutamax with 10% fetal bovine serum without IL-3 at 37°C in a 5% CO₂ incubator. About 10,000 to 20,000 Baf3Mu-1 cells were added to each well of a 96-well tissue culture plate and then incubated with an scFv or IgG for 30 minutes at 37°C. IL-21 (Wyeth, Giralda Farms, NJ) was then added to a concentration of 5 ng/ml and the cells were incubated for 24 hours. Cells were then pulse-labeled with 0.1 mCi/well ³H thymidine overnight at 37°C and subsequently harvested to measure thymidine incorporation as an indication of proliferation of cells. An alternative protocol, IL-21 was added to a concentration of 0.3 ng/ml and the cells were incubated for 48 hours. Cells were then warmed to room temperature, and 15 ml/well CellTiter-Glo (Promega, WI) were added. After mixing and a 10 minute incubation period, luminescence was measured on a Wallac MicroBeta 1450 TriLux counter (PerkinElmer, Boston, MA) as an indication of cell proliferation or viability.

[0176] An IC₅₀ value (i.e., concentration of an antibody required for 50% competition) for each scFv can be determined by plotting a measure of cell proliferation, e.g., thymidine incorporation, against the log concentration of IL-21. Typically, the lower an IC₅₀, the better affinity an antibody has for IL-21R. In one experiment depicted in FIG. 4, MUF inhibited cell response to IL-21 with an IC₅₀ of 268nM as an scFv and 3nM as an IgG. The IC₅₀ values of other scFv clones were subsequently compared with that of MUF, as summarized in Table 4 below.

Table 4: IC₅₀ values of various scFvs

Clone	IC ₅₀ Value (nM) ScFv
MUF	140
hIL21R18	473
18A5	213
18G4	522
19F5	91

(continued)

Clone	IC ₅₀ Value (nM) ScFv
CP5G2	329

Example 10: MUF Germlining

[0177] Sequence data for the scFv clones was used to identify the nearest germline sequence for the heavy and light chain of the MUF clone using VBASE. Mutations were made using standard site directed mutagenesis techniques with the appropriate mutagenic primers. Mutation of scFv sequences was confirmed by sequence analysis. Germlined scFv and V_H and V_L domain sequences for MUF are set forth in SEQ ID NO:85, 83 and 84, respectively.

[0178] The MUF scFv germlined sequence was subsequently assayed for its ability to block IL-21 induced hBaf3Mu-1 cell line proliferation in the assay described herein. There was no significant difference in the potency of the germlined MUF to block Baf3Mu-1 cell proliferation when compared to the non-germlined MUF scFv.

Example 11: Epitope Competition Assay

[0179] The scFv clones 18A5, 19F5 and 18G4 were further tested in an epitope competition assay in order to determine whether they bound the same or a different epitope than MUF. ScFv-containing periplasmic extracts were prepared as described above for the various clones. Final buffer used was 50 mM MOPS, pH 7.4, 0.5 mM EDTA, 0.5 M sorbitol. The scFv-containing crude periplasmic extracts were screened for the ability to inhibit the binding of biotinylated human IL-21R fusion protein (bio.hIL21R) to MuF IgG protein immobilized on plastic in a 96 well microtitre plate assay. Binding of bio.hIL21R was detected with Europium-labelled streptavidin and TRF detected using the DELFIA reagent kit (PerkinElmer). Positive clones were used in an epitope competition assay described herein.

[0180] The IC₅₀ values obtained for the various clones in the epitope competition assay are summarized in Table 5.

Table 5: Epitope Competition Assay

Clone	IC ₅₀ (nM)
MUF IgG	0.4
negative control	0.0
18A5	114
18G4	1.4
19F5	weak inhibition

Example 12: Treatment of Arthritis

[0181] IL-21 was used to study its effect on cells from the synovial membrane, the membrane that lines the joints. Human fibroblast-like synoviocytes (HFLS) (Cell Applications (San Diego, CA)) were isolated from synovial tissues of rheumatoid arthritis patients undergoing joint surgery. HFLS cells were cultured with human IL-21 for 48 hours, and the supernatants were removed and tested for chemokines MCP-1 (monocyte chemoattractant protein or CCL11), GRO (growth-regulated oncogene or CXC ligand 1), I-309 (CCL1), TARC (thymus and activation-regulated chemokine), Eotaxin, MDC (macrophage-derived chemokine or CCL22), LYMPH (lymphotactin or XCL1), SDF-1 B (stromal derived factor-1B or CXC ligand 12), IP-10 (CXC ligand 10), I-TAC (T-cell attracting chemokine or CXC ligand 11), MG (monokine induced by interferon or CXC ligand 9), MP3B (macrophage inhibitory protein) and cytokines IFN- α , TNF- α , IL-6, and IL-8 by ELISA. These chemokines and cytokines are known in the art to promote inflammation through a number of activities, and increased concentrations in the joints caused by IL-21 exacerbates inflammation and RA.

[0182] As shown in Figures 5A-5D, IL-21 repeatedly increased HFLS secretion of chemokines MCP-1, GRO, I-309, TARC, Eotaxin, MDC, LYMPH, SDF-1B, IP-10, I-TAC, MG, MP3B and cytokines IFN- α , TNF- α , IL-6, and IL-8. IL-21 was used to regulate the clinical progression of CIA (Collagen Induced Arthritis). CIA is the standard mouse and rat model for studying rheumatoid arthritis, see e.g., Holmdahl et al., (2002) Ageing Res. Rev., 1:135. On day 0, mice were injected with 100 μ g of Collagen Type II in complete Freund's adjuvant, and on day 21, the mice were boosted with 100 μ g of Collagen Type II in incomplete Freund's adjuvant. On day 21, the mice were also injected daily with 1 μ g of IL-21, and each day, the mice were examined for disease. The clinical signs were scored as follows: 0 = no swelling,

1 = 1 to 2 swollen digits or swollen ankle, 2 = more than 2 swollen digits or mild paw swelling, 3 = extensive paw swelling, and 4 = ankylosis of paw. As shown in Figure 5E, mice injected with PBS after the collagen injections progressively developed disease. Mice injected with IL-21 after the collagen injections progressively developed more severe disease. Because treatment with IL-21 specifically exacerbates CIA, treatment with anti-IL-21R antibodies is expected to suppress or delay CIA. Thus, since this model predicts treatment efficacy for RA, treatment with anti-IL-21R antibodies would also be expected to suppress or delay RA in humans.

Example 13: Treatment of Transplant Rejection

[0183] Transplant rejection is the immunological phenomenon where tissues from a donor are specifically "attacked" by immune cells of the host. One assay to study transplant rejection *in vitro* is the mixed lymphocyte reaction (MLR). In the MLR assay, "donor" cells and "host" cells are mixed *in vitro*, and the host cells become activated and proliferate. Between day 3 and 5, ³H-thymidine is added, and proliferation is measured by incorporated radioactivity using a liquid scintillation counter.

[0184] In Figure 6, C57BL/6J mouse spleen cells (500,000) and irradiated BDF1 mouse spleen cells (500,000) were suspended in 200 μ l of culture media in a microtiter plate well. Three duplicate wells were supplemented with different amounts of mouse IL-21. On day 4, ³H-thymidine was added, and day 5, incorporated radioactivity was measured using a LKB 1205 liquid scintillation counter. Samples "0" and "mock" indicate cultures without IL-21. In the absence of IL-21, C57BL/6J cells proliferated modestly (~6000 rads). In the presence of IL-21, C57BL/6J cells proliferated more strongly (~28,000-38,000 rads). Treatment with IL-21 augments the proliferation of C57BL/6J cells (the "host" or alloreactive cells), suggesting that IL-21 mediates MLR. Addition or treatment with anti-IL-21R antibodies is, therefore, expected to suppress or delay MLR and transplant rejection and related diseases (e.g., graft versus host disease).

SEQUENCE LISTING

[0185]

<110> WYETH

CAMBRIDGE ANTIBODY TECHNOLOGY

<120> ANTIBODIES AGAINST HUMAN IL-21 RECEPTOR AND USES THEREFOR

<130> 08702.0137-00304

<140>

<141>

<150> 60/454,336 <151> 2003-03-14

<160> 154

<170> PatentIn Ver. 3.2

<210> 1

<211> 113

<212> PRT

<213> Homo sapiens

<400> 1

EP 1 603 949 B9

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

<210> 2
 <211> 113
 <212> PRT
 <213> Homo sapiens

<400> 2

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

<210> 3
 <211> 253
 <212> PRT

EP 1 603 949 B9

<213> Homo sapiens

<400> 3

```

5      Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
      1          5          10          15

      Ser Val Arg Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Ile Tyr
          20          25          30

10     Ser Val Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
          35          40          45

      Gly Arg Ile Ile Pro Met Arg Asp Ile Ala Asn Tyr Ala Gln Arg Phe
          50          55          60

15     Gln Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Ser Gly Thr Ala Tyr
          65          70          75          80

      Met Glu Leu Arg Gly Leu Arg Ser Asp Asp Thr Ala Val Tyr Trp Cys
          85          90          95

20     Ala Thr Leu Ala Gly Pro Leu Asp Ser Trp Gly Gln Gly Thr Leu Val
          100          105          110

      Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
          115          120          125

25     Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
          130          135          140

      Val Gly Leu Gly Gln Thr Val Thr Ile Thr Cys Gln Gly Gly Ser Leu
          145          150          155          160

30

35     Arg Gln Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
          165          170          175

      Val Val Val Ile Tyr Gly Lys Asn Lys Arg Pro Ser Gly Ile Pro Asp
          180          185          190

40     Arg Phe Ser Gly Thr Thr Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
          195          200          205

      Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp
          210          215          220

45     Ser Ser Gly Asn His Pro Leu Tyr Val Phe Gly Ala Gly Thr Lys Leu
          225          230          235          240

      Thr Val Leu Gly Ala Ala Ala His His His His His His
          245          250

50

```

<210> 4

<211> 5

<212> PRT

<213> Homo sapiens

<400> 4

EP 1 603 949 B9

Ile Tyr Ser Val Ser
1 5

5 <210> 5
<211> 17
<212> PRT
<213> Homo sapiens

10 <400> 5

Arg Ile Ile Pro Met Arg Asp Ile Ala Asn Tyr Ala Gln Arg Phe Gln
1 5 10 15

15 Gly

<210> 6
<211> 7
20 <212> PRT
<213> Homo sapiens

<400> 6

25 Leu Ala Gly Pro Leu Asp Ser
1 5

<210> 7
30 <211> 11
<212> PRT
<213> Homo sapiens

<400> 7

35 Gln Gly Gly Ser Leu Arg Gln Tyr Tyr Ala Ser
1 5 10

40 <210> 8
<211> 7
<212> PRT
<213> Homo sapiens

45 <400> 8

Gly Lys Asn Lys Arg Pro Ser
1 5

50 <210> 9
<211> 13
<212> PRT
<213> Homo sapiens

55 <400> 9

EP 1 603 949 B9

Lys Ser Arg Asp Ser Ser Gly Asn His Pro Leu Tyr Val
1 5 10

5 <210> 10
<211> 339
<212> DNA
<213> Homo sapiens

10 <400> 10

15 cagggtccagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgagggtc 60
tcttgcaagg cttctggagg caccttcaac atctatagtg tcagctgggt gcgacaggcc 120
cctggacagg ggcttgagtg gatgggaagg atcatcccta tgcgtgatat tgcaaactac 180
gcgcagaggt tccagggcag ggtcacactt accgcggaac agtcctcggg gacagcctac 240
atggagttgc gcggcctgag atctgacgac acggccgtct attggtgtgc gacattggct 300
ggcccccttg actcctgggg ccagggcacc ctggtcacc 339

20 <210> 11
<211> 339
<212> DNA
<213> Homo sapiens

25 <400> 11

30 tcgtctgagc tgactcagga cccagctgtg tctgtgggct tgggacagac agtcacgata 60
acatgtcaag gcggcagcct cagacaatat tatgcaagtt ggtaccaaca gaagccagga 120
caggccccctg tgggtgtcat ctatggtaaa aataagcgac cctcagggat cccagaccga 180
ttctctggca ccacctcagg caacacagct tcttgacca tcactggggc tcaggcggaa 240
gatgaggctg actactattg taagtcccg gacagcagtg gtaaccatcc cttttatgtc 300
ttcggagcag ggaccaagct gaccgtccta ggtgagtca 339

35 <210> 12
<211> 759
<212> DNA
<213> Homo sapiens

40 <400> 12

45 cagggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgagggtc 60
tcttgcaagg cttctggagg caccttcaac atctatagtg tcagctgggt gcgacaggcc 120
cctggacagg ggcttgagtg gatgggaagg atcatcccta tgcgtgatat tgcaaactac 180
gcgcagaggt tccagggcag ggtcacactt accgcggaac agtcctcggg gacagcctac 240
atggagttgc gcggcctgag atctgacgac acggccgtct attggtgtgc gacattggct 300
ggcccccttg actcctgggg ccagggcacc ctggtcaccg tctcgagtgg aggcggcggg 360
tcaggcggag gtggctctgg cgggtggcga agtgactttt cttctgagct gactcaggac 420
ccagctgtgt ctgtgggctt gggacagaca gtcacgatca catgtcaagg cggcagcctc 480
agacaatat atgcaagttg gtaccaacag aagccaggac agggccctgt ggttgtcatc 540
tatggtaaaa ataagcgacc ctccaggatc ccagaccgat tctctggcac cacctcaggc 600
aacacagctt ccttgaccat cactggggct caggcgggaag atgaggctga ctactattgt 660
aagtcgccgg acagcagtg taaccatccc ctttatgtct tcggagctgg gaccaagctg 720
accgtcctag gtgcggccgc acatcatcat caccatcac 759

55 <210> 13
<211> 15
<212> DNA

<213> Homo sapiens
 <400> 13
 atctatagtg tcagc 15
 5
 <210> 14
 <211> 51
 <212> DNA
 <213> Homo sapiens
 10
 <400> 14
 aggatcatcc ctatgctga tattgcaaac tacgcgaga ggtccaggg c 51
 15
 <210> 15
 <211> 21
 <212> DNA
 <213> Homo sapiens
 20
 <400> 15
 ttggctggcc ccttgactc c 21
 25
 <210> 16
 <211> 33
 <212> DNA
 <213> Homo sapiens
 30
 <400> 16
 caaggcggca gcctcagaca atattatgca agt 33
 35
 <210> 17
 <211> 21
 <212> DNA
 <213> Homo sapiens
 40
 <400> 17
 ggtaaaaata agcgaccctc a 21
 45
 <210> 18
 <211> 39
 <212> DNA
 <213> Homo sapiens
 50
 <400> 18
 aagtccggg acagcagtg taaccatccc cttatgtc 39
 55
 <210> 19
 <211> 118
 <212> PRT
 <213> Homo sapiens
 <400> 19

EP 1 603 949 B9

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

25 <210> 20
 <211> 108
 <212> PRT
 <213> Homo sapiens

30 <400> 20

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

55 <210> 21
 <211> 242
 <212> PRT

EP 1 603 949 B9

<213> Homo sapiens

<400> 21

5	Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg	1 5 10 15
	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	20 25 30
10	Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35 40 45
	Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val	50 55 60
15	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	65 70 75 80
	Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys	85 90 95
20	Ala Arg His Gly Gln Tyr Ala Leu Asp Ile Trp Gly Gln Gly Thr Met	100 105 110
	Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly	115 120 125
25	Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser	130 135 140
	Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly	145 150 155 160
30	Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro	165 170 175
	Lys Val Leu Ile Tyr Lys Ala Ser Thr Leu Glu Ser Gly Val Pro Ser	180 185 190
35	Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser	195 200 205
40		
	Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr	210 215 220
45	Ser Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg	225 230 235 240
50	Ala Ala	

<210> 22

<211> 5

<212> PRT

<213> Homo sapiens

<400> 22

EP 1 603 949 B9

Ser Tyr Gly Met His
1 5

5 <210> 23
<211> 17
<212> PRT
<213> Homo sapiens

10 <400> 23

Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

15 Gly

<210> 24
<211> 9
20 <212> PRT
<213> Homo sapiens

<400> 24

25 His Gly Gln Tyr Ala Leu Asp Ile Trp
1 5

<210> 25
30 <211> 11
<212> PRT
<213> Homo sapiens

<400> 25

35 Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

40 <210> 26
<211> 7
<212> PRT
<213> Homo sapiens

45 <400> 26

Lys Ala Ser Thr Leu Glu Ser
1 5

50 <210> 27
<211> 9
<212> PRT
<213> Homo sapiens

55 <400> 27

EP 1 603 949 B9

Gln Gln Ser Tyr Ser Thr Pro Trp Thr
1 5

5 <210> 28
<211> 417
<212> DNA
<213> Homo sapiens

10 <400> 28

atgaaattct tagtcaacgt tgcccttgtt tttatggctg tgtacatttc ttacatctat 60
gcccaggtgc agctggtgga gtctggggga ggcgtgggtcc agcctgggag gtccctgaga 120
ctctcctgtg cagcctcttg attcaccttc agtagctatg gcatgcactg ggtccgccag 180
15 gctccaggca aggggctgga gtgggtggca gttatatcat atgatggaag taataaatac 240
tatgcagact ccgtgaaggg ccgattcacc atctccagag acaattccaa gaacacgctg 300
tatctgcaaa tgaacagcct gagagacgag gacacggctg tgtattactg tgcgaggcat 360
ggtcagtacg ctcttgatat ctggggggcaa gggacaatgg tcaccgtctc ctcaggt 417

20 <210> 29
<211> 381
<212> DNA
<213> Homo sapiens

25 <400> 29

atgggatgga gctgtatcat cctcttcttg gtagcaacag ctacaggcgc gcactccgac 60
atccagatga ccaggtctcc ttccaccctg tctgcatctg taggagacag agtcaccatc 120
30 acttgccggg ccagtcaggg tattagtagc tgggtggcct ggtatcagca gaaaccaggg 180
agagccccta aggtcttgat ctataaggca tctactttag aaagtggggg cccatcaagg 240
ttcagcggca gtggatctgg gacagatttc actctcacca tcagcagctc gcaacctgaa 300
gattttgcaa cttactactg tcaacagagt tacagtaccc cgtggacgtt cggccaaggg 360
accaagctcg agatcaaacg t 381

35 <210> 30
<211> 728
<212> DNA
40 <213> Homo sapiens

<400> 30

gaggtgcagc tgggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatac acagcctgag agacgaggac acggctgtgt attactgtgc gaggcattgt 300
cagtacgctc ttgatatact ggggcaaggg acaatgggtc ccgtctcttc aggtggaggc 360
50 gggtcaggcg gaggtggcag cggcgggtggc ggatcggaca tcgtgatgac ccagtctcct 420

55

EP 1 603 949 B9

tccaccctgt ctgcatctgt aggagacaga gtcaccatca cttgccgggc cagtcagggg 480
 attagtagct gggtggcctg gtatcagcag aaaccaggga gagcccctaa ggtcttgatc 540
 tataaggcat ctactttaga aagtgggggc ccatcaagggt tcagcggcag tggatctggg 600
 5 acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt 660
 caacagagtt acagtacccc gtggacgttc ggccaaggga ccaagctgga gatcaaactg 720
 gcggccgc 728

10 <210> 31
 <211> 18
 <212> DNA
 <213> Homo sapiens

15 <400> 31
 agtagctatg gcatgcac 18

20 <210> 32
 <211> 51
 <212> DNA
 <213> Homo sapiens

25 <400> 32
 gttatatcat atgatggaag taataaatac tatgcagact ccgtgaaggg c 51

30 <210> 33
 <211> 30
 <212> DNA
 <213> Homo sapiens

35 <400> 33
 aggcattggtc agtacgctct tgatatctgg 30

40 <210> 34
 <211> 33
 <212> DNA
 <213> Homo sapiens

45 <400> 34
 cgggccagtc aggtattag tagctggtg gcc 33

50 <210> 35
 <211> 21
 <212> DNA
 <213> Homo sapiens

55 <400> 35
 aaggcatcta ctttagaaag t 21

60 <210> 36
 <211> 27
 <212> DNA
 <213> Homo sapiens

65 <400> 36 27
 caacagagtt acagtacccc gtggacg 27

70 <210> 37

EP 1 603 949 B9

<211> 329
 <212> PRT
 <213> Homo sapiens

5 <400> 37

	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Gly	
	1				5					10					15		
10	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	
				20					25					30			
	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	
			35					40					45				
15	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	
	50						55					60					
	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	
	65					70					75					80	
20	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	
					85					90					95		
	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	
				100					105					110			
25	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	
				115				120					125				
	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	
	130					135						140					
	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	
	145					150					155					160	
35	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	
					165					170					175		
	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	
				180					185					190			
40	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	
			195					200					205				
	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	
	210						215					220					
45	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	
	225				230						235					240	
	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	
					245					250					255		
50																	
55																	

EP 1 603 949 B9

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
260 265 270

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
275 280 285

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
290 295 300

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
305 310 315 320

Lys Ser Leu Ser Leu Ser Pro Gly Lys
325

<210> 38
<211> 1599
<212> DNA
<213> Homo sapiens

<400> 38

```

g c c t c c a c c a   a g g g c c c a t c   g g t c t t c c c c   c t g g c a c c c t   c c t c c a a g a g   c a c c t c t g g g   60
g g c a c a g c g g   c c c t g g g c t g   c c t g g t c a a g   g a c t a c t t c c   c c g a a c c g g t   g a c g g t g t c g   120
t g g a a c t c a g   g c g c c c t g a c   c a g c g g c g t c   c a c a c c t t c c   c g g c t g t c c t   a c a g t c c t c a   180
g g a c t c t a c t   c c c t c a g c a g   c g t a g t g a c c   g t g c c c t c c a   g c a g c t t g g g   c a c c c a g a c c   240
t a c a t c t g c a   a c g t g a a t c a   c a a g c c c a g c   a a c a c c a a g g   t g g a c a a g a a   a g t t g g t g a g   300
a g g c c a g c a c   a g g g a g g g a g   g g t g t c t g c t   g g a a g c c a g g   c t c a g c g c t c   c t g c c t g g a c   360
g c a t c c c g g c   t a t g c a g c c c   c a g t c c a g g g   c a g c a a g g c a   g g c c c c g t c t   g c c t c t t c a c   420
c c g g a g g c c t   c t g c c c g c c c   c a c t c a t g c t   c a g g g a g a g g   g t c t t c t g g c   t t t t t c c c c a   480
g g c t c t g g g c   a g g c a c a g g c   t a g g t g c c c c   t a a c c c a g g c   c c t g c a c a c a   a a g g g g c a g g   540
t g c t g g g c t c   a g a c c t g c c a   a g a g c c a t a t   c c g g g a g g a c   c c t g c c c c t g   a c c t a a g c c c   600
a c c c c a a a g g   c c a a a c t c t c   c a c t c c c t c a   g c t c g g a c a c   c t t c t c t c c t   c c c a g a t t c c   660
a g t a a c t c c c   a a t c t t c t c t   c t c c a g a g c c   c a a a t c t t g t   g a c a a a a c t c   a c a c a t g c c c   720
a c c g t g c c c a   g g t a a g c c a g   c c c a g g c c t c   g c c c t c c a g c   t c a a g g c g g g   a c a g g t g c c c   780
t a g g t a g c c c   t g c a t c c a g g   g a c a g g c c c c   a g c c g g g t g c   t g a c a c g t c c   a c c t c c a t c t   840
c t t c c t c a g c   a c c t g a a c t c   c t g g g g g g a c   c g t c a g t c t t   c c t c t t c c c c   c c a a a a c c c a   900
a g g a c a c c c t   c a t g a t c t c c   c g g a c c c c t g   a g g t c a c a t g   c g t g g t g g t g   g a c g t g a g c c   960
a c g a a g a c c c   t g a g g t c a a g   t t c a a c t g g t   a c g t g g a c g g   c g t g g a g g t g   c a t a a t g c c a   1020
a g a c a a a g c c   g c g g g a g g a g   c a g t a c a a c a   g c a c g t a c c g   t g t g g t c a g c   g t c c t c a c c g   1080
t c c t g c a c c a   g g a c t g g c t g   a a t g g c a a g g   a g t a c a a g t g   c a a g g t c t c c   a a c a a a g c c c   1140
t c c c a g c c c c   c a t c g a g a a a   a c c a t c t c c a   a a g c c a a a g g   t g g g a c c c g t   g g g g t g c g a g   1200
g g c c a c a t g g   a c a g a g g c c g   g c t c g g c c c a   c c c t c t g c c c   t g a g a g t g a c   c g c t g t a c c a   1260
a c c t c t g t c c   c t a c a g g g c a   g c c c c g a g a a   c c a c a g g t g t   a c a c c c t g c c   c c c a t c c c g g   1320
g a t g a g c t g a   c c a a g a a c c a   g g t c a g c c t g   a c c t g c c t g g   t c a a a g g c t t   c t a t c c c a g c   1380
g a c a t c g c c g   t g g a g t g g g a   g a g c a a t g g g   c a g c c g g a g a   a c a a c t a c a a   g a c c a c g c c t   1440
c c c g t g c t g g   a c t c c g a c g g   c t c c t t c t t c   c t c t a c a g c a   a g c t c a c c g t   g g a c a a g a g c   1500
a g g t g g c a g c   a g g g g a a c g t   c t t c t c a t g c   t c c g t g a t g c   a t g a g g c t c t   g c a c a a c c a c   1560
t a c a c g c a g a   a g a g c c t c t c   c t t a a g t c c g   g g a a a a t a a a   1599

```

<210> 39
<211> 106
<212> PRT
<213> Homo sapiens

<400> 39

EP 1 603 949 B9

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

<210> 40

<211> 321

<212> DNA

25 <213> Homo sapiens

<400> 40

30 ggtcagccca aggctgcccc ctcggtcact ctgttcccgc cctcctctga ggagcttcaa 60
 gccacaag ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg 120
 gcctggaagg cagatagcag ccccgtaag gcgggagtgg agaccaccac accctccaaa 180
 caaagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag 240
 tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300
 gccctacag aatgttcata g 321
 35

<210> 41

<211> 105

<212> PRT

40 <213> Homo sapiens

<400> 41

45

50

55

EP 1 603 949 B9

```

-----
Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
 1          5          10          15

5    Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
      20          25          30

    Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
      35          40          45

10   Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
      50          55          60

    Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
      65          70          75          80

15

    Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
      85          90          95

    Thr Lys Ser Phe Asn Arg Gly Glu Cys
      100         105

25   <210> 42
      <211> 324
      <212> DNA
      <213> Homo sapiens

30   <400> 42

      ggaactgtgg ctgcaccatc tgtcttcac ttcgcccat ctgatgagca gttgaaatct 60
      ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120
      tggaagggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac 180
35   agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag 240
      aaacacaaaag tctacgcctg cgaagtcacc catcagggcc tgagttcacc ggtgacaaaag 300
      agcttcaaca ggggagagtg ttag                                324

40   <210> 43
      <211> 538
      <212> PRT
      <213> Homo sapiens

45   <400> 43

50

55

```


EP 1 603 949 B9

	Met	Pro	Arg	Gly	Trp	Ala	Ala	Pro	Leu	Leu	Leu	Leu	Leu	Leu	Gln	Gly
	1				5					10					15	
5	Gly	Trp	Gly	Cys	Pro	Asp	Leu	Val	Cys	Tyr	Thr	Asp	Tyr	Leu	Gln	Thr
				20					25					30		
	Val	Ile	Cys	Ile	Leu	Glu	Met	Trp	Asn	Leu	His	Pro	Ser	Thr	Leu	Thr
			35					40					45			
10	Leu	Thr	Trp	Gln	Asp	Gln	Tyr	Glu	Glu	Leu	Lys	Asp	Glu	Ala	Thr	Ser
		50					55					60				
	Cys	Ser	Leu	His	Arg	Ser	Ala	His	Asn	Ala	Thr	His	Ala	Thr	Tyr	Thr
	65					70					75					80
15	Cys	His	Met	Asp	Val	Phe	His	Phe	Met	Ala	Asp	Asp	Ile	Phe	Ser	Val
					85					90					95	
	Asn	Ile	Thr	Asp	Gln	Ser	Gly	Asn	Tyr	Ser	Gln	Glu	Cys	Gly	Ser	Phe
				100					105					110		
20	Leu	Leu	Ala	Glu	Ser	Ile	Lys	Pro	Ala	Pro	Pro	Phe	Asn	Val	Thr	Val
			115					120					125			
	Thr	Phe	Ser	Gly	Gln	Tyr	Asn	Ile	Ser	Trp	Arg	Ser	Asp	Tyr	Glu	Asp
25		130					135					140				
	Pro	Ala	Phe	Tyr	Met	Leu	Lys	Gly	Lys	Leu	Gln	Tyr	Glu	Leu	Gln	Tyr
	145					150					155					160

EP 1 603 949 B9

	Arg	Asn	Arg	Gly	Asp	Pro	Trp	Ala	Val	Ser	Pro	Arg	Arg	Lys	Leu	Ile	
					165					170					175		
5	Ser	Val	Asp	Ser	Arg	Ser	Val	Ser	Leu	Leu	Pro	Leu	Glu	Phe	Arg	Lys	
				180					185					190			
	Asp	Ser	Ser	Tyr	Glu	Leu	Gln	Val	Arg	Ala	Gly	Pro	Met	Pro	Gly	Ser	
			195					200					205				
10	Ser	Tyr	Gln	Gly	Thr	Trp	Ser	Glu	Trp	Ser	Asp	Pro	Val	Ile	Phe	Gln	
	210						215					220					
	Thr	Gln	Ser	Glu	Glu	Leu	Lys	Glu	Gly	Trp	Asn	Pro	His	Leu	Leu	Leu	
	225					230					235					240	
15	Leu	Leu	Leu	Leu	Val	Ile	Val	Phe	Ile	Pro	Ala	Phe	Trp	Ser	Leu	Lys	
					245					250					255		
	Thr	His	Pro	Leu	Trp	Arg	Leu	Trp	Lys	Lys	Ile	Trp	Ala	Val	Pro	Ser	
				260					265					270			
20	Pro	Glu	Arg	Phe	Phe	Met	Pro	Leu	Tyr	Lys	Gly	Cys	Ser	Gly	Asp	Phe	
			275					280					285				
	Lys	Lys	Trp	Val	Gly	Ala	Pro	Phe	Thr	Gly	Ser	Ser	Leu	Glu	Leu	Gly	
25		290					295					300					
	Pro	Trp	Ser	Pro	Glu	Val	Pro	Ser	Thr	Leu	Glu	Val	Tyr	Ser	Cys	His	
	305				310						315					320	
	Pro	Pro	Arg	Ser	Pro	Ala	Lys	Arg	Leu	Gln	Leu	Thr	Glu	Leu	Gln	Glu	
30				325						330					335		
	Pro	Ala	Glu	Leu	Val	Glu	Ser	Asp	Gly	Val	Pro	Lys	Pro	Ser	Phe	Trp	
				340					345					350			
35	Pro	Thr	Ala	Gln	Asn	Ser	Gly	Gly	Ser	Ala	Tyr	Ser	Glu	Glu	Arg	Asp	
			355					360					365				
	Arg	Pro	Tyr	Gly	Leu	Val	Ser	Ile	Asp	Thr	Val	Thr	Val	Leu	Asp	Ala	
		370					375					380					
40	Glu	Gly	Pro	Cys	Thr	Trp	Pro	Cys	Ser	Cys	Glu	Asp	Asp	Gly	Tyr	Pro	
	385					390					395					400	
	Ala	Leu	Asp	Leu	Asp	Ala	Gly	Leu	Glu	Pro	Ser	Pro	Gly	Leu	Glu	Asp	
				405						410					415		
45	Pro	Leu	Leu	Asp	Ala	Gly	Thr	Thr	Val	Leu	Ser	Cys	Gly	Cys	Val	Ser	
				420					425					430			
	Ala	Gly	Ser	Pro	Gly	Leu	Gly	Gly	Pro	Leu	Gly	Ser	Leu	Leu	Asp	Arg	
			435					440					445				
50	Leu	Lys	Pro	Pro	Leu	Ala	Asp	Gly	Glu	Asp	Trp	Ala	Gly	Gly	Leu	Pro	
		450					455					460					

EP 1 603 949 B9

	Trp	Gly	Gly	Arg	Ser	Pro	Gly	Gly	Val	Ser	Glu	Ser	Glu	Ala	Gly	Ser
	465					470					475					480
5	Pro	Leu	Ala	Gly	Leu	Asp	Met	Asp	Thr	Phe	Asp	Ser	Gly	Phe	Val	Gly
					485					490					495	
	Ser	Asp	Cys	Ser	Ser	Pro	Val	Glu	Cys	Asp	Phe	Thr	Ser	Pro	Gly	Asp
				500					505					510		
10	Glu	Gly	Pro	Pro	Arg	Ser	Tyr	Leu	Arg	Gln	Trp	Val	Val	Ile	Pro	Pro
			515					520					525			
	Pro	Leu	Ser	Ser	Pro	Gly	Pro	Gln	Ala	Ser						
15		530					535									
	<210> 44															
	<211> 2665															
	<212> DNA															
20	<213> Homo sapiens															
	<400> 44															
25	gtcgactgga	ggcccagctg	cccgtcatca	gagtgcacagg	tcttatgaca	gcctgattgg	60									
	tgactcgggc	tgggtgtgga	ttctcaccce	aggcctctgc	ctgctttctc	agaccctcat	120									
	ctgtcaccce	cacgtgaac	ccagctgcc	ccccagaag	cccatcagac	tgcccccagc	180									
	acacggaatg	gatttctgag	aaagaagccg	aaacagaagg	cccgtgggag	tcagcatgcc	240									
	gcgtggctgg	gcgcgccctt	tgctcctgct	gctgctccag	ggaggctggg	gctgccccga	300									
	cctcgtctgc	tacaccgatt	acctccagac	ggctcatctgc	atcctggaaa	tgtggaacct	360									
30	ccaccacagc	acgtccacc	ttacctggca	agaccagtat	gaagagctga	aggacgaggc	420									
	cacctcctgc	agcctccaca	ggctcgccca	caatgccacg	catgccacct	acacctgcca	480									
	catggatgta	ttccacttca	tggccgacga	cattttcagt	gtcaacatca	cagaccagtc	540									
	tggcaactac	tcccaggagt	gtggcagctt	tctcctggct	gagagcatca	agccggctcc	600									
	ccctttcaac	gtgactgtga	ccttctcagg	acagtataat	atctcctggc	gctcagatta	660									
35	cgaagaccct	gccttctaca	tgctgaagg	caagcttcag	tatgagctgc	agtacaggaa	720									
	ccggggagag	ccctgggctg	tgagtcagag	gagaaagctg	atctcagtg	actcaagaag	780									
	tgtctccctc	ctccccctgg	agttccgcaa	agactcgagc	tatgagctgc	aggtgcgggc	840									
	agggcccatg	cctggctcct	cctaccaggg	gacctggagt	gaatggagt	acccggctcat	900									
	ctttcagacc	cagtcagagg	agttaaagga	aggctggaac	cctcacctgc	tgcttctcct	960									
	cctgcttgct	atagtcttca	ttcctgcctt	ctggagcctg	aagaccatc	cattgtggag	1020									
40	gctatggaag	aagatatggg	ccgtccccag	ccctgagcgg	ttcttcatgc	ccctgtacaa	1080									
	gggctgcagc	ggagacttca	agaaatgggt	gggtgcaccc	ttcactggct	ccagcctgga	1140									
	gctgggaccc	tggagccag	agggtgcctc	cacctggag	gtgtacagct	gccaccaccc	1200									
	acggagcccg	gccaagaggc	tgagctcac	ggagctacaa	gaaccagcag	agctgggtgga	1260									
	gtctgacggg	gtgccaagc	ccagcttctg	gccagacagc	cagaactcgg	ggggctcagc	1320									
45	ttacagtgag	gagagggatc	ggccatacgg	cctgggtgtcc	attgacacag	tgactgtgct	1380									
	agatgcagag	gggccatgca	cctggccctg	cagctgtgag	gatgacggct	acccagccct	1440									
	ggacctggat	gctggcctgg	agcccagccc	aggcctagag	gacctactct	tggatgcagg	1500									
	gaccacagtc	ctgtcctgtg	gctgtgtctc	agctggcagc	cctgggctag	gagggccctt	1560									
	gggaagcctc	ctggacagac	taaagccacc	ccttgcatat	ggggaggact	gggctggggg	1620									
	actgccctgg	ggtggccggg	cacctggagg	ggtctcagag	agtgaggcgg	gctcaccctt	1680									
50	ggccggcctg	gatatggaca	cgtttgacag	tggctttgtg	ggctctgact	gcagcagccc	1740									
	tgtggagtgt	gacttcacca	gccccgggga	cgaaggaccc	ccccggagct	acctccgcca	1800									
	gtgggtggtc	attcctccgc	cactttcgag	ccctggaccc	caggccagct	aatgaggctg	1860									
	actggatgtc	cagagctggc	caggccactg	ggccttgagc	cagagacaag	gtcacctggg	1920									
	ctgtgatgtg	aagacacctg	cagcctttgg	tctcctggat	gggcctttga	gcctgatgtt	1980									
	tacagtgtct	gtgtgtgtgt	gtgcatatgt	gtgtgtgtgc	atatgcatgt	gtgtgtgtgt	2040									
55	gtgtgtctta	ggtgcgcagt	ggcatgtcca	cgtgtgtgtg	tgattgcacg	tgctgtgtgg	2100									
	cctgggataa	tgcccatggt	actccatgca	ttcacctgcc	ctgtgcatgt	ctggactcac	2160									

EP 1 603 949 B9

```

5      ggagctcacc catgtgcaca agtgtgcaca gtaaactgtt ttgtgggtcaa cagatgacaa 2220
      cagccgtcct ccctcctagg gtcttgtgtt gcaagttggt ccacagcatc tccgggggctt 2280
      tgtgggatca gggcattgcc tgtgactgag gcgagagccca gccctccagc gtctgcctcc 2340
      aggagctgca agaagtccat attgttcctt atcacctgcc aacaggaagc gaaaggggat 2400
      ggagtgaagg catggtgacc tcgggaatgg caattttttg ggcgggccct ggacgaagg 2460
      ctgaatcccg actctgatac cttctggctg tgctacctga gccaaagtgc cttccctctc 2520
      tgggctagag tttccttata cagacagtgg ggaaggcatg acacacctgg gggaaattgg 2580
      cgatgtcacc cgtgtacggt acgcagccca gagcagaccc tcaataaacg tcagcttcct 2640
10     tcaaaaaaaaa aaaaaaaaaat ctaga 2665

```

<210> 45

<211> 529

<212> PRT

15 <213> Mus musculus

<400> 45

```

20     Met  Pro  Arg  Gly  Pro  Val  Ala  Ala  Leu  Leu  Leu  Leu  Leu  Ile  Leu  His  Gly
      1              5              10              15

      Ala  Trp  Ser  Cys  Leu  Asp  Leu  Thr  Cys  Tyr  Thr  Asp  Tyr  Leu  Trp  Thr
              20              25              30

25     Ile  Thr  Cys  Val  Leu  Glu  Thr  Arg  Ser  Pro  Asn  Pro  Ser  Ile  Leu  Ser
              35              40              45

      Leu  Thr  Trp  Gln  Asp  Glu  Tyr  Glu  Glu  Leu  Gln  Asp  Gln  Glu  Thr  Phe
              50              55              60

30     Cys  Ser  Leu  His  Arg  Ser  Gly  His  Asn  Thr  Thr  His  Ile  Trp  Tyr  Thr
      65              70              75              80

      Cys  His  Met  Arg  Leu  Ser  Gln  Phe  Leu  Ser  Asp  Glu  Val  Phe  Ile  Val
              85              90              95

35     Asn  Val  Thr  Asp  Gln  Ser  Gly  Asn  Asn  Ser  Gln  Glu  Cys  Gly  Ser  Phe
              100              105              110

      Val  Leu  Ala  Glu  Ser  Ile  Lys  Pro  Ala  Pro  Pro  Leu  Asn  Val  Thr  Val
              115              120              125

40     Ala  Phe  Ser  Gly  Arg  Tyr  Asp  Ile  Ser  Trp  Asp  Ser  Ala  Tyr  Asp  Glu
      130              135              140

      Pro  Ser  Asn  Tyr  Val  Leu  Arg  Gly  Lys  Leu  Gln  Tyr  Glu  Leu  Gln  Tyr
45     145              150              155              160

      Arg  Asn  Leu  Arg  Asp  Pro  Tyr  Ala  Val  Arg  Pro  Val  Thr  Lys  Leu  Ile
              165              170              175

50     Ser  Val  Asp  Ser  Arg  Asn  Val  Ser  Leu  Leu  Pro  Glu  Glu  Phe  His  Lys
              180              185              190

      Asp  Ser  Ser  Tyr  Gln  Leu  Gln  Val  Arg  Ala  Ala  Pro  Gln  Pro  Gly  Thr
              195              200              205

55     Ser  Phe  Arg  Gly  Thr  Trp  Ser  Glu  Trp  Ser  Asp  Pro  Val  Ile  Phe  Gln
      210              215              220

```

EP 1 603 949 B9

Thr Gln Ala Gly Glu Pro Glu Ala Gly Trp Asp Pro His Met Leu Leu
 225 230 235 240
 5 Leu Leu Ala Val Leu Ile Ile Val Leu Val Phe Met Gly Leu Lys Ile
 245 250 255
 His Leu Pro Trp Arg Leu Trp Lys Lys Ile Trp Ala Pro Val Pro Thr
 260 265 270
 10 Pro Glu Ser Phe Phe Gln Pro Leu Tyr Arg Glu His Ser Gly Asn Phe
 275 280 285
 Lys Lys Trp Val Asn Thr Pro Phe Thr Ala Ser Ser Ile Glu Leu Val
 290 295 300
 15 Pro Gln Ser Ser Thr Thr Thr Ser Ala Leu His Leu Ser Leu Tyr Pro
 305 310 315 320
 Ala Lys Glu Lys Lys Phe Pro Gly Leu Pro Gly Leu Glu Glu Gln Leu
 325 330 335
 20 Glu Cys Asp Gly Met Ser Glu Pro Gly His Trp Cys Ile Ile Pro Leu
 340 345 350
 Ala Ala Gly Gln Ala Val Ser Ala Tyr Ser Glu Glu Arg Asp Arg Pro
 355 360 365
 25 Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Gly Asp Ala Glu Gly
 370 375 380
 Leu Cys Val Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro Ala Met
 385 390 395 400
 Asn Leu Asp Ala Gly Arg Glu Ser Gly Pro Asn Ser Glu Asp Leu Leu
 405 410 415
 35 Leu Val Thr Asp Pro Ala Phe Leu Ser Cys Gly Cys Val Ser Gly Ser
 420 425 430
 Gly Leu Arg Leu Gly Gly Ser Pro Gly Ser Leu Leu Asp Arg Leu Arg
 435 440 445
 40 Leu Ser Phe Ala Lys Glu Gly Asp Trp Thr Ala Asp Pro Thr Trp Arg
 450 455 460
 Thr Gly Ser Pro Gly Gly Gly Ser Glu Ser Glu Ala Gly Ser Pro Pro
 465 470 475 480
 45 Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Ala Gly Ser Asp Cys
 485 490 495
 Gly Ser Pro Val Glu Thr Asp Glu Gly Pro Pro Arg Ser Tyr Leu Arg
 500 505 510
 50
 Gln Trp Val Val Arg Thr Pro Pro Pro Val Asp Ser Gly Ala Gln Ser
 515 520 525
 55
 Ser

<210> 46
 <211> 2628
 <212> DNA
 <213> Homo sapiens

5

<400> 46

	gtcgacgcgg	cggtaccagc	tgtctgcccc	cttctcctgt	gggtgtgcctc	acgggtcactt	60
10	gcttgtctga	ccgcaagtct	gccccatccct	ggggcagcca	actggcctca	gcccgtgccc	120
	caggcgtagc	ctgtctctgt	ctggctgccc	cagccctact	gtcttcctct	gtgtaggctc	180
	tgcccagatg	ccgggtggt	cctcagcctc	aggactatct	cagcagtgac	tcccctgatt	240
	ctggacttgc	acctgactga	actcctgccc	acctcaaac	ttcacctccc	accaccacca	300
	ctccgagtcc	cgctgtgact	cccacgcccc	ggagaccacc	caagtgcccc	agcctaaaga	360
	atggctttct	gagaaaagacc	ctgaaggagt	aggtctggga	cacagcatgc	cccggggccc	420
15	actggctgcc	ttactcctgc	tgattctcca	tggagcttgg	agctgcctgg	acctcacttg	480
	ctacactgac	tacctctgga	ccatcacctg	tgtcctggag	acacggagcc	ccaaccccag	540
	catactcagt	ctcacctggc	aagatgaata	tgaggaactt	caggaccaag	agaccttctg	600
	cagcctacac	aggtctggcc	acaacaccac	acatatatgg	tacacgtgcc	atatgcgctt	660
	gtctcaattc	ctgtccgatg	aagttttcat	tgtcaatgtg	acggaccagt	ctggcaacaa	720
20	ctcccaagag	tgtggcagct	ttgtcctggc	tgagagcatc	aaaccagctc	cccccttgaa	780
	cgtgactgtg	gccttctcag	gacgctatga	tatctcctgg	gactcagctt	atgacgaacc	840
	ctccaactac	gtgctgaggg	gcaagctaca	atatgagctg	cagtatcgga	acctcagaga	900
	cccctatgct	gtgaggccgg	tgaccaagct	gatctcagtg	gactcaagaa	acgtctctct	960
	tctccctgaa	gagttccaca	aagattctag	ctaccagctg	cagggtgcggg	cagcgcctca	1020
25	gccaggcact	tcattcaggg	ggacctggag	tgagtggagt	gaccccgctc	tctttcagac	1080
	ccaggctggg	gagcccagg	caggctggga	ccctcacatg	ctgctgctcc	tggctgtctt	1140
	gatcattgtc	ctgggtttca	tgggtctgaa	gatccacctg	ccttggaggc	tatggaaaaa	1200
	gatatgggca	ccagtgccca	cccctgagag	tttcttccag	cccctgtaca	gggagcacag	1260
	cgggaacttc	aagaaatggg	ttaatacccc	tttcacggcc	tccagcatag	agttggtgcc	1320
	acagagttcc	acaacaacat	cagccttaca	tctgtcattg	tatccagcca	aggagaagaa	1380
30	gttcccgggg	ctgccgggtc	tggagagca	actggagtgt	gatggaatgt	ctgagcctgg	1440
	tcactgggtc	ataatcccct	tggcagctgg	ccaagcggtc	tcagcctaca	gtgaggagag	1500
	agaccggcca	tatggtctgg	tgtccattga	cacagtgact	gtgggagatg	cagagggcct	1560
	gtgtgtctgg	ccctgtagct	gtgaggatga	tggctatcca	gccatgaacc	tggatgctgg	1620
	ccgagagtct	ggccctaatt	cagaggatct	gctcttggtc	acagaccctg	cttttctgtc	1680
35	ttgctggctgt	gtctcaggta	gtggtctcag	gcttggaggc	tcccaggca	gcctactgga	1740
	caggttgagg	ctgtcatttg	caaaggaagg	ggactggaca	gcagacccaa	cctggagaac	1800
	tgggtcccca	ggagggggct	ctgagagtga	agcagggtcc	ccccctggct	tggacatgga	1860
	cacatttgac	agtggctttg	caggttcaga	ctgtggcagc	cccggtggaga	ctgatgaagg	1920
	accccctcga	agctatctcc	gccagtgggt	ggtcaggacc	cctccacctg	tggacagtgg	1980
	agcccagagc	agctagcata	taataaccag	ctatagttag	aagaggcctc	tgagcctggc	2040
40	atctacagtg	tgaacatgta	ggggtgtgtg	tgtgtgtgtg	tgtgtgtgtg	tgtgtgtgtg	2100
	tgtgtgtgtg	tgtgtgtgtg	tgtcttgggt	tgtgtgttag	cacatccatg	ttgggatttg	2160
	gtctgttgct	atgtattgta	atgctaaatt	ctctacccaa	agttctaggc	ctacgagtga	2220
	attctcatgt	ttacaaaactt	gctgtgtaaa	ccttgttcct	taatttaata	ccattgggtta	2280
	aataaaaattg	gctgcaacca	attactggag	ggatttagagg	tagggggcctt	ttgagttacc	2340
45	tgtttgagga	tgagagaagg	gagaggagag	accaagagga	gaaggaggaa	ggagaggaga	2400
	ggagaggaga	ggagaggaga	ggagaggaga	ggagaggaga	ggagaggaga	ggctgccgtg	2460
	aggggagagg	gaccatgagc	ctgtggccag	gagaaacagc	aagtatctgg	ggtacactgg	2520
	tgaggaggtg	gccaggccag	cagttagaag	agtagattag	gggtgacctc	cagtatttgt	2580
	caaagccaat	taaaataaca	aaaaaaaaaa	aaaagcggcc	gctctaga		2628

50

<210> 47
 <211> 116
 <212> PRT
 <213> Homo sapiens

55

<400> 47

EP 1 603 949 B9

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

<210> 48
 <211> 109
 <212> PRT
 <213> Homo sapiens

<400> 48

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

<210> 49
 <211> 242
 <212> PRT
 <213> Homo sapiens

<400> 49

EP 1 603 949 B9

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	
	1				5					10					15		
5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Asn	Ile	Tyr	
				20					25					30			
	Ser	Val	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
10	Gly	Arg	Ile	Ile	Pro	Met	Arg	Asp	Ile	Ala	Asn	Tyr	Ala	Gln	Arg	Phe	
	50						55					60					
	Gln	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Gly	Thr	Ala	Tyr	
	65					70					75					80	
15	Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Trp	Cys	
					85				90						95		
	Ala	Thr	Leu	Ala	Gly	Pro	Leu	Asp	Ser	Trp	Gly	Arg	Gly	Thr	Leu	Val	
			100						105					110			
20	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	
			115				120						125				
	Gly	Gly	Ser	Ala	Leu	Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	
	130					135						140					
25	Val	Ala	Leu	Gly	Gln	Thr	Val	Arg	Ile	Thr	Cys	Gln	Gly	Asp	Ser	Leu	
	145					150					155					160	
	Arg	Thr	Tyr	Tyr	Ala	Ser	Trp	Tyr	Gln	Lys	Arg	Pro	Gly	Gln	Ala	Pro	
30					165					170					175		
	Ile	Leu	Val	Met	Tyr	Gly	Arg	Asn	Lys	Arg	Pro	Ser	Gly	Ile	Pro	Asp	
			180					185						190			
	Arg	Phe	Ser	Gly	Ser	Phe	Ser	Gly	Asn	Arg	Ala	Ser	Leu	Thr	Ile	Thr	
35			195					200					205				
	Gly	Ala	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Lys	Ser	Arg	Ala	
	210						215					220					
40	Tyr	Ser	Gly	Asn	Leu	Val	Glu	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	
	225				230						235					240	

Leu Gly

45 <210> 50
 <211> 5
 <212> PRT
 <213> Homo sapiens

50 <400> 50

Ile Tyr Ser Val Ser
 1 5

55 <210> 51
 <211> 17
 <212> PRT

EP 1 603 949 B9

<213> Homo sapiens

<400> 51

5 Arg Ile Ile Pro Met Arg Asp Ile Ala Asn Tyr Ala Gln Arg Phe Gln
1 5 10 15

Gly

10

<210> 52

<211> 7

<212> PRT

<213> Homo sapiens

15

<400> 52

Leu Ala Gly Pro Leu Asp Ser
1 5

20

<210> 53

<211> 11

<212> PRT

<213> Homo sapiens

25

<400> 53

30 Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala Ser
1 5 10

<210> 54

<211> 7

<212> PRT

<213> Homo sapiens

35

<400> 54

40

Gly Arg Asn Lys Arg Pro Ser
1 5

<210> 55

<211> 11

<212> PRT

<213> Homo sapiens

45

<400> 55

50

Lys Ser Arg Ala Tyr Ser Gly Asn Leu Val Glu
1 5 10

55

<210> 56

<211> 348

<212> DNA

EP 1 603 949 B9

<213> Homo sapiens

<400> 56

```

5      gaggtgcagc  tgggtgcagtc  tggggctgag  gtgaagaagc  ctgggtcctc  ggtgaaggtc  60
      tcctgcaagg  cttctggagg  caccttcaac  atctatagtg  tcagctgggt  gcgacaggcc  120
      cctggacagg  ggcttgagtg  gatgggaagg  atcatcccta  tgcgtgatat  tgcaaaactac  180
      gcgcagaggt  tccagggcag  ggtcacactt  accgcggaca  agtcctcggg  gacagcctac  240
10     atggagtgc  gcagcctgag  atctgacgac  acggccgtct  attggtgtgc  gacattggct  300
      ggccccttgg  actcctgggg  cagaggaacc  ctggtcaccg  tctcgagt    348

```

<210> 57

<211> 327

15 <212> DNA

<213> Homo sapiens

<400> 57

```

20     tcttctgagc  tgactcagga  ccctgctgtg  tctgtggcct  tgggacagac  agtcaggatc  60
      acatgccagg  gagacagcct  cagaacttat  tatgcgagct  ggtaccagaa  gaggccagga  120
      caggccccta  tacttgatcat  gtatggtaga  aataagaggc  cctcagggat  cccagaccga  180
      ttctctggct  ccttctcagg  gaacagagct  tccttgacca  tctctggggc  tcaggcggaa  240
      gatgaggctg  actattactg  taaatcccgg  gcctacagtg  gtaacctcgt  agaattcggc  300
25     ggagggacca  agctgaccgt  cctaggt    327

```

<210> 58

<211> 726

30 <212> DNA

<213> Homo sapiens

<400> 58

```

35     gaggtgcagc  tgggtgcagtc  tggggctgag  gtgaagaagc  ctgggtcctc  ggtgaaggtc  60
      tcctgcaagg  cttctggagg  caccttcaac  atctatagtg  tcagctgggt  gcgacaggcc  120
      cctggacagg  ggcttgagtg  gatgggaagg  atcatcccta  tgcgtgatat  tgcaaaactac  180
      gcgcagaggt  tccagggcag  ggtcacactt  accgcggaca  agtcctcggg  gacagcctac  240
40     atggagtgc  gcagcctgag  atctgacgac  acggccgtct  attggtgtgc  gacattggct  300
      ggccccttgg  actcctgggg  cagaggaacc  ctggtcaccg  tctcgagtgg  aggcggcggt  360
      tcaggcggag  gtggctctgg  cggcggcgga  agtgcacttt  cttctgagct  gactcaggac  420
      cctgctgtgt  ctgtggcctt  gggacagaca  gtcaggatca  catgccaggg  agacagcctc  480
      agaacttatt  atgcgagctg  gtaccagaag  aggcaggac  agggccctat  acttgatcatg  540
      tatggtagaa  ataagaggcc  ctcagggatc  ccagaccgat  tctctggctc  cttctcaggg  600
45     aacagagctt  ccttgaccat  cactggggct  caggcgggag  atgaggctga  ctattactgt  660
      aaatcccggg  cctacagtgg  taacctcgta  gaattcggcg  gagggaccaa  gctgaccgtc  720
      ctaggt    726

```

50 <210> 59

<211> 15

<212> DNA

<213> Homo sapiens

55 <400> 59

atctatagtg tcagc 15

<210> 60

EP 1 603 949 B9

<211> 51
<212> DNA
<213> Homo sapiens

5 <400> 60
aggatcatcc ctatgcgtga tattgcaaac tacgcgcaga ggttcaggg c 51

<210> 61
<211> 21
<212> DNA
<213> Homo sapiens

<400> 61
ttggctggcc ccttggaactc c 21

<210> 62
<211> 33
<212> DNA
<213> Homo sapiens

<400> 62
caggagaca gcctcagaac ttattatgcg age 33

<210> 63
<211> 21
<212> DNA
<213> Homo sapiens

30 <400> 63
ggtagaaata agaggccctc a 21

<210> 64
<211> 33
<212> DNA
<213> Homo sapiens

<400> 64
aaatcccggg cctacagtgg taacctcgta gaa 33

40 <210> 65
 <211> 118
 <212> PRT
 <213> Homo sapiens

45 <400> 65

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

50 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Ser Ser Gly
20 25 30

55

EP 1 603 949 B9

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

20 <210> 66
 <211> 110
 <212> PRT
 <213> Homo sapiens

25 <400> 66

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

50 <210> 67
 <211> 245
 <212> PRT
 <213> Homo sapiens

55 <400> 67

EP 1 603 949 B9

1 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Thr Ser Glu
 5 1 5 10 15
 5 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Ser Ser Gly
 20 25 30
 10 Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45
 Ile Gly Ser Ile Ser His Thr Gly Asn Thr Tyr Tyr Asn Pro Pro Leu
 50 55 60
 15 Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
 65 70 75 80
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 20 Ala Arg Gly Gly Gly Ile Ser Arg Pro Glu Tyr Trp Gly Lys Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
 115 120 125
 25 Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Pro
 130 135 140
 Val Ser Val Ala Leu Gly Gln Thr Val Thr Leu Thr Cys Gln Gly Asp
 145 150 155 160
 30 Ser Leu Arg Thr Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Ser Gly Gln
 165 170 175
 Ala Pro Ile Leu Leu Leu Tyr Gly Lys His Lys Arg Pro Ser Gly Ile
 180 185 190
 35 Pro Asp Arg Phe Ser Gly Ser Thr Ser Gly Asp Thr Ala Ser Leu Thr
 195 200 205
 Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser
 210 215 220
 40 Arg Asp Ser Ser Gly Asn Pro His Val Leu Phe Gly Gly Gly Thr Gln
 225 230 235 240
 45 Leu Thr Val Leu Ser
 245

<210> 68

<211> 6

50 <212> PRT

<213> Homo sapiens

<400> 68

55 Ser Gly Tyr Tyr Trp Gly
 1 5

EP 1 603 949 B9

<210> 69
 <211> 16
 <212> PRT
 <213> Homo sapiens
 5
 <400> 69

 Ser Ile Ser His Thr Gly Asn Thr Tyr Tyr Asn Pro Pro Leu Lys Ser
 10 1 5 10 15

 <210> 70
 <211> 9
 <212> PRT
 15 <213> Homo sapiens

 <400> 70

 20 Gly Gly Gly Ile Ser Arg Pro Glu Tyr
 1 5

 <210> 71
 25 <211> 11
 <212> PRT
 <213> Homo sapiens

 <400> 71
 30

 Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala Ser
 1 5 10

 35 <210> 72
 <211> 7
 <212> PRT
 <213> Homo sapiens
 40
 <400> 72

 Gly Lys His Lys Arg Pro Ser
 45 1 5

 <210> 73
 <211> 12
 50 <212> PRT
 <213> Homo sapiens

 <400> 73

 55 Asn Ser Arg Asp Ser Ser Gly Asn Pro His Val Leu
 1 5 10

EP 1 603 949 B9

<210> 74
<211> 354
<212> DNA
<213> Homo sapiens

5

<400> 74

10

```
cagggtgcagc tgcaggagtc gggcccagga ctggtgaaga cttcggagac cctgtccctc 60
acctgcgctg tctctgggta ctccatcagc agtgggttact actggggctg gatccggcag 120
ccccagggga aggggttgga gtggattggg agtatctctc atactgggaa cacctactac 180
aaccgcgccc tcaagagtcg cgtcaccata tcagtagaca cgtccaagaa ccagttctcc 240
ctgaaaactga gctctgtgac cgccgcagac acggccgtgt attactgtgc gcgaggtggg 300
ggaattagca ggccggagta ctggggcaaa ggcaccctgg tcaccgtctc gagt 354
```

15

<210> 75
<211> 330
<212> DNA
<213> Homo sapiens

20

<400> 75

25

```
tcttctgagc tgactcagga ccctcctgtg tctgtggcct tgggacagac agtcacgctc 60
acatgccaaag gagacagcct cagaacctat tatgcaagct ggtaccagca gaagtcagga 120
caggccctta tactttctct ctatggtaaa cacaaacggc cctcagggat cccagaccgc 180
ttctctggct ccacctcagg agacacagct tccttgacca tcactggggc tcaggcggaa 240
gacgaggtcg actattactg taactcccgg gactccagtg gcaacccccca tgttctgttc 300
ggcgaggagg cccagctcac cgttttaagt 330
```

30

<210> 76
<211> 735
<212> DNA
<213> Homo sapiens

35

<400> 76

40

```
cagggtgcagc tgcaggagtc gggcccagga ctggtgaaga cttcggagac cctgtccctc 60
acctgcgctg tctctgggta ctccatcagc agtgggttact actggggctg gatccggcag 120
ccccagggga aggggttgga gtggattggg agtatctctc atactgggaa cacctactac 180
aaccgcgccc tcaagagtcg cgtcaccata tcagtagaca cgtccaagaa ccagttctcc 240
ctgaaaactga gctctgtgac cgccgcagac acggccgtgt attactgtgc gcgaggtggg 300
ggaattagca ggccggagta ctggggcaaa ggcaccctgg tcaccgtctc gagtggaggc 360
ggcggttcag gcggagggtg ctctggcggt ggcggaagtg cactttcttc tgagctgact 420
caggaccctc ctgtgtctgt ggccttggga cagacagtca cgctcacatg ccaaggagac 480
agcctcagaa cctattatgc aagctggtac cagcagaagt caggacaggc ccctatactt 540
ctcctctatg gtaaacacaa acggccctca gggatcccag accgcttctc tggctccacc 600
tcaggagaca cagcttcctt gaccatcact ggggctcagg cggaagacga ggctgactat 660
tactgtaact cccgggactc cagtggcaac ccccatgttc tgttcggcgg agggacccag 720
ctcaccgttt taagt 735
```

50

55

<210> 77
<211> 18
<212> DNA
<213> Homo sapiens

<400> 77

agtggttact actggggc 18

<210> 78
 <211> 48
 5 <212> DNA
 <213> Homo sapiens

<400> 78
 10 agtatctctc atactgggaa cacctactac aacccgcccc tcaagagt 48

<210> 79
 <211> 27
 <212> DNA
 15 <213> Homo sapiens

<400> 79
 ggtgggggaa ttagcaggcc ggagtac 27

<210> 80
 20 <211> 33
 <212> DNA
 <213> Homo sapiens

<400> 80
 25 caaggagaca gcctcagaac ctattatgca age 33

<210> 81
 <211> 21
 <212> DNA
 30 <213> Homo sapiens

<400> 81
 ggtaaacaca aacggccctc a 21

<210> 82
 35 <211> 36
 <212> DNA
 <213> Homo sapiens

<400> 82
 40 aactccggg actccagtgg caaccccat gttctg 36

<210> 83
 <211> 116
 45 <212> PRT
 <213> Homo sapiens

<400> 83

50

55

EP 1 603 949 B9

5
 10
 15
 20
 25
 30
 35
 40
 45
 50
 55
 60
 65
 70
 75
 80
 85
 90
 95
 100
 105
 110

25
 115

30
 <210> 84
 <211> 111
 <212> PRT
 <213> Homo sapiens
 <400> 84

35
 40
 45
 50
 55
 60
 65
 70
 75
 80
 85
 90
 95
 100
 105
 110

55
 <210> 85
 <211> 244
 <212> PRT
 <213> Homo sapiens

EP 1 603 949 B9

<400> 85

5 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Ile Tyr
20 25 30

10 Ser Val Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Ile Pro Met Arg Asp Ile Ala Asn Tyr Ala Gln Arg Phe
50 55 60

15 Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

20

Ala Thr Leu Ala Gly Pro Leu Asp Ser Trp Gly Gln Gly Thr Leu Val
100 105 110

25 Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser
130 135 140

30 Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Gly Ser Leu
145 150 155 160

Arg Gln Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175

35 Val Leu Val Ile Tyr Gly Lys Asn Lys Arg Pro Ser Gly Ile Pro Asp
180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr
195 200 205

40 Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp
210 215 220

45 Ser Ser Gly Asn His Pro Leu Tyr Val Phe Gly Ala Gly Thr Lys Leu
225 230 235 240

Thr Val Leu Gly

<210> 86

<211> 5

<212> PRT

<213> Homo sapiens

<400> 86

Ile Tyr Ser Val Ser
1 5

5 <210> 87
<211> 17
<212> PRT
<213> Homo sapiens

10 <400> 87

Arg Ile Ile Pro Met Arg Asp Ile Ala Asn Tyr Ala Gln Arg Phe Gln
1 5 10 15

15 Gly

<210> 88
<211> 7
20 <212> PRT
<213> Homo sapiens

<400> 88

25 Leu Ala Gly Pro Leu Asp Ser
1 5

<210> 89
30 <211> 11
<212> PRT
<213> Homo sapiens

<400> 89

35 Gln Gly Gly Ser Leu Arg Gln Tyr Tyr Ala Ser
1 5 10

40 <210> 90
<211> 7
<212> PRT
<213> Homo sapiens

45 <400> 90

Gly Lys Asn Lys Arg Pro Ser
1 5

50 <210> 91
<211> 13
<212> PRT
<213> Homo sapiens

55 <400> 91

EP 1 603 949 B9

Lys Ser Arg Asp Ser Ser Gly Asn His Pro Leu Tyr Val
1 5 10

5 <210> 92
<211> 348
<212> DNA
<213> Homo sapiens

10 <400> 92

15 caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcaac atctatagtg tcagctgggt gcgacaggcc 120
cctggacagg ggcttgagtg gatgggaagg atcatcccta tgcgtgatat tgcaaactac 180
gcgcagagggt tccagggcag ggtcacaatt accgcggaca agtccacgag cacagcctac 240
atggagttga gcagcctgag atctgaagac acggccgtct attattgtgc gacattggct 300
ggccccttgg actcctgggg ccagggcacc ctggtcaccg tctcgagt 348

20 <210> 93
<211> 333
<212> DNA
<213> Homo sapiens

25 <400> 93

30 tcttctgagc tgactcagga cccagctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgtcaag gcggcagcct cagacaatat tatgcaagtt ggtaccaaca gaagccagga 120
caggcccctg tgcttgtcat ctatggtaaa aataagcgac cctcagggat cccagaccga 180

35 ttctctggct cctcctcagg caacacagct tccttgacca tcaactggggc tcaggcggaa 240
gatgaggctg actactattg taagtcccgg gacagcagtg gtaaccatcc cctttatgtc 300
ttcggagctg ggaccaagct gaccgtccta ggt 333

40 <210> 94
<211> 732
<212> DNA
<213> Homo sapiens

<400> 94

45 caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcaac atctatagtg tcagctgggt gcgacaggcc 120
cctggacagg ggcttgagtg gatgggaagg atcatcccta tgcgtgatat tgcaaactac 180
gcgcagagggt tccagggcag ggtcacaatt accgcggaca agtccacgag cacagcctac 240
atggagttga gcagcctgag atctgaagac acggccgtct attattgtgc gacattggct 300
ggccccttgg actcctgggg ccagggcacc ctggtcaccg tctcgagtgg aggcggcgggt 360
tcaggcggag gtggctctgg cggcggcggg agtgcacttt cttctgagct gactcaggac 420
ccagctgtgt ctgtggcctt gggacagaca gtcaggatca catgtcaagg cggcagcctc 480
agacaatatt atgcaagttg gtaccaacag aagccaggac agggcccctgt gcttgtcatc 540
tatggtaaaa ataagcgacc ctcagggatc ccagaccgat tctctggctc ctccctcaggc 600
55 aacacagctt ccttgaccat cactggggct caggcgggaag atgaggctga ctactattgt 660
aagtcccggg acagcagtggt taaccatccc ctttatgtct tcggagctgg gaccaagctg 720
accgtcctag gt 732

<210> 95
 <211> 15
 <212> DNA
 <213> Homo sapiens
 5
 <400> 95
 atctatagtg tcagc 15
 <210> 96
 <211> 51
 <212> DNA
 <213> Homo sapiens
 10
 <400> 96
 aggatcatcc ctatgctga tattgcaaac tacgcgaga ggtccaggg c 51
 15
 <210> 97
 <211> 21
 <212> DNA
 <213> Homo sapiens
 20
 <400> 97
 ttggctggcc ccttgactc c 21
 25
 <210> 98
 <211> 33
 <212> DNA
 <213> Homo sapiens
 30
 <400> 98
 caaggcggca gcctcagaca atattatgca agt 33
 35
 <210> 99
 <211> 21
 <212> DNA
 <213> Homo sapiens
 40
 <400> 99
 ggtaaaaata agcgaccctc a 21
 45
 <210> 100
 <211> 39
 <212> DNA
 <213> Homo sapiens
 50
 <400> 100
 aagtcgggg acagcagtgg taaccatccc cttatgtc 39
 55
 <210> 101
 <211> 120
 <212> PRT
 <213> Homo sapiens
 <400> 101

EP 1 603 949 B9

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asp Asn
 5 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Pro Lys Thr Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 10 50 55 60
 Gln Gly Arg Val Ser Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
 65 70 75 80
 Met Asp Leu Ser Arg Leu Thr Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 15 85 90 95
 Thr Arg Ser Leu Ser Pro Tyr Gly Gly Gln Leu Leu Tyr Trp Gly Arg
 100 105 110
 Gly Thr Met Val Thr Val Ser Ser
 115 120

<210> 102
 <211> 110
 <212> PRT
 <213> Homo sapiens

<400> 102

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

<210> 103
 <211> 247
 <212> PRT
 <213> Homo sapiens

<400> 103

EP 1 603 949 B9

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	
	1				5					10					15		
5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ala	Phe	Thr	Asp	Asn	
				20					25					30			
	Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
10	Gly	Trp	Ile	Asn	Pro	Lys	Thr	Gly	Gly	Thr	Asn	Tyr	Ala	Gln	Lys	Phe	
		50					55					60					
	Gln	Gly	Arg	Val	Ser	Met	Thr	Arg	Asp	Thr	Ser	Ile	Asn	Thr	Ala	Tyr	
		65				70					75					80	
15	Met	Asp	Leu	Ser	Arg	Leu	Thr	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
					85					90					95		
	Thr	Arg	Ser	Leu	Ser	Pro	Tyr	Gly	Gly	Gln	Leu	Leu	Tyr	Trp	Gly	Arg	
				100					105					110			
20	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	
			115					120					125				
	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Leu	Ser	Ser	Glu	Leu	Thr	Gln	Asp	
25		130					135					140					
	Pro	Ala	Val	Ser	Val	Ala	Leu	Gly	Gln	Thr	Val	Arg	Ile	Thr	Cys	Gln	
	145					150					155					160	
30	Gly	Asp	Ser	Leu	Arg	Arg	Tyr	Tyr	Ala	Ser	Trp	Phe	Gln	Gln	Lys	Pro	
					165					170					175		
	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Phe	Gly	Lys	Asn	Asn	Arg	Pro	Ser	
35				180					185					190			
	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Ala	Ser	Ser	Ser	Gly	Asn	Thr	Ala	Ser	
			195					200					205				
40	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	
		210					215					220					
	Asn	Ser	Arg	Asp	Thr	Ser	Ile	Asn	His	Pro	Val	Ile	Phe	Gly	Gly	Gly	
	225					230					235					240	
45	Thr	Lys	Leu	Thr	Val	Leu	Gly										
					245												

<210> 104

<211> 5

50 <212> PRT

<213> Homo sapiens

<400> 104

55 Asp Asn Tyr Ile His
1 5

EP 1 603 949 B9

<210> 105
 <211> 17
 <212> PRT
 <213> Homo sapiens

5

<400> 105

10 Trp Ile Asn Pro Lys Thr Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

15 <210> 106
 <211> 11
 <212> PRT
 <213> Homo sapiens

20 <400> 106

Ser Leu Ser Pro Tyr Gly Gly Gln Leu Leu Tyr
 1 5 10

25 <210> 107
 <211> 11
 <212> PRT
 <213> Homo sapiens

30

<400> 107

Gln Gly Asp Ser Leu Arg Arg Tyr Tyr Ala Ser
 1 5 10

35

<210> 108
 <211> 7
 <212> PRT
 <213> Homo sapiens

40

<400> 108

Gly Lys Asn Asn Arg Pro Ser
 1 5

45

<210> 109
 <211> 12
 <212> PRT
 <213> Homo sapiens

50

<400> 109

55

Asn Ser Arg Asp Thr Ser Ile Asn His Pro Val Ile
 1 5 10

EP 1 603 949 B9

<210> 110
<211> 360
<212> DNA
<213> Homo sapiens

5

<400> 110

10

```
gaggtccagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgtaagg cttccggata cgccttcacc gacaactata tacactgggt gcgacaggcc 120
cctggacaag ggcttgaatg gatgggatgg atcaacccta agactgggtg cacaaactat 180
gcacaaaagt ttcagggcag ggtcagcatg accagggaca cgtccatcaa cacagcctac 240
atggacctaa gtaggctgac atctgacgac acggccgtct attactgtac gagaagcctt 300
tccccatatg gtggccaact cctctactgg ggccggggga caatggtcac cgtctcgagt 360
```

15

<210> 111
<211> 330
<212> DNA
<213> Homo sapiens

20

<400> 111

25

```
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaag gagacagcct cagaagatat tatgcaagct ggttccagca gaagccagga 120
caggcccttg tacttgtcat ctttggtaaa aacaaccggc cctcagggat cccagaccga 180
ttctctgcct ccagttcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa 240
gatgaggctg actattactg taactcccgg gacaccagta ttaaccatcc cgtgatattc 300
ggcgggggga ccaagctgac cgtcctagg 330
```

30

<210> 112
<211> 741
<212> DNA
<213> Homo sapiens

35

<400> 112

40

```
gaggtccagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgtaagg cttccggata cgccttcacc gacaactata tacactgggt gcgacaggcc 120
cctggacaag ggcttgaatg gatgggatgg atcaacccta agactgggtg cacaaactat 180
gcacaaaagt ttcagggcag ggtcagcatg accagggaca cgtccatcaa cacagcctac 240
atggacctaa gtaggctgac atctgacgac acggccgtct attactgtac gagaagcctt 300
tccccatatg gtggccaact cctctactgg ggccggggga caatggtcac cgtctcgagt 360
ggaggcggcg gttcaggcgg aggtggctct ggccggtggcg gaagtgcact ttcttctgag 420
ctgactcagg accctgctgt gtctgtggcc ttgggacaga cagtcaggat cacatgccaa 480
ggagacagcc tcagaagata ttatgcaagc tgggtccagc agaagccagg acaggccctt 540
gtacttgtca tctttggtaa aaacaaccgg cctcaggga tcccagaccg attctctgcc 600
tccagttcag gaaacacagc ttccttgacc atcactgggg ctcaggcgga agatgaggct 660
gactattact gtaactcccg ggacaccagt attaaccatc ccgtgatatt cggcgggggg 720
accaagctga ccgtcctagg t 741
```

50

<210> 113
<211> 15
<212> DNA
<213> Homo sapiens

55

<400> 113

gacaactata tacac 15

EP 1 603 949 B9

<210> 114
 <211> 54
 <212> DNA
 <213> Homo sapiens
 5
 <400> 114
 tggatcaadc ctaagactgg tggcacaac tatgcacaaa agtttcaggg cagg 54
 10
 <210> 115
 <211> 33
 <212> DNA
 <213> Homo sapiens
 15
 <400> 115
 agcctttccc catatggtgg ccaactcctc tac 33
 20
 <210> 116
 <211> 33
 <212> DNA
 <213> Homo sapiens
 25
 <400> 116
 caaggagaca gcctcagaag atattatgca agc 33
 30
 <210> 117
 <211> 21
 <212> DNA
 <213> Homo sapiens
 35
 <400> 117
 ggtaaaaaca accggccctc a 21
 40
 <210> 118
 <211> 36
 <212> DNA
 <213> Homo sapiens
 45
 <400> 118
 aactccggg acaccagtat taaccatccc gtgata 36
 50
 <210> 119
 <211> 118
 <212> PRT
 <213> Homo sapiens
 55
 <400> 119

EP 1 603 949 B9

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 5 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 10 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 15 85 90 95
 Ala Gly Gly Trp Lys Leu Pro Phe Phe Ala Tyr Trp Gly Arg Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115
 <210> 120
 <211> 110
 <212> PRT
 <213> Homo sapiens
 <400> 120
 Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1 5 10 15
 Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Thr Phe Tyr Ala
 20 25 30
 Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
 35 40 45
 Gly Lys Ser Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 50 55 60
 Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Arg Asp Arg Ser Gly Asn His
 85 90 95
 Leu Gly Met Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 <210> 121
 <211> 245
 <212> PRT
 <213> Homo sapiens

EP 1 603 949 B9

<400> 121

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

 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

10 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

15 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

20 Ala Gly Gly Trp Lys Leu Pro Phe Phe Ala Tyr Trp Gly Arg Gly Thr
 100 105 110

 Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 115 120 125

25 Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Ala
 130 135 140

 Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp
 145 150 155 160

30 Ser Leu Arg Thr Phe Tyr Ala Asn Trp Tyr Gln Gln Lys Pro Gly Gln
 165 170 175

 Ala Pro Ile Leu Val Ile Tyr Gly Lys Ser Asn Arg Pro Ser Gly Ile
 180 185 190

35 Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr
 195 200 205

40

 Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser
 210 215 220

45 Arg Asp Arg Ser Gly Asn His Leu Gly Met Phe Gly Gly Gly Thr Lys
 225 230 235 240

 Leu Thr Val Leu Gly
 245

<210> 122

<211> 5

<212> PRT

<213> Homo sapiens

<400> 122

EP 1 603 949 B9

Ser Tyr Ala Met Ser
 1 5

5 <210> 123
 <211> 17
 <212> PRT
 <213> Homo sapiens

10 <400> 123

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

15 Gly

<210> 124
 <211> 9
 20 <212> PRT
 <213> Homo sapiens

<400> 124

25 Gly Trp Lys Leu Pro Phe Phe Ala Tyr
 1 5

<210> 125
 30 <211> 11
 <212> PRT
 <213> Homo sapiens

<400> 125

35 Gln Gly Asp Ser Leu Arg Thr Phe Tyr Ala Asn
 1 5 10

40 <210> 126
 <211> 7
 <212> PRT
 <213> Homo sapiens

45 <400> 126

Gly Lys Ser Asn Arg Pro Ser
 1 5

50 <210> 127
 <211> 12
 <212> PRT
 <213> Homo sapiens

55 <400> 127

EP 1 603 949 B9

Tyr Ser Arg Asp Arg Ser Gly Asn His Leu Gly Met
1 5 10

5 <210> 128
<211> 354
<212> DNA
<213> Homo sapiens

10 <400> 128

15 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc ggggggggtgg 300
aaacttccat tttttgccta ctggggcccg ggcaccctgg tcaccgtctc gagt 354

20 <210> 129
<211> 330
<212> DNA
<213> Homo sapiens

25 <400> 129

30 tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
acatgccaaag gagacagcct cagaaccttt tatgcaaact ggtaccagca gaagccagga 120
caggccccta tacttgtcat ctatggtaaa agcaaccgtc cctcagggat ccagaccga 180
ttctctggct ccagctcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa 240
gatgaggctg actattactg ttactcccgg gacagaagtg gtaaccatct agggatgttc 300
ggcggagggga ccaagctgac cgtcctaggt 330

35 <210> 130
<211> 735
<212> DNA
<213> Homo sapiens

40 <400> 130

45 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc ggggggggtgg 300
aaacttccat tttttgccta ctggggcccg ggcaccctgg tcaccgtctc gagtggaggc 360
ggcgggttcag gcgagggttg ctctggcggg ggcggaagtg cactttcttc tgagctgact 420
caggaccctg ctgtgtctgt ggccttggga cagacagtca ggatcacatg ccaaggagac 480
50 agcctcagaa ccttttatgc aaactggtac cagcagaagc caggacaggc ccctatactt 540

55 gtcattctatg gtaaaagcaa ccgtccctca gggatcccag accgattctc tggtctccagc 600
tcaggaaaca cagcttcctt gaccatcact ggggctcagg cggaagatga ggctgactat 660
tactgttact cccgggacag aagtggtaac catctaggga tggtcggcgg agggaccaag 720
ctgaccgtcc taggt 735

<210> 131
 <211> 15
 <212> DNA
 <213> Homo sapiens
 5
 <400> 131
 agctatgcca tgagc 15
 <210> 132
 10 <211> 54
 <212> DNA
 <213> Homo sapiens
 <400> 132
 15 gctattagtg gtagtggtgg tagcacatac tacgcagact ccgtgaaggg ccgg 54
 <210> 133
 <211> 27
 <212> DNA
 20 <213> Homo sapiens
 <400> 133
 gggtggaac ttccatttt tgcctac 27
 25 <210> 134
 <211> 33
 <212> DNA
 <213> Homo sapiens
 30 <400> 134
 caaggagaca gcctcagaac ctttatgca aac 33
 <210> 135
 <211> 21
 35 <212> DNA
 <213> Homo sapiens
 <400> 135
 40 ggtaaaagca accgtccctc a 21
 <210> 136
 <211> 36
 <212> DNA
 <213> Homo sapiens
 45 <400> 136
 tactcccggg acagaagtgg taaccatcta gggatg 36
 <210> 137
 50 <211> 121
 <212> PRT
 <213> Homo sapiens
 <400> 137
 55

EP 1 603 949 B9

1 Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 5 5 10 15
 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 10 Ser Gly Ile Ser Gly Ser Gly Thr Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 15 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Thr His Ile Ser Glu Arg Pro Arg Gly Ala Phe Asp Ile Trp Gly
 100 105 110
 20 Arg Gly Thr Met Val Thr Val Ser Ser
 115 120

25 <210> 138
 <211> 109
 <212> PRT
 <213> Homo sapiens

30 <400> 138

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

50 Tyr Val Phe Gly Ala Gly Thr Lys Leu Thr Val Leu Gly
 100 105

55 <210> 139
 <211> 247
 <212> PRT

EP 1 603 949 B9

<213> Homo sapiens

<400> 139

5 Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
10 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Gly Ser Gly Thr Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
15 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
20 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Thr His Ile Ser Glu Arg Pro Arg Gly Ala Phe Asp Ile Trp Gly
100 105 110
25 Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln
130 135 140
30 Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys
145 150 155 160
Gln Gly Asp Ser Leu Arg Lys Tyr His Ala Thr Trp Tyr Gln Gln Lys
165 170 175
35 Pro Arg Gln Ala Pro Val Leu Val Val Tyr Gly Lys Asn Arg Arg Pro
180 185 190
Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala
195 200 205
40 Ser Leu Thr Ile Thr Gly Ala Gln Ala Gly Asp Glu Ala Asp Tyr Tyr
210 215 220
Cys Asn Ser Arg Asp Thr Ser Gly Leu His Tyr Val Phe Gly Ala Gly
225 230 235 240
45 Thr Lys Leu Thr Val Leu Gly
245

<210> 140

<211> 5

<212> PRT

<213> Homo sapiens

<400> 140

EP 1 603 949 B9

Ser Tyr Ala Met Ser
1 5

5 <210> 141
<211> 17
<212> PRT
<213> Homo sapiens

10 <400> 141

Gly Ile Ser Gly Ser Gly Thr Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

15 Gly

<210> 142
<211> 12
20 <212> PRT
<213> Homo sapiens

<400> 142

25 His Ile Ser Glu Arg Pro Arg Gly Ala Phe Asp Ile
1 5 10

<210> 143
30 <211> 11
<212> PRT
<213> Homo sapiens

<400> 143

35 Gln Gly Asp Ser Leu Arg Lys Tyr His Ala Thr
1 5 10

40 <210> 144
<211> 7
<212> PRT
<213> Homo sapiens

45 <400> 144

Gly Lys Asn Arg Arg Pro Ser
1 5

50 <210> 145
<211> 11
<212> PRT
<213> Homo sapiens

55 <400> 145

EP 1 603 949 B9

Asn Ser Arg Asp Thr Ser Gly Leu His Tyr Val
1 5 10

5 <210> 146
<211> 363
<212> DNA
<213> Homo sapiens

10 <400> 146

15 caggtgcagc tgcaggagtc ggggggagggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcc tgcagctgggt ccgccaggct 120
ccaggaagg ggctggagt ggtctcaggt attagtggta gtggtactag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaagac acggccgtat attactgtgc gacacatata 300
tcggaacgtc cacgtggtgc ttttgatata tggggccggg ggacaatggt caccgtctcg 360
agt 363

20 <210> 147
<211> 327
<212> DNA
<213> Homo sapiens

25 <400> 147

30 tcttctgagc tgactcagga ccctgctgtg tctgtggccc tgggacagac agtcaggatc 60
acatgccaaag gagacagcct cagaaaagtat catgcaactt ggtaccagca gaagccaagg 120
caggcccttg tacttgtcgt ctatggtaaa aacaggcgcc cctcagggat ccccgaccga 180
ttctctggct ccagctcagg aaacacagct tccctgacca tcaactggggc tcaggcgagg 240
gatgaggctg actattactg taactcccg gacaccagtgt gtcttcatta tgtcttcgga 300
gctgggacca agctgaccgt cctaggt 327

35 <210> 148
<211> 741
<212> DNA
<213> Homo sapiens

40 <400> 148

45 caggtgcagc tgcaggagtc ggggggagggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcc tgcagctgggt ccgccaggct 120
ccaggaagg ggctggagt ggtctcaggt attagtggta gtggtactag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaagac acggccgtat attactgtgc gacacatata 300
tcggaacgtc cacgtggtgc ttttgatata tggggccggg ggacaatggt caccgtctcg 360
agtggaggcg gcggttcagg cggagggtggc tctggcggtg gcggaagtgc actttcttct 420
gagctgactc aggaccctgc tgtgtctgtg gccctgggac agacagtcag gatcacatgc 480
caaggagaca gcctcagaaa gtatcatgca acttgggtacc agcagaagcc aaggcaggcc 540
cctgtacttg tcgtctatgg taaaaacagg cgccctcag ggatccccga ccgattctct 600
ggctccagct caggaaacac agcttccctg accatcaactg gggctcaggc gggagatgag 660
gctgactatt actgtaactc ccgggacacc agtgggtcttc attatgtctt cggagctggg 720
accaagctga ccgtcctagg t 741

55 <210> 149
<211> 15
<212> DNA

<213> Homo sapiens
 <400> 149
 agctatgcca tgagc 15
 5
 <210> 150
 <211> 51
 <212> DNA
 <213> Homo sapiens
 10
 <400> 150
 ggtattagtg gtagtggtac tagcacatac tacgcagact ccgtgaaggg c 51
 <210> 151
 <211> 36
 <212> DNA
 <213> Homo sapiens
 15
 <400> 151
 catatctcgg aacgtccacg tggcgcttt gatatc 36
 20
 <210> 152
 <211> 33
 <212> DNA
 <213> Homo sapiens
 25
 <400> 152
 caaggagaca gcctcagaaa gtatcatgca act 33
 30
 <210> 153
 <211> 21
 <212> DNA
 <213> Homo sapiens
 35
 <400> 153
 ggtaaaaaca ggcgcccctc a 21
 <210> 154
 <211> 33
 <212> DNA
 <213> Homo sapiens
 40
 <400> 154
 aactccggg acaccagtgg tcttcattat gtc 33
 45

Claims

1. An isolated antibody that antagonizes IL-21R activity, the antibody comprising an amino acid sequence which is at least 95% identical to an amino acid sequence selected from the group consisting of:
 50
 (a) SEQ ID NOs: 1 and 2;
 (b) SEQ ID NO: 3;
 (c) SEQ ID NOs: 19 and 20;
 55 (d) SEQ ID NO: 21;
 (e) SEQ ID NOs: 47 and 48;
 (f) SEQ ID NO: 49;
 (g) SEQ ID NOs: 65 and 66;

- (h) SEQ ID NO: 67;
- (i) SEQ ID NOs: 83 and 84;
- (j) SEQ ID NO: 85;
- (k) SEQ ID NOs: 101 and 102;
- (l) SEQ ID NO: 103;
- (m) SEQ ID NOs: 119 and 120;
- (n) SEQ ID NO: 121;
- (o) SEQ ID NOs: 137 and 138; and
- (p) SEQ ID NO:139,

wherein the antibody selectively binds to an extracellular domain of a human IL-21 receptor or of an IL-21 receptor which is at least 85% identical to an amino acid sequence shown as SEQ ID NO:45.

2. An isolated antibody that antagonizes IL-21R activity, the antibody encoded by a nucleotide sequence which is at least 95% identical to a nucleotide sequence selected from the group consisting of:

- (a) SEQ ID NOs: 10 and 11;
- (b) SEQ ID NO: 12;
- (c) SEQ ID NOs: 28 and 29;
- (d) SEQ ID NO: 30;
- (e) SEQ ID NOs: 56 and 57;
- (f) SEQ ID NO: 58;
- (g) SEQ ID NOs: 74 and 75;
- (h) SEQ ID NO: 76;
- (i) SEQ ID NO: 92 and 93;
- (j) SEQ ID NO: 94;
- (k) SEQ ID NOs: 110 and 111;
- (l) SEQ ID NO: 112;
- (m) SEQ ID NOs: 128 and 129;
- (n) SEQ ID NO: 130;
- (o) SEQ ID NOs: 146 and 147; and
- (p) SEQ ID NO: 148,

wherein the antibody selectively binds to an extracellular domain of a human IL-21 receptor or of an IL-21 receptor which is at least 85% identical to an amino acid sequence shown as SEQ ID NO:45.

3. An isolated antibody that antagonizes IL-21R activity, the antibody comprising:

- (a) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 4, 5, and 6, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs:7, 8 and 9;
- (b) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 22, 23, and 24, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs:25, 26, and 27;
- (c) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 50, 51, and 52, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 53, 54, and 55;
- (d) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 68, 69, and 70, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 71, 72, and 73;
- (e) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 86, 87, and 88, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 89, 90, and 91;
- (f) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 104, 105, and 106, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 107, 108, and 109;
- (g) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 122, 123, and 124, and a V_L domain which comprises CDR sequences at least 95% identical

to the amino acid sequences set forth in SEQ ID NOs: 125, 126, and 127; or

(h) a V_H domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 140, 141, and 142, and a V_L domain which comprises CDR sequences at least 95% identical to the amino acid sequences set forth in SEQ ID NOs: 143, 144, and 145,

wherein the antibody selectively binds to an extracellular domain of a human IL-21 receptor or of an IL-21 receptor which is at least 85% identical to an amino acid sequence shown as SEQ ID NO:45.

4. An isolated antibody that antagonizes IL-21R activity and competes with an antibody comprising an amino acid sequence selected from the group consisting of:

- (a) SEQ ID NOs: 1 and 2;
- (b) SEQ ID NO: 3;
- (c) SEQ ID NOs: 19 and 20;
- (d) SEQ ID NO: 21;
- (e) SEQ ID NOs: 47 and 48;
- (f) SEQ ID NO: 49;
- (g) SEQ ID NOs: 65 and 66;
- (h) SEQ ID NO: 67;
- (i) SEQ ID NOs: 83 and 84;
- (j) SEQ ID NO: 85;
- (k) SEQ ID NOs: 101 and 102;
- (l) SEQ ID NO: 103;
- (m) SEQ ID NOs: 119 and 120;
- (n) SEQ ID NO: 121;
- (o) SEQ ID NOs: 137 and 138; and
- (p) SEQ ID NO: 139,

wherein the antibody selectively binds to an extracellular domain of a human IL-21 receptor or of an IL-21 receptor which is at least 85% identical to an amino acid sequence shown as SEQ ID NO:45.

5. The antibody of claim 1, 2, 3, or 4, wherein the antibody selectively binds the extracellular domain of the polypeptide set forth in SEQ ID NO: 43.

6. The antibody of claim 1, 2, 3, or 4, wherein the antibody inhibits the binding of IL-21 to an extracellular domain of a human IL-21 receptor or of an IL-21 receptor which is at least 85% identical to an amino acid sequence shown as SEQ ID NO:45.

7. The antibody of claim 1, 2, 3, or 4, wherein the antibody is human.

8. The antibody of claim 1, 2, 3, or 4, wherein the antibody is an IgG₁ antibody.

9. The antibody of claim 8, wherein the antibody is IgG_{1λ} or IgG_{1κ}.

10. An isolated antibody that antagonizes IL-21R activity, the antibody expressed by a host cell having ATCC Deposit Designation No. PTA-5030 or PTA-5031.

11. A pharmaceutical composition comprising the antibody of claim 1, 2, 3, or 4, and a pharmaceutical excipient.

12. An isolated nucleic acid encoding the antibody of claim 1, 2, 3, or 4.

13. An expression vector comprising the nucleic acid of claim 12.

14. A host cell transformed with the vector of claim 13.

15. The host cell of claim 14, wherein the host cell is a bacteria, mammalian cell, yeast cell, plant cell, or an insect cell.

16. A host cell having ATCC Deposit Designation No. PTA-5030 or PTA-5031.

17. A method of producing an antibody that binds to an IL-21 receptor, the method comprising culturing the host cell of claim 16 under conditions that allow expression of the antibody, and isolating the antibody from the cell culture.

18. Use of the antibody of claim 1, 2, 3 or 4 for manufacture of a medicament for regulating an immune response, wherein the immune response comprises proliferation, cytolytic activity, cytokine secretion, or chemokine secretion of a cell.

19. The use of claim 18, wherein the cell is a leukocyte or a synovial cell.

20. The use of claim 19, wherein the leukocyte is a T cell, a B cell, a NK cell, or a macrophage.

21. Use of the antibody of claim 1, 2, 3 or 4, in an amount sufficient to treat or prevent an immune cell-associated disorder in a subject for the manufacture of a medicament for treating or preventing the immune cell-associated disorder in the subject, wherein the immune cell-associated disorder is selected from the group consisting of multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, transplant rejection, inflammatory bowel disease, psoriasis and Crohn's disease.

22. Use of claim 21, wherein the immune cell-associated disorder is selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, Crohn's disease and psoriasis.

23. Use of claim 21, wherein the medicament further comprises an additional therapeutic agent.

24. Use of claim 23, wherein the additional therapeutic agent is chosen from a cytokine inhibitor, a growth factor inhibitor, an immunosuppressant, an anti-inflammatory agent, a metabolic inhibitor, an enzyme inhibitor, a cytotoxic agent, and a cytostatic agent.

25. Use of claim 24, wherein the additional therapeutic agent is chosen from a TNF antagonist, an IL-12 antagonist, an IL-15 antagonist, an IL-17 antagonist, an IL-18 antagonist, an IL-22 antagonist, a T cell depleting agent, a B cell depleting agent, methotrexate, leflunomide, rapamycin, or an analog thereof, a Cox-2 inhibitor, a cPLA2 inhibitor, an NSAID, and a p38 inhibitor.

26. Use of the antibody of claim 1, 2, 3 or 4, for the manufacture of a medicament for treating or preventing a hyperproliferative disorder in a subject in an amount sufficient to inhibit or reduce hyperproliferation of IL-21- and/or IL-21 receptor-responsive cells in the subject, wherein the hyperproliferative disorder is selected from the group consisting of leukemic cancers and tumors of the blood, bone marrow, and lymph tissue.

27. Use of claim 26, wherein the subject is a mammal.

28. Use of claim 27, wherein the subject is a human.

29. Use according to claim 21 or claim 25, wherein the antibody is used in a range chosen from 1 µg/kg to 20 mg/kg, 1 µg/kg to 10 mg/kg, 1 µg/kg to 1 mg/kg, 10 µg/kg to 1 mg/kg, 10 µg/kg to 100 µg/kg, 100 µg/kg to 1 mg/kg, and 500 µg/kg to 1 mg/kg.

30. A diagnostic kit comprising the antibody of claim 1, 2, 3 or 4.

Patentansprüche

1. Isolierter Antikörper, der die IL-21R-Aktivität antagonisiert, wobei der Antikörper eine Aminosäuresequenz umfasst, die mindestens 95% identisch zu einer Aminosäuresequenz ist, die aus der Gruppe gewählt ist, die aus

- (a) SEQ ID NOs: 1 und 2;
- (b) SEQ ID NO: 3;
- (c) SEQ ID NOs: 19 und 20;
- (d) SEQ ID NO: 21;
- (e) SEQ ID NOs: 47 und 48;
- (f) SEQ ID NO: 49;

- (g) SEQ ID NOs: 65 und 66
- (h) SEQ ID NO: 67;
- (i) SEQ ID NOs: 83 und 84
- (j) SEQ ID NO: 85;
- (k) SEQ ID NOs: 101 und 102;
- (l) SEQ ID NO: 103;
- (m) SEQ ID NOs: 119 und 120;
- (n) SEQ ID NO: 121;
- (o) SEQ ID NOs: 137 und 138; und
- (p) SEQ ID NO: 139;

besteht, wobei der Antikörper selektiv an eine extrazelluläre Domäne eines humanen IL-21-Rezeptors oder eines IL-21-Rezeptors bindet, der mindestens 85% identisch zu einer Aminosäuresequenz, die als SEQ ID NO: 45 gezeigt ist, ist.

2. Isolierter Antikörper, der die IL-21R-Aktivität antagonisiert, wobei der Antikörper von einer Nukleotidsequenz codiert wird, die mindestens 95% identisch zu einer Nukleotidsequenz ist, die aus der Gruppe gewählt ist, die aus

- (a) SEQ ID NOs: 10 und 11;
- (b) SEQ ID NO: 12;
- (c) SEQ ID NOs: 28 und 29;
- (d) SEQ ID NO: 30;
- (e) SEQ ID NOs: 56 und 57;
- (f) SEQ ID NO: 58;
- (g) SEQ ID NOs: 74 und 75;
- (h) SEQ ID NO: 76;
- (i) SEQ ID NOs: 92 und 93;
- (j) SEQ ID NO: 94;
- (k) SEQ ID NOs: 110 und 111;
- (l) SEQ ID NO: 112;
- (m) SEQ ID NOs: 128 und 129;
- (n) SEQ ID NO: 130;
- (o) SEQ ID NOs: 146 und 147; und
- (p) SEQ ID NO: 148,

besteht, worin der Antikörper selektiv an eine extrazelluläre Domäne eines humanen IL-21-Rezeptors oder eines IL-21-Rezeptors bindet, der mindestens 85% identisch zu einer Aminosäuresequenz, die als SEQ ID NO: 45 gezeigt ist, ist.

3. Isolierter Antikörper, der die IL-21 R-Aktivität antagonisiert, wobei der Antikörper umfasst:

- (a) eine V_H -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 4, 5 und 6 dargelegt sind, sind und eine V_L -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 7, 8 und 9 dargelegt sind, sind;
- (b) eine V_H -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 22, 23 und 24 dargelegt sind, sind und eine V_L -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in SEQ ID NO: 25, 26 und 27 dargelegt sind, sind;
- (c) eine V_H -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 50, 51 und 52 dargelegt sind, sind und eine V_L -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 53, 54 und 55 dargelegt sind, sind;
- (d) eine V_H -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 68, 69 und 70 dargelegt sind, sind und eine V_L -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 71, 72 und 73 dargelegt sind, sind;
- (e) eine V_H -Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequen-

zen, die in den SEQ ID NOs: 86, 87 und 88 dargelegt sind, sind und eine V_L-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 89, 90 und 91 dargelegt sind, sind;

(f) eine V_H-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 104, 105 und 106 dargelegt sind, sind und eine V_L-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 107, 108 und 109 dargelegt sind, sind;

(g) eine V_H-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 122, 123 und 124 dargelegt sind, sind und eine V_L-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 125, 126 und 127 dargelegt sind, sind; oder

(h) eine V_H-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 140, 141 und 142 dargelegt sind, sind und eine V_L-Domäne, die CDR-Sequenzen umfasst, die mindestens 95% identisch zu den Aminosäuresequenzen, die in den SEQ ID NOs: 143, 144 und 145 dargelegt sind, sind,

besteht, wobei der Antikörper selektiv an eine extrazelluläre Domäne eines humanen IL-21-Rezeptors oder eines IL-21-Rezeptors bindet, der mindestens 85% identisch zu einer Aminosäuresequenz, die als SEQ ID NO: 45 gezeigt ist, ist.

4. Isolierter Antikörper, der die IL-2 1 R-Aktivität antagonisiert und mit einem Antikörper konkurriert, der eine Aminosäuresequenz umfasst, die aus der Gruppe gewählt ist, die aus

(a) SEQ ID NOs: 1 und 2;

(b) SEQ ID NO: 3;

(c) SEQ ID NOs: 19 und 20;

(d) SEQ ID NO: 21;

(e) SEQ ID NOs: 47 und 48;

(f) SEQ ID NO: 49;

(g) SEQ ID NOs: 65 und 66;

(h) SEQ ID NO: 67;

(i) SEQ ID NOs: 83 und 84;

(j) SEQ ID NO: 85;

(k) SEQ ID NOs: 101 und 102;

(l) SEQ ID NO: 103;

(m) SEQ ID NOs: 119 und 120;

(n) SEQ ID NO: 121;

(o) SEQ ID NOs: 137 und 138; und

(p) SEQ ID NO: 139,

besteht, worin der Antikörper selektiv an eine extrazelluläre Domäne eines humanen IL-21-Rezeptors oder eines IL-21-Rezeptors bindet, der mindestens 85% identisch zu einer Aminosäuresequenz, die als SEQ ID NO: 45 gezeigt ist, ist.

5. Antikörper nach Anspruch 1, 2, 3 oder 4, worin der Antikörper selektiv die extrazelluläre Domäne des Polypeptids, das in SEQ ID NO: 43 dargelegt ist, bindet.

6. Antikörper nach Anspruch 1, 2, 3 oder 4, worin der Antikörper die Bindung von IL-21 an eine extrazelluläre Domäne eines humanen IL-21-Rezeptors oder eines IL-21-Rezeptors, der mindestens 85% identisch zu einer Aminosäuresequenz, die in SEQ ID NO: 45 gezeigt ist, ist, inhibiert.

7. Antikörper nach Anspruch 1, 2, 3 oder 4, worin der Antikörper human ist.

8. Antikörper nach Anspruch 1, 2, 3 oder 4, worin der Antikörper ein IgG₁-Antikörper ist.

9. Antikörper nach Anspruch 8, worin der Antikörper IgG_{1λ} oder IgG_{1κ} ist.

10. Isolierter Antikörper, der die IL-2 1 R-Aktivität antagonisiert, wobei der Antikörper von einer Wirtszelle exprimiert

wird, die die ATCC-Hinterlegungsbezeichnungs-Nr. PTA-5030 oder PTA-5031 aufweist.

11. Pharmazeutische Zusammensetzung, die den Antikörper von Anspruch 1, 2, 3 oder 4 und einen pharmazeutischen Hilfsstoff umfasst.

12. Isolierte Nukleinsäure, die den Antikörper nach Anspruch 1, 2, 3 oder 4 codiert.

13. Expressionsvektor, der die Nukleinsäure nach Anspruch 12 umfasst.

14. Wirtszelle, die mit dem Vektor nach Anspruch 13 transformiert ist.

15. Wirtszelle nach Anspruch 14, worin die Wirtszelle ein Bakterium, eine Säugerzelle, Hefezelle, Pflanzenzelle oder eine Insektenzelle ist.

16. Wirtszelle mit der ATCC-Hinterlegungsbezeichnungs-Nr. PTA-5030 oder PTA-5031.

17. Verfahren zur Herstellung eines Antikörpers, der an einen IL-21-Rezeptor bindet, wobei das Verfahren das Kultivieren der Wirtszelle von Anspruch 16 bei Bedingungen, die die Expression des Antikörpers erlauben und das Isolieren des Antikörpers aus der Zellkultur umfasst.

18. Verwendung des Antikörpers nach Anspruch 1, 2, 3 oder 4 zur Herstellung eines Medikaments für die Regulation einer Immunantwort, worin die Immunantwort die Proliferation, cytolytische Aktivität, Cytokinsekretion oder Chemokinsekretion einer Zelle umfasst.

19. Verwendung nach Anspruch 18, worin die Zelle ein Leukozyt oder eine synoviale Zelle ist.

20. Verwendung nach Anspruch 19, worin der Leukozyt eine T-Zelle, eine B-Zelle, eine NK-Zelle oder ein Makrophage ist.

21. Verwendung des Antikörpers nach Anspruch 1, 2, 3 oder 4 in einer Menge, die ausreichend ist, um eine Immunzellen-verbundene Störung in einem Subjekt zu behandeln oder zu verhindern, für die Herstellung eines Medikaments für die Behandlung oder Verhinderung der Immunzellen-verbundenen Störung im Subjekt, worin die Immunzellen-verbundene Störung aus der Gruppe gewählt ist, die aus Multiple Sklerose, rheumatoide Arthritis, systemischer Lupus erythematoses, juvenile rheumatoide Arthritis, Osteoarthritis, psoriatische Arthritis, Spondylitis ankylosans, Transplantatabstoßung, entzündliche Darmkrankheit, Psoriasis und Morbus Crohn besteht.

22. Verwendung nach Anspruch 21, worin die Immunzellen-verbundene Störung aus der Gruppe gewählt ist, die aus rheumatoide Arthritis, entzündliche Darmerkrankung, Morbus Crohn und Psoriasis besteht.

23. Verwendung nach Anspruch 21, worin das Medikament weiterhin ein zusätzliches therapeutisches Mittel umfasst.

24. Verwendung nach Anspruch 23, worin das zusätzliche therapeutische Mittel aus einem Zytokininhibitor, einem Wachstumsfaktorinhibitor, einem Immunsuppressivum, einem entzündungshemmenden Mittel, einem metabolischen Inhibitor, einem Enzyminhibitor, einem cytotoxischen Mittel und einem cytostatischen Mittel gewählt ist.

25. Verwendung nach Anspruch 24, worin das zusätzliche therapeutische Mittel aus einem TNF-Antagonisten, einem IL-12-Antagonisten, einem IL-15-Antagonisten, einem IL-17-Antagonisten, einem IL-18-Antagonisten, einem IL-22-Antagonisten, einem T-Zellen depletierenden Mittel, einem B-Zellen depletierenden Mittel, Methotrexat, Leflunomid, Rapamycin oder einem Analogen davon, einem Cox-2-Inhibitor, einem cPLA2-Inhibitor, einem NSAID und einem p38-Inhibitor gewählt ist.

26. Verwendung des Antikörpers nach Anspruch 1, 2, 3 oder 4 zur Herstellung eines Medikaments zur Behandlung oder Verhinderung einer hyperproliferativen Störung in einem Subjekt in einer Menge, die ausreichend ist, um die Hyperproliferation von IL-21- und/oder IL-21-Rezeptor-reaktiven Zellen in dem Subjekt zu inhibieren oder zu reduzieren, worin die hyperproliferative Störung aus der Gruppe gewählt ist, die aus Leukämiekrebsarten und Tumoren des Bluts, Knochenmarks und Lymphgewebes besteht.

27. Verwendung nach Anspruch 26, worin das Subjekt ein Säuger ist.

28. Verwendung nach Anspruch 27, worin das Subjekt ein Mensch ist.

29. Verwendung nach Anspruch 21 oder Anspruch 25, worin der Antikörper in einem Bereich angewendet wird, der aus 1 µg/kg bis 20mg/kg, 1 µg/kg bis 10mg/kg, 1 µg/kg bis 1mg/kg, 10 µg/kg bis 1mg/kg, 10 µg/kg bis 100µg/kg, 100µg/kg bis 1mg/kg und 500µg/kg bis 1 mg/kg gewählt ist.

30. Diagnostischer Kit, der den Antikörper von Anspruch 1, 2, 3 oder 4 umfasst.

Revendications

1. Anticorps isolé qui antagonise l'activité du IL-21R, l'anticorps comprenant une séquence d'acides aminés au moins identique à 95 % à une séquence d'acides aminés choisie dans le groupe constitué par :

- (a) SEQ ID NO: 1 et 2 ;
- (b) SEQ ID NO: 3 ;
- (c) SEQ ID NO: 19 et 20 ;
- (d) SEQ ID NO: 21 ;
- (e) SEQ ID NO: 47 et 48 ;
- (f) SEQ ID NO: 49 ;
- (g) SEQ ID NO: 65 et 66 ;
- (h) SEQ ID NO: 67 ;
- (i) SEQ ID NO: 83 et 84 ;
- (j) SEQ ID NO: 85 ;
- (k) SEQ ID NO: 101 et 102 ;
- (l) SEQ ID NO : 103 ;
- (m) SEQ ID NO: 119 et 120 ;
- (n) SEQ ID NO: 121 ;
- (o) SEQ ID NO: 137 et 138 ; et
- (p) SEQ ID NO: 139,

lequel anticorps se lie de manière sélective à un domaine extracellulaire d'un récepteur humain de l'IL-21 ou d'un récepteur de l'IL-21 qui est au moins identique à 85 % à une séquence d'acides aminés indiquée par SEQ ID NO : 45.

2. Anticorps isolé qui antagonise l'activité du IL-21R, l'anticorps étant codé par une séquence nucléotidique qui est au moins identique à 95 % à une séquence nucléotidique choisie dans le groupe constitué par :

- (a) SEQ ID NO: 10 et 11 ;
- (b) SEQ ID NO: 12 ;
- (c) SEQ ID NO: 28 et 29 ;
- (d) SEQ ID NO: 30 ;
- (e) SEQ ID NO: 56 et 57 ;
- (f) SEQ ID NO: 58 ;
- (g) SEQ ID NO: 74 et 75 ;
- (h) SEQ ID NO: 76 ;
- (i) SEQ ID NO: 92 et 93 ;
- (j) SEQ ID NO: 94 ;
- (k) SEQ ID NO: 110 et 111 ;
- (l) SEQ ID NO: 112 ;
- (m) SEQ ID NO: 128 et 129 ;
- (n) SEQ ID NO: 130 ;
- (o) SEQ ID NO: 146 et 147 ; et
- (p) SEQ ID NO: 148,

lequel anticorps se lie de manière sélective à un domaine extracellulaire d'un récepteur humain de l'IL-21 ou d'un récepteur de l'IL-21 qui est au moins identique à 85 % à une séquence d'acides aminés indiquée par SEQ ID NO : 45.

3. Anticorps isolé qui antagonise l'activité du IL-21R, l'anticorps comprenant :

(a) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 4, 5 et 6, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 7, 8 et 9 ;

(b) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 22, 23 et 24, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 25, 26 et 27 ;

(c) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 50, 51 et 52, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 53, 54 et 55 ;

(d) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 68, 69 et 70, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 71, 72 et 73 ;

(e) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 86, 87 et 88, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 89, 90 et 91 ;

(f) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 104, 105 et 106, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 107, 108 et 109 ;

(g) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 122, 123 et 124, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 125, 126 et 127 ; ou

(h) un domaine V_H qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 140, 141 et 142, et un domaine V_L qui comprend des séquences CDR au moins identiques à 95 % aux séquences d'acides aminés décrites dans SEQ ID NO: 143, 144 et 145,

lequel anticorps se lie de manière sélective à un domaine extracellulaire d'un récepteur humain de l'IL-21 ou d'un récepteur de l'IL-21 qui est au moins identique à 85 % à une séquence d'acides aminés indiquée par SEQ ID NO: 45.

4. Anticorps isolé qui antagonise l'activité du IL-21R et concurrence un anticorps comprenant une séquence d'acides aminés choisie dans le groupe constitué par :

(a) SEQ ID NO: 1 et 2 ;

(b) SEQ ID NO: 3 ;

(c) SEQ ID NO: 19 et 20 ;

(d) SEQ ID NO: 21 ;

(e) SEQ ID NO: 47 et 48 ;

(f) SEQ ID NO: 49 ;

(g) SEQ ID NO: 65 et 66 ;

(h) SEQ ID NO: 67 ;

(i) SEQ ID NO: 83 et 84 ;

(j) SEQ ID NO: 85 ;

(k) SEQ ID NO: 101 et 102 ;

(l) SEQ ID NO: 103 ;

(m) SEQ ID NO: 119 et 120 ;

(n) SEQ ID NO: 121 ;

(o) SEQ ID NO: 137 et 138 ; et

(p) SEQ ID NO: 139,

lequel anticorps se lie de manière sélective à un domaine extracellulaire d'un récepteur humain de l'IL-21 ou d'un récepteur de l'IL-21 qui est au moins identique à 85 % à une séquence d'acides aminés indiquée par SEQ ID NO: 45.

5. Anticorps de la revendication 1, 2, 3 ou 4, lequel anticorps se lie de manière sélective au domaine extracellulaire du polypeptide décrit dans SEQ ID NO: 43.

6. Anticorps de la revendication 1, 2, 3 ou 4, lequel anticorps inhibe la liaison de l'IL-21 à un domaine extracellulaire d'un récepteur humain de l'IL-21 ou d'un récepteur de l'IL-21 qui est au moins identique à 85 % à une séquence d'acides aminés indiquée par SEQ ID NO: 45.

7. Anticorps de la revendication 1, 2, 3 ou 4, lequel anticorps est humain.
8. Anticorps de la revendication 1, 2, 3 ou 4, lequel anticorps est un anticorps IgG₁.
- 5 9. Anticorps de la revendication 8, lequel anticorps est une IgG_{1λ} ou IgG_{1κ}.
10. Anticorps isolé qui antagonise l'activité de l'IL-21R, l'anticorps étant exprimé par une cellule hôte ayant le numéro de désignation de dépôt à l'ATCC PTA-5030 ou PTA-5031.
- 10 11. Composition pharmaceutique comprenant l'anticorps de la revendication 1, 2, 3 ou 4, et un excipient pharmaceutique.
12. Acide nucléique isolé codant l'anticorps de la revendication 1, 2, 3 ou 4.
13. Vecteur d'expression comprenant l'acide nucléique de la revendication 12.
- 15 14. Cellule hôte transformée avec le vecteur de la revendication 13.
15. Cellule hôte de la revendication 14, laquelle cellule hôte est une bactérie, une cellule de mammifère, une cellule de levure, une cellule de plante ou une cellule d'insecte.
- 20 16. Cellule hôte ayant le numéro de désignation de dépôt à l'ATCC PTA-5030 ou PTA-5031.
17. Procédé de production d'un anticorps qui se lie à un récepteur de l'IL-21, le procédé comprenant la culture de la cellule hôte de la revendication 16 dans des conditions qui permettent l'expression de l'anticorps, et l'isolement de l'anticorps de la culture cellulaire.
- 25 18. Utilisation de l'anticorps de la revendication 1, 2, 3 ou 4 pour fabriquer un médicament permettant de réguler une réponse immunitaire, dans laquelle la réponse immunitaire comprend la prolifération, l'activité cytolytique, la sécrétion de cytokines ou la sécrétion de chimiokines d'une cellule.
- 30 19. Utilisation selon la revendication 18, dans laquelle la cellule est un leucocyte ou une cellule synoviale.
20. Utilisation selon la revendication 19, dans laquelle le leucocyte est un lymphocyte T, un lymphocyte B, une cellule tueuse naturelle ou un macrophage.
- 35 21. Utilisation de l'anticorps de la revendication 1, 2, 3 ou 4 dans une quantité suffisante pour traiter ou prévenir une maladie associée aux cellules immunitaires chez un sujet, pour fabriquer un médicament permettant de traiter ou de prévenir la maladie associée aux cellules immunitaires chez le sujet, dans laquelle la maladie associée aux cellules immunitaires est choisie dans le groupe constitué par la sclérose en plaques, la polyarthrite rhumatoïde, le lupus érythémateux systémique, la polyarthrite juvénile, l'arthrose, le rhumatisme psoriasique, la spondylarthrite ankylosante, le rejet de greffe, l'affection abdominale inflammatoire, le psoriasis et la maladie de Crohn.
- 40 22. Utilisation selon la revendication 21, dans laquelle la maladie associée aux cellules immunitaires est choisie dans le groupe constitué par la polyarthrite rhumatoïde, l'affection abdominale inflammatoire, la maladie de Crohn et le psoriasis.
- 45 23. Utilisation selon la revendication 21, dans laquelle le médicament comprend en outre un agent thérapeutique supplémentaire.
- 50 24. Utilisation selon la revendication 23, dans laquelle l'agent thérapeutique supplémentaire est choisi parmi un inhibiteur de cytokine, un inhibiteur du facteur de croissance, un immunosuppresseur, un agent anti-inflammatoire, un inhibiteur métabolique, un inhibiteur enzymatique, un agent cytotoxique et un agent cytostatique.
- 55 25. Utilisation selon la revendication 24, dans laquelle l'agent thérapeutique supplémentaire est choisi parmi un antagoniste de TNF, un antagoniste de l'IL-12, un antagoniste de l'IL-15, un antagoniste de l'IL-17, un antagoniste de l'IL-18, un antagoniste de l'IL-22, un agent déplétant les lymphocytes T, un agent déplétant les lymphocytes B, le méthotrexate, le léflunomide, la rapamycine, ou un analogue de ceux-ci, un inhibiteur de Cox-2, un inhibiteur de cPLA2, un AINS et un inhibiteur de p38.

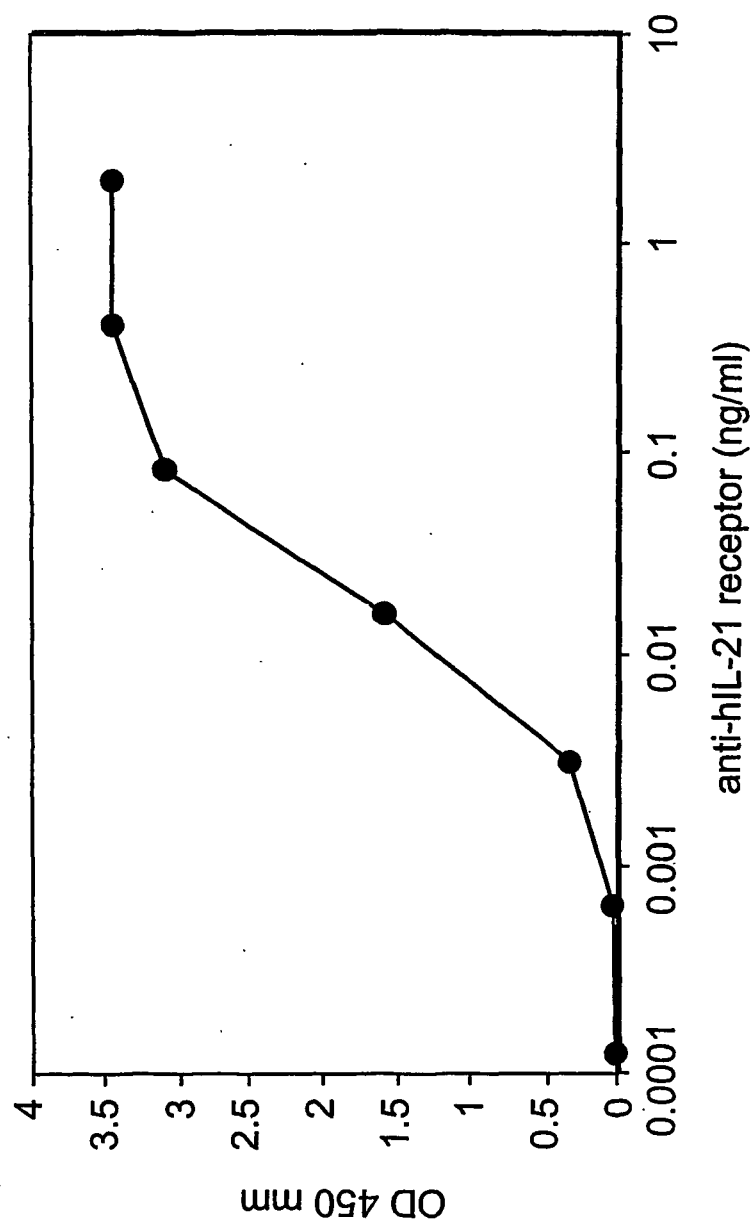
26. Utilisation de l'anticorps de la revendication 1, 2, 3 ou 4 pour fabriquer un médicament permettant de traiter ou de prévenir une maladie hyperproliférative chez un sujet dans une quantité suffisante pour inhiber ou réduire l'hyperprolifération des cellules sensibles à IL-21 et/ou aux récepteurs de l'IL-21 chez un sujet, dans laquelle la maladie hyperproliférative est choisie dans le groupe constitué par les cancers leucémiques et les tumeurs du sang, de la moelle osseuse et du tissu lymphatique.

27. Utilisation selon la revendication 26, dans laquelle le sujet est un mammifère.

28. Utilisation selon la revendication 27, dans laquelle le sujet est un humain.

29. Utilisation selon la revendication 21 ou 25, dans laquelle l'anticorps est utilisé dans une gamme choisie allant de 1 µg/kg à 20 mg/kg, de 1 µg/kg à 10 mg/kg, de 1 µg/kg à 1 mg/kg, de 10 µg/kg à 1 mg/kg, de 10 µg/kg à 100 µg/kg, de 100 µg/kg à 1 mg/kg, et de 500 µg/kg à 1 mg/kg.

30. Kit de diagnostic comprenant l'anticorps selon la revendication 1, 2, 3 ou 4.

**FIG. 1A**

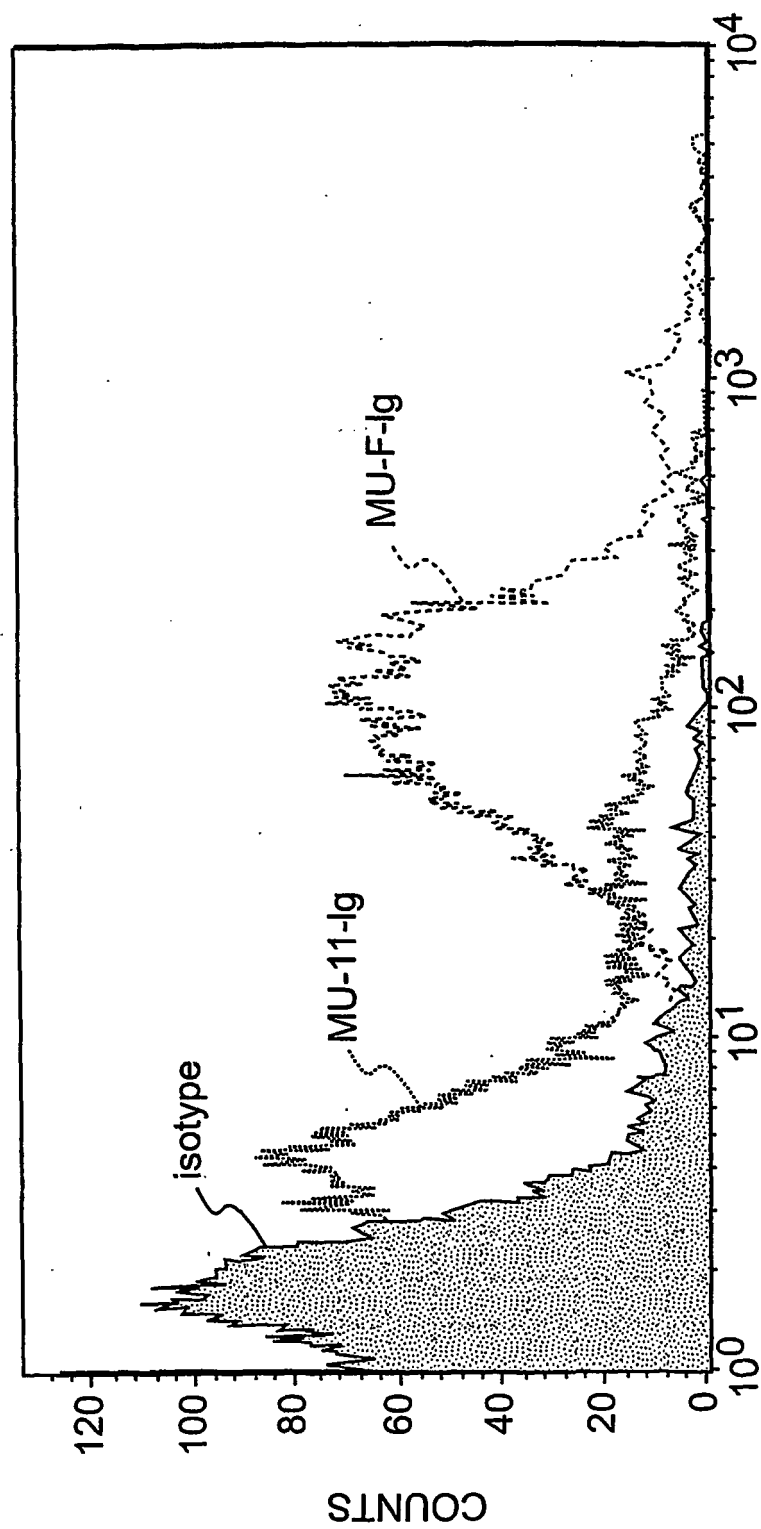


FIG. 1B

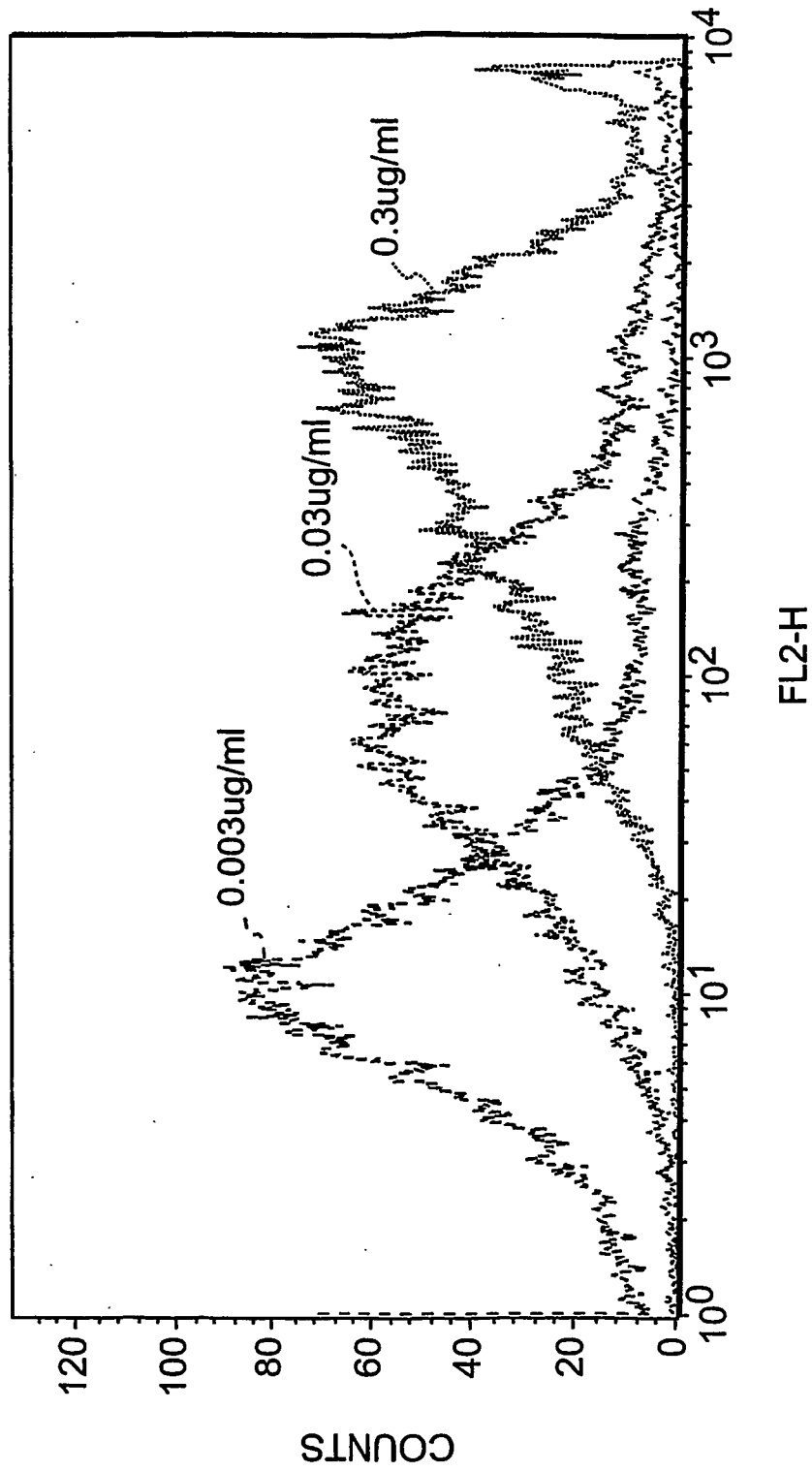
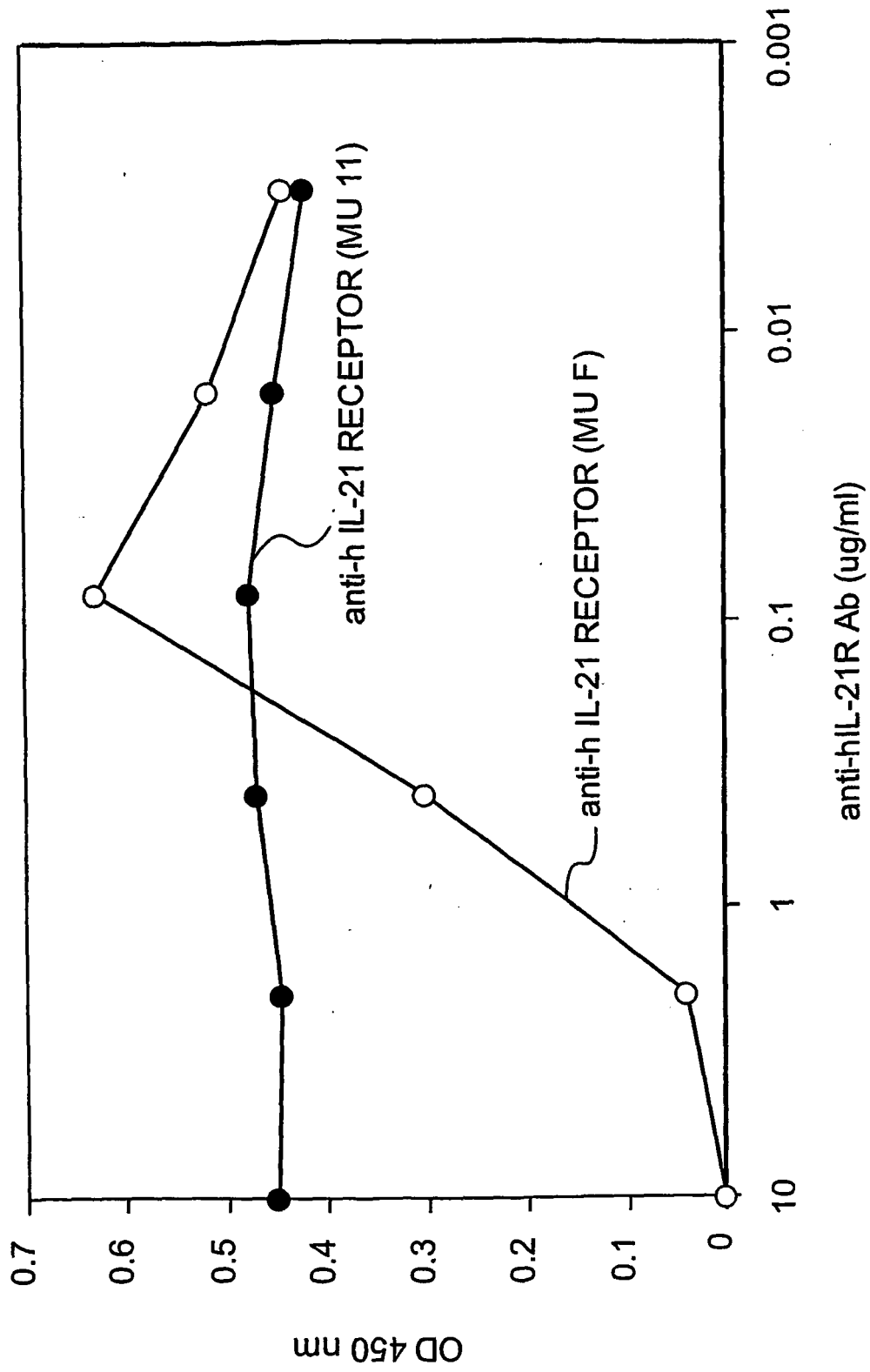


FIG. 1C

**FIG. 2**

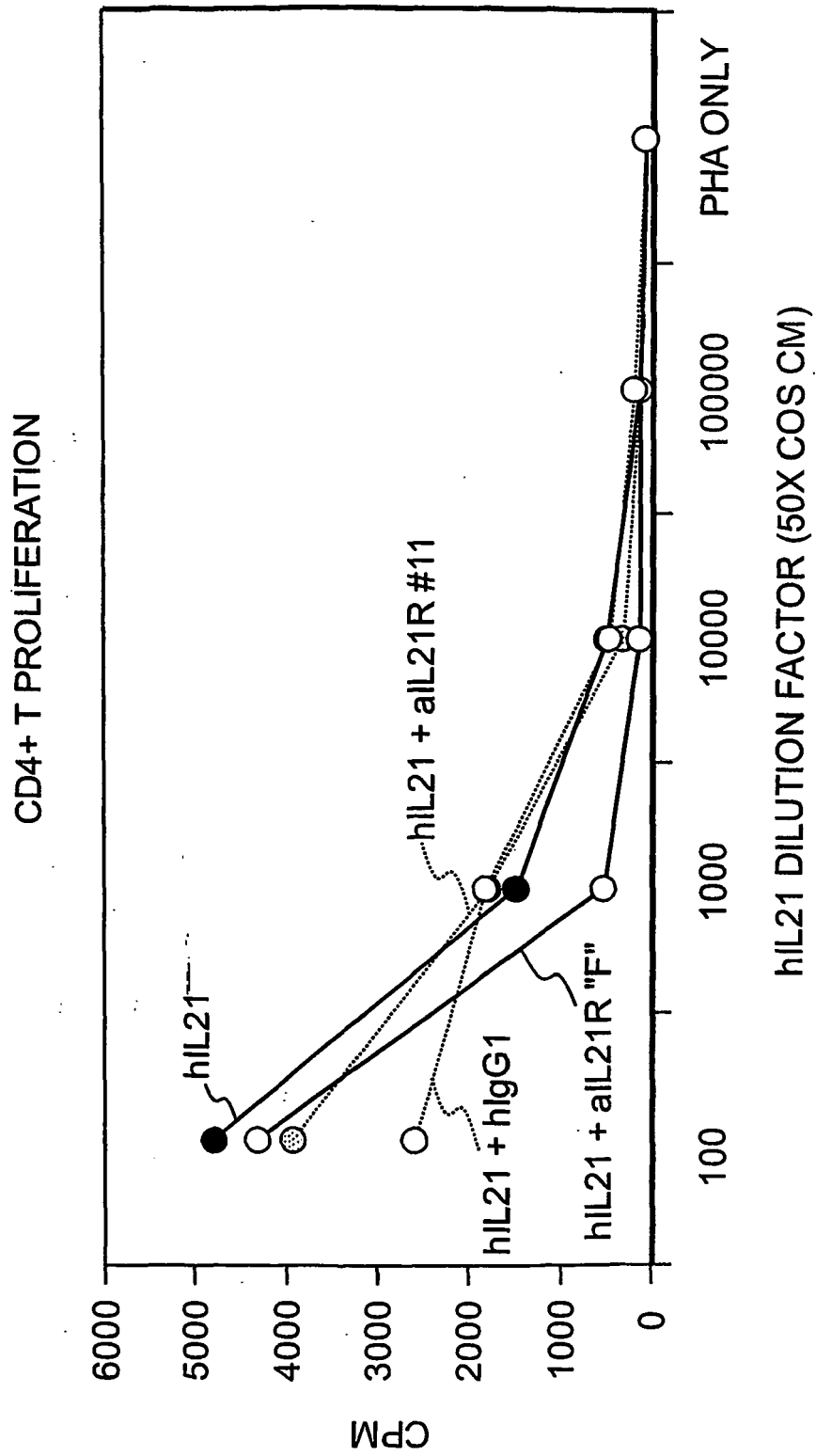


FIG. 3A

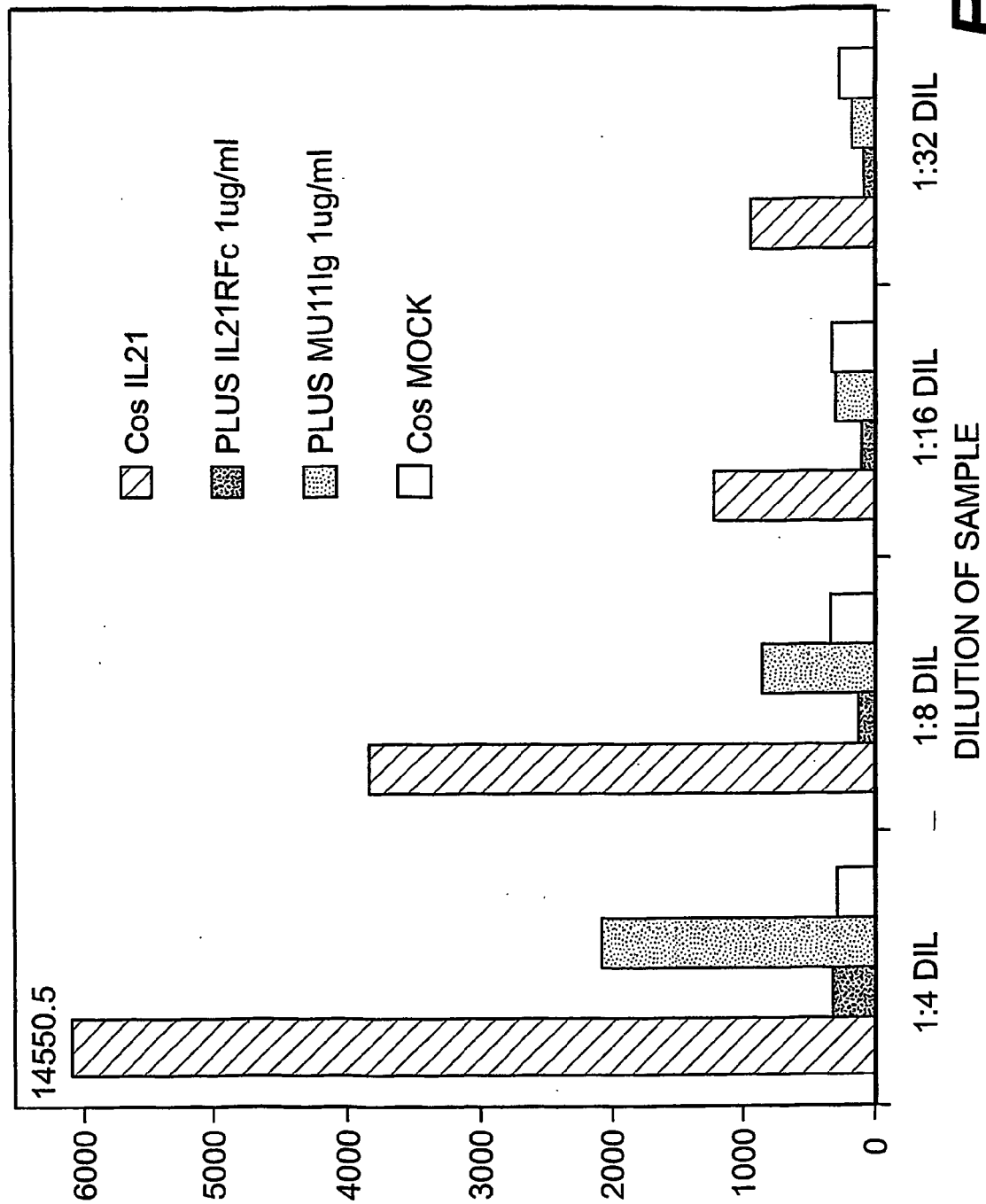
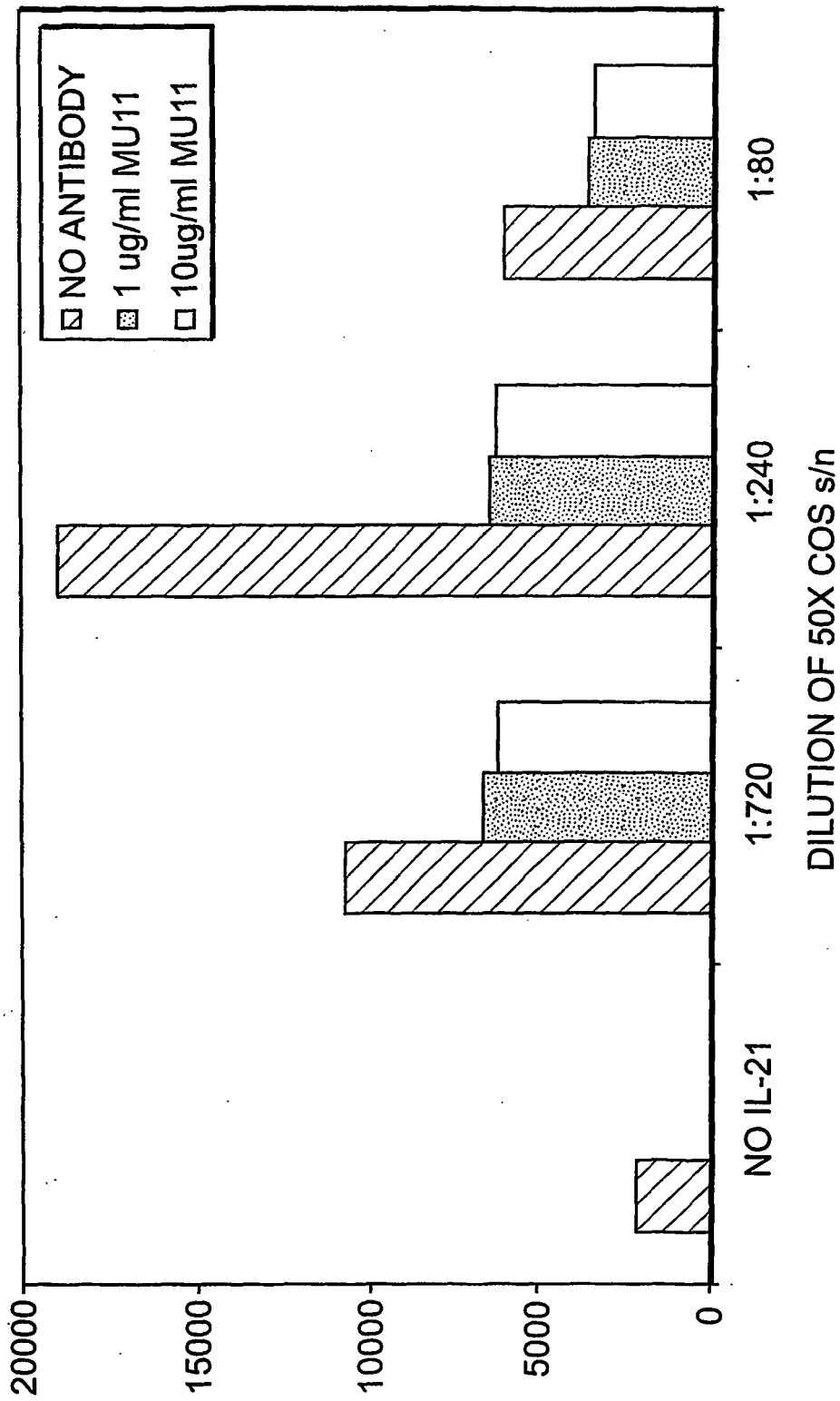
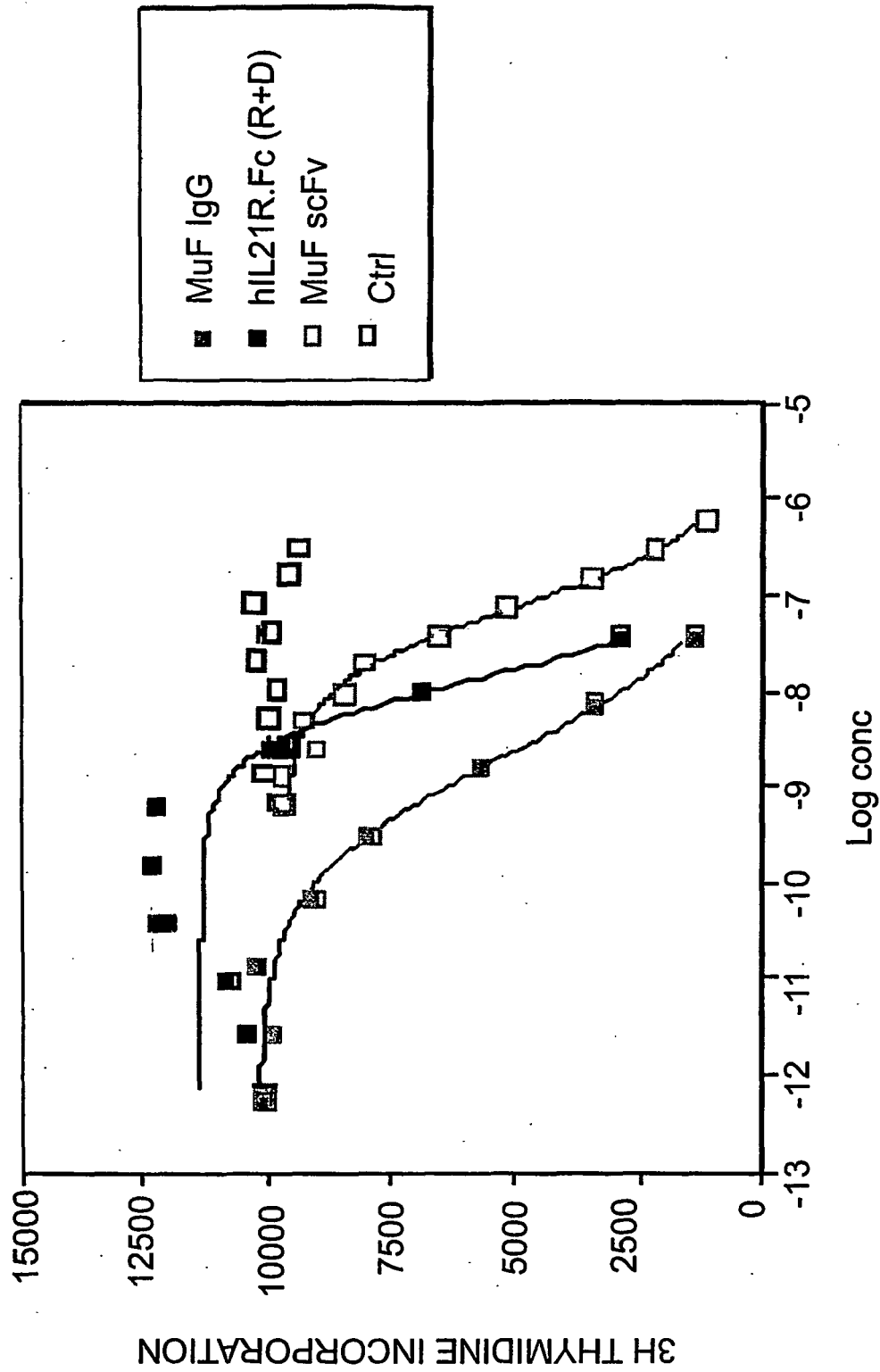


FIG. 3B

**FIG. 3C**

**FIG. 4**

CHEMOKINES

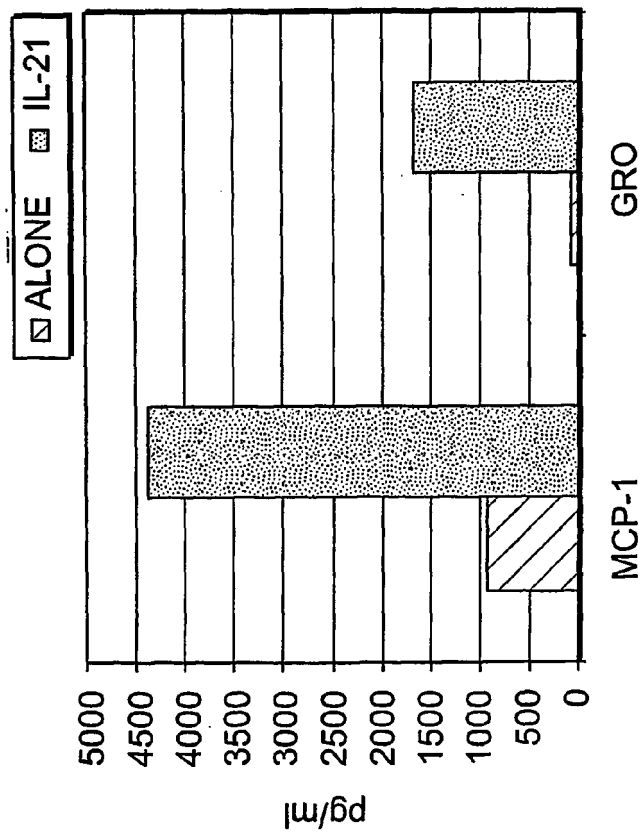


FIG. 5A

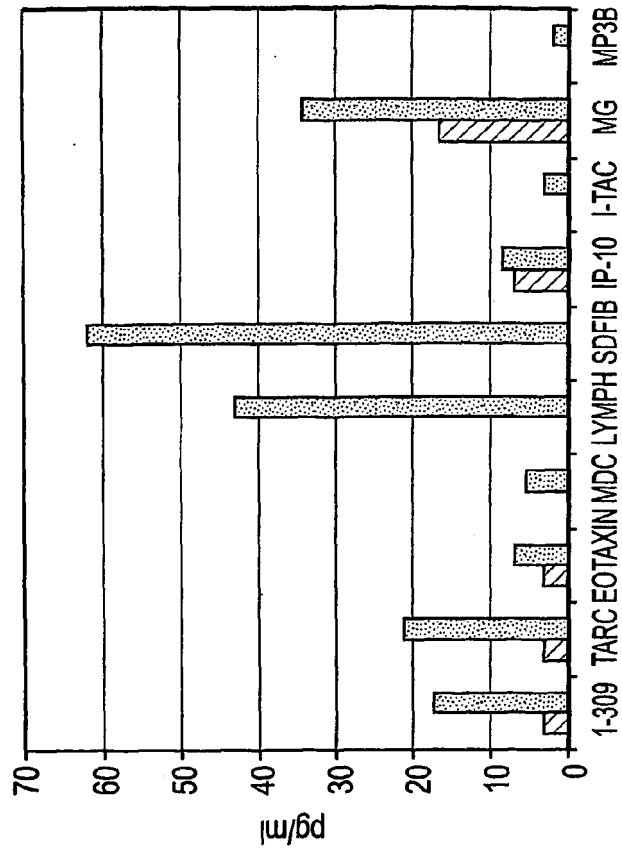


FIG. 5B

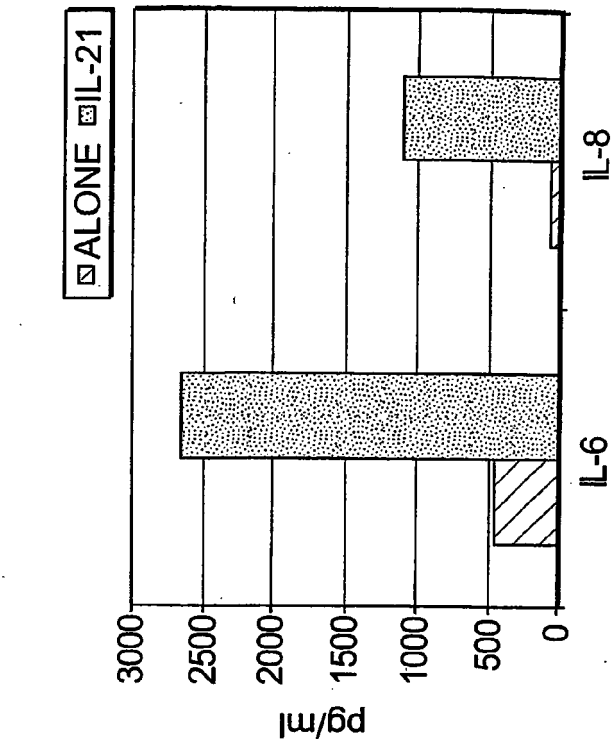


FIG. 5D

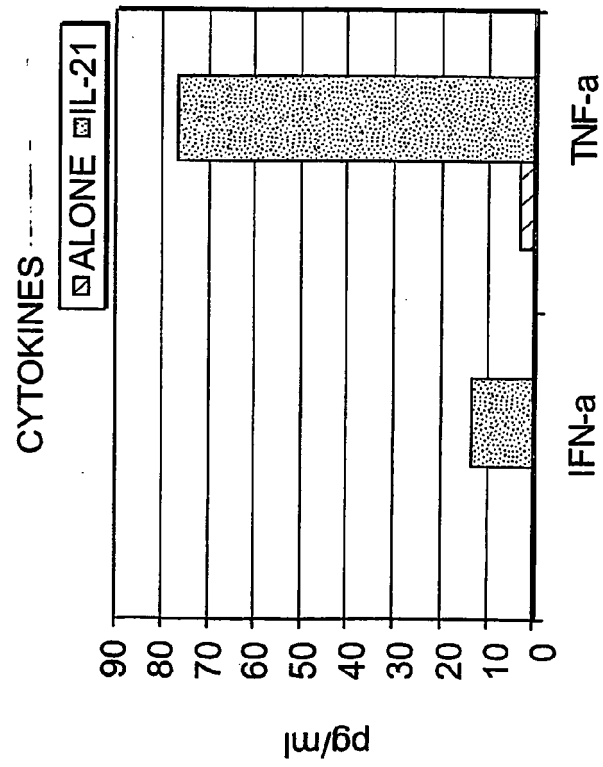


FIG. 5C

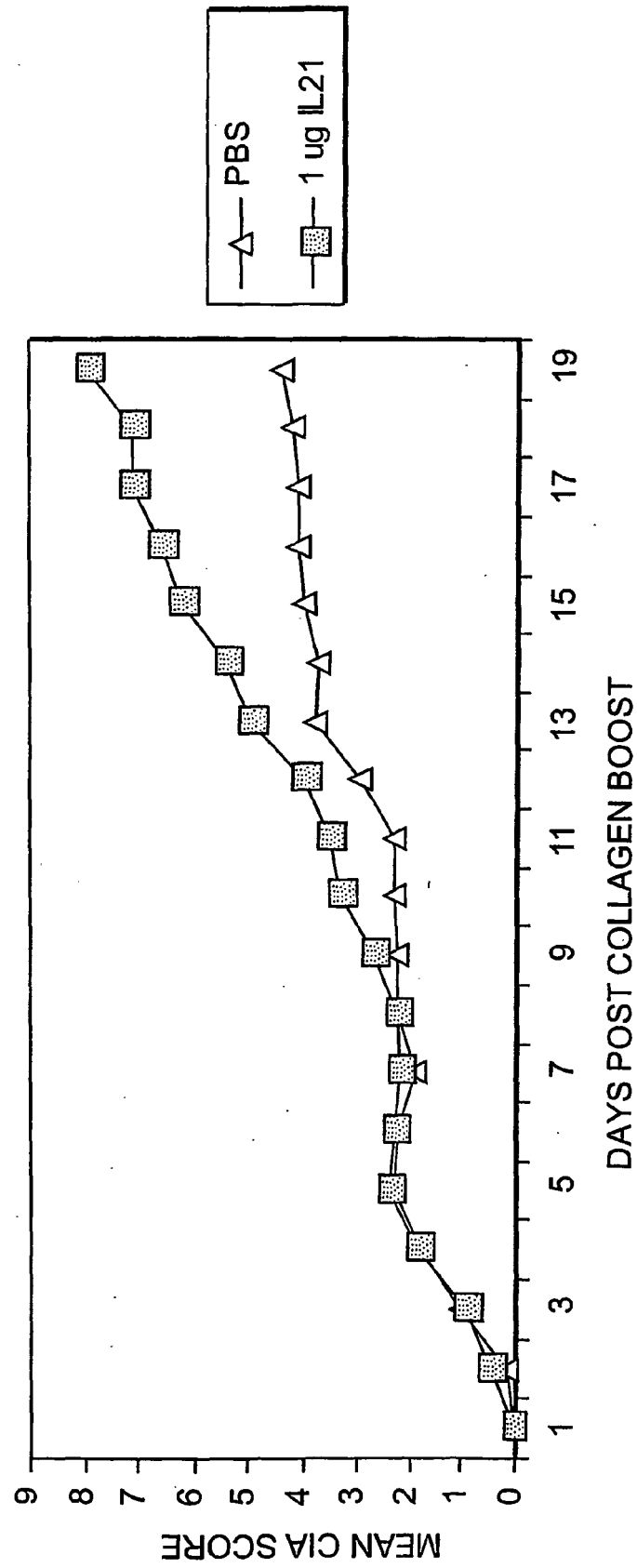
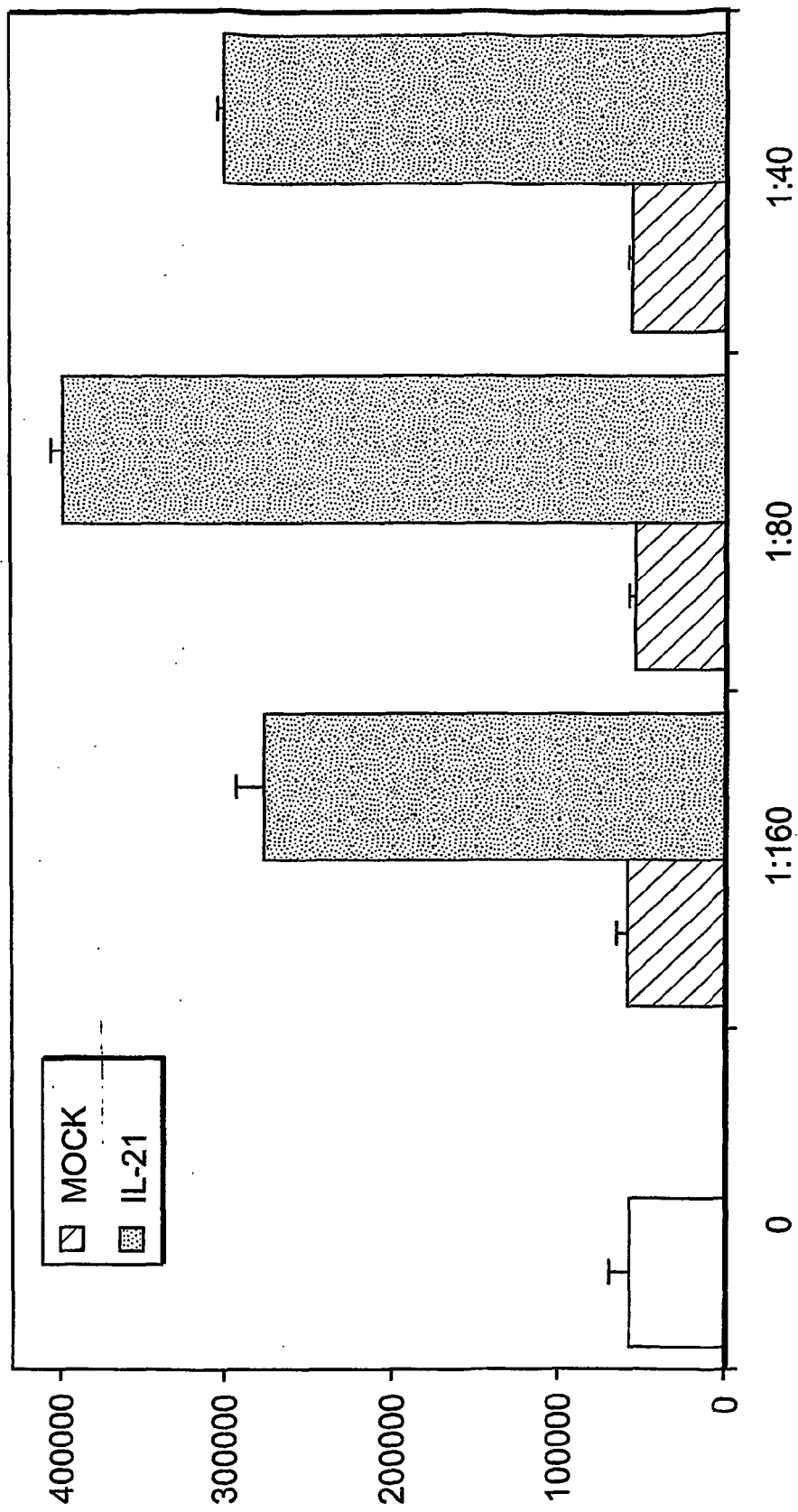


FIG. 5E

**FIG. 6**

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 0185792 A [0004] [0047]
- WO 0177171 A1 [0005]
- US 200210128446 A1 [0005]
- US 5565332 A [0051]
- US 4816567 A [0061]
- WO 9201047 A [0088] [0092]
- US 4640835 A [0093]
- US 4496689 A [0093]
- US 4301144 A [0093]
- US 4670417 A [0093]
- US 4791192 A [0093]
- US 4179337 A [0093]
- US 4766106 A [0093]
- US 4495285 A [0093]
- US 4609546 A [0093]
- WO 8705330 A [0094]
- EP 388151 A1 [0095]
- US 5624821 A [0095] [0096] [0097] [0099]
- US 5648260 A [0095]
- WO 9429351 A, Morgan [0099]
- WO 0056772 A [0123]
- US 6258562 B [0124]
- WO 0155112 A [0124]
- US 6350892 B [0127]
- US 4522811 A [0145]
- US 60454336 B [0185]

Non-patent literature cited in the description

- Parrish-Novak et al. *Nature*, 2000, vol. 408, 57-63 [0003] [0047]
- Ozaki et al. *Proc. Natl. Acad. Sci. USA*, 2000, vol. 97, 11439-11444 [0004]
- Asao et al. *J. Immunol.*, 2001, vol. 167, 1-5 [0004] [0047]
- Kasaian, M.T. et al. *Immunity*, 2002, vol. 16, 559-569 [0005]
- Ward et al. *Nature*, 1989, vol. 341, 544-546 [0042]
- Bird et al. *Science*, 1988, vol. 242, 423-426 [0042]
- Huston et al. *Proc. Natl. Acad. Sci. USA*, 1988, vol. 85, 5879-5883 [0042]
- Kabat et al. Sequences of Proteins of Immunological Interest. NIH Publication, 1991 [0044]
- Ozaki et al. *Proc. Natl. Acad. Sci. USA*, 2000, vol. 97, 11439-11444 [0047]
- Current Protocols in Molecular Biology. John Wiley & Sons, 1989, 6.3.1-6.3.6 [0053]
- Altshul et al. *J. Mol. Biol.*, 1990, vol. 215, 403-410 [0056]
- Needleman et al. *J. Mol. Biol.*, 1970, vol. 48, 444-453 [0056]
- Meyers et al. *Comput. Appl. Biosci.*, 1988, vol. 4, 11-17 [0056]
- E. Meyers ; W. Miller. *CABIOS*, 1989, vol. 4, 11-17 [0056]
- Kohler ; Milstein. *Nature*, 1975, vol. 256, 495-499 [0061]
- Clackson et al. *Nature*, 1991, vol. 352, 624-628 [0061]
- Marks et al. *J. Mol. Biol.*, 1991, vol. 222, 581-597 [0061]
- Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory, 1988 [0061]
- Immunoglobulin Genes. Academic Press, 1995 [0066]
- Epitope Mapping Protocols. Morris, Humana Press, 1996 [0077]
- Engstrom. *Biochem. Exp. Biol.*, 1974, vol. 11, 7-13 [0077]
- Molecular Biology. Cold Spring Harbor Laboratory [0077]
- Antibody Engineering. Oxford University Press, 1995 [0078]
- MacLennan et al. *Acta Physiol. Scand. Suppl.*, 1998, vol. 643, 55-67 [0081]
- Sasaki et al. *Adv. Biophys.*, 1998, vol. 35, 1-24 [0081]
- Marks et al. *BioTechnology*, 1992, vol. 10, 779-783 [0088]
- Gram et al. *Proc. Nat. Acad. Sci. U.S.A.*, 1992, vol. 89, 3576-3580 [0089]
- Barbas et al. *Proc. Nat. Acad. Sci. U.S.A.*, 1994, vol. 91, 3809-3813 [0090]
- Schier et al. *J. Mol. Biol.*, 1996, vol. 263, 551-567 [0090]
- Aplin et al. *CRC Crit. Rev. Biochem.*, 1981, vol. 22, 259-306 [0094]
- Hakimuddin et al. *Arch. Biochem. Biophys.*, 1987, vol. 259, 52 [0094]
- Edge et al. *Anal. Biochem.*, 1981, vol. 118, 131 [0094]
- Thotakura et al. *Meth. Enzymol.*, 1987, vol. 138, 350 [0094]

- **Fernandez et al.** Gene Expression Systems. Academic Press, 1999 [0110]
- **Sambrook et al.** Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 1989 [0110]
- Current Protocols in Molecular Biology. John Wiley & Sons, 1992 [0110]
- **Tuohy et al.** *J. Immunol.*, 1988, vol. 141, 1126-1130 [0114]
- **Sobel et al.** *J. Immunol.*, 1984, vol. 132, 2393-2401 [0114]
- **Traugott.** *Cell Immunol.*, 1989, vol. 119, 114-129 [0114]
- **Courtenay et al.** *Nature*, 1980, vol. 283, 666-628 [0115]
- **Williams et al.** *Immunol.*, 1995, vol. 84, 433-439 [0115]
- Current Protocols in Immunology. John Wiley & Sons, 1994 [0116]
- **Kasaian et al.** *Immunity*, 2002, vol. 16, 559-569 [0116]
- **Fulmer et al.** *Am. J. Anat.*, 1993, vol. 113, 273-285 [0116]
- **Lenschow et al.** *Science*, 1992, vol. 257, 789-792 [0116]
- Immunologic Defects in Laboratory Animals. Plenum Press, 1981 [0117]
- **Vaickus, L.** *Crit. Rev. in Oncol./Hematol.*, 1991, vol. 11, 267-97 [0118]
- **Yusuf-Makagiansar et al.** *Med Res Rev*, 2002, vol. 22 (2), 146-67 [0122]
- *Arthritis & Rheumatism*, 1994, vol. 37, S295 [0124]
- *J. Invest. Med.*, 1996, vol. 44, 235A [0124]
- *Arthritis & Rheumatism*, 1996, vol. 39 (9), S284 [0124]
- *Am. J. Physiol. Heart Circ. Physiol.*, 1995, vol. 268, 37-42 [0124]
- *Arthritis & Rheumatism*, 1993, vol. 36, 1223 [0125]
- *Cancer Res.*, 01 March 1990, vol. 50 (5), 1495-502 [0125]
- *Arthritis & Rheumatism*, 1996, vol. 39 (9), S280 [0126]
- *Neuro Report*, 1996, vol. 7, 1209-1213 [0126]
- *Arthritis & Rheumatism*, 1996, vol. 39 (9), S281 [0126]
- *Arthritis & Rheumatism*, vol. 39 (9), S131 [0126]
- *Inflammation Research*, vol. 45, 103-107 [0126]
- **Elit. L.** *Current Opinion Investig. Drugs*, 2002, vol. 3 (8), 1249-53 [0127]
- **Huang, S. et al.** *Current Opinion Investig. Drugs*, 2002, vol. 3 (2), 295-304 [0127]
- *Arthritis & Rheumatism*, 1996, vol. 39 (9), S81 [0127]
- *Arthritis & Rheumatism*, 1996, vol. 39 (9), S282 [0127]
- **Vaughan et al.** *Nature Biotech.*, 1996, vol. 14, 309-314 [0153]
- **Griffiths et al.** *EMBO J*, 1993, vol. 12, 725-734 [0155]
- **Takahashi et al.** *Cell*, 1982, vol. 29, 671 [0167]
- **Hieter et al.** *Nature*, 1982, vol. 294, 536 [0167]
- **Holmdahl et al.** *Ageing Res. Rev.*, 2002, vol. 1, 135 [0182]