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(54) **BIOMARKERS PREDICTIVE OF THE** RESPONSIVENESS TO TNFALPHA INHIBITORS IN AUTOIMMUNE DISORDERS

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- Provisional application No. 60/932,888, filed on May 31, 2007.

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(57)

The invention provides methods for predicting responsiveness to TNFα inhibitors in a subject suffering from an autoimmune disorder, such as rheumatoid arthritis. The methods involve assaying for expression of one or more biomarkers in the subject that are predictive of responsiveness to $TNF\alpha$ inhibitors. A preferred biomarker of the invention is CD11c. The methods can further comprise selecting a treatment regimen with a TNF α inhibitor in an autoimmune disorder subject based upon expression of the biomarker(s) in the subject. The methods can further comprise administering a TNFα inhibitor to the subject according to the selected treatment regimen. Kits that include means for measuring expression of one or more biomarkers that are predictive of responsiveness to TNFα inhibitors for an autoimmune disorder are also provided. Methods of preparing and using databases, and computer program products therefore, for selecting an autoimmune disorder subject for treatment with a TNF α inhibitor are also provided.

Figure 1

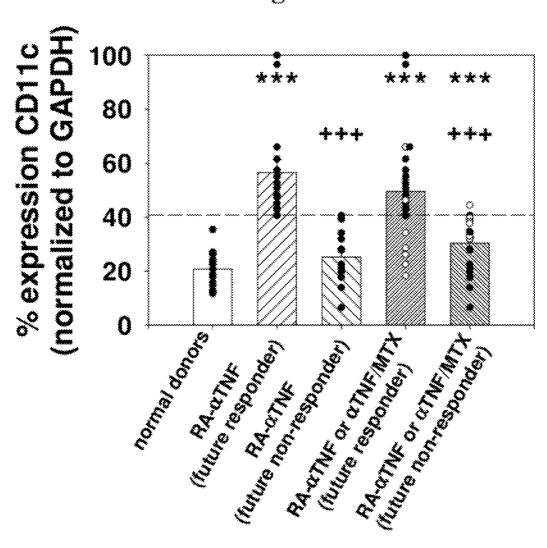


Figure 2

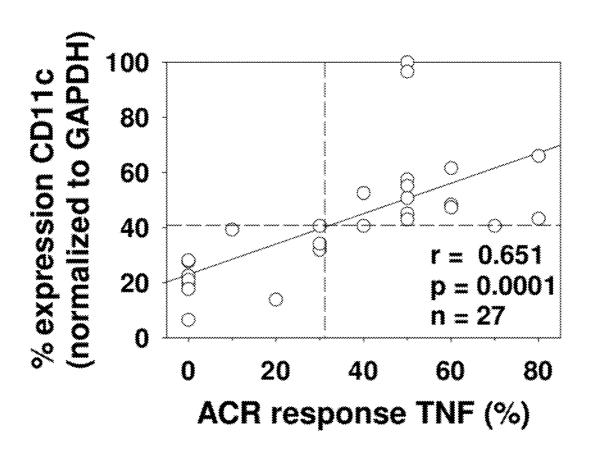
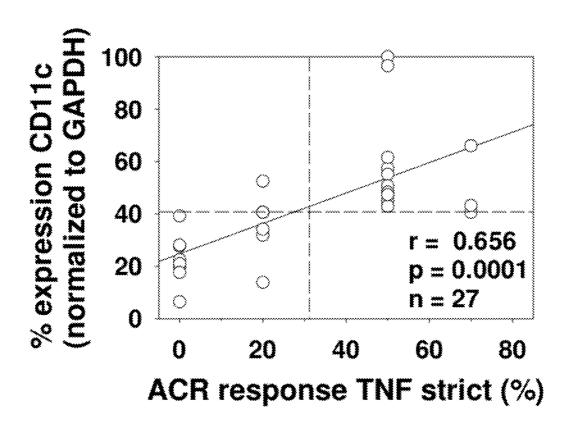


Figure 3



BIOMARKERS PREDICTIVE OF THE RESPONSIVENESS TO TNFALPHA INHIBITORS IN AUTOIMMUNE DISORDERS

RELATED APPLICATIONS

[0001] This application is a continuation application of U.S. patent application Ser. No. 12/130,373, filed on May 30, 2008, which claims the benefit of priority to U.S. provisional patent application No. 60/932,888 filed on May 31, 2007. The contents of the above-mentioned priority application is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Autoimmune disorders are a significant and widespread medical problem. For example, rheumatoid arthritis (RA) is an autoimmune disease affecting more than two million people in the United States. RA causes chronic inflammation of the joints and typically is a progressive illness that has the potential to cause joint destruction and functional disability. The cause of rheumatoid arthritis is unknown, although genetic predisposition, infectious agents and environmental factors have all been implicated in the etiology of the disease. In active RA, symptoms can include fatigue, lack of appetite, low grade fever, muscle and joint aches and stiffness. Also during disease flare ups, joints frequently become red, swollen, painful and tender, due to inflammation of the synovium. Furthermore, since RA is a systemic disease, inflammation can affect organs and areas of the body other than the joints, including glands of the eyes and mouth, the lung lining, the pericardium, and blood vessels.

[0003] Traditional treatments for the management of RA and other autoimmune disorders include fast acting "first line drugs" and slower acting "second line drugs." The first line drugs reduce pain and inflammation. Example of such first line drugs include aspirin, naproxen, ibuprofen etodolac and other nonsteroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroids, given orally or injected directly into tissues and joints. The second line drugs promote disease remission and prevent progressive joint destruction and are also referred to as disease-modifying anti-rheumatic drugs or DMARDs. Examples of second line drugs include gold, hydrochloroguine, azulfidine and immunosuppressive agents, such as methotrexate, azathioprine, cyclophosphamide, chlorambucil and cyclosporine. Many of these drugs, however, can have detrimental side-effects. Thus, additional therapies for rheumatoid arthritis and other autoimmune disorders have been sought.

[0004] More recently, biological therapies have been applied to the treatment of autoimmune disorders such as rheumatoid arthritis. For example, three TNF α inhibitors, REMICADETM (infliximab), a chimeric anti-TNFα mAb, ENBRELTM (etanercept), a TNFR-Ig Fc fusion protein, and HUMIRATM (adalimumab), a human anti-TNF α mAb, have been approved by the FDA for treatment of rheumatoid arthritis. While such biologic therapies have demonstrated success in the treatment of rheumatoid arthritis and other autoimmune disorders, not all subjects treated respond, or respond well, to a TNF α inhibitor. The use of TNF α inhibitors such as TNF α inhibitors typically is more expensive than traditional treatments and usually requires administration by injection, which, at least for certain agents, may require that the patient visit a medical office on a frequent basis. Thus, it would be very helpful to predict in advance of treatment whether a rheumatoid arthritis patient is likely to be responsive to treatment with a TNF α inhibitor. Accordingly, ways for predicting responsiveness to a TNF α inhibitor in patients having autoimmune disorders, such as rheumatoid arthritis patients, are of particular interest.

SUMMARY OF THE INVENTION

[0005] This invention provides methods and compositions for predicting responsiveness to a TNFα inhibitor in a subject having an autoimmune disorder, such as rheumatoid arthritis, based on the discovery that the expression patterns of particular biomarkers in the subject correlate with responsiveness to a TNFα inhibitor. Using microarray analysis of monocytes from representative rheumatoid arthritis (RA) patients treated with an anti-TNFα monoclonal antibody, 82 differentially expressed genes predictive of responsiveness to TNFα inhibitor treatment were identified by pairwise comparisons between future RA responders and future RA non-responders to anti-TNFα therapy. Furthermore, hierarchical clustering and TaqMan®-PCR of RA responders/non-responders pretreatment identified one gene of particular interest, CD11c, which was fully predictive of future response to anti-TNF α treatment.

[0006] Accordingly, in one aspect, the invention pertains to a method for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder (e.g., rheumatoid arthritis). The method comprises: (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on expression of the one or more biomarkers in the subject, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (corresponding to the sequences set forth in Table 9)

[0007] Within SEQ ID NOs: 1-82, certain genes were found to be upregulated in RA responders to TNF α inhibitors. Accordingly, in one embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43-47, 49, 51, 54, 55, 57, 59, 61, 62, 64, 70, 75, 79 and 82 (corresponding to sequences from Table 9 that are increased in ≥80% of responders vs. non-responders). More preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 37, 44, 47, 62 and 70 (corresponding to sequences from Table 9 that are increased in ≥90% of responders vs. non-responders). Even more preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 44. (corresponding to CD11c, from Table 9, which is increased in 100% of responders vs. non-responders). In each of these embodiments, increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor.

[0008] Within SEQ ID NOs: 1-82, certain genes were found to be downregulated in RA responders to TNFα inhibitors. Accordingly, in one embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 11-14, 18, 20, 21, 23, 25, 26, 28-30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 65-69, 71-74, 76-78, 80 and 81. (corresponding to sequences from Table 9

that are decreased in $\geq 80\%$ of responders vs. non-responders). More preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 29, 65, 73 and 74 (corresponding to sequences from Table 9 that are decreased in $\geq 90\%$ of responders vs. non-responders). Even more preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 11 or SEQ ID NO: 74 (corresponding to sequences from Table 9 that are decreased in 100% of responders vs. non-responders). In each of these embodiments, decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor.

[0009] In another aspect, the invention provides a method for predicting responsiveness to a TNFα inhibitor in a subject having an autoimmune disorder, the method comprising: (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to a TNFα inhibitor in an autoimmune disorder, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on expression of the one or more biomarkers in the subject, wherein the one or more biomarkers is selected from the group consisting of Aquaporin 3 (Genbank Accession No. NM_004925); Similar to ribosomal protein S24, clone MGC:8595 (Genbank Accession No. NM_033022); Transmembrane emp24 domain trafficking protein 2 (Genbank Accession No. NM_006815; Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (Genbank Accession No. NM_000454); Calmodulin 1 (phosphorylase kinase, delta) (Genbank Accession No. NM_006888); Guanine nucleotide binding protein (G protein), beta polypeptide 1 (Genbank Accession No. NM_002074); Prothymosin, alpha (gene sequence 28) (Genbank Accession No. NM_002823); Homo sapiens isocitrate dehydrogenase 1 (NADP+) soluble (IDH1) (Genbank Accession No. NM_005896); Tumor protein D52 (Genbank Accession Nos. NM_001025252, NM_001025253, NM_005079); Early growth response 1 (Genbank Accession No. NM 001964); Homo sapiens predicted osteoblast protein (GS3786) (Genbank Accession Nos. NM_014888, NM_001040020); Cytochrome c oxidase subunit VIIb (Genbank Accession No. NM_001866); CUG triplet repeat, RNA binding protein 2 (Genbank Accession No. NM_001025077, NM 001025076, NM 006561); Ubiquinol-cytochrome c reductase hinge protein (Genbank Accession No. NM_006004); Homo sapiens leptin receptor gene-related protein (HS0BRGRP) (Genbank Accession NM_017526); Wiskott-Aldrich syndrome protein interacting protein (Genbank Accession Nos. NM 001077269, NM_003387); CD97 antigen (Genbank Accession Nos. NM_001025160, NM_001784, NM_078481); Glutamatecysteine ligase, catalytic subunit (Genbank Accession No. NM_001498); Crystallin, zeta (quinone reductase) (Genbank Accession No. NM_001889); Rap guanine nucleotide exchange factor (GEF) 2 (Genbank Accession No. NM_014247); Ataxin 1 (Genbank Accession No. NM_000332); Adaptor-related protein complex 1, sigma 2 subunit (Genbank Accession No. NM 003916); Ectonucleotide pyrophosphatase/phosphodiesterase 4 (Genbank Accession No. NM_014936); Desmocollin 2 (Genbank Accession Nos. NM_024422, NM_004949); MAL, T-cell differentiation protein (Genbank Accession NM_002371, NM_022438, NM_022439, NM_022440); Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (Genbank Accession No. NM_005476); Chemokine (C—C motif) ligand 3 (Genbank Accession Nos. NM_001001437, NM_021006); Carboxypeptidase A3 (Genbank Accession No. NM_001870); Charcot-Leyden crystal protein (Genbank Accession No. NM_001828); NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7 kDa (Genbank Accession No. NM_004545); Interleukin 8 receptor, beta (Genbank Accession No. NM 001557); Platelet factor 4 variant 1 (Genbank Accession No. NM 002620); Poly(A) binding protein interacting protein 1 (Genbank Accession No. NM 006451); ATP-binding cassette, subfamily C (CFTR/MRP), member 3 (Genbank Accession No. NM_003786); Actinin, alpha 1 (Genbank Accession No. NM_001102); NAD kinase (Genbank Accession No. NM_023018); Platelet/endothelial cell adhesion molecule (CD31 antigen) (Genbank Accession No. NM 000442); Esterase D/formylglutathione hydrolase (Genbank Accession No. NM_001984); Chromosome 20 open reading frame 111 (Genbank Accession No. NM_016470); Sterol-C4-meoxidase-like (Genbank Accession NM_001017369, NM_006745); PIM-1 oncogene (Genbank Accession No. NM 002648); GATA binding protein 2 (Genbank Accession No. NM_032638); Cathepsin Z (Genbank Accession No. NM_001336); Integrin alpha-X (antigen CD11c) (Genbank Accession No. NM 000887); Lectin, galactoside-binding, soluble, 8 (galectin 8) (Genbank Accession Nos. NM_006499, NM_201545); CD86 antigen (CD28 antigen ligand 2, B7-2 antigen) (Genbank Accession Nos. NM_006889, NM_175862); Interleukin 8 (Genbank Accession No. NM_000584); Fc fragment of IgE, high affinity I, receptor for alpha polypeptide (Genbank Accession No. NM_002001); Actin, gamma 1 (Genbank Accession No. NM_001614); KIAA0746 protein (Genbank Accession No. NM_015187); Glucosamine (N-acetyl)-6-sulfatase (Sanfilippo disease IIID) (Genbank Accession No. NM_002076); Transcription factor 4 (Genbank Accession Nos. BF592782, CR612521); Major histocompatibility complex, class II, DQ alpha 1 (Genbank Accession Nos. NM_002122, NM 020056); Cell division cycle 2-like 6 (CDK8-like) (Genbank Accession No. NM_015076); Major histocompatibility complex, class II, DQ beta 1 (Genbank Accession No. XM_942240); Phospholipase C-like 2 (Genbank Accession No. NM_015184); Coagulation factor II (thrombin) receptor-like 1 (Genbank Accession No. NM 005242); TM2 domain containing 1 (Genbank Accession NM_032027); Splicing factor 3b, subunit 1, 155 kDa (Genbank Accession No. NM_012433); SUB1 homolog (S. cerevisiae) (Genbank Accession No. NM_006713); MRNA; cDNA DKFZp564O0862 (Genbank Accession No. AI278204); Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease) (Genbank Accession Nos. NM_201413, NM_000484, NM_201414); Cytochrome b-5 (Genbank Accession Nos. NM_001914, NM_148923); Cold autoinflammatory syndrome 1 (Genbank Accession No. NM_183395); Neugrin, neurite outgrowth associated (Genbank Accession Nos. NM_016645, NM_001033088); Ribosomal protein S26, 40S ribosomal protein (Genbank Accession No. XM 941927); CCR4-NOT transcription complex, subunit 6 (Genbank Accession No. NM_015455); Ubiquinol-cytochrome c reductase complex (7.2 kD) (Genbank Accession Nos. NM_013387, NM_001003684); Hepatocellular carcinoma-associated antigen 112 (Genbank Accession No. NM_018487); Kruppel-like factor 11 (Genbank Accession No. XM_001129527); GGA binding partner

(Genbank Accession No. NM_018318); Cornichon homolog 4 (Drosophila) (Genbank Accession No. NM_014184); Hypothetical protein FLJ21616 (Genbank Accession No. NM_024567); Homo sapiens hypothetical protein FLJ10134 (Genbank Accession No. NM_018004); Nuclear prelamin A recognition factor (Genbank Accession Nos. NM_012336, NM_001038618); Erythroblast membraneassociated protein (Genbank Accession Nos. NM_018538, NM_001017922); LR8 protein (Genbank Accession No. NM_014020); Likely ortholog of mouse limb-bud and heart gene (LBH) (Genbank Accession No. NM_030915); Calmin (calponin-like, transmembrane) (Genbank Accession No. NM_024734); Chromosome 14 open reading frame 156 (Genbank Accession No. NM_031210); Guanine nucleotide binding protein (G protein) alpha 12 (Genbank Accession No. NM_007353); and SRY (sex determining region Y)-box 18 (Genbank Accession No. NR_003287) (corresponding to biomarkers listed in Table 9).

[0010] Within the above-listed biomarkers, certain genes were found to be upregulated in RA responders to TNF α inhibitors. Accordingly, in one embodiment, the one or more biomarkers is selected from the group consisting of Guanine nucleotide binding protein (G protein), beta polypeptide 1; Prothymosin, alpha (gene sequence 28); Early growth response 1; Homo spaiens leptin receptor gene-related protein (HS0BRGRP); Wiskott-Aldrich syndrome protein interacting protein; CD97 antigen; Crystallin, zeta (quinone reductase); Adaptor-related protein complex 1, sigma 2 subunit; Desmocollin 2; Chemokine (C—C motif) ligand 3; Interleukin 8 receptor, beta; ATP-binding cassette, sub-family C (CFTR/MRP), member 3; Actinin, alpha 1; NAD kinase; Platelet/endothelial cell adhesion molecule (CD31 antigen); Esterase D/formylglutathione hydrolase; Chromosome 20 open reading frame 111; Cathepsin Z; Integrin alpha-X (antigen CD11c); Lectin, galactoside-binding, soluble, 8 (galectin 8); CD86 antigen (CD28 antigen ligand 2, B7-2 antigen); Interleukin 8; Actin, gamma 1; Glucosamine (N-acetyl)-6-sulfatase (Sanfilippo disease IIID); Cell division cycle 2-like 6 (CDK8-like); Major histocompatibility complex, class II, DQ beta 1; Coagulation factor II (thrombin) receptor-like 1; Splicing factor 3b, subunit 1, 155 kDa; mRNA; cDNA DKEZp564O0862; Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease); Cold autoinflammatory syndrome 1; Kruppel-like factor 11; Nuclear prelamin A recognition factor; Calmin (calponinlike, transmembrane); and SRY (sex determining region Y)-box 18 (corresponding to biomarkers from Table 9 that are increased in ≥80% of responders vs. non-responders). More preferably, the one or more biomarkers is selected from the group consisting of Interleukin 8 receptor, beta; Platelet/endothelial cell adhesion molecule (CD31 antigen); Integrin alpha-X (antigen CD11c); Interleukin 8; Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease); and Kruppel-like factor 11 (corresponding to biomarkers from Table 9 that are decreased in ≥80% of responders vs. non-responders). Even more preferably, the one or more biomarkers is Integrin alpha-X (antigen CD11c) (corresponding to a biomarker from Table 9 that is increased in 100% of responders vs. non-responders). In each of these embodiments, increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibi-

[0011] Within the above-listed biomarkers, certain genes were found to be downregulated in RA responders to TNF α

inhibitors. Accordingly, in one embodiment, the one or more biomarkers is selected from the group consisting of Aquaporin 3; Similar to ribosomal protein S24, clone MGC:8595; Transmembrane emp24 domain trafficking protein 2; Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1; Calmodulin 1 (phosphorylase kinase, delta); Homo sapiens isocitrate dehydrogenase 1 (NADP+) soluble (IDH1); Tumor protein D52; Homo sapiens predicted osteoblast protein (GS3786); Cytochrome c oxidase subunit VIIb; CUG triplet repeat, RNA binding protein 2; Ubiquinol-cytochrome c reductase hinge protein; Glutamate-cysteine ligase, catalytic subunit; Rap guanine nucleotide exchange factor (GEF) 2; Ataxin 1; Ectonucleotide pyrophosphatase/phosphodiesterase 4; MAL, T-cell differentiation protein; Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase; Carboxypeptidase A3; Charcot-Leyden crystal protein; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7 kDa; Platelet factor 4 variant 1; Poly(A) binding protein interacting protein 1; Sterol-C4-methyl oxidase-like; PIM-1 oncogene; GATA binding protein 2; Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide; KIAA0746 protein; Transcription factor 4; Major histocompatibility complex, class II, DQ alpha 1; Phospholipase C-like 2; TM2 domain containing 1; SUB1 homolog (S. cerevisiae); Cytochrome b-5; Neugrin, neurite outgrowth associated; Ribosomal protein S26, 40S ribosomal protein; CCR4-NOT transcription complex, subunit 6; Ubiquinol-cytochrome c reductase complex (7.2 kD); Hepatocellular carcinoma-associated antigen 112; GGA binding partner; Cornichon homolog 4 (Drosophila); Hypothetical protein FLJ21616; Homo sapiens hypothetical protein FLJ10134; Erythroblast membrane-associated protein; LR8 protein; Likely ortholog of mouse limb-bud and heart gene (LBH); Chromosome 14 open reading frame 156; and Guanine nucleotide binding protein (G protein) alpha 12 (corresponding to biomarkers from Table 9 that are decreased in ≥80% of responders vs. non-responders). More preferably, the one or more biomarkers is selected from the group consisting of Homo sapiens predicted osteoblast protein (GS3786); Charcot-Leyden crystal protein; Neugrin, neurite outgrowth associated; Hypothetical protein FLJ21616; and Homo sapiens hypothetical protein FLJ10134 (corresponding to biomarkers from Table 9 that are decreased in $\geq 90\%$ of responders vs. non-responders). Even more preferably, the one or more biomarkers is Homo sapiens predicted osteoblast protein (GS3786) or Homo sapiens hypothetical protein FLJ10134 (corresponding to biomarkers from Table 9 that are decreased in 100% of responders vs. non-responders). In each of these embodiments, decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor.

[0012] In yet another aspect, the invention provides a method for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, the method comprising: (i) assaying the subject for increased expression of a biomarker, which biomarker is CD11c, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on increased expression of CD11c in the subject.

[0013] In yet another aspect, the invention provides a method for predicting responsiveness to a TNF α inhibitor, which TNF α inhibitor is adalimumab, in a subject having an autoimmune disorder, the method comprising: (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to adalimumab in an autoimmune disorder, and (ii) predicting responsiveness of the subject to

adalimumab based on expression of the one or more biomarkers in the subject. Preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (corresponding to biomarkers set forth in Table 9).

[0014] In one embodiment of the methods of the invention, a sample from the subject is assayed for expression of mRNA encoding the one or more biomarkers. In another embodiment of the methods of the invention, a sample from the subject is assayed for protein expression of the one or more biomarkers.

[0015] In one embodiment, the methods of the invention further comprise selecting a treatment regimen with the TNF α inhibitor based upon expression of the one or more biomarkers in the subject. In another embodiment, the methods of the invention further comprise administering the TNF α inhibitor to the subject according to the treatment regimen such that autoimmune disorder is inhibited in the subject.

[0016] A preferred TNF α inhibitor of the invention is an anti-tumor necrosis factor-alpha (TNFα) antibody, or antigen-binding portion thereof. The anti-TNF α antibody, or antigen-binding portion thereof, can be, for example, a humanized antibody, a chimeric antibody or a multivalent antibody. For example, the anti-TNFa antibody, or antigenbinding portion thereof, can be infliximab or golimumab. In another embodiment, the anti-TNF α antibody, or antigenbinding portion thereof, is a human antibody. For example, the anti-TNF α antibody, or antigen-binding portion thereof, can be an isolated human antibody that dissociates from human TNF α with a K_d of 1×10⁻⁸ M or less and a K_{off} rate constant of 1×10⁻³ s⁻¹ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard in vitro L929 assay with an IC $_{50}$ of 1×10^{-7} M or less. In another embodiment, the anti-TNF α antibody, or antigen-binding portion thereof, is an isolated human antibody with the following characteristics:

[0017] a) dissociates from human TNF α with a K_{off} rate constant of $1\times10^{-3}~{\rm s}^{-1}$ or less, as determined by surface plasmon resonance;

[0018] b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 305, or modified from SEQ ID NO: 305 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

[0019] c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 306, or modified from SEQ ID NO: 306 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or

[0020] In another embodiment, the anti-TNF α antibody, or antigen-binding portion thereof, is an isolated human antibody with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 303 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 304. In yet another embodiment, the anti-TNF α antibody, or antigen-binding portion thereof, is adalimumab. Yet another example of a TNF α inhibitor is etanercept.

[0021] Preferably, in the methods of the invention, the subject is a human.

[0022] In another aspect, the invention pertains to a kit for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder (e.g., rheumatoid arthritis). The kit comprises:

[0023] a) means for isolating monocytes;

[0024] b) means for measuring expression in the subject of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder;

[0025] c) means for measuring expression of at least one housekeeping gene; and

[0026] d) instructions for use of the kit to predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82

[0027] In one embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43-47, 49, 51, 54, 55, 57, 59, 61, 62, 64, 70, 75, 79 and 82, more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 37, 44, 47, 62 and 70, even more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 44 (CD11c). In each of these embodiments, the instructions for use of the kit instruct that increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNFα inhibitor.

[0028] In another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 11-14, 18, 20, 21, 23, 25, 26, 28-30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 65-69, 71-74, 76-78, 80 and 81, more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 29, 65, 73 and 74, even more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 11 or SEQ ID NO: 74. In each of these embodiments, the instructions for use of the kit instruct that decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNFα inhibitor.

[0029] In one embodiment of the kit, the means for measuring expression in the subject of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder comprises a nucleic acid preparation sufficient to detect expression of mRNA encoding the biomarker in a sample from the subject. In another embodiment of the kit, the means for measuring expression in the subject of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder comprises an antibody preparation sufficient to detect protein expression of the biomarker in a sample from the subject. The kit can further comprise a TNF α inhibitor for treating the autoimmune disorder in the subject.

[0030] In another aspect, the invention pertains to methods of monitoring an autoimmune disorder (e.g., RA) in a subject having the autoimmune disorder (e.g., RA). These methods are based, at least in part, on microarray analysis of monocytes from representative rheumatoid arthritis (RA) patients treated with an anti-TNF α monoclonal antibody, including (i) hierarchical clustering with the genes resulting from a simultaneous comparison between RA versus ND and RA responders pre- versus post-anti-TNF α therapy, (ii) prediction analy-

sis of microarrays (PAM); and (iii) hierarchical clustering based on the comparison between RA responders and nonresponders post-treatment.

[0031] Accordingly, in another aspect, the invention provides a method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 83-133 (corresponding to biomarkers set forth in Table 3), thereby monitoring the autoimmune disorder in the subject.

[0032] In another aspect, the invention provides a method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 134-177, 110, 112, 118, 123 and 131 (corresponding to biomarkers set forth in Table 4), thereby monitoring the autoimmune disorder in the subject. In one embodiment, preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 134-150, 112, 118 and 131 (upregulated biomarkers from Table 4), wherein expression of the one or more biomarkers is increased in the subject. In another embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 151-177, 110 and 123 (downregulated biomarkers from Table 4), wherein expression of the one or more biomarkers is decreased in the subject.

[0033] In another aspect, the invention provides a method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 178-292, 91 and 97 (corresponding to biomarkers set forth in Table 5), thereby monitoring the autoimmune disorder in the subject. In one embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 178-185; 187-200, 202, 203, 205-207; 211, 213, 214, 216, 220, 221, 226, 228, 229, 231, 232, 234, 235, 238-247, 249, 250, 253, 262-265, 268-282 and 285-288 (upregulated biomarkers from Table 5), wherein expression of the one or more biomarkers is increased in the subject. In another embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 186, 201, 204, 208, 209, 91, 210, 212, 97, 215, 217-219, 222-225, 227, 230, 233, 236, 237, 248, 251, 252, 254-261, 266, 267, 283, 284 and 289-292 (downregulated biomarkers from Table 5), wherein expression of the one or more biomarkers is decreased in the subject.

[0034] In another aspect, the invention provides a method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 87, 97, 101, 293, 92, 272, 93, 107, 108, 121 and 123 (corresponding to pre-treatment biomarkers

set forth in Table 6), and wherein the subject is monitored prior to treatment with a TNF α inhibitor, thereby monitoring the autoimmune disorder in the subject.

[0035] In another aspect, the invention provides a method of monitoring an autoimmune disorder in a subject having the autoimmune disorder the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 290, 209, 98, 112, 116, 121, 130, 155, 92, 289, 216 and 131 (corresponding to post-treatment biomarkers set forth in Table 6), and wherein the subject is monitored after treatment with a TNF α inhibitor, thereby monitoring the autoimmune disorder in the subject.

[0036] In yet another aspect, the invention provides a method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 97, 102, 29, 294, 295, 91, 131, 290, 100, 134, 296, 297, 298, 299, 136, 174 and 300 (corresponding to biomarkers set forth in Table 7), thereby monitoring the autoimmune disorder in the subject.

[0037] In yet another aspect, the invention pertains to a method of building a database for use in selecting a subject having an autoimmune disorder (e.g., RA) for treatment with a TNFα inhibitor. The method comprises: receiving, in a computer system, biomarker expression patterns from a plurality of subjects having an autoimmune disorder; and storing the biomarker expression pattern from each subject such that the biomarker expression pattern is associated with an identifier of the subject, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82. The identifier of the subject can be, for example, a numerical identifier coded to an identity of the subject. In a preferred embodiment, the method further comprises receiving, in the computer system, one or more treatment regimens for treatment of the autoimmune disorder in a subject such that the treatment regimen is associated with the biomarker expression pattern of the subject and the identifier of the subject.

[0038] The invention also pertains to a computer program product containing executable instructions that when executed cause a processor to perform operations comprising: receiving, in a computer system, a biomarker expression pattern of a subject at one or more biomarkers predictive of responsiveness to a TNFα inhibitor in an autoimmune disorder; and storing the biomarker expression pattern such that the biomarker expression pattern is associated with an identifier of the subject, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82. The computer program can further cause the processor to perform an operation comprising: receiving, in the computer system, a treatment regimen for treatment of the autoimmune disorder in the subject such that the treatment regimen is associated with the biomarker expression pattern of the subject and the identifier of the subject.

[0039] In yet another aspect, the invention pertains to a method of selecting an autoimmune disorder subject for treatment with a TNFα inhibitor, the method comprising: (i) identifying, in a database comprising a plurality of autoimmune disorder subjects, a subject whose database entry is associated with a biomarker expression pattern that is predictive of responsiveness to treatment with a TNFα inhibitor, and (ii) selecting the subject for treatment with a TNF α inhibitor, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82. The method can further comprise selecting a treatment regimen by identifying, in the database, a treatment regimen that has been associated with the biomarker expression pattern of the subject and with an identifier of the subject.

[0040] The invention also pertains to a computer program product containing executable instructions that when executed cause a processor to perform operations comprising: (i) identifying, in a database including a plurality of autoimmune disorder subjects associated with biomarker expression patterns, a subject that is associated with a biomarker expression pattern that is predictive of responsiveness to treatment with a TNFα inhibitor; and (ii) outputting the identified subject as a subject to be treated with a TNF α inhibitor; wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82. In one embodiment, the computer program further causes the processor to perform an operation comprising outputting a treatment regimen that is associated with the subject to be treated with the TNFa inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] FIG. 1 is a bar graph showing the results of experiments validating the predictive gene CD11c by quantitative real-time PCR. mRNA expression was compared in monocytes from normal donors (n=16), as well as future responders and future non-responders to therapy with anti-TNFα (RA-ATNF; filled circles ●; 15 responders and 12 non-responders) or to combination therapy with anti-TNF α /methotrexate (RA-αTNF/MTX; empty circles 0; 7 responders and 9 nonresponders) The expression of CD11c is expressed as the means±standard error of the mean normalized to that of the house keeping gene glycerol-aldehyd-3-phosphate dehydrogenase (GAPDH; % expression). Except for 1 RA patient with a borderline ACR response of 30 and a CD11c mRNA level directly at the distinction threshold (who was therefore classified as a false negative), the threshold level (40%) almost fully distinguished future responders from nonresponders (100% specificity, 94% sensitivity, and 96% power). The threshold level to distinguish future responders from non-responders is indicated by a broken line (----); * $P \leq 0.05$, ** $P \leq 0.01$ as compared to normal donors; +++ P≦0.005 as compared to future responders to anti-TNFα therapy.

[0042] FIG. 2 is a graph showing the correlation between the mRNA expression of predictive CD11c in pre-treatment RA patients and their individual future ACR response (continuous ACR score). The horizontal and vertical broken lines indicate the thresholds for the separation between RA-responders and RA-non-responders, both in terms of the pre-treatment CD11c mRNA levels (40%) and their ACR

response (continuous ACR score \leq 30). Responders (continuous American College of Rheumatology [ACR] score \geq 40; clustered as ND) and non-responders to anti-TNF therapy (continuous ACR score \leq 30; clustered as RA) were defined according to the criteria of the ACR.

[0043] FIG. 3 is a graph showing the correlation between the mRNA expression of predictive CD11c in pre-treatment RA patients and their individual future strict ACR response in the following conventional used steps: $\geq 0\%$, $\geq 20\%$, and $\geq 70\%$ (continuous ACR score).

DETAILED DESCRIPTION OF THE INVENTION

[0044] This invention provides methods for predicting responsiveness to a TNF α inhibitor in a subject suffering from an autoimmune disorder, and methods for selecting a treatment regimen with a TNFα inhibitor, based on expression of particular biomarkers in the subject to be treated. The invention is based, at least in part, on the observation that altered expression of particular biomarkers in a subject suffering from rheumatoid arthritis is associated with increased or decreased responsiveness to therapy with a TNF α inhibitor. Microarray analysis, hierarchical clustering and Taq-Man®-PCR analysis were used to examine normal donors (NA) and rheumatoid arthritis (RA) patients, who were categorized as being responsive to treatment with an anti-TNF α antibody (RA responders) or nonresponsive to treatment with an anti-TNFα antibody (RA nonresponders). A panel of 82 genes were identified whose expression was altered (upregulated or downregulated) in patients identified as either future RA responders or future RA nonresponders, demonstrating the ability of these genes to act as biomarkers for predicting responsiveness to TNFα inhibitor treatment. In particular, one gene, encoding the antigen CD11c, was identified as fully predicting the future response to anti-TNF α treatment. Accordingly, the expression pattern of one or more biomarkers can be assessed in RA subjects for which TNFα inhibitor therapy is being considered, or subjects suffering from other autoimmune disorders amenable to TNF α inhibitor therapy, to thereby predict responsiveness of the subject to such therapy and/or to aid in the selection of an appropriate treatment regimen.

[0045] Furthermore, additional patterns of biomarker expression were identified by (i) hierarchical clustering with the genes resulting from a simultaneous comparison between RA versus ND and RA responders pre- versus post-anti-TNF α therapy; (ii) prediction analysis of microarrays; and (iii) hierarchical clustering based on the comparison between RA responders and non-responders post-treatment. Accordingly, the biomarker expression patterns described herein also can be using in monitoring an autoimmune disorder in a subject, e.g., monitoring the responsiveness of the subject to a particular therapy or assisting in the diagnosis or prognosis of the autoimmune disorder (e.g., RA) in the subject.

[0046] 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.

[0047] The term "predicting responsiveness to a TNF α inhibitor", as used herein, is intended to refer to an ability to assess the likelihood that treatment of a subject with a TNF α inhibitor will or will not be effective in (e.g., provide a measurable benefit to) the subject. In particular, such an ability to assess the likelihood that treatment will or will not be effective typically is exercised before treatment with the TNF α inhibitor is begun in the subject. However, it is also possible

that such an ability to assess the likelihood that treatment will or will not be effective can be exercised after treatment has begun but before an indicator of effectiveness (e.g., an indicator of measurable benefit) has been observed in the subject.

[0048] The term "TNF α inhibitor" as used herein is intended to encompass agents including proteins, antibodies, antibody fragments, fusion proteins (e.g., Ig fusion proteins or Fc fusion proteins), multivalent binding proteins (e.g., DVD Ig), small molecule TNFα antagonists and similar naturally- or nonnaturally-occurring molecules, and/or recombinant and/or engineered forms thereof, that, directly or indirectly, inhibits TNFa activity, such as by inhibiting interaction of TNF α with a cell surface receptor for TNF α , inhibiting TNFα protein production, inhibiting TNFα gene expression, inhibiting TNFα secretion from cells, inhibiting TNFα receptor signaling or any other means resulting in decreased TNFa activity in a subject. The term "TNFa inhibitor" also includes agents which interfere with TNFa activity. Examples of TNFa inhibitors include etanercept (ENBRELTM, Amgen), infliximab (REMICADETM, Johnson and Johnson), human anti-TNF monoclonal antibody adalimumab (D2E7/HUMIRATM, Abbott Laboratories), CDP 571 (Celltech), and CDP 870 (Celltech), as well as other compounds which inhibit TNFa activity, such that when administered to a subject suffering from or at risk of suffering from a disorder in which TNF α activity is detrimental (e.g., RA), the disorder is treated. The term also includes each of the anti-TNFα human antibodies and antibody portions described herein as well as those described in U.S. Pat. Nos. 6,090,382; 6,258,562; 6,509,015, and in U.S. patent application Ser. Nos. 09/801,185 (U.S. Publication No. 20030092059) and 10/302,356 (U.S. Publication No. 20030219438), each incorporated by reference herein.

[0049] The term "antibody" as referred to herein includes whole antibodies and any antigen binding fragment (i.e., "antigen-binding portion") or single chains thereof. An "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, C_{H1} , C_{H2} and C_{H3} . Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, C_L . The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each \mathbf{V}_H and \mathbf{V}_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[0050] The term "antibody" is also intended to encompass dual-specific antibodies and bispecific antibodies. The term "dual-specific antibody", as used herein, refers to full-length antibodies that can bind two different antigens (or epitopes) in each of its two binding arms (a pair of HC/LC) (see e.g., PCT

publication WO 02/02773). Accordingly a dual-specific binding protein has two identical antigen binding arms, with identical specificity and identical CDR sequences, and is bi-valent for each antigen it binds to. The term "bispecific antibody", as used herein, refers to full-length antibodies that are generated by quadroma technology (see Milstein, C. and A. C. Cuello (1983) Nature, 305:537-40), by chemical conjugation of two different mAbs (see Staerz, U. D., et al. (1985) Nature 314: 628-31), or by knob-into-hole or similar approaches which introduces mutations in the Fc region (see Holliger, P., T. Prospero, and G. Winter (1993) Proc. Natl. Acad. Sci. USA 90:6444-8), resulting in multiple different immunogloblin species of which only one is the functional bispecific antibody. By molecular function, a bispecific antibody binds one antigen (or epitope) on one of its two binding arms (one pair of HC/LC), and binds a different antigen (or epitope) on its second arm (a different pair of HC/LC). By this definition, a bispecific antibody has two distinct antigen binding arms (in both specificity and CDR sequences), and is mono-valent for each antigen it binds to. Thus, when used herein, a "bispecific" antibody of the invention has one binding arm that is specific for an epitope of TNF α and a second binding arm that is specific for a different antigen or epitope.

[0051] The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. It has been shown that the antigenbinding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (vi) 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). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. 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.

[0052] The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0053] The terms "chimeric antibody" or "chimeric monoclonal antibody" are intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

Such "chimeric antibodies" can be prepared by standard recombinant technology well established in the art. For example, a nucleic acid encoding a V_H region from a mouse antibody can be operatively linked to a nucleic acid encoding the heavy chain constant regions from a human antibody and, likewise, a nucleic acid encoding a V_L region from a mouse antibody can be operatively linked to a nucleic acid encoding the light chain constant region from a human antibody.

[0054] The terms "humanized antibody" or "humanized monoclonal antibody" are intended to refer to antibodies in which CDR sequences derived from the germline of a nonhuman mammalian species, such as a mouse, have been grafted onto human framework sequences. Additional framework region modifications may be made within the human framework sequences. Such "humanized antibodies" can be prepared by standard recombinant technology well established in the art. For example, nucleic acids encoding the CDR1, CD2 and CDR3 regions from a V_H region of a mouse antibody can be operatively linked to nucleic acids encoding the FR1, FR2, FR3 and FR4 regions of a human V_H region, and the entire "CDR-grafted" \mathbf{V}_{H} region can be operatively linked to nucleic acid encoding the heavy chain constant regions from a human antibody. Likewise, nucleic acids encoding the CDR1, CD2 and CDR3 regions from a V_L region of a mouse antibody can be operatively linked to nucleic acids encoding the FR1, FR2, FR3 and FR4 regions of a human V_L region, and the entire "CDR-grafted" V_L region can be operatively linked to nucleic acid encoding the light chain constant region from a human antibody.

[0055] The term "human antibody", as used herein, is intended to refer to antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. Human antibodies 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).

[0056] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Human monoclonal antibodies can be produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell. The term "human monoclonal antibody", as used herein, also includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. Such recombinant human antibodies, however, can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the \mathbf{V}_H and \mathbf{V}_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo. [0057] The terms "Ig fusion protein" and "Fc fusion protein" are intended to refer to a recombinant, composite protein comprising a polypeptide of interest operatively linked to a constant region portion of immunoglobulin, typically the hinge, CH₂ and CH₃ domains of heavy chain constant region, more typically the human IgG1 hinge, CH₂ and CH₃ domains. The polypeptide of interest operatively linked to the Fc portion can be, for example, a full-length protein or only a portion of a full-length protein, such as one or more extracellular domains of a protein, e.g., one or more extracellular domains of a cell-surface protein. Such "Ig fusion proteins" can be prepared by standard recombinant technology well established in the art. For example, a nucleic acid encoding the polypeptide of interest can be operatively linked to a nucleic

acid encoding the hinge, CH₂ and CH₃ domains of a heavy

chain constant region.

[0058] The term "multivalent binding protein", as a form of TNF α inhibitor, is used in this specification to denote a binding protein comprising two or more antigen binding sites. Examples of multivalent binding proteins include dual variable domain (DVD) binding proteins. The multivalent binding protein is preferably engineered to have three or more antigen binding sites, and is generally not a naturally occurring antibody. A multivalent binding protein also can be a "multispecific binding protein." The term "multispecific binding protein" refers to a binding protein capable of binding two or more related or unrelated targets (wherein, with respect to this specification at least one of the targets is $TNF\alpha$). Dual variable domain (DVD) binding proteins, as used herein, are binding proteins that comprise two or more antigen binding sites and are tetravalent or multivalent binding proteins. Such DVDs may be monospecific, i.e., capable of binding one antigen (e.g., TNFα) or multispecific, i.e., capable of binding two or more antigens (e.g., TNF α and one or more other antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as "DVD Ig." Each half of a DVD Ig comprises a heavy chain DVD polypeptide, and a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. DVD binding proteins and methods of making DVD binding proteins are disclosed in US. Publication No. 20070071675, the entire contents of which are specifically incorporated herein by reference.

[0059] As used herein, the term "biomarker" is intended to encompass a substance that is used as an indicator of a biologic state and includes genes (and nucleotide sequences of such genes), mRNAs (and nucleotide sequences of such mRNAs) and proteins (and amino acid sequences of such proteins). A "biomarker expression pattern" is intended to refer to a quantitative or qualitative summary of the expression of one or more biomarkers in a subject, such as in comparison to a standard or a control.

[0060] The terms "increased" or "increased expression" and "decreased" or "decreased expression", with respect to the expression pattern of a biomarker(s), are used herein as

meaning that the level of expression is increased or decreased relative to a constant basal level of expression of a household, or housekeeping, gene, whose expression level does not significantly vary under different conditions. A nonlimiting example of such a household, or housekeeping, gene is GAPDH. Other suitable household, or housekeeping, gene are well-established in the art.

[0061] As used herein, the term "CD11c" refers to a protein having a full-length amino acid sequence as set forth at Genbank Accession No. NP_000878 (also shown as SEQ ID NO: 302) and encoded by a full-length nucleotide sequence as set forth at Genbank Accession No. NM_000887 (also shown as SEQ ID NO: 301). CD11c is also known in the art as CD11C, CD11c antigen, Integrin alpha X, complement component 3 receptor 4 subunit, ITGAX, LeuM5, Integrin alpha X precursor, Leukocyte adhesion glycoprotein p150,p95 alpha chain, and Leukocyte adhesion receptor p150 subunit, which terms may be used interchangeably herein to refer to CD11c.

[0062] As used herein, the term "Affymetrix ID" refers to a numerical identifier that corresponds to a sequence entry in an Affymetrix database, which entry includes the sequence as well as additional information relating to the sequence and corresponding protein. The sequence entries, and additional information in the entries, for each Affymetrix ID are publicly available (e.g., by entering the Affymetrix ID number into the Affymetrix database search engine, e.g., at https://www.affymetrix.com/analysis/netaffx/index.affx). All sequence entries (such as Genbank Accession numbers), and additional information provided for each entry, corresponding to each of the Affymetrix ID numbers disclosed herein are hereby specifically incorporated by reference in their entirety.

[0063] As used herein, the term "subject" includes humans, and non-human animals amenable to $TNF\alpha$ inhibitor therapy, e.g., preferably mammals, such as non-human primates, sheep, dogs, cats, horses and cows.

[0064] As used herein, the term "autoimmune disorder subject" or "AD subject" is intended to refer to a subject (e.g., human patient) suffering from an autoimmune disorder.

[0065] As used herein, the term "rheumatoid arthritis subject" or "RA subject" is intended to refer to a subject (e.g., human patient) suffering from rheumatoid arthritis.

[0066] As used herein, the term "treatment regimen" is intended to refer to one or more parameters selected for the treatment of a subject, e.g., with a TNF α inhibitor, which parameters can include, but are not necessarily limited to, the type of agent chosen for administration, the dosage, the formulation, the route of administration and the frequency of administration.

[0067] Various aspects of the invention are described in further detail in the following subsections.

Prediction of Responsiveness to a TNF α Inhibitor for Autoimmune Disorders

[0068] In one aspect, the invention pertains to a method for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, such as rheumatoid arthritis. Typically, the method comprises (i) assaying the subject for the expression of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on expression of the one or more biomarkers in the subject. As used herein, the term "one or more biomarkers" is intended to mean that at least one biomarker in a disclosed list of biomarkers is assayed and, in various

embodiments, more than one biomarker set forth in the list may be assayed, such as two, three, four, five, ten, twenty, thirty, forty, fifty, more than fifty, or all the biomarkers in the list may be assayed.

[0069] Predicting responsiveness of the subject to the TNFα inhibitor "based on expression of the one or more biomarkers in the subject" typically involves comparing the level, or pattern, of expression of the one or more biomarkers in the subject to a known standard or control (which known standard or control may be derived from, for example, a normal subject, a pre-established TNFα inhibitor responder or a pre-established TNFα inhibitor non-responder). In a preferred embodiment, the level of expression of the biomarker(s) is measured in parallel with measurement of the level of expression of one or more "housekeeping" genes, such as GAPDH, whose expression level is not altered by the autoimmune disorder. The level of expression of the biomarker(s) is determined to be "increased" or "decreased" relative to a constant basal level of expression of the housekeeping gene. Examples of suitable housekeeping genes, such as GAPDH, that can be used for comparison purposes are well known in the art.

[0070] Preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (corresponding to sequences of the biomarkers set forth in Table 9). Thus, at least one of the biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 is assayed and, in various embodiments, for example, two, three, four, five, ten, twenty, thirty, forty, fifty, more than fifty, or all the biomarkers in the list may be assayed.

[0071] In a preferred embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43-47, 49, 51, 54, 55, 57, 59, 61, 62, 64, 70, 75, 79 and 82 (corresponding to sequences from Table 9 that are increased in ≥80% of responders vs. non-responders). More preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 37, 44, 47, 62 and 70 (corresponding to sequences from Table 9 that are increased in ≥90% of responders vs. non-responders). Even more preferably, at least one of the biomarkers to be assayed is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 44 (corresponding to the biomarker CD11c, which, as set forth in Table 9, is increased in 100% of responders vs. non-responders). In each of these embodiments, increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNFα inhibitor (e.g., increased expression relative to a standard or control level of expression, which standard or control level of expression can be based, for example, on the level of expression in previously established TNFα inhibitor non-responder RA subjects).

[0072] In another preferred embodiment, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 11-14, 18, 20, 21, 23, 25, 26, 28-30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 65-69, 71-74, 76-78, 80 and 81 (corresponding to sequences from Table 9 that are decreased in $\ge 80\%$ of responders vs. non-responders). More preferably, the one or more biomarkers is encoded

by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 29, 65, 73 and 74 (corresponding to sequences from Table 9 that are decreased in $\geq 90\%$ of responders vs. non-responders). Even more preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 11 or SEQ ID NO: 74 (corresponding to sequences from Table 9 that are decreased in 100% of responders vs. non-responders). In each of these embodiments, decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor (e.g., decreased expression relative to a standard or control level of expression can be based, for example, on the level of expression in previously established TNF α inhibitor non-responder RA subjects).

[0073] In another aspect, the invention provides a method for predicting responsiveness to a TNFα inhibitor in a subject having an autoimmune disorder, the method comprising: (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to a TNFα inhibitor in the autoimmune disorder, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on expression of the one or more biomarkers in the subject, wherein the one or more biomarkers is selected from the group consisting of Aquaporin 3 (Genbank Accession No. NM 004925); Similar to ribosomal protein S24, clone MGC:8595 (Genbank Accession No. NM_033022); Transmembrane emp24 domain trafficking protein 2 (Genbank Accession No. NM_006815; Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (Genbank Accession No. NM_000454); Calmodulin 1 (phosphorylase kinase, delta) (Genbank Accession No. NM_006888); Guanine nucleotide binding protein (G protein), beta polypeptide 1 (Genbank Accession No. NM_002074); Prothymosin, alpha (gene sequence 28) (Genbank Accession No. NM_002823); Homo sapiens isocitrate dehydrogenase 1 (NADP+) soluble (IDH1) (Genbank Accession No. NM_005896); Tumor protein D52 (Genbank Accession Nos. NM 001025252, NM 001025253, NM_005079); Early growth response 1 (Genbank Accession No. NM_001964); Homo sapiens predicted osteoblast protein (GS3786) (Genbank Accession Nos. NM_014888, NM_001040020); Cytochrome c oxidase subunit VIIb (Genbank Accession No. NM 001866); CUG triplet repeat, RNA binding protein 2 (Genbank Accession No. NM_001025077, NM_001025076, NM_006561); Ubiquinol-cytochrome c reductase hinge protein (Genbank Accession No. NM_006004); Homo sapiens leptin receptor gene-related (HS0BRGRP) (Genbank Accession NM_017526); Wiskott-Aldrich syndrome protein interacting protein (Genbank Accession Nos. NM_001077269, NM_003387); CD97 antigen (Genbank Accession Nos. NM_001025160, NM_001784, NM_078481); Glutamatecysteine ligase, catalytic subunit (Genbank Accession No. NM_001498); Crystallin, zeta (quinone reductase) (Genbank Accession No. NM_001889); Rap guanine nucleotide exchange factor (GEF) 2 (Genbank Accession No. NM_014247); Ataxin 1 (Genbank Accession No. NM_000332); Adaptor-related protein complex 1, sigma 2 subunit (Genbank Accession No. NM_003916); Ectonucleotide pyrophosphatase/phosphodiesterase 4 (Genbank Accession No. NM_014936); Desmocollin 2 (Genbank Accession Nos. NM_024422, NM_004949); MAL, T-cell differentiation protein (Genbank Accession

NM_002371, NM_022438, NM_022439, NM_022440); Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (Genbank Accession No. NM_005476); Chemokine (C—C motif) ligand 3 (Genbank Accession Nos. NM_001001437, NM_021006); Carboxypeptidase A3 (Genbank Accession No. NM_001870); Charcot-Leyden crystal protein (Genbank Accession No. NM_001828); NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7 kDa (Genbank Accession No. NM 004545); Interleukin 8 receptor, beta (Genbank Accession No. NM 001557); Platelet factor 4 variant 1 (Genbank Accession No. NM 002620); Poly(A) binding protein interacting protein 1 (Genbank Accession No. NM_006451); ATP-binding cassette, subfamily C (CFTR/MRP), member 3 (Genbank Accession No. NM_003786); Actinin, alpha 1 (Genbank Accession No. NM_001102); NAD kinase (Genbank Accession No. NM 023018); Platelet/endothelial cell adhesion molecule (CD31 antigen) (Genbank Accession No. NM_000442); Esterase D/formylglutathione hydrolase (Genbank Accession No. NM_001984); Chromosome 20 open reading frame 111 (Genbank Accession No. NM 016470); Sterol-C4-meoxidase-like (Genbank Accession NM_001017369, NM_006745); PIM-1 oncogene (Genbank Accession No. NM_002648); GATA binding protein 2 (Genbank Accession No. NM 032638); Cathepsin Z (Genbank Accession No. NM 001336); Integrin alpha-X (antigen CD11c) (Genbank Accession No. NM_000887); Lectin, galactoside-binding, soluble, 8 (galectin 8) (Genbank Accession Nos. NM_006499, NM_201545); CD86 antigen (CD28 antigen ligand 2, B7-2 antigen) (Genbank Accession Nos. NM_006889, NM_175862); Interleukin 8 (Genbank Accession No. NM_000584); Fc fragment of IgE, high affinity I, receptor for alpha polypeptide (Genbank Accession No. NM_002001); Actin, gamma 1 (Genbank Accession No. NM_001614); KIAA0746 protein (Genbank Accession No. NM_015187); Glucosamine (N-acetyl)-6-sulfatase (Sanfilippo disease IIID) (Genbank Accession No. NM_002076); Transcription factor 4 (Genbank Accession Nos. BF592782, CR612521); Major histocompatibility complex, class II, DQ alpha 1 (Genbank Accession Nos. NM_002122, NM_020056); Cell division cycle 2-like 6 (CDK8-like) (Genbank Accession No. NM_015076); Major histocompatibility complex, class II, DQ beta 1 (Genbank Accession No. XM 942240): Phospholipase C-like 2 (Genbank Accession No. NM_015184); Coagulation factor II (thrombin) receptor-like 1 (Genbank Accession No. NM_005242); TM2 domain containing 1 (Genbank Accession NM_032027); Splicing factor 3b, subunit 1, 155 kDa (Genbank Accession No. NM 012433); SUB1 homolog (S. cerevisiae) (Genbank Accession No. NM_006713); mRNA; cDNA DKFZp564O0862 (Genbank Accession No. AI278204); Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease) (Genbank Accession Nos. NM_201413, NM_000484, NM_201414); Cytochrome b-5 (Genbank Accession Nos. NM_001914, NM_148923); Cold autoinflammatory syndrome 1 (Genbank Accession No. NM_183395); Neugrin, neurite outgrowth associated (Genbank Accession Nos. NM 016645, NM 001033088); Ribosomal protein S26, 40S ribosomal protein (Genbank Accession No. XM_941927); CCR4-NOT transcription complex, subunit 6 (Genbank Accession No. NM_015455); Ubiquinol-cytochrome c reductase complex (7.2 kD) (Genbank Accession Nos. NM_013387, NM_001003684); Hepatocellular carcinoma-associated antigen 112 (Genbank

Accession No. NM_018487); Kruppel-like factor 11 (Genbank Accession No. XM_001129527); GGA binding partner (Genbank Accession No. NM_018318); Cornichon homolog 4 (Drosophila) (Genbank Accession No. NM_014184); Hypothetical protein FLJ21616 (Genbank Accession No. NM_024567); Homo sapiens hypothetical protein FLJ10134 (Genbank Accession No. NM_018004); Nuclear prelamin A recognition factor (Genbank Accession Nos. NM_012336, NM_001038618); Erythroblast membraneassociated protein (Genbank Accession Nos. NM_018538, NM_001017922); LR8 protein (Genbank Accession No. NM_014020); Likely ortholog of mouse limb-bud and heart gene (LBH) (Genbank Accession No. NM_030915); Calmin (calponin-like, transmembrane) (Genbank Accession No. NM_024734); Chromosome 14 open reading frame 156 (Genbank Accession No. NM_031210); Guanine nucleotide binding protein (G protein) alpha 12 (Genbank Accession No. NM_007353); and SRY (sex determining region Y)-box 18 (Genbank Accession No. NR_003287) (corresponding to biomarkers listed in Table 9).

[0074] In a preferred embodiment, the one or more biomarkers is selected from the group consisting of Guanine nucleotide binding protein (G protein), beta polypeptide 1; Prothymosin, alpha (gene sequence 28); Early growth response 1; Homo spaiens leptin receptor gene-related protein (HS0BRGRP); Wiskott-Aldrich syndrome protein interacting protein; CD97 antigen; Crystallin, zeta (quinone reductase); Adaptor-related protein complex 1, sigma 2 subunit; Desmocollin 2; Chemokine (C—C motif) ligand 3; Interleukin 8 receptor, beta; ATP-binding cassette, sub-family C (CFTR/MRP), member 3; Actinin, alpha 1; NAD kinase; Platelet/endothelial cell adhesion molecule (CD31 antigen); Esterase D/formylglutathione hydrolase; Chromosome 20 open reading frame 111; Cathepsin Z; Integrin alpha-X (antigen CD11c); Lectin, galactoside-binding, soluble, 8 (galectin 8); CD86 antigen (CD28 antigen ligand 2, B7-2 antigen); Interleukin 8; Actin, gamma 1; Glucosamine (N-acetyl)-6sulfatase (Sanfilippo disease IIID); Cell division cycle 2-like 6 (CDK8-like); Major histocompatibility complex, class II, DQ beta 1; Coagulation factor II (thrombin) receptor-like 1; Splicing factor 3b, subunit 1, 155 kDa; mRNA; cDNA DKEZp564O0862; Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease); Cold autoinflammatory syndrome 1; Kruppel-like factor 11; Nuclear prelamin A recognition factor; Calmin (calponin-like, transmembrane); and SRY (sex determining region Y)-box 18 (corresponding to biomarkers listed in Table 9 that are increased in $\ge 80\%$ of responders vs. non-responders). More preferably, the one or more biomarkers is selected from the group consisting of Interleukin 8 receptor, beta; Platelet/endothelial cell adhesion molecule (CD31 antigen); Integrin alpha-X (antigen CD11c); Interleukin 8; Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease); and Kruppel-like factor 11 (corresponding to biomarkers listed in Table 9 that are increased in ≥90% of responders vs. non-responders). Even more preferably, at least one of the biomarkers is Integrin alpha-X (antigen CD11c) (corresponding to a biomarker listed in Table 9 that is increased in 100% of responders vs. nonresponders). In each of the embodiments, increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor.

[0075] In another preferred embodiment, the one or more biomarkers is selected from the group consisting of Aquaporin 3; Similar to ribosomal protein S24, clone MGC:8595;

Transmembrane emp24 domain trafficking protein 2; Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1; Calmodulin 1 (phosphorylase kinase, delta); Homo sapiens isocitrate dehydrogenase 1 (NADP+) soluble (IDH1); Tumor protein D52; Homo sapiens predicted osteoblast protein (GS3786); Cytochrome c oxidase subunit VIIb; CUG triplet repeat, RNA binding protein 2; Ubiquinol-cytochrome c reductase hinge protein; Glutamate-cysteine ligase, catalytic subunit; Rap guanine nucleotide exchange factor (GEF) 2; Ataxin 1; Ectonucleotide pyrophosphatase/phosphodiesterase 4; MAL, T-cell differentiation protein; Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase; Carboxypeptidase A3; Charcot-Leyden crystal protein; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7 kDa; Platelet factor 4 variant 1; Poly(A) binding protein interacting protein 1; Sterol-C4-methyl oxidase-like; PIM-1 oncogene; GATA binding protein 2; Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide; KIAA0746 protein; Transcription factor 4; Major histocompatibility complex, class II, DQ alpha 1; Phospholipase C-like 2; TM2 domain containing 1; SUB1 homolog (S. cerevisiae); Cytochrome b-5; Neugrin, neurite outgrowth associated; Ribosomal protein S26, 40S ribosomal protein; CCR4-NOT transcription complex, subunit 6; Ubiquinol-cytochrome c reductase complex (7.2 kD); Hepatocellular carcinoma-associated antigen 112; GGA binding partner; Cornichon homolog 4 (Drosophila); Hypothetical protein FLJ21616; Homo sapiens hypothetical protein FLJ10134; Erythroblast membrane-associated protein; LR8 protein; Likely ortholog of mouse limb-bud and heart gene (LBH); Chromosome 14 open reading frame 156; and Guanine nucleotide binding protein (G protein) alpha 12 (corresponding to biomarkers listed in Table 9 that are decreased in ≧80% of responders vs. non-responders). More preferably, the one or more biomarkers is selected from the group consisting of *Homo sapiens* predicted osteoblast protein (GS3786); Charcot-Leyden crystal protein; Neugrin, neurite outgrowth associated; Hypothetical protein FLJ21616; and Homo sapiens hypothetical protein FLJ10134 (corresponding to biomarkers listed in Table 9 that are decreased in ≥90% of responders vs. non-responders). Even more preferably, the one or more biomarkers is Homo sapiens predicted osteoblast protein (GS3786) or Homo sapiens hypothetical protein FLJ10134 (corresponding to biomarkers listed in Table 9 that are decreased in 100% of responders vs. non-responders). In each of these embodiments, decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor.

[0076] In a particularly preferred aspect, the invention provides a method for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder the method comprising: (i) assaying the subject for increased expression of a biomarker, which biomarker is CD11c, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on increased expression of CD11c in the subject.

[0077] In yet another particularly preferred embodiment, the invention provides a method for predicting responsiveness to a TNF α inhibitor, which TNF α inhibitor is adalimumab, in a subject having an autoimmune disorder the method comprising: (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to adalimumab in the autoimmune disorder, and (ii) predicting responsiveness of the subject to adalimumab based on expression of the one or more biomarkers in the subject. Preferably,

the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (or selected from the group consisting of the biomarkers set forth in Table 9). In more preferred embodiments, the subsets of sequences within SEQ ID NO: 1-82 that are either increased or decreased, as set forth in detail above, can be assayed.

[0078] In the methods of the invention for predicting responsiveness to a TNFα inhibitor in a subject having an autoimmune disorder, the expression of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in the autoimmune disorder can be assayed in the subject using techniques well-established in the art. In a preferred embodiment, the expression of the one or more biomarkers in the subject is assayed by obtaining an mRNA sample from the subject (e.g., isolated from peripheral blood mononuclear cells, by standard methods) and detecting the expression of mRNA(s) encoding the one or more biomarkers in the mRNA sample using standard molecular biology techniques, such as PCR analysis. A preferred method of PCR analysis is revers transcriptase-polymerase chain reaction (RT-PCR). Other suitable systems for mRNA sample analysis include microarray analysis (e.g., using Affymetrix's microarray system or Illumina's BeadArray Technology).

[0079] Additionally or alternatively, in certain situations it may be possible to assay for the expression of one or more biomarkers at the protein level, using a detection reagent that detects the protein product encoded by the mRNA of the biomarker(s). For example, if an antibody reagent is available that binds specifically to the biomarker protein product to be detected, and not to other proteins, then such an antibody reagent can be used to detect the expression of the biomarker of interest in a cellular sample from the subject, or a preparation derived from the cellular sample, using standard antibody-based techniques known in the art, such as FACS analysis, ELISA and the like.

[0080] It will be readily understood by the ordinarily skilled artisan that essentially any technical means established in the art for detecting biomarkers, at either the nucleic acid or protein level, can be adapted to detection of the biomarkers discussed herein and applied in the methods of the current invention for predicting responsiveness to a $TNF\alpha$ inhibitor in a subject having an autoimmune disorder.

[0081] The biomarkers described herein were originally identified in patients having rheumatoid arthritis (see the Examples) and thus a particularly preferred autoimmune disorder in which to apply the methods of the invention is rheumatoid arthritis. The mechanism of action of the TNFα pathway, however, is thought to be common to a large number of autoimmune disorders and TNF α inhibitors have been shown to be effective therapy in a variety of different autoimmune disorders. Accordingly, the method of the invention for predicting responsiveness to a TNF α inhibitor can be applied to essentially any autoimmune disorder in which TNFα inhibitor therapy is applied. Other preferred autoimmune disorders include Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, juvenile arthritis and ankylosing spondilitis, Other non-limiting examples of autoimmune disorders include autoimmune diabetes, multiple sclerosis, systemic lupus erythematosus, rheumatoid spondylitis, gouty arthritis, allergy, autoimmune uveitis, nephrotic syndrome, multisystem autoimmune diseases, autoimmune hearing loss, adult respiratory distress syndrome, shock lung, chronic pulmonary inflammatory disease, pulmonary sarcoidosis, pulmonary fibrosis, silicosis, idiopathic interstitial lung disease, chronic obstructive pulmonary disease, asthma, restenosis, spondyloarthropathies, Reiter's syndrome, autoimmune hepatitis, inflammatory skin disorders, vasculitis of large vessels, medium vessels or small vessels, endometriosis, prostatitis and Sjogren's syndrome.

Biomarkers for Monitoring an Autoimmune Disorder in a Subject

[0082] In another aspect, the invention provides methods of monitoring an autoimmune disorder in a subject having the autoimmune disorder based on biomarker expression patterns established using microarray analysis of, for example, RA subjects vs. normal donors, RA subjects vs. RA subjects treated with a TNF α inhibitor and/or RA subjects treated with a TNF α inhibitor vs. RA responders to TNF α inhibitors. In these monitoring methods, the subject is assayed for expression of one or more biomarkers (using techniques, for example, as described in the previous section), thereby monitoring the autoimmune disorder in the subject.

[0083] In one embodiment of the monitoring method, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 83-133 (or the biomarkers set forth by name in Table 3, namely v-maf musculoaponeurotic fibrosarcoma oncogene homolog F; Diphtheria toxin receptor (DTR); DEAH (Asp-Glu-Ala-His) box polypeptide 15; Ribonucleotide reductase M2 polypeptide; Solute carrier family 6, member 8; 6-phosphofructo-2-kinase/fructose-2,6biphosphatase 3; Ferrochelatase (protoporphyria); Nuclear factor, interleukin 3 regulated; Thrombomodulin; Major histocompatibility complex, class II, DM beta; Forkhead box O3A; Hemoglobin, gamma A, gamma G; Synuclein, alpha (non A4 component of amyloid precursor); Hemoglobin, gamma A; Amphiregulin (schwannoma-derived growth factor); Lipoyltransferase 1; Solute carrier family 4, anion exchanger, member 1; S100 calcium binding protein A12 (calgranulin C); Keratin 1 (epidermolytic hyperkeratosis); Carbonic anhydrase I; CD1C antigen, c polypeptide; Tumor necrosis factor, alpha-induced protein 6; Ribonuclease, RNase A family, 2; Hemoglobin, delta; Transferrin receptor (p90, CD71); Ring finger protein 10; Chromosome 1 open reading frame 63; Hemoglobin, alpha 1, alpha 2; CD69 antigen (p60, early T-cell activation antigen; APEX nuclease (multifunctional DNA repair enzyme) 1; Membrane-spanning 4-domains, subfamily A, member 3; Heat shock 70 kDa protein 8; Hypothetical protein MGC12760; GABA(A) receptor-associated protein like 1, like 3; Aminolevulinate, delta-, synthase 2; Major histocompatibility complex, class II, DP alpha 1; Morf4 family associated protein 1-like 1; Aldehyde dehydrogenase 1 family, member A1; Formin binding protein 4; Zinc finger protein 24 (KOX 17); Hypothetical protein L0054103; Selenium binding protein 1; Hematopoietically expressed homeobox; Major histocompatibility complex, class II, DM alpha; Eukaryotic translation initiation factor 2-alpha kinase 1; Ankyrin repeat domain 49; Hypothetical protein FLJ20701; Zinc finger protein 331; Membrane-spanning 4-domains, subfamily A, member 4; Tensin 1; and Family with sequence similarity 46, member A, respectively).

[0084] In another embodiment of the monitoring method, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 134-177, 110, 112, 118, 123

and 131 (or the biomarkers set forth by name in Table 4, namely Uncharacterized hypothalamus protein HT007; Dual specificity phosphatase 22; Proteasome (prosome, macropain) subunit, beta type, 7; Membrane-spanning 4-domains, subfamily A, member 4; DKFZP434C171 protein; Protein phosphatase 1, catalytic subunit, beta isoform; Splicing factor, arginine/serine-rich 5; Sorting nexin 11; Farnesyltransferase, CAAX box, alpha; Peroxisomal D3,D2-enoyl-CoA isomerise; Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide; UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 1; Hypothetical protein FLJ11259; APEX nuclease (multifunctional DNA repair enzyme) 1; Geranylgeranyl diphosphate synthase 1; Down syndrome critical region gene 5; Calpain 7; Major histocompatibility complex, class II, DP alpha 1; Brix domain containing 5; Chromosome 21 open reading frame 59; Tumor necrosis factor (ligand) superfamily, member 10; Chromosome 10 open reading frame 86; CD1D antigen, d polypeptide; Ewing sarcoma breakpoint region 1; Ribonuclease P 40 kDa subunit; PHD finger protein 20; Thioredoxin interacting protein; Ubiquinol-cytochrome c reductase core protein II; Hypothetical protein FLJ22662; Preimplantation protein 3; DKFZP564G2022 protein; Dipeptidase 2; Hemoglobin, alpha 1, alpha 2; Frequently rearranged in advanced T-cell lymphomas; DEAD (Asp-Glu-Ala-Asp) box polypeptide 48; Tumor necrosis factor, alpha-induced protein 2; Nucleophosmin (nucleolar phosphoprotein B23, numatrin); Interleukin 13 receptor, alpha 1; Leukocyte specific transcript 1, LST1; CGI-121 protein; RAS p21 protein activator 4/hypothetical protein FLJ21767; Cathepsin S; CD63 antigen (melanoma 1 antigen); JTV1 gene; KIAA0174; Thrombospondin 1; Hypothetical protein L0054103; Interferon regulatory factor 1; and SEC11-like 1 (S. cerevisiae)).

[0085] More preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 134-150, 112, 118 (or the biomarkers set forth by name in Table 4 as being upregulated, namely Uncharacterized hypothalamus protein HT007; Dual specificity phosphatase 22; Proteasome (prosome, macropain) subunit, beta type, 7; Membrane-spanning 4-domains, subfamily A, member 4; DKEZP434C171 protein; Protein phosphatase 1, catalytic subunit, beta isoform; Splicing factor, arginine/serine-rich 5; Sorting nexin 11; Farnesyltransferase, CAAX box, alpha; Peroxisomal D3,D2-enoyl-CoA isomerise; Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide; UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1; Hypothetical protein FLJ11259; APEX nuclease (multifunctional DNA repair enzyme) 1; Geranylgeranyl diphosphate synthase 1; Down syndrome critical region gene 5; Calpain 7; Major histocompatibility complex, class II, DP alpha 1; Brix domain containing 5; and Chromosome 21 open reading frame 59), wherein expression of the one or more biomarkers is increased in the subject.

[0086] Additionally or alternatively, more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 151-177, 110 and 123 (or the biomarkers set forth by name in Table 4 as being downregulated, namely Tumor necrosis factor (ligand) superfamily, member 10; Chromosome 10 open reading frame 86; CD1D antigen, d polypeptide; Ewing sarcoma breakpoint region 1; Ribonuclease P 40 kDa subunit; PHD finger protein 20; Thioredoxin interacting protein; Ubiquinol-cytochrome c

reductase core protein II; Hypothetical protein FLJ22662; Preimplantation protein 3; DKFZP564G2022 protein; Dipeptidase 2; Hemoglobin, alpha 1, alpha 2; Frequently rearranged in advanced T-cell lymphomas; DEAD (Asp-Glu-Ala-Asp) box polypeptide 48; Tumor necrosis factor, alphainduced protein 2; Nucleophosmin (nucleolar phosphoprotein B23, numatrin); Interleukin 13 receptor, alpha 1; Leukocyte specific transcript 1, LST1; CGI-121 protein; RAS p21 protein activator 4/hypothetical protein FLJ21767; Cathepsin S; CD63 antigen (melanoma 1 antigen); JTV1 gene; KIAA0174; Thrombospondin 1; Hypothetical protein L0054103; Interferon regulatory factor 1; and SEC11-like 1 (S. cerevisiae), wherein expression of the one or more biomarkers is decreased in the subject.

[0087] In yet another embodiment of the monitoring method, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 178-292, 91 and 97 (or the biomarkers set forth by name in Table 5, namely HLA-B associated transcript-1 (D6S81E); Interleukin enhancer binding factor 2, 45 kD (ILF2); Isolate Liv chaperone protein HSP90 beta (HSP90BETA) mRNA; Lysyl-tRNA synthetase mRNA, complete cds; nuclear gene for mitochondrial product; alternatively spliced; Tryptophanyl-tRNA synthetase (WARS); Profilin 1 (PFN1), mRNA; Seryl-tRNA synthetase (SARS); Similar to KIAA1007 protein, clone MGC: 692, mRNA, complete cds; CD59 antigen p18-20 (antigen identified by monoclonal antibodies 16.3A5, EJ16, EJ30, EL32 and G344); Homo sapiens KIAA0064 gene product (KIAA0064), mRNA; Chromosome segregation 1 (yeast homolog)-like (CSE1L), mRNA; Protein phosphatase 1, regulatory subunit 7 (PPP1R7), mRNA; DEADH (Asp-Glu-Ala-AspHis) box polypeptide 1 (DDX1), mRNA; ThreonyltRNA synthetase (TARS), mRNA; Dead box protein 15 mRNA, complete cds; SRY (sex determining region Y)-box 4/DEF=Human DNA sequence from clone RP3-322L4 on chromosome 6; Galactosidase, beta 1 (GLB1), mRNA; ATPbinding cassette, sub-family E (OABP), member 1; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14 kD, B14) (NDUFA6), mRNA; Pericentriolar material 1 (PCM1), mRNA; Excision repair cross-complementing rodent repair deficiency, complementation group 3 (ERCC3), mRNA; KIAA0907 protein (KIAA0907), mRNA; v-crk avian sarcoma virus CT10 oncogene homolog; 6-phosphofructo-2kinasefructose-2,6-biphosphatase 3 (PFKFB3), mRNA./ PROD=6-phosphofructo-2-kinase-fructose-2,6-

biphosphatase 3; KIAA0766 gene product (KIAA0766), mRNA; N-acetylgalactosaminidase, alpha- (NAGA), mRNA; Protein tyrosine phosphatase, non-receptor type substrate 1 (PTPNS1), mRNA; Crystallin, zeta (quinone reductase) (CRYZ), mRNA; KIAA0429 gene product (KIAA0429), mRNA; SET domain, bifurcated 1 (SETDB1), mRNA; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3 (12 kD, B12) (NDUFB3), mRNA; Diphtheria toxin receptor (DTR); Thrombomodulin (THBD), mRNA; Protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), mRNA; CD37 antigen (CD37), mRNA; Hemoglobin, gamma G (HBG2), mRNA; Protein phosphatase 1D magnesium-dependent, delta isoform (PPM1D), mRNA; Hematopoietically expressed homeobox (HHEX), mRNA; Amphiregulin (schwannoma-derived growth factor) (AREG), mRNA; Early growth response 2 (Krox-20 (Drosophila) homolog) (EGR2), mRNA; 2,5-oligoadenylate synthetase 1 (40-46 kD) (OAS1), transcript variant E16, mRNA;

Early growth response 3 (EGR3), mRNA./PROD=early growth response 3; Homo sapiens MD-2 protein (MD-2), mRNA; Homo sapiens MAX dimerization protein (MAD), mRNA; DKEZP586A011 protein (DKEZP586A011), mRNA; 78 kDa gastrin-binding protein mRNA, complete cds; Transferrin receptor (p90, CD71), clone MGC:3151, mRNA, complete cds; Homo sapiens mRNA; cDNA DKFZp564N1272 (from clone DKFZp564N1272); complete cds; GABA-A receptor-associated protein like 1 (GABARAPL1) mRNA, complete cds; Translocation protein 1; Homo sapiens clone 016b03 My027 protein mRNA, complete cds; Protein kinase-related oncogene (PIM1) mRNA, complete cds; MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C); eIF-2-associated p67 homolog mRNA, complete cds; Human mRNA for hCREM (cyclic AMP-responsive element modulator) type 2 protein, complete cds; Apurinic endonuclease (APE) mRNA. complete cds./PROD=apurinic endonuclease; TATA box binding protein (TBP)-associated factor, RNA polymerase II, D, 100 kD; Human mRNA for ZFM1 protein alternatively spliced product, complete cds./PROD=ZFM1 protein, alternatively spliced product; Trachea cellular apoptosis susceptibility protein (CSE1) mRNA, complete cds; Similar to eukaryotic translation initiation factor 3, subunit 8 (110 kD), clone MGC:8693, mRNA, complete cds; GABA-A receptorassociated protein mRNA, complete cds./PROD=GABA-A receptor-associated protein; Human (clone 2-5) synuclein (NACP) mRNA, complete cds; Human putative ribosomal protein 51 mRNA; Aldehyde dehydrogenase 1, soluble (ALDH1), mRNA./PROD=aldehyde dehydrogenase 1, soluble; Homo sapiens mRNA for KIAA1057 protein, partial cds; RBP1-like protein; Ring finger protein 4; KIAA0197 protein; Homo sapiens mRNA; cDNA DKFZp586F1323 (from clone DKFZp586F1323); Homo sapiens mRNA; cDNA DKFZp5641052 (from clone DKFZp5641052); Homo sapiens mRNA for Hmob33 protein, 3 untranslated region; Homo sapiens mRNA; cDNA DKFZp586F1019 (from clone DKFZp586F1019); partial cds; Myosin, light polypeptide 4, alkali; atrial, embryonic; H. sapiens novel gene from PAC 117P20, chromosome 1; Homo sapiens clone 24582 mRNA sequence; Heterogeneous nuclear ribonucleoprotein H1 (H); Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide; Cyclin T2; cDNA: FLJ23227 fis, clone CAE00645, highly similar to AF052138; Hypothetical protein FLJ12619; C-terminal binding protein 1; SEC22, vesicle trafficking protein (S. cerevisiae)-like 1; Hemoglobin, alpha 1; Homo sapiens clone 24659 mRNA sequence/DEF=Homo sapiens clone 24659 mRNA sequence; Calcium channel, voltage-dependent, PQ type, alpha 1A subunit; H. sapiens SMAS mRNA; H. sapiens HEX gene encoding homeobox related protein; Mitogen-activated protein kinase kinase kinase 4; Serine palmitoyltransferase (LCB2) mRNA, partial cds; KIAA0971 protein/DEF=Homo sapiens cDNA FLJ11495 fis, clone HEMBA1001950, highly similar to Homo sapiens mRNA for KIAA0971 protein; ESTs, Hs.97109; ESTs, Weakly similar to ALU7_HUMAN ALU; DEAD-box protein abstrakt (ABS), mRNA; KIAA1513 protein (KIAA1513), mRNA; Cell division protein FtsJ (FJH1), mRNA; F-box only protein 3 (FBXO3), mRNA; Purinergic receptor (family A group 5) (P2Y5), mRNA; Integral inner nuclear membrane protein (MAN1), mRNA; Fanconi anemia, complementation group F (FANCF), mRNA; Hypothetical protein FLJ12820 (FLJ12820), mRNA; Hypothetical protein FLJ13119 (FLJ13119), mRNA; Hypothetical protein FLJ20189 (FLJ20189), mRNA; Hypothetical protein FLJ20701 (FLJ20701), mRNA; Homo sapiens chromosome 12 open reading frame 5 (C12ORF5), mRNA; Hypothetical protein FLJ22555 (FLJ22555), mRNA; Hypothetical protein protein FLJ11110 (FLJ11110), mRNA; CGI-12 (LOC51001), mRNA; Triggering receptor expressed on myeloid cells 1 (TREM1), mRNA; betaGlcNAc beta 1,4galactosyltransferase. polypeptide 5; PNAS-25 mRNA, complete cds.; Homo sapiens mRNA for FLJ00043 protein, partial cds; Homo sapiens cDNA: FLJ21737 fis, clone COLF3396; Homo sapiens cDNA FLJ13399 fis, clone PLACE1001395/DEF=Homo sapiens cDNA FLJ13399 fis, clone PLACE1001395; Novel MAFF (v-maf musculoaponeurotic fibrosarcoma (avian) oncogene family, protein F) LIKE protein; Heparin-binding EGF-like growth factor mRNA, complete cds; E. coli 7,8-diamino-pelargonic acid (bioA), biotin synthetase (bioB), 7-keto-8-amino-pelargonic acid synthetase (bioF), bioC protein, and dethiobiotin synthetase (bioD), complete cds; Escherichia coli/REF=J04423/ DEF=E. coli bioC protein corresponding to nucleotides 4609-4883 of J04423/LEN=777 (-5 and -3 represent transcript regions 5 prime and 3 prime respectively)).

[0088] More preferably, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 178-185; 187-200, 202, 203, 205-207; 211, 213, 214, 216, 220, 221, 226, 228, 229, 231, 232, 234, 235, 238-247, 249, 250, 253, 262-265, 268-282 and 285-288 (or the biomarkers set forth by name in Table 5 as being upregulated, namely HLA-B associated transcript-1 (D6S81E); Interleukin enhancer binding factor 2, 45 kD (ILF2); Isolate Liv chaperone protein HSP90 beta (HSP90BETA) mRNA; Lysyl-tRNA synthetase mRNA, complete cds; nuclear gene for mitochondrial product; alternatively spliced; Tryptophanyl-tRNA synthetase (WARS); Profilin 1 (PFN1), mRNA; Seryl-tRNA synthetase (SARS); Similar to KIAA1007 protein, clone MGC: 692, mRNA, complete cds; Homo sapiens KIAA0064 gene product (KIAA0064), mRNA; Chromosome segregation 1 (yeast homolog)-like (CSE1L), mRNA; Protein phosphatase 1, regulatory subunit 7 (PPP1R7), mRNA; DEADH (Asp-Glu-Ala-AspHis) box polypeptide 1 (DDX1), mRNA; Threonyl-tRNA synthetase (TARS), mRNA; Dead box protein 15 mRNA, complete cds; SRY (sex determining region Y)-box 4/DEF=Human DNA sequence from clone RP3-322L4 on chromosome 6; Galactosidase, beta 1 (GLB1), mRNA; ATPbinding cassette, sub-family E (OABP), member 1; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14 kD, B14) (NDUFA6), mRNA; Pericentriolar material 1 (PCM1), mRNA; Excision repair cross-complementing rodent repair deficiency, complementation group 3 (ERCC3), mRNA; KIAA0907 protein (KIAA0907), mRNA; v-crk avian sarcoma virus CT10 oncogene homolog; KIAA0766 gene product (KIAA0766), mRNA; N-acetylgalactosaminidase, alpha-(NAGA), mRNA; Crystallin, zeta (quinone reductase) (CRYZ), mRNA; KIAA0429 gene product (KIAA0429), mRNA; SET domain, bifurcated 1 (SETDB1), mRNA; CD37 antigen (CD37), mRNA; Protein phosphatase 1D magnesium-dependent, delta isoform (PPM1D), mRNA; Hematopoietically expressed homeobox (HHEX), mRNA; 2,5-oligoadenylate synthetase 1 (40-46 kD) (OAS1), transcript mRNA; E16, DKFZP586A011 (DKFZP586A011), mRNA; 78 kDa gastrin-binding protein mRNA, complete cds; Homo sapiens clone 016b03 My027

protein mRNA, complete cds; MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C); eIF-2-associated p67 homolog mRNA, complete cds; Apurinic endonuclease (APE) mRNA, complete cds./ PROD=apurinic endonuclease; TATA box binding protein (TBP)-associated factor, RNA polymerase II, D, 100 kD; Trachea cellular apoptosis susceptibility protein (CSE1) mRNA, complete cds; Similar to eukaryotic translation initiation factor 3, subunit 8 (110 kD), clone MGC:8693, mRNA, complete cds; Human putative ribosomal protein 51 mRNA; Aldehyde dehydrogenase 1, soluble (ALDH1), mRNA./PROD=aldehyde dehydrogenase 1, soluble; Homo sapiens mRNA for KIAA1057 protein, partial cds; RBP1like protein; Ring finger protein 4; KIAA0197 protein; Homo sapiens mRNA; cDNA DKFZp586F1323 (from clone DKFZp586F1323); Homo sapiens mRNA; cDNA DKFZp5641052 (from clone DKFZp5641052); Homo sapiens mRNA for Hmob33 protein, 3 untranslated region; Homo sapiens mRNA; cDNA DKFZp586F1019 (from clone DKFZp586F1019); partial cds; H. sapiens novel gene from PAC 117P20, chromosome 1; Homo sapiens clone 24582 mRNA sequence; Cyclin T2; H. sapiens HEX gene encoding homeobox related protein; Mitogen-activated protein kinase kinase kinase 4; Serine palmitoyltransferase (LCB2) mRNA, partial cds; KIAA0971 protein/DEF=Homo sapiens cDNA FLJ11495 fis, clone HEMBA1001950, highly similar to Homo sapiens mRNA for KIAA0971 protein; DEAD-box protein abstrakt (ABS), mRNA; KIAA1513 protein (KIAA1513), mRNA; Cell division protein FtsJ (FJH1), mRNA; F-box only protein 3 (FBXO3), mRNA; Purinergic receptor (family A group 5) (P2Y5), mRNA; Integral inner nuclear membrane protein (MAN1), mRNA; Fanconi anemia, complementation group F (FANCF), mRNA; Hypothetical protein FLJ12820 (FLJ12820), mRNA; Hypothetical protein FLJ13119 (FLJ13119), mRNA; Hypothetical protein FLJ20189 (FLJ20189), mRNA; Hypothetical protein FLJ20701 (FLJ20701), mRNA; Homo sapiens chromosome 12 open reading frame 5 (C12ORF5), mRNA; Hypothetical protein FLJ22555 (FLJ22555), mRNA; Hypothetical protein FLJ11110 (FLJ11110), mRNA; CGI-12 (LOC51001), mRNA; PNAS-25 mRNA, complete cds.; Homo sapiens mRNA for FLJ00043 protein, partial cds; Homo sapiens cDNA: FLJ21737 fis, clone COLF3396; Homo sapiens cDNA FLJ13399 fis, clone PLACE1001395/ DEF=Homo sapiens cDNA FLJ13399 fis, clone PLACE1001395), wherein expression of the one or more biomarkers is increased in the subject.

[0089] Additionally or alternatively, more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 186, 201, 204, 208, 209, 91, 210, 212, 97, 215, 217-219, 222-225, 227, 230, 233, 236, 237, 248, 251, 252, 254-261, 266, 267, 283, 284 and 289-292 (or the biomarkers set forth by name in Table 5 as being downregulated, namely CD59 antigen p18-20 (antigen identified by monoclonal antibodies 16.3A5, EJ16, EJ30, EL32 and G344); 6-phosphofructo-2-kinasefructose-2,6-biphosphatase 3 (PFKFB3), mRNA./PROD=6-phosphofructo-2-kinase-fructose-2,6-biphosphatase 3; Protein tyrosine phosphatase, non-receptor type substrate 1 (PTPNS1), mRNA; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3 (12 kD, B12) (NDUFB3), mRNA; Diphtheria toxin receptor (DTR); Thrombomodulin (THBD), mRNA; Protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), mRNA; Hemoglobin, gamma G (HBG2), mRNA; Amphiregulin (schwannoma-derived growth factor) (AREG), mRNA; Early growth response 2 (Krox-20 (Drosophila) homolog) (EGR2), mRNA; Early growth response 3 (EGR3), mRNA./PROD=early growth response 3; Homo sapiens MD-2 protein (MD-2), mRNA; Homo sapiens MAX dimerization protein (MAD), mRNA; Transferrin receptor (p90, CD71), clone MGC:3151, mRNA, complete cds; Homo sapiens mRNA; cDNA DKFZp564N1272 (from clone DKFZp564N1272); complete cds; GABA-A receptor-associated protein like 1 (GABARAPL1) mRNA, complete cds; Translocation protein 1; Protein kinase-related oncogene (PIM1) mRNA, complete cds; Human mRNA for hCREM (cyclic AMP-responsive element modulator) type 2 protein, complete cds; Human mRNA for ZFM1 protein alternatively spliced product, complete cds./PROD=ZFM1 protein, alternatively spliced product; GABA-A receptor-associated protein mRNA, complete cds./PROD=GABA-A receptor-associated protein; Human (clone 2-5) synuclein (NACP) mRNA, complete cds; Myosin, light polypeptide 4, alkali; atrial, embryonic; Heterogeneous nuclear ribonucleoprotein H1 (H); Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide; cDNA: FLJ23227 fis, clone CAE00645, highly similar to AF052138; Hypothetical protein FLJ12619; C-terminal binding protein 1; SEC22, vesicle trafficking protein (S. cerevisiae)-like 1; Hemoglobin, alpha 1; Homo sapiens clone 24659 mRNA sequence/DEF=Homo sapiens clone 24659 mRNA sequence; Calcium channel, voltage-dependent, PQ type, alpha 1A subunit; H. sapiens SMA5 mRNA; ESTs, Hs.97109; ESTs, Weakly similar to ALU7_HUMAN ALU; Triggering receptor expressed on myeloid cells 1 (TREM1), betaGlcNAc beta 1,4-galactosyltransferase. polypeptide 5; Novel MAFF (v-maf musculoaponeurotic fibrosarcoma (avian) oncogene family, protein F) LIKE protein; Heparin-binding EGF-like growth factor mRNA, complete cds; E. coli 7,8-diamino-pelargonic acid (bioA), biotin synthetase (bioB), 7-keto-8-amino-pelargonic acid synthetase (bioF), bioC protein, and dethiobiotin synthetase (bioD), complete cds; Escherichia coli/REF=J04423/DEF=E. coli bioC protein corresponding to nucleotides 4609-4883 of J04423/LEN=777 (-5 and -3 represent transcript regions 5 prime and 3 prime respectively)), wherein expression of the one or more biomarkers is decreased in the subject.

[0090] In yet another embodiment of the monitoring method, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 87, 97, 101, 293, 92, 272, 93, 107, 108, 121 and 123 (or the biomarkers set forth by name in Table 6 as pre-treatment biomarkers, namely Solute carrier family 6; Amphiregulin; Keratin 1; Hemoglobin, alpha 1; MHC-II, DM beta; Purinergic receptor P2Y, G-protein coupled 5; Forkhead box O3A; Transferrin receptor (p90, CD71); Ring finger protein 10; Formin binding protein 4; and Hypothetical protein LOC54103), wherein the subject is monitored prior to treatment with a TNFα inhibitor. [0091] In yet another embodiment of the monitoring method, the one or more biomarkers is encoded by a nucleic

method, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 290, 209, 98, 112, 116, 121, 130, 155, 92, 289, 216 and 131 (or the biomarkers set forth by name in Table 6 as post-treatment biomarkers, namely Diphteria toxin receptor; Heparin-binding EGF-like growth factor; Lipoyltransferase 1; APEX nuclease (multi-

funct. DNA repair enzyme) 1; GABA(A) receptor-associated protein like 1/3; Formin binding protein 4; Zinc finger protein 331; Ribonuclease P 40 kDa subunit; MHC class II, DM beta; v-maf fibrosarc. oncogene homolog F (avian); 2',5'-oligoad-enylate synthetase 1, 40/46 kDa; and Membrane-spanning 4-domains, subfam. A, memb. 4), wherein the subject is monitored after treatment with a TNF α inhibitor.

[0092] In yet another embodiment of the monitoring method, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 97, 102, 29, 294, 295, 91, 131, 290, 100, 134, 296, 297, 298, 299, 136, 174 and 300 (or the biomarkers set forth by name in Table 7, namely Amphiregulin; Carbonic anhydrase 1; Charcot-Leyden crystal protein; Clusterin C; Tumor necrosis factor alpha induced protein 6; Thrombomodulin; Membrane-spanning 4-domains, subfamily A, member 4; Diptheria toxin receptor; S100 calcium binding protein A1; Uncharacterized hypothalamus protein HT007; MHC-class-II; HLA-DR alpha; Hypothetical protein L0054103; Tumor necrosis factor alpha; Interleukin 1 beta; Proteasome subunit beta type 7 precursor; and Protein KIAA0174; Microsomal signal peptidase 18 kDa subunit).

[0093] A preferred autoimmune disorder in which to apply the methods of the invention for monitoring an autoimmune disorder is rheumatoid arthritis. However, the monitoring methods can be applied to essentially any autoimmune disorder in which TNF α inhibitor therapy is applied, including the autoimmune disorders listed in the previous section.

Selection and Use of Treatment Regimens with TNF α Inhibitors

[0094] Given the observation that the expression pattern of particular biomarkers in an autoimmune disorder subject influences the responsiveness of the subject to a TNF α inhibitor, one can select an appropriate treatment regimen for the subject based on the expression of one or more biomarkers in the subject. Accordingly, in one embodiment, the above-described method for predicting the responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder further comprises selecting a treatment regimen with the TNF α inhibitor based upon expression of the one or more biomarkers in the subject. In another aspect, the method still further comprises administering the TNF α inhibitor to the subject according to the treatment regimen such that the autoimmune disorder is inhibited in the subject.

[0095] In another embodiment, the invention provides a method for selecting a treatment regimen for therapy with a TNF α inhibitor in a subject having an autoimmune disorder, the method comprising:

[0096] assaying the subject for expression of one or more biomarkers predictive of responsiveness to a TNF α inhibitor for treatment of the autoimmune disorder; and

[0097] selecting a treatment regimen with a TNF α inhibitor based upon expression of the one or more biomarkers in the subject.

[0098] In yet another embodiment, the invention provides a method of treating a subject having an autoimmune disorder with a TNF α inhibitor, the method comprising:

[0099] assaying the subject for expression of one or more biomarkers predictive of responsiveness to a TNF α inhibitor for treatment of the autoimmune disorder;

[0100] selecting a treatment regimen with a TNF α inhibitor based upon expression of the one or more biomarkers in the subject; and

[0101] administering the $TNF\alpha$ inhibitor according to the treatment regimen such that the subject is treated for the autoimmune disorder.

[0102] The treatment regimen that is selected typically includes at least one of the following parameters and more typically includes many or all of the following parameters: the type of agent chosen for administration, the dosage, the formulation, the route of administration and/or the frequency of administration.

[0103] Particularly preferred TNF α inhibitors are biologic agents that have been approved by the FDA for use in humans in the treatment of rheumatoid arthritis, which agents include adalimumab (HUMIRATM), infliximab (REMICADETM) and etanercept (ENBRELTM), most preferably adalimumab (HUMIRATTM).

[0104] In one embodiment, the TNF α inhibitor is an antitumor necrosis factor-alpha (TNF α) antibody, or antigenbinding portion thereof. For example, the anti-TNF α antibody, or antigen-binding portion thereof, can be a humanized antibody, a chimeric antibody or a multivalent antibody.

[0105] In another embodiment, the anti-TNF α antibody, or antigen-binding portion thereof, is a human antibody, preferably a human antibody, or antigen-binding portion thereof, that binds to human TNF α with high affinity and a low off rate, and has a high neutralizing capacity. Preferably, the human antibodies are recombinant, neutralizing human antihTNFα antibodies. The most preferred recombinant, neutralizing antibody used in the method of the invention is referred to herein as adalimumab, also referred to as HUMIRA® or D2E7 (the amino acid sequence of the adalimumab VL region is shown in SEQ ID NO: 303; the amino acid sequence of the adalimumab VH region is shown in SEQ ID NO: 304). The properties of D2E7 (adalimumab; Humira®) have been described in Salfeld et al., U.S. Pat. Nos. 6,090,382, 6,258, 562, and 6,509,015, which are each incorporated by reference herein.

[0106] Other examples of TNFα antibodies include chimeric and humanized murine anti-hTNFα antibodies which have undergone clinical testing for treatment of rheumatoid arthritis (see e.g., Elliott et al. (1994) *Lancet* 344:1125-1127; Elliot et al. (1994) *Lancet* 344:1105-1110; Rankin et al. (1995) *Br. J. Rheumatol.* 34:334-342). In another embodiment, the TNFα antibody used in the invention is infliximab (Remicade®, Johnson and Johnson; described in U.S. Pat. No. 5,656,272, incorporated by reference herein), CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment), an anti-TNF dAb (Peptech), and CNTO 148 (golimumab; Medarex and Centocor, see also WO 02/12502).

[0107] In one embodiment, the TNF α inhibitors used in the methods of the invention include adalimumab antibodies and antibody portions, adalimumab-related antibodies and antibody portions, adalimumab-related DVD-Ig or dual specific antibodies, and other human antibodies and antibody portions with equivalent properties to adalimumab, such as high affinity binding to hTNF α with low dissociation kinetics and high neutralizing capacity. In one embodiment, a treatment regimen of the invention provides treatment with an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNF α with a K $_d$ of 1×10^{-8} M or less and a K $_{off}$ rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard in vitro L929 assay with an IC $_{50}$ of 1×10^{-7} M or less. More preferably, the isolated human anti-

body, or antigen-binding portion thereof, dissociates from human TNF α with a K $_{off}$ of 5×10^{-4} s $^{-1}$ or less, or even more preferably, with a K $_{off}$ of 1×10^{-4} s $^{-1}$ or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, neutralizes human TNF α cytotoxicity in a standard in vitro L929 assay with an IC $_{50}$ of 1×10^{-8} M or less, even more preferably with an IC $_{50}$ of 1×10^{-9} M or less and still more preferably with an IC $_{50}$ of 1×10^{-10} M or less. In a preferred embodiment, the antibody is an isolated human recombinant antibody, or an antigen-binding portion thereof.

[0108] It is well known in the art that antibody heavy and light chain CDR3 domains play an important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, in another aspect, the TNF α inhibitor used in the treatment method of the invention is a human anti-TNF α antibody that has slow dissociation kinetics for association with hTNFα and that has light and heavy chain CDR3 domains that structurally are identical to or related to those of adalimumab. Position 9 of the adalimumab VL CDR3 can be occupied by Ala or Thr without substantially affecting the $K_{\it off}$. Accordingly, a consensus motif for the adalimumab VL CDR3 comprises the amino acid sequence: Q-R-Y-N-R-A-P-Y-(T/A) (SEQ ID NO: 305). Additionally, position 12 of the adalimumab VH CDR3 can be occupied by Tyr or Asn, without substantially affecting the $K_{\it off}$. Accordingly, a consensus motif for the adalimumab VH CDR3 comprises the amino acid sequence: V-S-Y-L-S-T-A-S-S-L-D-(Y/N) (SEQ ID NO: 306). Moreover, as demonstrated in Example 2 of U.S. Pat. No. 6,090,382, the CDR3 domain of the adalimumab heavy and light chains is amenable to substitution with a single alanine residue (at position 1, 4, 5, 7 or 8 within the VL CDR3 or at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 within the VH CDR3) without substantially affecting the Koff Still further, the skilled artisan will appreciate that, given the amenability of the adalimumab VL and VH CDR3 domains to substitutions by alanine, substitution of other amino acids within the CDR3 domains may be possible while still retaining the low off rate constant of the antibody, in particular substitutions with conservative amino acids. Preferably, no more than one to five conservative amino acid substitutions are made within the adalimumab VL and/or VH CDR3 domains. More preferably, no more than one to three conservative amino acid substitutions are made within the adalimumab VL and/or VH CDR3 domains. Additionally, conservative amino acid substitutions should not be made at amino acid positions critical for binding to hTNF α . Positions 2 and 5 of the adalimumab VL CDR3 and positions 1 and 7 of the adalimum ab VH CDR3 appear to be critical for interaction with hTNF α and thus, conservative amino acid substitutions preferably are not made at these positions (although an alanine substitution at position 5 of the adalimumab VL CDR3 is acceptable, as described above) (see U.S. Pat. No. 6,090,382).

[0109] Accordingly, in another embodiment, the antibody or antigen-binding portion thereof preferably contains the following characteristics:

[0110] a) dissociates from human TNF α with a K_{off} rate constant of $1\times10^{-3}~{\rm s}^{-1}$ or less, as determined by surface plasmon resonance;

[0111] b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 305, or modified from SEQ ID NO: 305 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

[0112] c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 306, or modified from SEQ ID NO: 306 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

[0113] More preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNF α with a K_{off} of $5\times 10^{-4}~s^{-1}$ or less. Even more preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNF α with a K_{off} of $1\times 10^{-4}~s^{-1}$ or less.

[0114] In yet another embodiment, the antibody or antigenbinding portion thereof preferably contains a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 305, or modified from SEQ ID NO: 305 by a single alanine substitution at position 1, 4, 5, 7 or 8, and with a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 306, or modified from SEQ ID NO: 306 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11. Preferably, the LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 307 (i.e., the adalimumab VL CDR2) and the HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 308 (i.e., the adalimumab VH CDR2). Even more preferably, the LCVR further has CDR1 domain comprising the amino acid sequence of SEQ ID NO: 309 (i.e., the adalimumab VL CDR1) and the HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 310 (i.e., the adalimumab VH CDR1). The framework regions for VL preferably are from the V_rI human germline family, more preferably from the A20 human germline Vk gene and most preferably from the adalimumab VL framework sequences shown in FIGS. 1A and 1B of U.S. Pat. No. 6,090,382. The framework regions for VH preferably are from the V₁₁3 human germline family, more preferably from the DP-31 human germline VH gene and most preferably from the adalimumab VH framework sequences shown in FIGS. 2A and 2B of U.S. Pat. No. 6,090,382.

[0115] Accordingly, in another embodiment, the antibody or antigen-binding portion thereof preferably contains a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 303 (i.e., the adalimumab VL) and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 304 (i.e., the adalimumab VH). In certain embodiments, the antibody comprises a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. Preferably, the heavy chain constant region is an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. Furthermore, the antibody can comprise a light chain constant region, either a kappa light chain constant region or a lambda light chain constant region. Preferably, the antibody comprises a kappa light chain constant region. Alternatively, the antibody portion can be, for example, a Fab fragment or a single chain Fv

[0116] In other embodiments, the TNF α inhibitor of the invention is etanercept (described in WO 91/03553 and WO 09/406,476), infliximab (described in U.S. Pat. No. 5,656, 272), CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment), D2E7 (a human anti-TNF mAb), soluble TNF receptor Type I, or a pegylated soluble TNF receptor Type I (PEGs TNF-R1).

[0117] The TNF α antibody of the invention can be modified. In some embodiments, the TNF α antibody or antigen binding fragments thereof, is chemically modified to provide a desired effect. For example, pegylation of antibodies and antibody fragments of the invention may be carried out by any of the pegylation reactions known in the art, as described, for example, in the following references: Focus on Growth Factors 3:4-10 (1992); EP 0 154 316; and EP 0 401 384 (each of which is incorporated by reference herein in its entirety). Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive polyethylene glycol molecule (or an analogous reactive water-soluble polymer). A preferred water-soluble polymer for pegylation of the antibodies and antibody fragments of the invention is polyethylene glycol (PEG). As used herein, "polyethylene glycol" is meant to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol.

[0118] Methods for preparing pegylated antibodies and antibody fragments of the invention will generally comprise the steps of (a) reacting the antibody or antibody fragment with polyethylene glycol, such as a reactive ester or aldehyde derivative of PEG, under conditions whereby the antibody or antibody fragment becomes attached to one or more PEG groups, and (b) obtaining the reaction products. It will be apparent to one of ordinary skill in the art to select the optimal reaction conditions or the acylation reactions based on known parameters and the desired result.

[0119] In yet another embodiment of the invention, TNFα antibodies or fragments thereof can be altered wherein the constant region of the antibody is modified to reduce at least one constant region-mediated biological effector function relative to an unmodified antibody. To modify an antibody of the invention such that it exhibits reduced binding to the Fc receptor, the immunoglobulin constant region segment of the antibody can be mutated at particular regions necessary for Fc receptor (FcR) interactions (see e.g., Canfield, S. M. and S. L. Morrison (1991) *J. Exp. Med.* 173:1483-1491; and Lund, J. et al. (1991) *J. Immunol.* 147:2657-2662). Reduction in FcR binding ability of the antibody may also reduce other effector functions which rely on FcR interactions, such as opsonization and phagocytosis and antigen-dependent cellular cytotoxicity.

[0120] An antibody or antibody portion of the invention can be derivatized or linked to another functional molecule (e.g., another peptide or protein). Accordingly, the antibodies and antibody portions of the invention are intended to include derivatized and otherwise modified forms of the anti-TNF α antibodies described herein, including immunoadhesion molecules. For example, an antibody or antibody portion of the invention can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate associate of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

[0121] One type of derivatized antibody is produced by crosslinking two or more antibodies (of the same type or of different types, e.g., to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide

ester) or homobifunctional (e.g., disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

[0122] Useful detectable agents with which an antibody or antibody portion of the invention may be derivatized include fluorescent compounds. Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody may also be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding.

[0123] Selection of the particular parameters of the treatment regimen can be based on known treatment parameters for the TNF α inhibitor previously established in the art. For example, a non-limiting example of a treatment regimen for adalimumab (HUMIRATM) is 40 mg every other week by subcutaneous injection. A non-limiting example of a treatment regimen for etanercept (ENBRELTM) is 50 mg/week by subcutaneous injection. A non-limiting example of a treatment regimen for infliximab (REMICADETM) is 3 mg/kg by intravenous infusion at weeks 0, 2 and 6, then every 8 weeks. A treatment regimen can include administration of the TNF α inhibitor alone or can include combination of the $\ensuremath{\mathsf{TNF}}\alpha$ inhibitor with other therapeutic agents, such as methotrexate (e.g., 10-20 mg/week) or prednisolone (e.g., 10 mg/week). Other suitable treatment regimens for the TNF α inhibitors discussed herein will be readily apparent to the ordinarily skilled artisan based on prior studies of preferred administration parameters for the TNF α inhibitor.

[0124] For administration to a subject, a TNF α inhibitor typically is formulated into a pharmaceutical composition containing the TNF α inhibitor and a pharmaceutically acceptable carrier. Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. Pharmaceutical compositions also can be administered in combination therapy, i.e., combined with other agents, such as other TNF α inhibitors and/or other therapeutic agents, such as traditional therapeutic agents for the treatment of autoimmune disorders, such as rheumatoid arthritis.

[0125] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

[0126] The pharmaceutical compositions may include one or more pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see e.g., Berge, S. M., et al. (1977) *J. Pharm. Sci.* 66:1-19). Examples of such

salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

[0127] A pharmaceutical composition also may include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0128] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0129] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0130] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0131] A TNF α inhibitor of the present invention can be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. A preferred route of administration, particularly for antibody agents, is by intravenous injection or infusion. Other preferred routes of administration include intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other

parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. Alternatively, a TNF α inhibitor of the invention can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

[0132] In a preferred embodiment, the subject to be treated with the TNF α inhibitor is a human subject.

[0133] A preferred autoimmune disorder in which to apply the methods of the invention for selecting and using a treatment regimen is rheumatoid arthritis. However, these methods can be applied to essentially any autoimmune disorder in which $TNF\alpha$ inhibitor therapy is applied, including the autoimmune disorders listed in the previous sections

Kits of the Invention

[0134] In another aspect, the invention pertains to kits for carrying out the methods of the invention. For example, in one embodiment, the invention provides a kit for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder. In one embodiment, the kit comprises: [0135] a) means for isolating monocytes;

[0136] b) means for measuring expression in the subject of one or more biomarkers predictive of responsiveness to a $TNF\alpha$ inhibitor in an autoimmune disorder;

[0137] c) means for measuring expression of at least one housekeeping gene; and

[0138] d) instructions for use of the kit to predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (or the biomarkers set forth by name in Table 9, as described above)

[0139] In one embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43-47, 49, 51, 54, 55, 57, 59, 61, 62, 64, 70, 75, 79 and 82 (or the biomarkers set forth by name in Table 9 as being increased in ≥80% of responders vs. non-responders, as described above), more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 37, 44, 47, 62 and 70 (or the biomarkers set forth by name in Table 9 as being increased in ≥90% of responders vs. non-responders, as described above), and even more preferably at least one of the biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 44 (or the CD11c biomarkers set forth by name in Table 9 as being increased in 100% of responders vs. non-responders). In each of these embodiments, preferably the instructions for use of the kit instruct that increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNFα inhibitor.

[0140] In another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising

a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 11-14, 18, 20, 21, 23, 25, 26, 28-30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 65-69, 71-74, 76-78, 80 and 81 (or the biomarkers set forth by name in Table 9 as being decreased in ≥80% of responders vs. non-responders, as described above), more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 29, 65, 73 and 74 (or the biomarkers set forth by name in Table 9 as being decreased in ≥90% of responders vs. non-responders, as described above), and even more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 11 or SEQ ID NO: 74 (or the biomarkers set forth by name in Table 9 as being decreased in 100% of responders vs. non-responders, as described above). In each of these embodiments, preferably the instructions for use of the kit instruct that decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNFα inhibitor.

[0141] In another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 83-133 (or the biomarkers set forth by name in Table 3, as described above).

[0142] In yet another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 134-177, 110, 112, 118, 123 and 131 (or the biomarkers set forth by name in Table 4, as described above), more preferably SEQ ID NO: 134-150, 112, 118 (or the biomarkers set forth by name in Table 4 as being upregulated, as described above), wherein the instructions instruct that expression of the one or more biomarkers is increased in the subject, and/or more preferably SEQ ID NO: 151-177, 110 and 123 (or the biomarkers set forth by name in Table 4 as being downregulated, as described above), wherein the instructions instruct that expression of the one or more biomarkers is decreased in the subject.

[0143] In yet another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 178-292, 91 and 97 (or the biomarkers set forth by name in Table 5, as described above), more preferably SEQ ID NO: 178-185; 187-200, 202, 203, 205-207; 211, 213, 214, 216, 220, 221, 226, 228, 229, 231, 232, 234, 235, 238-247, 249, 250, 253, 262-265, 268-282 and 285-288 (or the biomarkers set forth by name in Table 5 as being upregulated, as described above), wherein the instructions instruct that expression of the one or more biomarkers is increased in the subject, and/or more preferably SEQ ID NO: 186, 201, 204, 208, 209, 91, 210, 212, 97, 215, 217-219, 222-225, 227, 230, 233, 236, 237, 248, 251, 252, 254-261, 266, 267, 283, 284 and 289-292 (or the biomarkers set forth by name in Table 5 as being downregulated, as described above), wherein the instructions instruct that expression of the one or more biomarkers is decreased in the subject.

[0144] In yet another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 87, 97, 101, 293, 92, 272, 93, 107, 108, 121 and 123 (or the biomarkers set forth by name in Table 6 as pre-treatment biomarkers, as described above), wherein the instructions instruct that the subject is monitored prior to

treatment with a TNF α inhibitor. In yet another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 290, 209, 98, 112, 116, 121, 130, 155, 92, 289, 216 and 131 (or the biomarkers set forth by name in Table 6 as post-treatment biomarkers, as described above), wherein the instructions instruct that the subject is monitored after treatment with a TNF α inhibitor.

[0145] In yet another embodiment of the kit, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 97, 102, 29, 294, 295, 91, 131, 290, 100, 134, 296, 297, 298, 299, 136, 174 and 300 (or the biomarkers set forth by name in Table 7, as described above). [0146] In a preferred embodiment, the means for measuring expression in the subject of the one or more biomarkers predictive of responsiveness to a TNFa inhibitor in an autoimmune disorder comprises a nucleic acid preparation sufficient to detect expression of mRNA encoding the one or more biomarkers in a sample from the subject, such as a peripheral blood mononuclear cell sample from which mRNA is obtained by standard methods. This nucleic acid preparation includes at least one, and may include more than one, nucleic acid probe or primer, the sequence(s) of which is designed such that the nucleic acid preparation can detect the expression of mRNA encoding the biomarker(s) of interest in the sample from the subject. A preferred nucleic acid preparation includes two or more PCR primers that allow for PCR amplification of a segment of the mRNA encoding the biomarker(s) of interest. In a particularly preferred embodiment, the kit comprises a nucleic acid preparation sufficient to detect expression of CD11c mRNA in a sample from the subject.

[0147] Alternatively, the means for detecting expression in the subject of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder can comprise a reagent that detects the gene product of the mRNA encoding the biomarker(s) of interest sufficient to distinguish it from other gene products in a sample from the subject. A non-limiting example of such a reagent is a monoclonal antibody preparation (comprising one or more monoclonal antibodies) sufficient to detect protein expression of the biomarker(s) of interest in a sample from the subject, such as a peripheral blood mononuclear cell sample. In a particularly preferred embodiment, the kit comprises a monoclonal antibody preparation sufficient to detect expression of CD11c protein in a sample from the subject.

[0148] The means for measuring expression of the one or more biomarkers can also include, for example, buffers or other reagents for use in an assay for evaluating biomarker expression (e.g., at either the mRNA or protein level). The instructions can be, for example, printed instructions for performing the assay for evaluating the expression of the one or more biomarkers.

[0149] In a preferred embodiment, the means for measuring expression of at least one housekeeping gene comprises a nucleic acid preparation sufficient to detect expression of mRNA of the housekeeping gene (e.g., GAPDH) in a sample from the subject, such as a peripheral blood mononuclear cell sample from which mRNA is obtained by standard methods. This nucleic acid preparation includes at least one, and may include more than one, nucleic acid probe or primer, the sequence(s) of which is designed such that the nucleic acid preparation can detect the expression of mRNA of the house-

keeping gene(s) in the sample from the subject. A preferred nucleic acid preparation includes two or more PCR primers that allow for PCR amplification of a segment of the mRNA of the housekeeping gene(s). Alternatively, the means for detecting expression in the subject of at least one housekeeping gene can comprise a reagent that detects the gene product of housekeeping gene sufficient to distinguish it from other gene products in a sample from the subject. A non-limiting example of such a reagent is a monoclonal antibody preparation (comprising one or more monoclonal antibodies) sufficient to detect protein expression of housekeeping gene product in a sample from the subject, such as a peripheral blood mononuclear cell sample.

[0150] The means for isolating monocytes can comprise one or more reagents that can be used to separate monocytes from other cell types in a sample of peripheral blood mononuclear cells, for example by positive selection of the monocytes or by negative selection in which all other cell types other than monocytes are removed. In one embodiment, a reagent that binds CD14 on monocytes (e.g., an anti-CD14 antibody) is included in the kit as means to isolate monocytes via positive selection. Alternatively, in another embodiment, reagents such as those commercially available in the Monocyte Isolation Kit II (Miltenyi Biotec, Auburn, Calif.) can be used for negative selection, in which non-monocytes (T cells, B cells, NK cells, dendritic cells, basophils) are indirectly magnetically labeled using a cocktail of biotin-conjugated antibodies against CD3, CD7, CD16, CD19, CD56, CD123 and CD235a (Glycophorin A), as well as anti-biotin Micro-Beads, and then highly pure unlabeled monocytes are obtained by depletion of the magnetically labeled cells.

[0151] In another embodiment, the kit can further comprise a TNF α inhibitor for treating an autoimmune disorder in the subject. Preferred TNF α inhibitors for use in the kit include the TNF α inhibitors described in detail above with respect to treatment regimens, in particular anti-TNF α antibodies such as adalimumab, infliximab and/or golimumab, and/or Ig fusion proteins such as etanercept.

[0152] Preferably, the kit is designed for use with a human subject.

Databases and Computer Programs

[0153] In another aspect, the invention pertains to methods of building a database for use in selecting an autoimmune disorder subject for treatment with a TNFa inhibitor, or for use in selecting or monitoring a treatment regimen in an autoimmune disorder subject. The method can comprise receiving, in a computer system, biomarker expression patterns from a plurality of subjects having an autoimmune disorder; and storing the biomarker expression pattern from each subject such that the biomarker expression pattern is associated with an identifier of the subject, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (or the biomarkers set forth by name in Table 9, as described above). The identifier of the subject can be, for example, the name of the subject or a numerical or symbolic identifier coded to the identity of the subject. The method can further comprise receiving, in the computer system, one or more treatment regimens for treatment of an autoimmune disorder in a subject such that the treatment regimen is associated with the biomarker expression pattern of the subject and the identifier of the subject. A user can enter the subject's biomarker expression pattern, and optionally the subject's treatment regimen(s), into the computer system. Alternatively, the subject's biomarker expression pattern can be received directly from equipment used in determining the expression of one or more biomarkers in a sample from the subject.

[0154] In another aspect, the invention provides a computer program product useful for building a database for use in selecting or monitoring an autoimmune disorder subject for treatment with a TNFα inhibitor. The computer program can contain executable instructions that when executed cause a processor to perform operations comprising: receiving, in a computer system, a biomarker expression pattern of a subject at one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder; and storing the biomarker expression pattern such that the biomarker expression pattern is associated with an identifier of the subject, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (or the biomarkers set forth by name in Table 9, as described above). Optionally, the computer program can further cause the processor to perform an operation comprising: receiving, in the computer system, a treatment regimen for treatment of an autoimmune disorder in the subject such that the treatment regimen is associated with the biomarker expression pattern of the subject and the identifier of the subject.

[0155] In another aspect, the invention provides a method of selecting an autoimmune disorder subject for a treatment with a TNF α inhibitor. The method can comprise: (i) identifying, in a database comprising a plurality of autoimmune disorder subjects, a subject whose database entry is associated with a biomarker expression pattern that is predictive of responsiveness to treatment with a TNF α inhibitor, and (ii) selecting the subject for treatment with a TNFα inhibitor, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (or the biomarkers set forth by name in Table 9, as described above). The method can further comprise selecting a treatment regimen by identifying, in the database, a treatment regimen that has been associated with the biomarker expression pattern of the subject and with an identifier of the subject.

[0156] In yet another aspect, the invention provides a computer program product useful for identifying and/or selecting a subject for treatment with a TNF α inhibitor. The computer program can contain executable instructions that when executed cause a processor to perform operations comprising: (i) identifying, in a database including a plurality of autoimmune disorder subjects associated with biomarker expression patterns, a subject that is associated with a biomarker expression pattern that is predictive of responsiveness to treatment with a TNF a inhibitor; and (ii) outputting the identified subject as a subject to be treated with a TNF α inhibitor; wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82 (or the biomarkers set forth by name in Table 9, as described above). The computer program can further cause the processor to perform

an operation comprising outputting a treatment regimen that is associated with the subject to be treated with the $TNF\alpha$ inhibitor.

[0157] In one embodiment of the above-described methods and computer program, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43-47, 49, 51, 54, 55, 57, 59, 61, 62, 64, 70, 75, 79 and 82 (or the biomarkers set forth by name in Table 9 as being increased in ≥80% of responders vs. non-responders, as described above), more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 37, 44, 47, 62 and 70 (or the biomarkers set forth by name in Table 9 as being increased in ≥90% of responders vs. non-responders, as described above), and even more preferably at least one of the biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 44 (or the biomarker, CD11c antigen, set forth by name in Table 9 as being increased in 100% of responders vs. non-responders, as described above). In each of these embodiments, increased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α inhibitor.

[0158] In another embodiment of the above-described methods and computer programs, the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 11-14, 18, 20, 21, 23, 25, 26, 28-30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 65-69, 71-74, 76-78, 80 and 81 (or the biomarkers set forth by name in Table 9 as being decreased in ≥80% of responders vs. non-responders, as described above), more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 29, 65, 73 and 74 (or the biomarkers set forth by name in Table 9 as being decreased in ≥90% of responders vs. non-responders, as described above), and even more preferably the one or more biomarkers is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 11 or SEQ ID NO: 74 (or the biomarkers set forth by name in Table 9 as being decreased in 100% of responders vs. non-responders, as described above). In each of these embodiments, decreased expression of the one or more biomarkers is predictive of responsiveness of the subject to a TNF α

[0159] In another embodiment of the above-described methods and/or computer programs, the biomarker expression pattern(s) can be for one or more biomarkers selected from the group consisting of SEQ ID NO: 83-133 (or the biomarkers set forth by name in Table 3, as described above). [0160] In yet another embodiment of the above-described methods and/or computer programs, the biomarker expres-

[0160] In yet another embodiment of the above-described methods and/or computer programs, the biomarker expression pattern(s) can be for one or more biomarkers selected from the group consisting of SEQ ID NO: 134-177, 110, 112, 118, 123 and 131 (or the biomarkers set forth by name in Table 4, as described above), more preferably SEQ ID NO: 134-150, 112, 118 (or the biomarkers set forth by name in Table 4 as having increased expression, as described above), wherein expression of the one or more biomarkers is increased in the subject, and/or more preferably SEQ ID NO: 151-177, 110 and 123 (or the biomarkers set forth by name in

Table 4 as having decreased expression, as described above), wherein expression of the one or more biomarkers is decreased in the subject.

[0161] In vet another embodiment of the above-described methods and/or computer programs, the biomarker expression pattern(s) can be for one or more biomarkers selected from the group consisting of SEQ ID NO: 178-292, 91 and 97 (or the biomarkers set forth by name in Table 5, as described above), more preferably SEQ ID NO: 178-185; 187-200, 202, 203, 205-207; 211, 213, 214, 216, 220, 221, 226, 228, 229, 231, 232, 234, 235, 238-247, 249, 250, 253, 262-265, 268-282 and 285-288 (or the biomarkers set forth by name in Table 5 as having increased expression, as described above), wherein expression of the one or more biomarkers is increased in the subject, and/or more preferably SEQ ID NO: 186, 201, 204, 208, 209, 91, 210, 212, 97, 215, 217-219, 222-225, 227, 230, 233, 236, 237, 248, 251, 252, 254-261, 266, 267, 283, 284 and 289-292 (or the biomarkers set forth by name in Table 5 as having decreased expression, as described above), wherein expression of the one or more biomarkers is decreased in the subject.

[0162] In yet another embodiment of the above-described methods and/or computer programs, the biomarker expression pattern(s) can be for one or more biomarkers selected from the group consisting of SEQ ID NO: 87, 97, 101, 293, 92, 272, 93, 107, 108, 121 and 123 (or the biomarkers set forth by name in Table 6 as pre-treatment biomarkers, as described above), wherein the subject is monitored prior to treatment with a TNFα inhibitor. In yet another embodiment of the above-described methods and/or computer programs, the biomarker expression pattern(s) can be for one or more biomarkers selected from the group consisting of SEQ ID NO: 290, 209, 98, 112, 116, 121, 130, 155, 92, 289, 216 and 131 (or the biomarkers set forth by name in Table 6 as post-treatment biomarkers, as described above), wherein the subject is monitored after treatment with a TNFα inhibitor.

[0163] In yet another embodiment of the above-described methods and/or computer programs, the biomarker expression pattern(s) can be for one or more biomarkers selected from the group consisting of SEQ ID NO: 97, 102, 29, 294, 295, 91, 131, 290, 100, 134, 296, 297, 298, 299, 136, 174 and 300 (or the biomarkers set forth by name in Table 7, as described above).

[0164] Computer systems and database software well established in the art can be adapted for use in the methods and computer program products of the invention for building and searching a database for use in selecting or monitoring a treatment regimen for a subject having an autoimmune disorder or for selecting a particular autoimmune disorder subject for treatment with a $TNF\alpha$ inhibitor.

[0165] The present invention is further illustrated by the following examples which should not be construed as further limiting. The contents of all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference in their entirety.

EXAMPLES

Example 1

Materials and Methodologies

[0166] In this example, the materials and methodologies used in the subsequent Examples are described.

Patients

[0167] Purified monocytes (MO) derived from a total of 84 RA patients were used. The clinical data for the RA patients,

pre- and post-anti-TNFα treatment, is summarized in Table 1. All patients fulfilled the revised American College of Rheumatology (ACR) criteria (Arnett, F. C. et al. (1988) *Arthritis Rheum.* 31:315-324). Patients were defined as responders (≧continuous ACR score 40) or non-responders (≦continuous ACR score 30) to anti-TNFα monotherapy, MTX monotherapy or combination therapy. In order to account for a gradual transition from clinical responders to non-responders to therapy, a continuous ACR response evaluation was performed by applying the ACR criteria, but by defining 10% response steps instead of the usual 20, 50, and 70% steps. This was also done to allow more detailed analyses of the correlation between the ACR response and the mRNA expression levels of the predictive marker CD11c.

[0168] For Affymetrix® microarray analysis, MO samples from 7 RA patients (RA1-RA7; all females) undergoing the Abbott DE011 trial were used (ReACT; monoclonal antibody Adalimumab®). In this multicenter, double-blinded study patients received Adalimumab® (20 mg weekly or 40 mg biweekly) in the outpatient Rheumatology Clinic of the Charite University Hospital in Berlin, Germany, for a total of 2 years. Non-steroidal anti-inflammatory drugs and 10 mg prednisolone-equivalent per week were allowed in addition to the anti-TNFα therapy. For TaqMan® real-time PCR, 26 patients (RA8-RA84 from the Abbott DE013 trial were used (ATTRACT). In this study Adalimumab®, methotrexate (MTX; 10-20 mg/week) or a combination of both therapeutics was applied.

[0169] The mean time interval between the two MO samples (blood sampling before and during therapy) was 9.4±1.8 months (mean±SEM; range 4-13.5 months), the mean age 50.3±3.9 years (range 39-70), and the mean disease duration 18.6±5.3 years (range 4-38). As controls, healthy individuals were recruited (n=7; 6 females, 1 male; mean age 36.1±7.4 years). RA patients RA1-RA84 were recruited from the Rheumatology Clinic of the Charité University Clinic, the Rheumaklinik of the Charité in Berlin-Buch, and from the Schlossparklinik in Berlin.

Separation of Peripheral Blood Mononuclear Cells, Purification of Monocytes, RNA Isolation

[0170] Peripheral blood (30 to 35 ml) was obtained by venopuncture, immediately stored in heparin-containing vacutainers (Beckton-Dickinson, Rutherford, N.J., USA), and cooled to 4° C. Blood samples were subjected to a Ficoll-Hypaque gradient (d=1.077 g/ml; Biochrom, Berlin, Germany). To enrich MO, negative selection magnetic cell sorting (MACS; Miltenyi; Bergisch Gladbach, Germany) was subsequently applied. Successful purification of MO (purity of 83-90%; 1.3-3.2×10⁶ MO/patient) was validated by FACS analysis using CD14 and CD45 antibodies (Beckman-Coulter, Krefeld, Germany). In all cases, purified MO showed >98% vitality using propidiumiodide staining (Pharmingen, San-Diego, Calif., USA). MO preparation was performed at 4° C. After purification, MO were lysed in RLT lysis buffer and total RNA was isolated using the RNeasy mini elute kit (Quiagen, Düsseldorf, Germany; yield 1.5-3.2 µg/sample). Ouantification and quality control of RNA was performed at 260/280 nm using a Bioanalyzer 2100 unit (Agilent, Palo Alto, Calif., USA).

RNA Amplification and Labeling

[0171] For target synthesis, 500 ng of total RNA were amplified using the standard protocol of the manufacturer

(Affymetrix®, Palo Alto, Calif., USA) and the Megascript kit (Ambion, Camhridgeshire, UK).

Biotin-Labeling of cRNA and Gene-Chip Hybridization

[0172] Biotinylated cRNA target was generated from amplified cRNAs using the Bioarray high-yield transcription kit (Enzo, New York, N.Y., USA). Samples were hybridized to Affymetrix® test and HG-U133A GeneChip arrays.

[0173] Following washing and staining, arrays were scanned twice at 3 µm resolution using a confocal scanner with an argon laser instrument (Agilent® G2500A GeneArray Scanner; Agilent, CA, USA).

Bioinformatic Analysis of Differentially Expressed Genes in ND and RA Patients Pre- and Post Anti-TNF α Treatment

[0174] All GeneChips were analyzed for signal calculation and pairwise comparisons using the GCOS 1.4 software package with standard settings provided by Affymetrix®. Scaling was performed to a target value of 150 and normalization was set to "1". Pairwise comparison data were grouped to generate a percentage level of increased and decreased comparisons. Fold-changes were calculated from the mean of the SLR values in pairwise comparisons. Filtering was performed on the basis of "increased/decreased" comparisons with a percentage cutoff as indicated in the results. For hierarchical clustering, the software tool "Gene Expression Similarity Investigation Suite" (Genesis; Sturn, A. et al. (2002) Bioinformatics 18:207-208; http://genome. tugraz.at/Software/GenesisCenter.html) was applied using normalized signal intensities, Pearson distance correlation, and complete linkage clustering. Prediction analysis was performed using the PAM software (http://www.bioconductor. org; Khan, J. et al. (2001) Nat. Med. 7:673-679).

Data Sets of Publication

[0175] The complete ASCI-file datasets have been deposited in the microarray GEO database (http://www.ncbi.nlm.nih.gov/geo/).

TaqMan® Real Time PCR

[0176] Real-time PCR (RT-PC) was performed using a TaqMan® 7500 system and pre-designed TaqMan® low density gene expression primers (Applied Biosystems; Foster City, Calif., USA) or, in the case of CD11c, the primer Hs01015072_g1 (commercially available from Applied Biosystems) in a Bio-Rad iQ real time PCR system (Icycler; Bio-Rad; München, Germany). The housekeeping gene GAPDH was used for normalization of the cDNA content. Quantification was performed using the SDS 2.2.0 software (Applied Biosystems); results were expressed as relative quantities of the logarithm of the $\Delta\Delta$ CT values (log RQ), as the relative quantity of expression (RQ; fold-change in comparison to normal donor expression), or as the % expression as normalized to GAPDH.

Literature-Associated Pathway Analysis Using Ingenuity

[0177] Gene ontology and gene interaction analyses were executed using the Ingenuity® Pathway analysis tool v.4.0 (Ingenuity, Redwood City, Calif., USA; Jenssen, T. K. et al. (2001) *Nat. Genet.* 28:21-28; http://www.ingenuity.com). Highest scoring neighborhood analysis of literature-based gene connections was performed by comparing up- and downregulated genes in anti-TNFα responders and non-responders (pre- and post-treatment). Significantly regulated

genes in both comparisons were merged from the networks 1 to 5, complemented by transcription factors and finally overlayed with their relative expression values.

Expression-Based Pathway Analysis Using Kyoto Encyclopedia of Genes and Genomes (KEGG)

[0178] The KEGG pathway analysis (Kanehisa, M. and Bork, P. (2003) *Nat. Genet.* 33:305-310) was performed using selected genes from the comparison of microarray data in responders and non-responders either pre- or post-treatment with anti-TNF α . Upregulated genes and downregulated genes within the illustrated pathways were color-coded in a gradient fashion (SLR 0.5 to \ge 1.5). A total of 4 pathways out of the 8 most highly ranked pathways were selected for illustration

Statistical Analysis

[0179] The non-parametric Mann-Whitney U test was applied to analyze differences between data from RA patients and normal donors, from untreated and anti-TNFα-treated RA patients, and from responders and non-responders to anti-TNFα-therapy. Correlation analyses between experimental and clinical/laboratory parameters of the patients were performed using the Pearson test and the software SPSS 13.0^{TM} (SPSS Inc., Chicago, Ill., USA). For the U test, statistically significant differences were accepted for P \leq 0.05; for correlation analyses, the acceptance level was reduced to P \leq 0.01 to account for multiple comparisons.

Example 2

Clinical and Laboratory Assessments for RA Patients and Normal Donors

[0180] Two of the seven anti-TNFα-treated RA patients used for microarray analysis, i.e., patients RA4 and RA6, were non-responders to therapy according to the ACR improvement criteria (\leq continuous ACR 30 score). In general, this was also reflected in the respective percent-reduction of other clinical parameters of local or systemic inflammation. The group of seven RA patients employed for microarray analysis in the present study constituted a representative RA cohort, as demonstrated by well-known correlations among clinical parameters pre- and post-anti-TNFα treatment, as summarized in Table 2.

[0181] The identification of patients RA4 and RA6 as nonresponders was also confirmed by hierarchical clustering of clinical parameters.

Example 3

Gene Expression Profiling and Analysis

Differential Gene Expression in Responders Versus Non-Responders to Anti-TNFα-Therapy

[0182] A total of 119 differentially-expressed genes was identified by comparing RA and normal donors (ND; n=7 each; total of 49 comparisons). Hierarchical clustering of ND, as well as RA patients pre- and post-treatment with these genes also identified 5 responders and 2 non-responders (RAantiTNF4 and RAantiTNF6).

[0183] In order to select therapeutically relevant genes, a subpopulation of 51 differentially-expressed genes was then identified by the simultaneous comparison between RA versus normal donors (ND; total of 49 comparisons) and RA

responders (n=5) pre- versus post-anti-TNF α therapy (25 comparisons). These genes showed an increase or decrease of the signal log ratio (SLR; between -4.36 and 4.61) in >70% of the pair-wise comparisons between RA and ND. These genes are summarized in Table 3.

[0184] Hierarchical clustering with these genes resulted in precise (100%) classification of ND, RA patients pre-treatment, and clinically-defined responders (≧continuous ACR score 40; clustered as ND) or non-responders (≦continuous ACR score 30; clustered as RA; note RAantiTNF4 and RAantiTNF6). This was confirmed by supervised pattern discovery using prediction analysis of microarrays (PAM analysis) at a threshold value of 4.3 in order to minimize the misclassification error. Table 4 summarizes the results of the PAM analysis, showing 49 selected genes, five of them overlapping with genes listed in Table 3. In this case, both non-responders (RAantiTNF4 and RAantiTNF6) were classified as RA patients, whereas the responders, RAantiTNF1-3, RAantiTNF5, and RAantiTNF7, were classified either as normals or as anti-TNFa-treated RA patients. Notably, ND showed the lowest misclassification error at the threshold value (0.00; i.e., the highest similarity among individuals), followed by pre-treatment RA patients (0.14), and anti-TNFα-treated RA patients (0.42).

[0185] Identification of responders/non-responders was also confirmed by hierarchical clustering of RA patients post-treatment. A total of 117 genes differentially expressed in RA responders versus RA non-responders was identified in post-anti-TNF α therapy samples, which showed an increase or decrease in 100% of the respective pair-wise comparisons (total of 10 comparisons). The 117 genes identified in this analysis are summarized in Table 5, three of which genes overlap with the genes summarized in Table 3. Hierarchical clustering with these genes resulted in precise (100%) classification of responders and non-responders to therapy.

[0186] A number of the differentially-expressed genes showed highly significant correlations with clinical or laboratory parameters pre- and/or post-anti-TNF α treatment, indicating a potential clinical relevance of the genes and contributing to the selection of genes for validation with TaqMan® real-time RT-PCR. These genes are summarized in Table 6.

Example 4

Real-Time RT-PCR Validation of Genes Differentiating Responders and Non-Responders

[0187] Sixteen genes with a likely pathogenetic importance in RA (and 6 control genes) from Affymetrix® gene expression profiling were selected for validation by TaqMan® realtime RT-PCR (n=10 anti-TNFα-treated RA patients prior to therapy; n=14 ND). The RT-PCR results confirmed the results of Affymetrix® gene expression profiling for 17 of 22 genes (approx. 77%), summarized in Table 7. This applied to genes regarded as differentially expressed in RA versus ND by Affymetrix® analysis (decreased: <-70%; increased: >70%) and to equally expressed control genes. By real-time RT-PCR, 18 genes showed significantly differential expression $(p \le 0.000 \text{ for } 7 \text{ genes}; p \le 0.041 \text{ for the remaining}) \text{ in MO}$ from RA patients responding to anti-TNFα therapy versus ND, including genes 10 upregulated in RA (Amphiregulin, Charcot-Leyden crystal protein, TNFα-induced protein 6, thrombomodulin, membrane-spanning 4-domains, subfamily A—member 4, S100 calcium binding protein A1, TNFα, IL-1β, lipoyltransferase 1, and interferon regulatory protein 1), as well as 8 genes downregulated in RA (Uncharacterized hypothalamus protein HT007, MHC class II HLA-DR-alpha, hypothetical protein L0054103, proteasome subunit beta type 7 precursor, protein KIAA0174, microsomal signal peptidase 18 kDa subunit, ring zinc finger protein 361, and protein phosphatase 1, catalytic subunit, beta isoform). However, the expression for these genes showed no significant differences for the direct comparison between RA responders and non-responders to anti-TNF α therapy.

[0188] The potential clinical relevance of some of the differentially expressed genes is underlined by a significant correlation with the ACR response at different time points during anti-TNF α therapy, as summarized in Table 8.

[0189] Validation of the 22 selected genes by TaqMan® real-time RT-PCR confirmed the results of Affymetrix® gene expression profiling for 17 of 22 genes (approx. 77% true positives or negatives), in accordance with the rates reported in other gene expression studies and therefore underlining the validity of the present data. The 18 genes showing significantly differential expression in MO from RA patients responding to anti-TNF α therapy versus ND included several genes with a likely pathogenetic importance in RA (e.g., amphiregulin, TNF α -induced protein 6, thrombomodulin, membrane-spanning 4-domains, subfamily A—member 4, S100 calcium binding protein A1, TNF α , IL-1 β , lipoyltransferase 1, interferon regulatory protein 1, MHC class II HLA-DR-alpha).

Example 5

Gene Expression Profiling and Analysis

Differential Gene Expression in Responders Versus Non-Responders Prior to Anti-TNF α -Therapy (Predictive Genes)

[0190] Using a threshold of ≥80% for the pairwise comparisons between future RA responders and future RA nonresponders prior to anti-TNFα therapy, a total of 82 predictive genes was identified (11 genes for a threshold of ≥90%; 3 genes for 100%). These genes are summarized in Table 9. The latter group (100%) consisted of 2 known proteins (Homo sapiens predicted osteoblast protein (GS3786); integrin alpha-X (antigen CD11c) and an unknown protein (Homo sapiens hypothetical protein FLJ10134). In particular the antigen CD11e appears highly interesting, since it is a surface molecule on human MO (and other cells of the myelomonocytic lineage), and since it has known inflammatory functions. Hierarchical clustering with the selected genes resulted again in precise (100%) predictive classification of future responders and non-responders to therapy. Marginal co-clustering of the patient RA5 with the non-responders RA4 and RA6 at the threshold values 80% and 100% possibly identified RA5 as a 'weak' responder, as also indicated by a marginal position in the hierarchical clustering of clinical parameters.

[0191] Interestingly, future responders to anti-TNFα-therapy (when directly compared to non-responders) showed a pattern shift from the recently described 'inflammatory' MO to 'resident' MO subsets (Gordon, S. et al. (2005) *Nat. Immunol.* 5:953-963) both prior to therapy and post-treatment. Although most of the individual molecules showed an identical pattern shift in both pre-treatment and post-treatment comparisons, in particular the activating (CD16a,b) and inhibiting Fcγ-receptors (CD32) displayed an opposite

behavior. This pattern shift was observed despite the fact that all pre-treatment or post-treatment comparisons between RA patients (all, future responders, future non-responders) and ND indicated a dominance of 'inflammatory' MO in the respective RA groups. Post-treatment, strikingly, responders to anti-TNF α -therapy became barely distinguishable from ND in contrast to non-responders, which still showed a clear 'inflammatory' predominance. These results indicate that successful anti-TNF α -therapy acts by blocking TNF α signaling via TNF α -receptors 1 and 2 and by subsequent induction of a major change in the composition of pro-inflammatory and other MO subsets.

Example 6

Real-Time RT-PCR Validation of Predictive CD11c

[0192] TaqMan® real-time RT-PCR confirmed the discrimination of future RA responders (n=15) from future non-responders (n=12) to anti-TNF monotherapy (at the level of continuous ACR score 30) on the basis of their CD11c mRNA expression in monocytes.

[0193] TaqMan® real-time RT-PCR confirmed the separation of future RA responders n=55 from future non-responders n=12 to anti-TNFα monotherapy on the basis of their CD11c mRNA expression in MO. The results are summarized in the bar graph of FIG. 1. This clear separation was lost in the case of combination therapy with anti-TNFa/MTX, possibly due to a differential importance of the CD11c mRNA expression for the anti-TNF α and MTX components. [0194] Of the 3 genes identified by pairwise comparison between RA responders and RA non-responders prior to treatment at the level of 100% (and confirmed by TaqMan® real-time RT-PCR), the antigen CD11c appears of particular interest, since it is expressed on the surface of human MO (and other cells of the myelomonocytic lineage, e.g. dendritic cells), and since it has known functions in inflammatory reactions (e.g., as the complement receptor 4) and cell adhesion. [0195] The validity of CD11c as a predictive biomarker is further underlined by a significant correlation (r=0.651, P=<0.0001, n=27) between the CD11c expression prior to therapy and the future percentage of the ACR response, illustrated in the graph of FIG. 2.

[0196] Except for 1 RA patient with a borderline ACR response of 30 and a CD11c mRNA level directly at the distinction threshold (who was therefore classified as a false negative), the threshold level (40%) almost fully distinguished future responders from nonresponders (100% specificity, 94% sensitivity, and 96% power). This clear separation was lost in the case of combination therapy with anti-TNF/ methotrexate (MTX), possibly owing to a differential importance of the CD11c mRNA expression for the anti-TNF and MTX treatment components. This was further underlined by the fact that: i) future responders to MTX monotherapy did not significantly differ in their CD11c mRNA expression level from future nonresponders to MTX monotherapy; and ii) there was no significant correlation between the future ACR response of RA patients treated with MTX monotherapy and their CD11c mRNA expression (data not shown). [0197] Strikingly, this was true not only for the continuous ACR score, but also for the clinically applied, discrete ACR criteria.

[0198] A significant correlation (r=0.656, P=<0.0001, n=27) was observed between CD11c expression and the future percentage of strict ACR response, illustrated in the

graph in FIG. 3. This finding complements and expands previous reports on the identification of molecules capable of predicting a future response to anti-TNF α therapy (Lequerre, T. et al. (2006) *Arthritis Res. Ther.* 8:R105; Toh, M. L. et al. (2006) *Arthritis Rheum.* 54:2109-2118).

Example 7

Ingenuity® Pathway Analysis

[0199] Ingenuity® pathway analysis of the genes in Tables 3 and 5 indicated a direct or indirect influence of anti-TNF α therapy on several molecules thought to be relevant for the pathogenesis and/or severity of RA, e.g., HLA-DMA/B (Morel, J. et al. (2004) Ann. Rheum. Dis. 63:1581-1586), CD69 (Marzio, R. et al. (1999) Immunopharmacol. Immunotoxicol. 2:565-582) thrombomodulin (Cobankara, V. et al. (2004) Clin. Rheumatol. 23:430-434), membrane-spanning 4-domains, subfamily A—member 4 (Fujikado, N. et al. (2006) Arthritis Res. Ther. 8:1-13), and forkhead box 03a (Jonsson, H. et al. (2005) *Nat. Med.* 11:666-671). The present approach, therefore, represents a powerful tool to identify gene regulation patterns applicable for diagnosis, as well as for therapy stratification and monitoring in rheumatic diseases, in particular in view of the fact that blood MO are much more easily available than synovial tissue samples. This is further supported by the fact that a high number of individual genes show significant correlations with clinical parameters in RA patients pre- and/or post-anti-TNFα treatment (see Table 6). [0200] Pairwise comparison between RA responders and RA non-responders prior to treatment yielded a number of genes suitable for the prediction of a future response to anti-TNF α therapy (82 genes for a threshold of $\ge 80\%$; 11 genes for ≥90%; 3 genes for 100%; summarized in Table 9), resulting in exact classification of future responders and non-responders upon hierarchical clustering. Using all genes differentially expressed in the above comparison at a threshold level of 70% (256 pre-treatment; 1295 post-treatment) for Ingenuity® pathway analysis, the differences between responders and non-responders either pre-treatment or posttreatment were concentrated in the functional gene ontology terms cellular movement, haematological system development, immune response, cell-to-cell signaling and interaction, as well as immunological disease.

[0201] In particular, numerous relevant mediators were identified: i) pro-inflammatory cytokines (e.g., interleukin-8 [IL8], chemokine (C—C motif) ligand 5 [CCL5], chemokine

(C-X-C motif) ligand 5 [CXCL5], and chemokine (C—X—C motif) ligand 10 [CXCL10]); ii) pro-destructive enzymes (e.g., matrix metalloproteinase 9 [MMP9]); iii) adhesion molecules and Fcy-receptors (galectin-8 [LGALS8], integrin alpha-X [ITGAX] or CD11c, Fc-gamma receptor IIb [FCGR2B] or CD32, CD86 [CD86] and platelet/ endothelial cell adhesion molecule 1 [PECAM1] or CD31); iv) signal transduction molecules (e.g., protein kinase B [AKT1], apoptosis regulator Bel-2 [BCL2], p21-activated protein kinase 1 [PAK1]); and v) transcription factors (e.g., Mad-related protein 2 [SMAD2], interferon regulatory factor 1 [IRF1], c-myb [MYB], early growth response protein 1 [EGR1], signal transducer and activator of transcription 1 [STAT1], and nuclear factor NF-κB 1 [NFKB1]; for the remaining abbreviations see the respective gene cards [http:// www.genecards.org/index.shtml]). These molecules were differentially expressed between RA responders and RA nonresponders either pre-treatment or post-treatment and in some cases even inverted their expression upon anti-TNF α -therapy (see interleukin-8 receptor beta [IL8RB], Amyloid-beta A4 precursor [APP]; overexpressed in RA responders pre-treatment and underexpressed post-treatment). Similar opposite variations in transcript levels between RA responders and RA non-responders have recently been reported when comparing baseline to 3-month results (Lequerre, T. et al. (2006) Arthritis Res. Ther. 8:R105).

[0202] Most strikingly, the transcription of TNF α itself, as well the transcription of members of the subsequent NFKB-pathway (NFKB1 and inhibitor of NF- κ B [IKBKB]), was upregulated in RA responders post-treatment. This previously unreported finding at first sight questions the central pro-inflammatory role of TNF α in RA. However, several caveats should be considered: i) The mRNA expression levels of TNF α measured in the present study may not be proportional to the levels of circulating TNF α protein and/or bioactivity, the latter apparently predictive of the clinical response to TNF α inhibition (Marotte, H. et al. (2005) *Arthritis Res. Ther.* 7:R149-155); ii) TNF α , in addition to its well-established pro-inflammatory properties, may also exhibit phase-dependent immunosuppressive properties (Kassiotis, G. et al. (2001) *J. Exp. Med.* 193:427-434).

[0203] Several interesting pathways with potential importance for the mechanisms underlying susceptibility to anti-TNF α -therapy were identified by KEGG pathway analysis; including Apotosis and the MAPK pathways.

TABLE 1

Clinical parameters of patients before and after anti-TNF treatment										
Patient	Methods Affymetrix (A) real-time (R/P)	Duration of treatment, mo	Disease duration, y	Age,	Gender	RF	Morning stiffness, min (% reduction)	Swollen joint count 68 (% reduction)	Painful joint count 68 (% reduction)	
RA1-1110006211	A/P	0	4	52	F	+	320	10	19	
RA1-aTNF	A	13.5					15 (95)	3 (70)	8 (58)	
RA2-1110005181	A/P	0	9	53	F	+	180	16	50	
RA2-aTNF	A	6					0 (100)	1 (94)	19 (62)	
RA3-1110005291	A/P	0	18	39	F	+	0	10	28	
RA3-aTNF	\mathbf{A}	5.5					0 (0)	2 (80)	8 (29)	
RA4-1110005031	A/P	0	12	47	F	+	720	20	43	
RA4-aTNF	A	17					60 (92)	19 (5)	35 (19)	
RA5-1110004141	A/P	0	38	70	F	+	120	11	56	
RA5-aTNF	\mathbf{A}	15					120(0)	2 (82)	61 (0)	
RA6-1110004131	A/P	0	38	51	F	+	60	12	27	

TABLE 1-continued

Clinical parameters of patients before and after anti-TNF treatment									
RA6-aTNF	A	4					60 (0)	4 (67)	28 (0)
RA7-1110006221	A/P	0	11	40	F	+	150	18	44
RA7-aTNF	A	4.5					10 (93)	5 (72)	25 (43)
RA8-06507	R	0	<1	28	F	-	120	14	17
RA8-aTNF/MTX RA9-06513	R R	6 0	1	53	F	_	0 (100) 120	0 (100)	3 (82) 20
RA9-aTNF/MTX	R R	4.5	1	33	Г	_	15 (87)	16 12 (25)	16 (20)
RA10-05602	R	0	1	48	F	+	180	8	40
RA10-MTX	R	3.5		10	•		240 (0)	10 (0)	29 (27)
RA11-05610	R/P	0	<1	38	F	_	360	14	22
RA11-aTNF	R	6					30 (92)	3 (79)	9 (59)
RA12-05609	R/P	0	1	63	F	+	60	17	29
RA12-aTNF	R	6	2	4.4			10 (83)	5 (71)	9 (69)
RA13-05608 RA13-aTNF/MTX	R R	0 6	2	44	F	+	45 0 (100)	12 0 (100)	24 1 (96)
RA14-05612	R/P	0	1	29	F	+	60	8	11
RA14-aTNF/MTX	R	6	1	27	•		0 (100)	0 (100)	0 (100)
RA15-06504	R/P	ō	2	47	F	+	60	10	23
RA15-aTNF	R	6					20 (67)	2 (80)	3 (87)
RA16-06308	R/P	0	<1	60	F	+	120	17	29
RA16-aTNF/MTX	R	6					15 (87)	1 (94)	16 (45)
RA17-06516	R	0	1	36	F	+	30	17	17
RA11-aTNF	R/P	6			-		15 (50)	11 (35)	0 (100)
RA18-06309	R	0	1	83	F	-	30	11	27
RA18-aTNF/MTX RA19-05613	R R/P	6 0	2	63	F		0 (100) 120	0 (100) 25	0 (100)
RA19-03013	R	6	2	0.5	Г	+	15 (87)	9 (64)	43 17 (60)
RA20-06304	R/P	0	<1	50	F	_	60	12	29
RA20-aTNF	R	6	-1	50	•		0 (100)	2 (83)	5 (83)
RA21-06514	R/P	Ö	2	56	F	_	30	21	52
RA21-aTNF/MTX	R	6					30(0)	15 (29)	16 (69)
RA22-05606	R/P	0	<1	36	F	+	60	12	22
RA22-aTNF/MTX	R	6					0 (100)	2 (83)	9 (83)
RA23-06306	R/P	0	1	34	F	+	30	13	27
RA23-aTNF	R	3		10			30 (0)	18 (0)	27 (0)
RA24-06305 RA24-MTX	R R	0 6	n.d.	18	F	+	30 60 (0)	14 2 (86)	20
RA25-06515	R/P	0	<1	54	M	_	45	2 (80)	8 (60) 43
RA25-aTNF	R	6	~1	27	141		20 (66)	7 (68)	28 (35)
RA26-06506	R/P	Ö	1	50	F	_	60	9	23
RA26-aTNF	R	6					120(0)	20(0)	45 (0)
RA27-05601	R/P	0	1	42	F	+	60	8	24
RA27-aTNF	R	6.5					60 (0)	7 (12)	30 (0)
RA28-1110004171	P	0	n.d.	34	F	+	60	20	47
RA28-aTNF	D	3.5	1.1	62			0 (100)	4 (80)	4 (91)
RA29-1110011271 RA29-aTNF/MTX	P	0 0.5	11	62	F	+	120 120 (0)	8 9 (0)	35 44 (0)
RA30-1110010101	P	0.5	7	35	F	+	120 (0)	8	12
RA30-aTNF/MTX	1	10	r	33			0 (100)	2 (75)	7 (42)
RA31-1110004121	P	0	13	33	F	+	30	11	27
RA31-aTNF		6					20 (67)	2 (82)	7 (74)
RA32-1110008092	P	0	20	43	F	+	60	14	38
RA32-aTNF		6.5					0 (100)	6 (57)	7 (72)
RA33-1110005121	P	0	8	61	F	-	180	19	59
RA33-aTNF	_	17.5			_		120 (66)	2 (89)	12 (81)
RA34-1110111281	P	0	12	66	F	+	90	10	5
RA34-MTX	P	12		63		_	120 (0)	8 (20)	9 (0)
RA35-1110112121 RA35-MTX	Р	0 9	6	63	F	+	180 0	8 3 (63)	20 4 (80)
RA36-1110201231	P	0	10	36	F	0	60	30	19
RA36-MTX	1	4	10	30	1	0	30 (50)	0 (100)	0 (100)
RA37-1110211051	P	o o	1	59	F	+	180	2	21
RA37-MTX		3					15 (92)	0 (100)	4 (81)
RA38-1110309012	P	0	<1	32	F	+	180	7	29
RA38-MTX		3					0 (100)	1 (85)	3 (90)
RA39-1110309122	P	0	1	26	F	+	180	6	23
RA39-MTX		3					15 (92)	1 (83)	9 (41)
RA40-1110310302	P	0	1	45	F	+	10	10	17
RA40-MTX	TD.	4	1	50	т-		0 (100)	0 (100)	2 (88)
RA41-1110411251	P	0	<1	58	F	0	180	6 (100)	16
RA41-MTX RA42-1110409071	P	3 0	1	52	F	0	0 (100) 0	0 (100) 9	2 (88) 4
RA42-1110409071	Г	3	1	32	I.	V	0 (0)	0 (100)	0 (100)
RA43-1110409141	P	0	<1	58	M	+	10	8	22
1110 1071 11	*	~			~**				

TABLE 1-continued

Clinical parameters of patients before and after anti-TNF treatment									
D 442 3 (TV)		•	icis of path	onts octor	c and ar	cer anti-		0 (100)	5 (77)
RA43-MTX RA44-1110409223	P	3 0	1	67	F	0	10 (0) 60	0 (100) 12	5 (77) 20
RA44-MTX	P	3	~1	44	F	0	0 (100)	0 (100)	4 (80)
RA45-1110411291 RA45-MTX	P	3	<1	44	7	0	30 0 (100)	25 9 (64)	43 17 (60)
RA46-1110602212	P	0	10	45	F	+	120	3	13
RA46-aTNF/MTX RA47-1110503081	P	6 0	21	57	F	+	120 (0) 360	0 (100) 8	21 (0) 10
RA47-TNF	1	6	21	31	1	т	180 (50)	7 (14)	11 (0)
RA48-1110703082	P	0	7	60	F	+	240	0	10
RA48-TNF RA49-1110309122	P	6 0	1	26	F	+	120 (50) 180	0 (0) 6	5 (50) 24
RA49-MTX	_	9					15 (92)	1 (83)	9 (62)
RA50-1100308202 RA50-MTX	P	0	6	63	F	+	0 0 (0)	0 1 (0)	18 2 (89)
RA51-1110309111	P	0	2	45	M	+	180	16	30
RA51-MTX	P	3 0	1	62	F		120 (33) 0	9 (44) 0	24 (20)
RA52-1110401081 RA52-MTX	Г	5.5	1	02	Г	+	0 (0)	0 (0)	18 0 (100)
RA53-1110406011	P	0	1	61	F	+	30	10	33
RA53-MTX RA54-1110406112	P	3 0	3	61	M	+	5 (83) 10	0 (100) 6	1 (97) 22
RA54-MTX		3	5	01	111	•	0 (100)	0 (100)	5 (77)
RA55-1110406111	P	0	<1	57	F	+	60	2	12
RA55-MTX RA56-1110407131	P	0	1	63	F	+	0 (100) 30	0 (100) 9	2 (83) 30
RA56-MTX	_	3					0 (100)	0 (100)	6 (80)
RA57-1110407281 RA57-MTX	P	0	2	56	F	+	0 (0)	7 0 (100)	19 2 (89)
RA58-1110409201	P	0	1	61	F	+	10	5	16
RA58-MTX RA59-1110410271	P	3 0	6	35	M		0 (100) 15	0 (100) 0	4 (75) 5
RA59-MTX	Г	3	Ü	33	IVI	+	0 (100)	0 (0)	2 (60)
RA60-1110503231	P	0	1	71	F	+	30	6	23
RA60-MTX RA61-1110504061	P	3	1	51	F	+	0 (100) 45	0 (100) 12	5 (78) 27
RA61-MTX		3	-				0 (100)	0 (100)	0 (100)
RA62-1110505301 RA62-MTX	P	0	1	59	F	0	120 0 (100)	2 0 (100)	9 12 (0)
RA63-1110507281	P	0	2	43	F	+	30	10	17
RA63-MTX	D	3	~1	60	E		0 (100)	6 (40)	15 (12)
RA64-1110511281 RA64-MTX	P	0	<1	69	F	+	90 0 (100)	7 1 (86)	21 2 (90)
RA65-1110405273	P	0	5	55	F	+	0	0	2
RA65-aTNF/MTX RA66-1110502091	P	4	36	62	F	+	10 (0) 30	6 (0) 13	16 (0) 14
RA66-aTNF/MTX		30				•	15 (50)	2 (85)	14 (0)
RA67-1110507261 RA67-aTNF/MTX	P	0 25	25	43	F	+	0 0 (0)	4 0 (100)	5 1 (80)
RA68-1110603141	P	0	12	72	F	+	30	7	7
RA68-aTNF	D	12	2	22			60 (0)	0 (100)	0 (100)
RA69-1110510181 RA69-aTNF/MTX	P	0 12	2	33	F	+	50 0 (100)	6 0 (100)	6 0 (100)
RA70-06303	P	0	1	53	F	+	30	14	17
RA70-aTNF/MTX RA71-06516	P	6 0	3	79	F	+	10 (66) 30	0 (100) 17	0 (100) 17
RA71-TNF		6		,,,			15 (50)	0 (100)	11 (35)
RA72-06510 RA72-TNF	P	0 6	3	68	F	+	10 10 (0)	25 2 (92)	34 0 (100)
RA73-06309	P	0	1	36	F	0	45	2 (92) 11	27
RA73-TNF/MTX		6			-		0 (100)	0 (100)	0 (100)
RA74-06310 RA74-TNF	P	0 12	3	48	F	0	360 15	14 6 (57)	22 14 (36)
RA75-06307	P	0	2	51	F	+	360	16	22
RA75-MTX RA76-06311	P	6 0	3	43	F	+	0 (100) 120	2 (87) 14	3 (86) 36
RA76-06311 RA76-TNF	Г	3	3	+3	I.	+	0 (100)	0 (100)	0 (100)
RA77-06513	P	0	1	53	F	0	120	16	20
RA77-TNF/MTX RA78-06512	P	4.5 0	1	83	F	0	15 (87) 30	12 (25) 15	16 (20) 53
RA78-MTX		5.5				-	15 (50)	27 (0)	63 (0)
RA79-06514 RA79-TNF/MTX	P	0 6	2	56	F	0	30 30 (0)	21 15 (29)	52 16 (69)
RA80-1110505241	P	0	4	47	F	+	24	5	9

TABLE 1-continued

	Clinical p	parameters of patient	s before and after	anti-TNF treatmer	nt	
RA80-TNF/MTX	3	1.5		36 (0)	4 (20)	4 (56)
RA81-06305	P 0		18 F	+ 30	8	20
RA81-MTX	6			60 (0)	2 (75)	14 (70)
RA82-05602	P 0		48 F	+ 180	29	40
RA82-MTX RA83-05607	P 0	5.5) 3	61 M	240 (0) + 120	10 (66) 25	8 (20) 40
RA83-MTX	8		01 141	0 (100)	3 (88)	3 (92)
RA84-06302	P 0		42 F	+ 60	16	39
RA84-MTX	6	i		10 (83)	6 (62)	18 (51)
						ACR
		ESR,	CRP,			improvement
		mm/hr	mg/L	HAQ score	DAS28	(% continuous
	Patient	(% reduction)	(% reduction)	(% reduction)	(% reduction)	score)
	RA1-1110006211	69	57.5	2.0	6.0	
	RA1-aTNF	8 (88)	2.0 (97)	1.3 (35)	3.1 (48)	50
	RA2-1110005181	46	52.2	1.6	6.3	
	RA2-aTNF	12 (74)	2.8 (94)	1.0 (37)	2.9 (54)	60
	RA3-1110005291 RA3-aTNF	72 16 (78)	61.1 3.9 (93)	1.5 1.0 (33)	6.1 4.1 (33)	60
	RA4-1110005031	58	85.3	2.1	6.9	00
	RA4-aTNF	40 (31)	20.0 (77)	1.3 (38)	6.5 (6)	0
	RA5-1110004141	80	41.5	2.1	6.3	
	RA5-aTNF	11 (86)	4.5 (88)	1.4 (33)	4.0 (37)	50
	RA6-1110004131	46	36.0	1.6	5.9	10
	RA6-aTNF RA7-1110006221	32 (30) 30	22.3 (39) 17.3	1.6 (0) 1.9	5.1 (14) 6.0	10
	RA1-aTNF	14 (53)	11.3 (35)	1.3 (32)	4.1 (32)	40
	RA8-06507	30	<3.5	1.6	6.1	
	RA8-aTNF/MTX	4 (87)	<3.5 (0)	0.0 (100)	2.4 (61)	70
	RA9-06513	34	<3.5	1.3	6.2	
	RA9-aTNF/MTX	14 (59)	<3.5 (0)	1.4 (0)	5.2 (26)	20
	RA10-05602 RA10-MTX	31 39 (0)	<3.5 <3.5 (0)	2.2 2.3 (0)	7.1 6.8 (4)	0
	RA11-05610	40	39.2	1.4	6.5	O
	RA11-aTNF	45 (0)	36.4 (7)	0.3 (79)	4.3 (34)	50
	RA12-05609	22	14.3	0.5	6.6	
	RA12-aTNF	30 (0)	<3.5 (100)	0.3 (40)	4.3 (35)	50
	RA13-05608	32	5.1	0.8	6.1	00
	RA13-aTNF/MTX RA14-05612	Z 28 (12) 35	<3.5 (100) 13.1	0.0 (100) 1.0	2.7 (56) 5.0	90
	RA14-03012		<3.5 (100)	0.0 (100)	1.7 (66)	100
	RA15-06504	28	<3.5	1.8	6.3	
	RA15-aTNF	24 (14)	4.1(0)	1.3 (28)	3.5 (44)	50
	RA16-06308	56	<3.5	1.8	7.3	
	RA16-aTNF/MTX	\ /	<3.5 (0)	1.3 (28)	4.8 (44)	40
	RA17-06516 RA17-aTNF	80 24 (30)	22.8 27.5 (0)	1.8 0.6 (67)	6.5 3.2 (51)	30
	RA18-06309	24 (30)	39.4	1.3	6.5	30
	RA18-aTNF/MTX		8.5 (78)	0.6 (54)	1.9 (71)	70
	RA19-05613	53	31.5	2.3	8.5	
	RA19-aTNF	85 (0)	40.0 (0)	1.3 (43)	5.6 (34)	60
	RA20-06304	24	10.0	1.0	6.6	20
	RA20-aTNF RA21-06514	16 (33) 34	10.0 (0) <3.5	1.0 (0) 1.4	3.8 (42) 8.3	30
	RA21-aTNF/MTX		<3.5 (0)	0.9 (36)	5.4 (35)	20
	RA22-05606	40	23.1	2.4	6.2	
	RA22-aTNF/MTX		7.3 (68)	0.8 (67)	4.2 (32)	50
	RA23-06306	90	61.1	2.1	7.1	
	RA23-aTNF	62 (33)	53.4 (23)	2.0 (5)	7.2 (0)	0
	RA24-06305 RA24-MTX	22 20 (10)	29.1 31.3 (0)	0.3 0.1 (33)	4.7 4.1 (13)	20
	RA25-06515	34	<3.5	1.0	8.0	20
	RA25-aTNF	9 (74)	<3.5 (0)	1.6 (0)	5.8 (27)	0
		16	<3.5	1.5	5.9	
	RA26-06506	10		4 0 (0)	9.2 (0)	0
	RA26-aTNF	50 (0)	<3.5 (0)	1.9(0)	8.3 (0)	U
	RA26-aTNF RA27-05601	50 (0) 30	6.8	1.1	5.8	
	RA26-aTNF RA27-05601 RA27-aTNF	50 (0) 30 58 (0)	6.8 16.9 (0)	1.1 1.5 (0)	5.8 6.7 (0)	0
	RA26-aTNF RA27-05601 RA27-aTNF RA28-111000417	50 (0) 30 58 (0) 1 30	6.8 16.9 (0) 7.0	1.1 1.5 (0) 1.8	5.8 6.7 (0) 6.2	0
	RA26-aTNF RA27-05601 RA27-aTNF RA28-111000417 RA28-aTNF	50 (0) 30 58 (0) 1 30 16 (47)	6.8 16.9 (0) 7.0 6.9 (1)	1.1 1.5 (0) 1.8 0.4 (78)	5.8 6.7 (0) 6.2 3.6 (42)	
	RA26-aTNF RA27-05601 RA27-aTNF RA28-111000417	50 (0) 30 58 (0) 1 30 16 (47) 1 19	6.8 16.9 (0) 7.0	1.1 1.5 (0) 1.8	5.8 6.7 (0) 6.2	0

TABLE 1-continued

Clinical para		before and after a	anti-TNF treatme	nt	
RA30-aTNF/MTX	17 (63)	10.1 (76)	n.d.	2.6 (51)	50
RA31-1110004121	33	7.8	1.3	5.2	
RA31-aTNF	18 (45)	5.9 (24)	0.9 (31)	3.4 (35)	40
RA32-1110008092 RA32-aTNF	29 28 (3)	18.4 21.0 (0)	n.d. n.d.	6.8 3.4 (50)	50
RA33-1110005121	28 (3)	22.4	1.8	6.3	30
RA33-aTNF	26 (7)	14.0 (36)	1.9(0)	4.1 (35)	20
RA34-1110111281	18	9.0	1.43	4.29	
RA34-MTX	13 (28)	12.0 (0)	0.74 (49)	5.10 (0)	0
RA35-1110112121 RA35-MTX	17	66.0	2.67	6.3	60
RA35-M1X RA36-1110201231	12 (29) 38	<3.5 (100) 45.0	0.67 (76) 2.33	3.5 (45) 6.3	60
RA36-MTX	17 (55)	5.0 (89)	0.33 (86)	2.1 (67)	80
RA37-1110211051	27	11.0	2.44	5.5	
RA37-MTX	8 (70)	5.0 (55)	1.44 (41)	2.9 (47)	40
RA38-1110309012	20	8.1	1.11	5.4	
RA38-MTX	10 (50)	1.2 (85)	0.44 (60)	2.5 (54)	70
RA39-1110309122 RA39-MTX	101 81 (20)	33.0 44.5 (0)	2.67 2.10 (21)	6.5 5.6 (14)	20
RA40-1110310302	72	77.6	2.10 (21)	6.8	20
RA40-MTX	18 (75)	6.9 (91)	1.1 (49)	3.4 (50)	50
RA41-1110411251	17	<3.5	2.4	5.4	
RA41-MTX	12 (29)	<3.5 (0)	0 (100)	3.1 (43)	80
RA42-1110409071	37	22.0	2.1	5.7	90
RA42-MTX RA43-1110409141	5 (87) 27	6.6 (70) 32.0	0.4 (81) 2.3	1.1 (81) 5.9	80
RA43-MTX	3 (89)	4.6 (86)	2.0 (13)	1.7 (71)	70
RA44-1110409223	55	62.6	1.33	3.13	
RA44-MTX	12 (78)	3.80 (94)	1.40(0)	4.93 (0)	70
RA45-1110411291	34	18.0	1.4	4.9	
RA45-MTX	20 (41)	12.6 (30)	0 (100)	2.2 (65)	60
RA46-1110602212 RA46-aTNF/MTX	74 20 (63)	17.8 2.7 (85)	1.7 1.1 (35)	5.8 4.4 (24)	30
RA47-1110503081	74	<3.5	2.0	6.5	30
RA47-TNF	20 (0)	<3.5 (0)	2.8 (0)	6.7 (0)	0
RA48-1110703082	28	106.0	1.1	6.2	
RA48-TNF	120 (12)	83.6 (21)	1.0 (9)	4.1 (34)	0
RA49-1110309122	40	33.0 34.5 (0)	0.9	6.6	10
RA49-MTX RA50-1100308202	40 (0) 28	9.8	0.7 (22) 1.4	5.7 (14) 4.6	10
RA50-MTX	21 (25)	9.9 (0)	1.7 (0)	4.0 (13)	0
RA51-1110309111	10	4.0	2.2	6.1	
RA51-MTX	5 (50)	1.3 (77)	2.1 (5)	5.1 (16)	0
RA52-1110401081	30	6.5	1.1	4.4	00
RA52-MTX RA53-1110406011	25 (17) 10	4.8 (26) 23.0	0.1 (91) 1.78	2.3 (48) 6.4	90
RA53-HT10400011 RA53-MTX	0 (100)	3.1 (87)	0.3 (83)	2.4 (62)	80
RA54-1110406112	10	9.0	0.7	5.2	
RA54-MTX	20 (0)	16.7(0)	1.9(0)	3.3 (37)	40
RA55-1110406111	25	24.8	1.9	5.4	
RA55-MTX	12 (52) 55	6.7 (73)	0.3 (84)	2.4 (56)	80
RA56-1110407131 RA56-MTX	33 14 (75)	37.8 1.0 (97)	1.67 1.10 (34)	8.8 3.7 (58)	30
RA57-1110407281	21	3.9	1.6	5.5	50
RA57-MTX	10 (52)	<3.5 (100)	0.2 (87)	2.5 (55)	70
RA58-1110409201	20	<3.5	2.2	4.3	
RA58-MTX	14 (30)	<3.5 (0)	0.4 (82)	2.0 (53)	70
RA59-1110410271 RA59-MTX	12 25 (0)	<3.5 7.9 (0)	0.8 0.8 (0)	2.6 2.7 (0)	30
RA60-1110503231	14	5.6	0.8 (0)	5.9	30
RA60-MTX	8 (43)	4.9 (12)	0.9 (55)	3.1 (47)	40
RA61-1110504061	16	<3.5	2.5	7.0	
RA61-MTX	4 (75)	<3.5 (0)	0.4 (84)	1.0 (86)	70
RA62-1110505301	10	<3.5	2.1	4.7	40
RA62-MTX RA63-1110507281	6 (40) 68	<3.5 (0) 42.0	1.1 (48) 1.8	3.2 (26) 6.0	40
RA63-111050/281 RA63-MTX	20 (71)	42.0 33.0 (21)	1.8	4.0 (33)	30
RA64-1110511281	25	14.5	1.1 (39)	5.8	50
RA64-MTX	10 (60)	27.0 (0)	0.9 (25)	3.0 (48)	20
RA65-1110405273	6	<3.5	1.2	3.0	

TABLE 1-continued

Clinical parameters of patients before and after anti-TNF treatment									
	RA65-aTNF/MTX	12 (0)	<3.5 (0)	0.8 (33)	4.7 (0)	0			
	RA66-1110502091	10	<3.5	1.9	4.2				
	RA66-aTNF/MTX	12(0)	4.2(0)	0 (100)	4.1(2)	40			
	RA67-1110507261	32	11.4	1.7	4.4				
	RA67-aTNF/MTX	16 (50)	7.7 (32)	1.1 (35)	2.8 (36)	30			
	RA68-1110603141	72	4.8	1.3	4.7				
	RA68-aTNF	4 (94)	<3.5 (100)	0.0 (100)	2.4 (49)	30			
	RA69-1110510181	12	9.0	3.0	4.7				
	RA69-aTNF/MTX	26(0)	<3.5 (100)	1.1 (63)	2.4 (49)	80			
	RA70-06303	26	31.9	1.3	5.8				
	RA70-aTNF/MTX	6 (77)	0 (100)	0.1 (92)	1.6 (73)	70			
	RA71-06516	80	22.8	1.8	6.5				
	RA71-TNF	24 (70)	7.5 (67)	0.6 (67)	3.2 (49)	30			
	RA72-06510	80	41.6	2.1	8.2				
	RA72-TNF	58 (27)	21.4 (49)	1.5 (29)	2.6 (68)	70			
	RA73-06309	24	39.4	1.3	6.5				
	RA73-TNF/MTX	8 (75)	8.5 (78)	0.6 (54)	1.9 (71)	70			
	RA74-06310	30	21.9	3.0	8.1				
	RA74-TNF	13 (57)	14.3 (35)	2.3 (23)	2.9 (64)	50			
	RA75-06307	64	83.4	2.6	7.0				
	RA75-MTX	22 (66)	11.5 (86)	0.8 (69)	2.2 (69)	70			
	RA76-06311	32	53.1	0.8	7.0				
	RA76-TNF	8 (75)	4.9 (91)	0.1 (87)	1.7 (75)	80			
	RA77-06513	34	<3.5	1.3	6.2				
	RA77-TNF/MTX	14 (59)	<3.5 (0)	1.4(0)	5.3 (15)	20			
	RA78-06512	33	7.4	2.4	6.7				
	RA78-MTX	8 (76)	4.9 (34)	3.0 (0)	8.3 (0)	0			
	RA79-06514	34	<3.5	1.3	8.3	-			
	RA79-TNF/MTX	6 (82)	<3.5 (0)	0.9 (31)	5.4 (35)	20			
	RA80-1110505241	24	10.2	1.3	4.4				
	RA80-TNF/MTX	36 (0)	<3.5 (100)	1.1 (15)	4.1 (7)	20			
	RA81-06305	22	29.1	0.3	6.0	20			
	RA81-MTX	20 (9)	31.3 (0)	0.1 (33)	4.1 (32)	20			
	RA82-05602	31	<3.5	2.1	4.0	20			
	RA82-MTX	39 (0)	<3.5 (0)	2.3 (0)	6.5 (0)	0			
	RA83-05607	29	4.6	2.5	7.8	•			
	RA83-MTX	12 (59)	0 (100)	1.3 (52)	3.1 (60)	60			
	RA84-06302	30	9.6	2.5	7.4	00			
	RA84-MTX	24 ()	<3.5 (100)	0.8 (68)	5.3 (28)	60			

A = Affymetrix; R = real-time RT-PCR (validation of gene expression); P = real-time RT-PCR (validation of predictive gene); RF = rheumatoid factor;; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein concentration, HAQ = Health Assessment Questionnaire; DAS28 = disease activity score (28 joints); + = positive; - = negative; n.d. = not determined; aTNF = anti-TNF monoclonal antibody therapy; MTX = methotrexate therapy

TABLE 2 TABLE 2-continued

Correlations among clinical parameters (Pea pre- and post-anti-TNFα treat		on test;	Correlations among clinical parameters (Pearson correlation test; pre- and post-anti-TNF $lpha$ treatment)				
	r-value	p-value		r-value	p-value		
Morning stiffness/Swollen joint count 28	0.718	0.004	DAS 28/Swollen joint count 68	0.878	0.000		
Morning stiffness/Swollen joint count 68	0.664	0.010	DAS 28/Painful joint count 28	0.660	0.010		
Swollen joint count 28/Swollen joint count 68	0.990	0.000	VAS (physician)/Swollen joint count 68	0.672	0.008		
Painful joint count 28/Painful joint count 68	0.794	0.001	VAS (physician)/Painful joint count 28	0.697	0.006		
ESR/CRP	0.854	0.000	VAS (physician)/DAS 28	0.790	0.001		
ESR/VAS (physician)	0.764	0.001					
ESR/DAS 28	0.813	0.000	Different clinical parameters showed correlations in RA treatment (n = 14 in all cases).	A patients pre- and p	ost anti-TNFo		
CRP/Morning stiffness	0.733	0.003	ESR = erythrocyte sedimentation rate;				
CRP/Swollen joint count 28	0.762	0.002	CRP = C-reactive protein;				
CRP/Swollen joint count 68	0.728	0.003	DAS 28 = disease activity score (28 joints); and				
CRP/DAS 28	0.786	0.001	VAS (physician) = visual analogue score (physican's gl	obal assessment)			
DAS 28/Swollen joint count 28	0.891	0.000	4 , ,				

TABLE 3

	Genes differentially regulated in peripheral blood monocytes of both RA patients versus normal donors and RA patients pre-versus post-anti-TNF $lpha$										
Affymetrix		Increased (%)	Decreased (%)	Fold change	SLR						
ID	Gene name	. ,	RA vs. N								
36711_at	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F	71.43	14.29	3.44	1.78						
38037_at	Diphtheria toxin receptor (DTR)	71.43	10.20	2.87	1.52						
201386_s_at	DEAH (Asp-Glu-Ala-His) box polypeptide 15	2.04	73.47	-1.66	-0.73						
201890_at 202219_at	Ribonucleotide reductase M2 polypeptide Solute carrier family 6, member 8	81.63 71.43	8.16 8.16	4.39 8.44	2.13						
202219_at 202464_s_at	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	81.63	—	2.74	1.46						
203115_at	Ferrochelatase (protoporphyria)	83.67	8.16	3.87	1.95						
203574_at	Nuclear factor, interleukin 3 regulated	77.55	_	2.16	1.11						
203887_s_at	Thrombomodulin	71.43	16.33	2.49	1.32						
203932_at	Major histocompatibility complex, class II, DM beta	2.04	75.51	-1.82	-0.87						
204131_s_at	Forkhead box O3A	77.55	4.08	2.21	1.14						
204419_x_at	Hemoglobin, gamma A, gamma G	75.51	6.12	2.88	1.52						
204467_s_at	Synuclein, alpha (non A4 component of amyloid precursor)	71.43	4.08	3.60	1.85						
204848_x_at 205239_at	Hemoglobin, gamma A Amphiregulin (schwannoma-derived growth	75.51 81.63	6.12 4.08	3.83 6.13	1.94 2.62						
205239_at 205571_at	factor) Lipoyltransferase 1	-	79.59	-1.90	-0.93						
205592_at	Solute carrier family 4, anion exchanger, member 1	77.55	10.20	4.83	2.27						
205863_at	S100 calcium binding protein A12 (calgranulin C)	71.43	4.08	1.69	0.76						
205900_at	Keratin 1 (epidermolytic hyperkeratosis)	75.51	6.12	4.03	2.01						
205950_s_at	Carbonic anhydrase I	81.63	4.08	5.88	2.56						
205987_at	CD1C antigen, c polypeptide		87.76	-2.93	-1.55						
206025_s_at	Tumor necrosis factor, alpha-induced protein 6 Ribonuclease, RNase A family, 2	71.43	_	3.85 1.95	1.94 0.97						
206111_at 206834_at	Hemoglobin, delta	73.47 83.67	10.20	4.08	2.03						
207332_s_at	Transferrin receptor (p90, CD71)	81.63	2.04	2.35	1.23						
208632_at	Ring finger protein 10	71.43	6.12	2.06	1.04						
209007_s_at	Chromosome 1 open reading frame 63	4.08	73.47	-2.14	-1.10						
209458_x_at 209795_at	Hemoglobin, alpha 1, alpha 2 CD69 antigen (p60, early T-cell activation	85.71 71.43	2.04 12.24	3.00 2.95	1.59 1.56						
210027_s_at	antigen APEX nuclease (multifunctional DNA repair	_	75.51	-1.93	-0.94						
210254_at	enzyme) 1 Membrane-spanning 4-domains, subfamily A,	73.47	16.33	3.41	1.77						
210338_s_at	member 3 Heat shock 70 kDa protein 8	6.12	71.43	-2.09	-1.06						
211038_s_at	Hypothetical protein MGC12760		71.43	-2.07	-1.05						
211458_s_at	GABA(A) receptor-associated protein like 1, like 3	71.43	_	1.95	0.96						
211560_s_at	Aminolevulinate, delta-, synthase 2	87.76	4.08	24.35	4.61						
211991_s_at	Major histocompatibility complex, class II, DP alpha 1	4.08	79.59	-3.01	-1.59						
212199_at	Morf4 family associated protein 1-like 1	2.04	75.51	-1.94	-0.96						
212224_at	Aldehyde dehydrogenase 1 family, member A1	4.08	75.51	-2.56	-1.36						
212232_at	Formin binding protein 4		77.55	-1.83	-0.87						
212534_at	Zinc finger protein 24 (KOX 17)	6.12	71.43	-1.49	-0.58						
213142_x_at	Hypothetical protein LOC54103	4.08	73.47	-1.77	-0.82						
214433_s_at 215933_s_at	Selenium binding protein 1 Hematopoietically expressed homeobox	71.43	10.20 75.51	4.59 -1.83	2.20 -0.87						
217478_s_at	Major histocompatibility complex, class II,	4.08	73.47	-2.02	-1.01						
217736_s_at	DM alpha Eukaryotic translation initiation factor 2-alpha kinase 1	75.51	_	1.97	0.98						
219069_at	Ankyrin repeat domain 49	_	73.47	-1.59	-0.67						
219093_at	Hypothetical protein FLJ20701	_	85.71	-3.32	-1.73						
219228_at	Zinc finger protein 331	77.55	8.16	3.94	1.98						
219607_s_at	Membrane-spanning 4-domains, subfamily A, member 4	91.84	_	2.96	1.57						
221748_s_at	Tensin 1	81.63	4.08	4.29	2.10						
221766_s_at	Family with sequence similarity 46, member A		71.43	-1.71	-0.77						

TABLE 3-continued

Genes differentially regulated in peripheral blood monocytes of both RA patients versus normal donors and RA patients pre-versus post-anti-TNFa

patient	ts versus nor	mal donors a	nd RA pat	ients pr	e-versus pos	t-anti-TNFα		
	Increased	Decreased	Fold		Increased	Decreased	Fold	
Affymetrix	(%)	(%)	change	SLR	(%)	(%)	change	SLR
ID	R.	A-aTNF vs. I	RA (all)		RA-a	TNF vs. RA	(responde	r)
36711_at	28.57	61.22	-2.78	-1.48	12.00	80.00	-5.88	-2.56
38037_at	12.24	73.47	-2.59	-1.37	_	84.00	-3.70	-1.89
201386_s_at	44.90	14.29	1.43	0.51	60.00	_	1.81	0.85
201890_at	2.04	69.39	-3.86	-1.95	4.00	64.00	-3.88	-1.96
202219_at	12.24	59.18	-5.17	-2.37	4.00	72.00	-6.96	-2.80
202464_s_at	12.24	69.39	-2.18	-1.12	_	84.00	-3.01	-1.59
203115_at	20.41	63.27	-2.18	-1.12	16.00	72.00	-2.25	-1.17
203574_at	10.20	53.06	-1.54	-0.62	_	76.00	-2.06	-1.04
203887_s_at	12.24	65.31	-2.34	-1.23	_	76.00	-3.14	-1.65
203932_at	63.27	4.08	1.64	0.71	84.00	_	1.68	0.75
204131_s_at	18.37	55.10	-1.42	-0.50	4.00	64.00	-1.41	-0.50
204419_x_at	14.29	75.51	-3.18	-1.67	8.00	92.00	-4.16	-2.04
204467_s_at	24.49	65.31	-2.26	-1.18	16.00	80.00	-2.93	-1.55
204848_x_at	16.33	65.31	-3.22	-1.69	4.00	80.00	-4.63	-2.21
205239_at	20.41	71.43	-3.36	-1.75	_	96.00	-5.91	-2.56
205571_at	51.02	12.24	1.35	0.44	72.00	_	1.61	0.69
205592_at	16.33	65.31	-3.81	-1.93	8.00	76.00	-5.63	-2.49
205863_at	14.29	55.10	-1.49	-0.58	8.00	56.00	-1.56	-0.64
205900_at	20.41	67.35	-2.31	-1.21	16.00	84.00	-3.18	-1.67
205950_s_at	22.45	67.35	-2.87	-1.52	16.00	84.00	-4.14	-2.05
205987_at	63.27	2.04	1.72	0.79	68.00	_	1.72	0.78
206025_s_at	12.24	59.18	-1.97	-0.98	4.00	72.00	-2.74	-1.46
206111_at	8.16	67.35	-1.59	-0.67	_	72.00	-1.68	-0.75
206834_at	20.41	65.31	-3.13	-1.64	16.00	80.00	-4.59	-2.20
207332_s_at	2.04	79.59	-2.45	-1.29	_	84.00	-2.57	-1.36
208632_at	12.24	59.18	-1.71	-0.78	4.00	68.00	-1.69	-0.76
209007_s_at	57.14	14.29	1.54	0.62	76.00	4.00	1.87	0.90
209458_x_at	8.16	63.27	-2.09	-1.06	4.00	76.00	-2.60	-1.38
209795_at	14.29	75.51	-3.18	-1.67	16.00	76.00	-3.77	-1.92
210027_s_at	67.35	10.20	1.64	0.72	84.00	_	2.02	1.02
210254_at	14.29	79.59	-4.56	-2.19	20.00	76.00	-3.69	-1.88
210338_s_at	55.10	18.37	1.57	0.66	68.00	4.00	2.04	1.03
211038_s_at	42.86	16.33	1.29	0.37	56.00	4.00	1.46	0.55
211458_s_at	16.33	65.31	-1.92	-0.94	_	84.00	-2.75	-1.46
211560_s_at	16.33	75.51	-10.81	-3.43	8.00	80.00	-20.53	-4.36
211991_s_at	75.51	8.16	2.37	1.24	80.00	4.00	2.54	1.34
212199_at	59.18	10.20	1.56	0.64	80.00	_	2.11	1.08
212224_at	71.43	12.24	2.28	1.19	92.00	_	2.74	1.45
212232_at	48.98	14.29	1.27	0.35	72.00	_	1.57	0.65
212534_at	53.06	4.08	1.35	0.43	76.00	_	1.45	0.53
213142_x_at	51.02	12.24	1.25	0.32	72.00		1.51	0.60
214433_s_at	18.37	65.31	-3.08	-1.62	12.00	68.00	-3.55	-1.83
215933_s_at	55.10	6.12	1.51	0.59	76.00	0.00	1.85	0.88
217478_s_at	61.22	12.24	1.68	0.75	64.00	8.00	1.85	0.88
217736_s_at	14.29	51.02	-1.46	-0.54	8.00	60.00	-1.41	-0.50
219069_at	57.14	12.24	1.30	0.38	84.00	_	1.58	0.66
219093_at	71.43	8.16	2.43	1.28	84.00		2.59	1.37
219228_at	10.20	71.43	-3.26	-1.70	12.00	80.00	-4.62	-2.21
219607_s_at	6.12	73.47	-1.95	-0.96		80.00	-2.06	-1.04
221748_s_at	24.49	65.31	-2.12	-1.08	16.00	80.00	-2.42	-1.28
221766_s_at	53.06	10.20	1.30	0.38	80.00	_	1.66	0.73

The table presents the percentage of pairwise comparisons between the respective groups showing an increase or decrease for the fold-change/Signal Log Ratio (SLR; 51 candidate genes were selected); n = 7 each for the comparisons RA vs. ND and RA- α TNF vs. RA (all); n = 5 for the comparison RA- α TNF vs. RA (all) is shown in the central 4 columns to assess the effect of treatment on differential gene expression in all TNF α -treated RA patients.

RA = rheumatoid arthritis (pre-anti-TNF α treatment); ND = normal donor; RA- α TNF = rheumatoid arthritis (post-anti-TNF α treatment)

TABLE 4

Genes differentially regulated in peripheral blood monocytes of both RA patients versus normal donors and RA patients pre-versus post-anti-TNF α therapy (PAM analysis)

Affymetrix ID	Gene title	RA score
221622_s_at	Uncharacterized hypothalamus protein HT007	0.7405
218845_at	Dual specificity phosphatase 22	0.6694
200786_at	Proteasome (prosome, macropain) subunit, beta type, 7	0.5297
219607_s_at	Membrane-spanning 4-domains, subfamily A, member 4	0.4449
212886_at	DKFZP434C171 protein	0.2690
201407_s_at	Protein phosphatase 1, catalytic subunit, beta isoform	0.2653
212266_s_at	Splicing factor, arginine/serine-rich 5	0.1771
53912_at	Sorting nexin 11	0.1277
200090_at	Farnesyltransferase, CAAX box, alpha	0.1167
218025_s_at	Peroxisomal D3,D2-enoyl-CoA isomerase	0.1032
204232_at	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	0.0993
201722_s_at	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1	0.0942
218627_at	Hypothetical protein FLJ11259	0.0841
210027_s_at	APEX nuclease (multifunctional DNA repair enzyme) 1	0.0817
202322_s_at	Geranylgeranyl diphosphate synthase 1	0.0646
221689_s_at	Down syndrome critical region gene 5	0.0549
203356_at	Calpain 7	0.0535
211991_s_at	Major histocompatibility complex, class II, DP alpha 1	0.0515
218462_at	Brix domain containing 5	0.0378
218123_at	Chromosome 21 open reading frame 59	0.0173
214329_x_at	Tumor necrosis factor (ligand) superfamily, member 10	-0.0025
219067_s_at	Chromosome 10 open reading frame 86	-0.0046
205789_at	CD1D antigen, d polypeptide	-0.0104
209214_s_at	Ewing sarcoma breakpoint region 1	-0.0111
213427_at	Ribonuclease P 40 kDa subunit	-0.0471
209422_at/206567_s_at	PHD finger protein 20	-0.0480/-0.0698
201010_s_at	Thioredoxin interacting protein	-0.0520
200883 at	Ubiquinol-cytochrome c reductase core protein II	-0.0521
218454_at	Hypothetical protein FLJ22662	-0.0544
202918 s at	Preimplantation protein 3	-0.0574
212204 at	DKFZP564G2022 protein	-0.0698
219452 at	Dipeptidase 2	-0.0800
209458 x at	Hemoglobin, alpha 1, alpha 2	-0.0809
219889_at	Frequently rearranged in advanced T-cell lymphomas	-0.0832
201303 at	DEAD (Asp-Glu-Ala-Asp) box polypeptide 48	-0.0832
_		-0.0872
202510_s_at	Tumor necrosis factor, alpha-induced protein 2	
221923_s_at	Nucleophosmin (nucleolar phosphoprotein B23, numatrin)	-0.0902
201887_at	Interleukin 13 receptor, alpha 1	-0.1075
211582_x_at	Leukocyte specific transcript 1, LST1	-0.1193
219030_at	CGI-121 protein	-0.1259
212706_at	RAS p21 protein activator 4/hypothetical protein FLJ21767	-0.1393
202902_s_at	Cathepsin S	-0.1644
200663_at	CD63 antigen (melanoma 1 antigen)	-0.1764
202138_x_at/209971_x_at	JTV1 gene	-0.1950/-0.2868
200851_s_at	KIAA0174	-0.2019
201109_s_at	Thrombospondin 1	-0.2079
213142_x_at	Hypothetical protein LOC54103	-0.2285
202531_at	Interferon regulatory factor 1	-0.2904
216274 s at	SEC11-like 1 (S. cerevisiae)	-0.6951
2102/1 <u>0</u> 40	SECTI III (S. COLONDINO)	0.0001

Positive RA scores indicate genes overexpressed in RA,

negative RA scores indicate those underexpressed in RA.
PAM = Prediction analysis of microarrays;

bold and underlined letters indicate genes overlapping with the 51 genes identified by Affymetrix ® gene expression profiling and analysis (see Table 3).

TABLE 5

	Genes differentially regulated in RA-anti-TNF α responders versus RA-anti-TNF α non-responders (post anti-TNF α therapy)					
Affymetrix ID	In- creased (%)	De- creased (%)	Gene title	Fold change	SLR	
200041_s_at	100	0	HLA-B associated transcript-1 (D6S81E)	2.53	1.34	
200052_s_at	100	0	Interleukin enhancer binding factor 2, 45 kD (ILF2)	3.73	1.90	
200064_at	100	0	Isolate Liv chaperone protein HSP90 beta (HSP90BETA) mRNA	2.66	1.41	
200079_s_at	100	0	Lysyl-tRNA synthetase mRNA, complete cds; nuclear gene for mitochondrial product; alternatively spliced	2.16	1.11	

TABLE 5-continued

	In-	De-			
Affymetrix ID	creased (%)		Gene title	Fold change	SLR
200629 at	100	0	Tryptophanyl-tRNA synthetase (WARS)	2.14	1.10
200634_at	100	0	Profilin 1 (PFN1), mRNA	2.16	1.11
200802_at	100	0	Seryl-tRNA synthetase (SARS)	2.20	1.14
200860_s_at	100	0	Similar to KIAA1007 protein, clone MGC: 692, mRNA, complete cds	2.11	1.08
200983_x_at	0	100	CD59 antigen p18-20 (antigen identified by monoclonal antibodies 16.3A5, EJ16, EJ30, EL32 and G344)	-2.43	-1.28
200991_s_at	100	0	Homo sapiens KIAA0064 gene product (KIAA0064), mRNA	2.71	1.44
201112_s_at	100	0	Chromosome segregation 1 (yeast homolog)-like (CSE1L), mRNA	2.01	1.01
201214_s_at	100 100	0 0	Protein phosphatase 1, regulatory subunit 7 (PPP1R7), mRNA DEADH (Asp-Glu-Ala-AspHis) box polypeptide 1 (DDX1), mRNA	2.17 2.30	1.12 1.20
201241_at 201263_at	100	0	Threonyl-tRNA synthetase (TARS), mRNA	2.14	1.10
201205_at 201386_s_at	100	ő	Dead box protein 15 mRNA, complete cds	2.22	1.15
201417_at	100	0	SRY (sex determining region Y)-box 4 /DEF = Human DNA sequence from clone RP3-322L4 on chromosome 6	3.18	1.67
201576_s_at	100	0	Galactosidase, beta 1 (GLB1), mRNA	2.00	1.00
201872_s_at	100	0	ATP-binding cassette, sub-family E (OABP), member 1	2.28	1.19
201892_s_at	100	0	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14 kD, B14) (NDUFA6), mRNA	2.19	1.13
202174_s_at	100	0	Pericentriolar material 1 (PCM1), mRNA	2.08	1.06
202176_at	100	0	Excision repair cross-complementing rodent repair deficiency, complementation group 3 (ERCC3), mRNA	2.93	1.55
202220_at	100	0	KIAA0907 protein (KIAA0907), mRNA	2.39	1.26
202225_at	100	0	v-crk avian sarcoma virus CT10 oncogene homolog	2.10	1.07
202464_s_at	0	100	6-phosphofructo-2-kinasefructose-2,6-biphosphatase 3 (PFKFB3), mRNA. /PROD = 6-phosphofructo-2-kinase-fructose-2,6-biphosphatase 3	-3.25	-1.70
202545_at	100	0	KIAA0766 gene product (KIAA0766), mRNA	1.38	0.46
202838_at	100	100	N-acetylgalactosaminidase, alpha-(NAGA), mRNA	1.82	0.86
202896_s_at 202950_at	0 100	100 0	Protein tyrosine phosphatase, non-receptor type substrate 1 (PTPNS1), mRNA Crystallin, zeta (quinone reductase) (CRYZ), mRNA	-2.00 2.51	-1.00 1.33
203037_s_at	100	0	KIAA0429 gene product (KIAA0429), mRNA	2.41	1.27
203155_at	100	ő	SET domain, bifurcated 1 (SETDB1), mRNA	4.23	2.08
203371_s_at	0	100	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3 (12 kD, B12) (NDUFB3), mRNA	-2.13	-1.09
203821_at	0	100	Diphtheria toxin receptor (DTR)	-3.63	-1.86
203887_s_at	0	100	Thrombomodulin (THBD), mRNA	-2.75	-1.46
203966_s_at	0	100	Protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform (PPM1A), mRNA	-2.73	-1.45
204192_at	100	0	CD37 antigen (CD37), mRNA	3.66	1.87
204419_x_at	0	100	Hemoglobin, gamma G (HBG2), mRNA	-5.50	-2.46
204566_at	100	0	Protein phosphatase 1D magnesium-dependent, delta isoform (PPM1D), mRNA	2.00	1.00
204689_at	100 0	0 100	Hematopoietically expressed homeobox (HHEX), mRNA	2.04 -3.38	1.03 -1.04
205239_at 205249_at	0	100	Amphiregulin (schwannoma-derived growth factor) (AREG), mRNA Early growth response 2 (Krox-20 (<i>Drosophila</i>) homolog) (EGR2), mRNA	-2.55	-1.35
205552 s at	100	0	2,5-oligoadenylate synthetase 1 (40-46 kD) (OAS1), transcript variant E16, mRNA	2.08	1.06
206115_at	0	100	Early growth response 3 (EGR3), mRNA. /PROD = early growth response 3	-6.54	-2.71
206584_at	0	100	Homo sapiens MD-2 protein (MD-2), mRNA	-2.16	-1.11
206877_at	0	100	Homo sapiens MAX dimerization protein (MAD), mRNA	-3.92	-1.97
207170_s_at	100	0	DKFZP586A011 protein (DKFZP586A011), mRNA	2.20	1.14
208631_s_at	100	0	78 kDa gastrin-binding protein mRNA, complete cds	2.04	1.03
208691_at	0	100	Transferrin receptor (p90, CD71), clone MGC: 3151, mRNA, complete cds	-2.30	-1.20
208868_s_at	0	100	Homo sapiens mRNA; cDNA DKFZp564N1272 (from clone DKFZp564N1272); complete cds	-3.18	-1.67
208869_s_at	0	100	GABA-A receptor-associated protein like 1 (GABARAPL1) mRNA, complete cds	-3.29	-1.72
208942_s_at	0	100	Translocation protein 1	-2.93	-1.55
209092_s_at	100 0	0 100	Homo sapiens clone 016b03 My027 protein mRNA, complete cds	2.07	1.05
209193_at 209200_at	100	0	Protein kinase-related oncogene (PIM1) mRNA, complete cds MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	-2.51 2.48	-1.33 1.31
209200_at 209861_s_at	100	0	eIF-2-associated p67 homolog mRNA, complete cds	2.55	1.35
209967_s_at	0	100	Human mRNA for hCREM (cyclic AMP-responsive element modulator) type 2 protein, complete cds	-3.07	-1.62
210027_s_at	100	0	Apurinic endonuclease (APE) mRNA, complete cds. /PROD = apurinic endonuclease	2.23	1.16
210053_at	100	0	TATA box binding protein (TBP)-associated factor, RNA polymerase II, D, 100 kD	2.23	1.16
210172_at	0	100	Human mRNA for ZFM1 protein alternatively spliced product, complete cds. /PROD = ZFM1 protein, alternatively spliced product	-2.16	-1.11
210766_s_at	100	0	Trachea cellular apoptosis susceptibility protein (CSE1) mRNA, complete cds	2.28	1.19
210949_s_at	100	0	Similar to eukaryotic translation initiation factor 3, subunit 8 (110 kD), clone MGC:	2.53	1.34
211458_s_at	0	100	8693, mRNA, complete cds GABA-A receptor-associated protein mRNA, complete cds. /PROD = GABA-A	-3.18	-1.67
			receptor-associated protein		
					_
211546_x_at 212199_at	0 100	100 0	Human (clone 2-5) synuclein (NACP) mRNA, complete cds Human putative ribosomal protein S1 mRNA	-4.92 2.22	-2.30 1.15

TABLE 5-continued

	In-	De-			
Affymetrix ID	creased (%)	creased (%)	Gene title	Fold change	SLR
			1, soluble		
212388_at	100	0	Homo sapiens mRNA for KIAA1057 protein, partial cds	3.10	1.63
212591_at	100	ŏ	RBP1-like protein	2.03	1.02
212696_s_at	100	0	Ring finger protein 4	3.05	1.6
212709_at	100	0	KIAA0197 protein	2.10	1.0
212714_at	100	0	Homo sapiens mRNA; cDNA DKFZp586F1323 (from clone DKFZp586F1323)	2.13	1.09
212893_at	100	0	Homo sapiens mRNA; cDNA DKFZp564I052 (from clone DKFZp564I052)	2.01	1.0
212989_at 213410_at	100 100	0 0	Homo sapiens mRNA for Hmob33 protein, 3 untranslated region	2.25 2.53	1.1′
213410_at 213515_x_at	0	100	Homo sapiens mRNA; cDNA DKFZp586F1019 (from clone DKFZp586F1019); partial cds Myosin, light polypeptide 4, alkali; atrial, embryonic	-4.69	-2.2
213515_x_at 213528 at	100	0	H. sapiens novel gene from PAC 117P20, chromosome 1	2.87	1.5
213604_at	100	ŏ	Homo sapiens clone 24582 mRNA sequence	2.07	1.05
213619_at	0	100	Heterogeneous nuclear ribonucleoprotein H1 (H)	-2.48	-1.3
213655_at	0	100	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein,	-3.03	-1.60
			epsilon polypeptide		
213743_at	100	0	Cyclin T2	2.08	1.00
213788_s_at	0	100	cDNA: FLJ23227 fis, clone CAE00645, highly similar to AF052138	-2.20	-1.14
213872_at	0	100	Hypothetical protein FLJ12619	-4.29	-2.1
213979_s_at	0	100	C-terminal binding protein 1	-4.41	-2.14
214257_s_at	0	100	SEC22, vesicle trafficking protein (S. cerevisiae)-like 1	-2.97	-1.57
214414_x_at	0	100	Hemoglobin, alpha 1	-2.04	-1.03
214696_at	0	100	Homo sapiens clone 24659 mRNA sequence /DEF = Homo sapiens clone 24659	-2.93	-1.55
214022	0	100	mRNA sequence	2.17	
214933_at	0	100	Calcium channel, voltage-dependent, PQ type, alpha 1A subunit	-2.17	-1.13
215043_s_at	0 100	100 0	H. sapiens SMA5 mRNA	-4.08 2.17	-2.03 1.12
215933_s_at 216199_s_at	100	0	H. sapiens HEX gene encoding homeobox related protein Mitogen-activated protein kinase kinase kinase 4	2.17	1.17
216202_s_at	100	0	Serine palmitoyltransferase (LCB2) mRNA, partial cds	2.75	1.46
216996_s_at	100	0	KIAA0971 protein /DEF = <i>Homo sapiens</i> cDNA FLJ11495 fis, clone HEMBA1001950,	2.20	1.14
210))0_5_4t	100	v	highly similar to Homo sapiens mRNA for KIAA0971 protein	2.20	1.1-
217554_at	0	100	ESTs, Hs.97109	-3.63	-1.80
217682_at	0	100	ESTs, Weakly similar to ALU7_HUMAN ALU	-3.01	-1.59
217840_at	100	0	DEAD-box protein abstrakt (ABS), mRNA	2.39	1.20
218229_s_at	100	0	KIAA1513 protein (KIAA1513), mRNA	2.07	1.05
218356_at	100	0	Cell division protein FtsJ (FJH1), mRNA	2.20	1.14
218432_at	100	0	F-box only protein 3 (FBXO3), mRNA	2.16	1.13
218589_at	100	0	Purinergic receptor (family A group 5) (P2Y5), mRNA	2.68	1.42
218604_at	100	0	Integral inner nuclear membrane protein (MAN1), mRNA	2.04	1.03
218689_at	100	0	Fanconi anemia, complementation group F (FANCF), mRNA	8.94	3.16
218889_at	100	0	Hypothetical protein FLJ12820 (FLJ12820), mRNA	2.01	1.0
218973_at	100	0	Hypothetical protein FLJ13119 (FLJ13119), mRNA	2.07	1.0
219069_at	100	0	Hypothetical protein FLJ20189 (FLJ20189), mRNA	2.23	1.16
219093_at	100	0	Hypothetical protein FLJ20701 (FLJ20701), mRNA	3.32	1.73
219099_at	100	0 0	Homo sapiens chromosome 12 open reading frame 5 (C12ORF5), mRNA Hypothetical protein FLJ22555 (FLJ22555), mRNA	2.13	1.09
219176_at 219243_at	100 100	0	Hypothetical protein FLJ12110 (FLJ11110), mRNA	2.13 2.07	1.09
219243_at 219363_s_at	100	0	CGI-12 protein (LOC51001), mRNA	2.31	1.01
219434_at	0	100	Triggering receptor expressed on myeloid cells 1 (TREM1), mRNA	-4.35	-2.12
221485_at	0	100	betaGlcNAc beta 1,4-galactosyltransferase. polypeptide 5	-2.71	-1.4
221652_s_at	100	0	PNAS-25 mRNA, complete cds.	2.55	1.3
221755_at	100	0	Homo sapiens mRNA for FLJ00043 protein, partial cds	3.44	1.09
221970_s_at	100	0	Homo sapiens cDNA: FLJ21737 fis, clone COLF3396	2.41	1.27
222127_s_at	0.1	0	Homo sapiens cDNA FLJ13399 fis, clone PLACE1001395 /DEF = Homo sapiens cDNA FLJ13399 fis, clone PLACE1001395	2.31	1.2
36711_at	0	100	Novel MAFF (v-maf musculoaponeurotic fibrosarcoma (avian) oncogene family, protein F) LIKE protein	-3.54	-1.10
38037_at	0	100	Heparin-binding EGF-like growth factor mRNA, complete cds	-3.63	-1.86
AFFX-BioB-M_at	0	100	E. coli 7,8-diamino-pelargonic acid (bioA), biotin synthetase (bioB), 7-keto-8-amino-	-4.69	-2.5
_			pelargonic acid synthetase (bioF), bioC protein, and dethiobiotin synthetase (bioD), complete cds		
AFFX-r2-Ec-bioC-3_at	0	100	Escherichia coli /REF = J04423 /DEF = E coli bioC protein corresponding to mucleotides 4609-4883 of J04423 /LEN = 777 (-5 and -3 represent transcript regions 5 prime and 3 prime respectively)	-4.22	-1.80

TABLE 6

Correlations between clinical parameters and differentially expressed genes (Pearson correlation test; pre- and post-anti-TNF α treatment; n = 7 for all; bold letters identify genes occurring twice, bold and italics letters identify genes occurring ≥ 3 times)

	Affymetrix_ID	Gene title	r-value	p-value
		Pre-anti-TNF α treatment		
Leuko/	202219_at 205239_at	Solute carrier family 6 Amphiregulin	0.901 0.879	0.006** 0.009**
Thromb/	205900_at	Keratin 1	0.923	0.003**
Mono/	204018_x_at	Hemoglobin, alpha 1	-0.908	0.005**
GPT/	203932_at	MHC-II, DM beta	-0.912	0.004**
	218589_s_at	Purinergic receptor P2Y, G-protein coupled 5	-0.919	0.003**
Hb/	205900_at	Keratin 1	-0.944	0.001**
MoStiff/	202219_ at	Solute carrier family 6	0.893	0.007**
	203932_at	MHC-II, DM beta	-0.898	0.006**
	204131_s_at	Forkhead box O3A	0.917	0.004**
	205239_at	Amphiregulin	0.954	0.001**
	207332_s_at	Transferrin receptor (p90, CD71)	0.926	0.003**
	208632_at	Ring finger protein 10	0.913	0.004**
DisDur/	212232_at	Formin binding protein 4	0.955	0.001**
	213142_x_at	Hypothetical protein LOC54103	0.877	0.009**
		Post-anti-TNFα treatment		
ESR/	38037_at	Diphteria toxin receptor	0.928	0.003 **
	203821_at	Heparin-binding EGF-like growth factor	0.928	0.003 **
	205571_at	Lipoyltransferase 1	-0.898	0.006 **
	210027_s_at	APEX nuclease (multifunct. DNA repair enzyme) 1	-0.944	0.001 **
	211458_s_at	GABA(A) receptor-associated protein like 1/3	0.947	0.001 **
	212232_at	Formin binding protein 4	-0.890	0.007 **
	219228_at	Zinc finger protein 331	0.894	0.007**
CRP/	38037_at	Diphteria toxin receptor	0.968	0.000 **
	203821_at	Heparin-binding EGF-like growth factor	0.963	0.001 **
	205571_at	Lipoyltransferase 1	-0.946	0.001 **
	210027_s_at	APEX nuclease (multifunct. DNA repair enzyme) 1	-0.950	0.001 **
	211458_s_at	GABA(A) receptor-associated protein like 1/3	0.948	0.001 **
	212232 at	Formin binding protein 4	-0.908	0.005 **
Thromb/	205571 at	Lipoyltransferase 1	-0.934	0.002 **
	212232 at	Formin binding protein 4	-0.921	0.003 **
Granulo/	213427_at	Ribonuclease P 40 kDa subunit	-0.875	0.010**
Hb/	38037_at	Diphteria toxin receptor	-0.930	0.002 **
1107	203821 at	Heparin-binding EGF-like growth factor	-0.948	0.001 **
	203932 at	MHC class II, DM beta	0.885	0.008**
	210027_s_at	APEX nuclease (multifunct. DNA repair enzyme) 1	0.971	0.000 **
	211458_s_at	GABA(A) receptor-associated protein like 1/3	-0.951	0.001 **
Dis_act/	36711_at	v-maf fibrosarc. oncogene homolog F (avian)	0.932	0.002**
Dis_act	205552 s at	2',5'-oligoadenylate synthetase 1, 40/46 kDa	-0.951	0.002
	203552_s_at 211458 s at	GABA(A) receptor-associated protein like 1/3	0.896	0.001 **
	211438_3_ui 212232 at	Formin binding protein 4	-0.898	0.006 **
DAG20/	_	5.		
DAS28/	36711	v-maf fibrosarc. oncogene homolog F (avian)	0.940	0.002**
	205552_s_at	2',5'-oligoadenylate synthetase 1, 40/46 kDa	-0.898	0.006**
	205571_at	Lipoyltransferase 1	-0.937	0.002 **
	211458_s_at	GABA(A) receptor-associated protein like 1/3	0.897	0.006 **
	212232_at	Formin binding protein 4	-0.973	0.000 **
Sw28/	219607_s_at	Membrane-spanning 4-domains, subfam. A, memb. 4	0.931	0.002**

GPT = glutamate pyruvic transferase;

Hb = haemoglobin;

MoStiff = Morning stiffness (minutes);

 $DisDur = Disease \ duration \ (years);$

ESR = erythrocyte sedimentation rate;

CRP = C-reactive protein;

DAS 28 = disease activity score (28 joints);

Sw = number of swollen joints (28 joints)

TABLE 7

		raqivian i CK V	andation in allti	-TNFα-treated RA p			
					PCF	<u> </u>	
Time point	Gene Description	Gene title		Applera ID	RA-αTNF (responder) versus ND (RQ; Means ± S	$Max - \Delta R$	
			,	Validated genes			
BL	AREG	Amphiregulin		Hs00155832_m1	10.23 ± 2.93	-7.60	0.000
BL	CA-1	Carbonic anhydrase	1	Hs00266139_m1	6.83 ± 3.49		n.s.
BL	CLC	Charcot-Leyden cry		Hs00171342_m1	5.36 ± 4.82		0.041
3L	CLU	Clusterin C	•	Hs00156548_m1	3.94 ± 2.87	-2.77	n.s.
3L	TNFAIP6	Tumor necrosis fact induced protein 6	or alpha	Hs00218482_m1	1.71 ± 0.40	0.82	0.000
ВL	THBD	Thrombomodulin		Hs00264920_s1	1.58 ± 1.08	-0.53	0.041
BL	MS4A4A	Membrane-spanning		Hs00254770_m1	1.54 ± 0.42		0.041
3L	DTR	subfamily A, memb Diptheria toxin rece		Hs00181813_m1	1.21 ± 0.44	-1.10	n.s.
3L	S100A12	S100 calcium bindir		Hs00194525_m1	1.07 ± 0.21		0.041
BL	HT007	Uncharacterized hy		Hs00218482_m1	0.51 ± -0.0		0.000
		protein HT007					
3L	HLA-DR	MHC-class-II; HLA		Hs00219578_m1	0.59 ± -0.1		0.000
3L	LOC54103	Hypothetical protein		Hs00367929_m1	0.90 ± -0.2		0.041
3L	TNF	Tumor necrosis fact	or aipna	Hs00174128_m1	1.22 ± 0.53		0.041
BL BL	IL1B PSMB7	Interleukin 1 beta Proteasome subunit	heta tune 7	Hs00174097_m1 Hs00160607_m1	1.14 ± 0.42 0.72 ± -0.1		0.041 0.041
) L	1 SNID/	precursor	octa type 7	11800100007_III1	0.72 ± -0.1	9 0.10	0.041
3L	KIAA0174	Protein KIAA0174		Hs00796085_sh	0.89 ± 0.30	0.08	0.041
BL	SPC18	Microsomal signal p	eptidase	Hs00819308_m1	0.96 ± 0.11	-0.25	0.041
		18 kDa subunit Di	screpancies betw	veen Affymetrix and	TaqMan PCR		
.,	I IDE	T' 1: C 1	-	H 00276062 1	2.17 0.54	0.60	0.000
BL	LIPT1	Lipoyltransferase 1	4-1- 261	Hs00376962_m1	2.17 ± 0.54		0.000
BL BL	ZNF361 THBS1	Ring zinc finger pro Thrombospondin-1	tem 301	Hs00367929_m1	0.55 ± -0.1 0.88 ± 0.25		0.000
BL	IRF1		r mustain 1	Hs00170236_m1	0.88 ± 0.23 4.95 ± 0.18		n.s. 0.000
3L	PPP1CB	Interferon regulator Protein phosphatase	•	Hs00233698_m1 Hs00160349_m1	0.93 ± 0.18		0.000
) <u>L</u>	TITIED	subunit, beta isoforr		118001003 4 2_1111	0.93 ± 0.09	-0.26	0.041
					Affymetrix		
				RA-αTNF	FC RA-αTNF		FC RA-αTN
				(responder)	(responder)	RA-αTNF all	all
		Time	Affymetrix	versus ND	versus ND	versus ND	versus ND
		point	•	(% of comp.)	(Means)	(% of comp.)	(Means)
					Validated genes		
					vanuated genes		
		BL	205239_at	82.86	5.48	81.63	6.13
		BL	205950_s_a		4.92	81.63	5.88
		BL	206207_at	62.86	2.46	73.47	3.97
		BL	222043_at	68.57	2.57	75.51	2.68
		BL	206026_s_a		2.07	73.27	2.24
		BL BL	203887_s_a		2.64	71.43	2.49
		BL BL	219607_s_at 38037_at	t 88.57 68.57	2.66 2.91	91.84 71.43	2.96 2.87
		BL	205863_at	62.86	1.50	71.43	1.69
		BL	221622_s_at		-1.74	-85.71	-1.66
		BL	208894_at	-65.71	-1.77	-75.51	-2.15
		BL	222150_s_at		-1.84	-73.47	-1.71
		BL	207113_s_a		1.03	-46.94	-1.28
			205067_at	57.14	1.62	57.02	1.44
		$_{ m BL}$	203007_40			-57.74	-1.27
		BL BL	200786_at	-54.29	-1.27	-37.74	1.2,
					-1.27 -1.17	-46.94	-1.23
		$_{ m BL}$	200786_at	t -42.86 -17.14	-1.17 -1.04	-46.94 -72.24	
		BL BL	200786_at 200851_s_a	t -42.86 -17.14	-1.17	-46.94 -72.24	-1.23
		BL BL BL	200786_at 200851_s_a	t -42.86 -17.14 Discrepancies be	-1.17 -1.04	-46.94 -72.24	-1.23 -1.03
		BL BL BL	200786_at 200851_s_at 201290_at	t -42.86 -17.14 Discrepancies be -74.29 77.14	-1.17 -1.04 tween Affymetrix a	-46.94 -72.24 and TaqMan PCR	-1.23 -1.03

TABLE 7-continued

TaqMan PCR validation in anti-TNFα-treated RA patients and normal donors					
	202531_at	-40.00	-1.30	-55.70	-1.44
	201409_s_at	60.00	1.63	57.14	1.69

Validation of 22 selected genes from Affymetrix 8 gene expression profiling by Taqman real-time RT-PCR (10 anti-TNF α -treated RA patients prior to therapy; 14 normal donors – ND); genes differentially expressed (decreased: <-70%; increased: >70%) in RA versus ND according to the Affymetrix 8 analysis are shown in normal type, equally-expressed genes are displayed in italics; RQ = relative quantity; FC = fold-change; BL = baseline (pre-antiTNF α therapy)

TABLE 8

Correlations between TaqMan PCR results and the ACR response in anti-TNF α -treated RA patients							
Gene description	Time point	Gene title	Applera ID	r-value	р	n	
CA1	w 12	Carbonic anhydrase 1	Hs00266139_m1	0.642	0.045	10	
CA1	w 26			0.962	0.000	9	
CLC	w 4	Charcot-Leyden crystal protein	Hs00171342_m1	0.766	0.027	8	
THBD	w 4	Thrombomodulin	Hs00264920_s1	0.766	0.027	8	
THBS1	w 26	Thrombospondin 1	Hs00170236_m1	-0.710	0.032	9	
IRF1	w 4	Interferon regulatory factor 1	Hs00233698 m1	0.778	0.023	8	

TABLE 9

Genes differentially regulated in RA-anti-TNF α responders versus RA-anti-TNF α non-responders (pre-anti-TNF α therapy; predictive genes)

Affymetrix ID	Gene title	Increased (%)	Decreased (%)	Fold- Change	SLR
39248_at	Aquaporin 3	10	80	-4.6	-2.19
200061_s_at	Similar to ribosomal protein S24, clone MGC: 8595	0	80	-1.39	-0.47
200087_s_at	Transmembrane emp24 domain trafficking protein 2	0	80	-1.6	-0.63
200642_at	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1	0	80	-1.8	-0.84
200655_s_at	Calmodulin 1 (phosphorylase kinase, delta)	0	80	-1.5	-0.59
200745_s_at	Guanine nucleotide binding protein (G protein), beta polypeptide 1	80	0	1.6	0.66
200772_x_at	Prothymosin, alpha (gene sequence 28)	80	0	1.7	0.75
201193_at	Homo sapiens isocitrate dehydrogenase 1 (NADP+) soluble (IDH1)	0	80	-1.4	-0.49
201690_s_at	Tumor protein D52	0	80	-3.3	-1.73
201693_s_at	Early growth response 1	80	0	3.1	1.61
201889_at	Homo sapiens predicted osteoblast protein (GS3786)	0	<u> 100</u>	-1.7	-0.74
202110_at	Cytochrome c oxidase subunit VIIb	0	80	-1.6	-0.64
202157_s_at	CUG triplet repeat, RNA binding protein 2	0	80	-1.6	-0.64
202233_s_at	Ubiquinol-cytochrome c reductase hinge protein	0	80	-1.7	-0.74
202378_s_at	Homos spaiens leptin receptor gene-related protein (HS0BRGRP)	80	20	1.15	0.20
202664_at	Wiskott-Aldrich syndrome protein interacting protein	80	0	1.9	0.91
202910_s_at	CD97 antigen	80	10	1.6	0.70
202922_at	Glutamate-cysteine ligase, catalytic subunit	0	80	-2.3	-1.17
202950_at	Crystallin, zeta (quinone reductase)	80	0	2.2	1.16
203097 s at	Rap guanine nucleotide exchange factor (GEF) 2	20	80	-1.3	-0.38
203231_s_at	Ataxin 1	0	80	-8.2	-3.03
203300 x at	Adaptor-related protein complex 1, sigma 2 subunit	80	20	1.9	0.89
204160 s at	Ectonucleotide pyrophosphatase/phosphodiesterase 4	10	80	-2.4	-1.27
204750 s at	Desmocollin 2	80	0	12.9	3.69
204777 s at	MAL, T-cell differentiation protein	10	80	-2.6	-1.39
205042_at	Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase	0	80	-1.9	-0.95
205114 s at	Chemokine (C—C motif) ligand 3	80	0	2.0	0.96
205624 at	Carboxypeptidase A3	0	80	-4.0	-2.00
206207 at	Charcot-Leyden crystal protein	0	90	-4.9	-2.29
206790 s at	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7 kDa	0	80	-1.5	-0.61
207008 at	Interleukin 8 receptor, beta	90	0	4.0	2.00
207815 at	Platelet factor 4 variant 1	20	80	-2.4	-1.28
208051_s_at	Poly(A) binding protein interacting protein 1	0	80	-1.6	-0.68
208161_s_at	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	80	0	4.3	2.10
208637_x_at	Actinin, alpha 1	80	Ö	2.4	1.24
208918 s at	NAD kinase	80	0	1.5	0.59
208982_at	Platelet/endothelial cell adhesion molecule (CD31 antigen)	90	0	1.6	0.71
209009_at	Esterase D/formylglutathione hydrolase	80	20	1.5	0.71
209009_at 209020_at	Chromosome 20 open reading frame 111	80	20	1.5	0.54
209020_at 209146 at	Sterol-C4-methyl oxidase-like	0	80	-1.9	-0.89
209140_at 209193_at	PIM-1 oncogene	10	80	-2.3	-1.19
202123_at	That I oncogone	10	30	2.3	1.17

TABLE 9-continued

Genes differentially regulated in RA-anti-TNF α responders versus RA-anti-TNF α non-responders (pre-anti-TNF α therapy; predictive genes)

Affymetrix ID	Gene title	Increased (%)	Decreased (%)	Fold- Change	SLR
209710_at	GATA binding protein 2	20	80	-3.5	-1.81
210042_s_at	Cathepsin Z	80	20	1.9	0.94
210184_at	Integrin alpha-X (antigen CD11c)	<u>100</u>	0	2.3	1.22
210732_s_at	Lectin, galactoside-binding, soluble, 8 (galectin 8)	80	0	2.4	1.23
210895_s_at	CD86 antigen (CD28 antigen ligand 2, B7-2 antigen)	80	10	1.9	0.92
211506_s_at	Interleukin 8	90	0	3.2	1.67
211734_s_at	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	0	80	-5.0	-2.31
211995_x_at	Actin, gamma 1	80	0	1.4	0.46
212314_at	KIAA0746 protein	10	80	-1.7	-0.73
212335_at	Glucosamine (N-acetyl)-6-sulfatase (Sanfilippo disease IIID)	80	0	1.5	0.54
212386_at	Transcription factor 4	0	80	-2.5	-1.29
212671_s_at	Major histocompatibility complex, class II, DQ alpha 1	10	80	-3.3	-1.72
212897_at	Cell division cycle 2-like 6 (CDK8-like)	80	0	1.8	0.83
212999_x_at	Major histocompatibility complex, class II, DQ beta 1	80	20	1.8	0.88
213309_at	Phospholipase C-like 2	0	80	-1.9	-0.9
213506_at	Coagulation factor II (thrombin) receptor-like 1	80	0	2.4	1.23
213883_s_at	TM2 domain containing 1	10	80	-1.4	-0.46
214305_s_at	Splicing factor 3b, subunit 1, 155 kDa	80	20	1.5	0.62
214512_s_at	SUB1 homolog (S. cerevisiae)	0	80	-1.7	-0.76
214807_at	MRNA; cDNA DKFZp564O0862	80	10	1.7	0.79
214953_s_at	Amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)	90	0	1.9	0.93
215726_s_at	Cytochrome b-5	0	80	-2.1	-1.08
216016_at	Cold autoinflammatory syndrome 1	80	0	6.1	2.60
217722_s_at	Neugrin, neurite outgrowth associated	0	90	-1.9	-0.91
217753_s_at	Ribosomal protein S26, 40S ribosomal protein	10	80	-2.9	-1.51
217970_s_at	CCR4-NOT transcription complex, subunit 6	0	80	-1.9	-0.91
218190_s_at	Ubiquinol-cytochrome c reductase complex (7.2 kD)	0	80	-2.0	-1.03
218345_at	Hepatocellular carcinoma-associated antigen 112	10	80	-3.9	-1.95
218486_at	Kruppel-like factor 11	90	0	2.1	1.06
218545_at	GGA binding partner	0	80	-1.6	-0.67
218728_s_at	Cornichon homolog 4 (Drosophila)	0	80	-1.8	-0.84
219269_at	Hypothetical protein FLJ21616	0	90	-2.1	-1.06
219410_at	Homo sapiens hypothetical protein FLJ10134	0	<u> 100</u>	-4.7	-2.33
219862_s_at	Nuclear prelamin A recognition factor	80	0	1.5	0.62
219905_at	Erythroblast membrane-associated protein	0	80	-1.8	-0.85
220532_s_at	LR8 protein	10	80	-5.2	-2.39
221011_s_at	Likely ortholog of mouse limb-bud and heart gene (LBH)	0	80	-2.8	-1.47
221042_s_at	Calmin (calponin-like, transmembrane)	80	0	1.9	0.89
221434_s_at	Chromosome 14 open reading frame 156	0	80	-1.7	-0.72
221737_at	Guanine nucleotide binding protein (G protein) alpha 12	10	80	-2.0	-1.96
AFFX-M27830_5_at	SRY (sex determining region Y)-box 18	80	0	4.3	2.09

The criterion for gene selection (total of 82) was the percentage of pairwise comparisons between future RA responders and future RA non-responders to anti-TNF α therapy showing an increase or decrease for the fold-change/Signal Log Ratio prior to therapy; bold letters indicate a percentage of 80% for the pairwise comparisons (total of 10), bold and italic letters 90%, bold, italic, and underlined letters. 100% in the latter case, also the gene names are shown in bold, italic, and underlined letters.

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SUMMARY OF SEQUENCE LISTING

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303 Adalimumab ${ m V}_L$	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
adilinamas V _L	Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg
	Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
	Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala
	Ala Ser Thr Leu Gln Ser Gly Val Pro Ser
	Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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	Tyr Asn Arg Ala Pro Tyr Thr Phe Gly Gln
	Gly Thr Lys Val Glu Ile Lys
204	
304 dalimumah W	Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Arg Leu
Adalimumab V_H	Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp
	Asp Tyr Ala Met His Trp Val Arg Gln Ala
	Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
	Ile Thr Trp Asn Ser Gly His Ile Asp Tyr
	Ala Asp Ser Val Glu Gly Arg Phe Thr Ile
	Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
	Thr Ala Val Tyr Tyr Cys Ala Lys Val Ser
	Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr
	Trp Gly Gln Gly Thr Leu Val Thr Val Ser
	Ser
305	Gln Arg Tyr Asn Arg Ala Pro Tyr Xaa
Adalimumab	Xaa = Thr or Ala
V_L CDR3	
306	Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu
Adalimumab	Asp Xaa
V _H CDR3	Xaa = Tyr or Asn
307	Ala Ala Ser Thr Leu Gln Ser
Adalimumab	
V_L CDR2	
308	Ala Ile Thr Trp Asn Ser Gly His Ile Asp
Adalimumab	Tyr Ala Asp Ser Val Glu Gly
V_H CDR2	_
0.00	
309	Arg Ala Ser Gln Gly Ile Arg Asn Tyr Leu
Adalimumab V_L CDR1	Ala
VL CDRI	
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V_H CDR1	

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ccttttgctg aactcacagt tagacaatcc atggtttaat gcacatgaaa ttacctatat
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catgaaaggc actgagtttt gtaaatcagg accctaaatg tttaattgta aataagtttc
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                                                                      120
agaagtactg gctacaattt tttatcccat tgttggtggt gattctgttt gctgtggaca
caggattatt tatctcaact cagcagcagg tcacatttct cttgaagatt aagagaacca
                                                                      240
ggaaaggctt cagacttctg aacccacatc ctaagccaaa ccccaaaaac aactgatata
attactcaag aaatatttgc aacattagtt tttttccagc atcagcaatt gctactcaat
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<223 > OTHER INFORMATION: AffymetrixID: 211995_x_at
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ggattagcaa gcaggagtac gacgagtcgg gcccctccat cgtccaccgc aaatgcttct
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aaacggactc agcagatgcg tagcatttgc tgcatgggtt aattgagaat agaaatttgc
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ccctggcaaa tgcacacacc tcatgctagc ctcacgaaac tggaataagc cttcgaaaag
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aaattgtcct tgaagcttgt atctgatatc agcactggat tgtagaactt gttgctgatt
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ttgaccttgt attgaagtta actgttcccc ttggtatttg tttaataccc tgtacatatc
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tttgagttca acctttagta cgtgtggctt ggtcacttcg tggctaaggt aagaacgtgc
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ttgtggaaga caagtctgtg gcttggtgag tctgtgtggc cagcagcctc tgatctgtgc
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: AffymetrixID: 212314_at
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                                                                      120
atgcagggag ggcaatagct ttgtaaattg gtttacattt ttctccttga atttttctag
                                                                      180
ggtcctagtg cttccgaatc atttaatggc attgtcggat atcttttaca tttcaattgc
                                                                      240
aatccatgaa attacattta gaagattett agtacttaac tgtagtette tecatgaatt
                                                                      300
acacgttaga atagactggc agcaacngaa tatgcagcaa gtaagcctct agcttatagt
                                                                      360
ttcatcccta cccctcatgc ctgcgtgagt ctgtacaggg atatgtgtgt gtgtgtgt
                                                                      420
gtgtgtgtgt tagagaggaa gaggaagagc agaatgtctg tatactacat gctgctaagg
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<213 > ORGANISM: Homo sapiens
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: AffymetrixID: 212335_at
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gctqtqqttt qtaacttqtt caactcaqqc aataaqcqat tttaqcttta tttaaaqtct
                                                                      180
totqtocaqo tttaaqoact ttqtaaqaca tqqctqaaaq taqcttttct atcaqaattq
                                                                      240
cagatagtca tgttgggcta acagtcaatt ggatatattc ctttacctca catgacccca
                                                                      300
qcaactqtqq tqqtatctaq aqqtqaaaca qqcaaqtqaa atqqacacct ctqctqtqaa
                                                                      360
tqttttaqaq aaqqaaattc aaaaaatqtt qtaactqaaa qcactqttqa atatqqqtat
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eggetttett ttteactttg actettaaca ttateagtea actteeacat taatg
                                                                      475
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ttttgctata aaatagactg tagtacaccc tagtaggaaa aaaaaaaaac taaatttaaa
                                                                      120
aataaaaaat atatttggct tatttttcgc aggagcaatc cttttatacc atgaatatt
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<223> OTHER INFORMATION: AffymetrixID: 212671_s_at
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aacaccctca tetgtettgt ggacaacate ttteeteetg tggteaacat caentggetg
                                                                       120
agcaatgggc actcagtcac agaaggtgtt tctgagacca gcttcctctc caagagtgat
                                                                       180
catteettet teaagateag ttaceteace tteeteeett etgntgatga gatttatgae
                                                                       240
tgcaaggtgg agcactgggg cctggatgag cctcttctga aacactggga gcctg
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<211> LENGTH: 565
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(565)
<223> OTHER INFORMATION: AffymetrixID: 212897_at
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atttctcttt qaaatttatt aqatactqtt atqtccccca aqqqtacaqq aqqqqcatcc
                                                                       120
ctcagcctat gggnaacacc caaactagga ggggttattg acaggaagga atgaatccaa
                                                                       180
gtgaaggett tetgetette gtgttacaaa ceagttteag agttagettt etggggaggt
                                                                       240
gtgtgtttgt gaaaggaatt caagtgttgc aggacagatg agctcaaggt aaggtagctt
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tggcagcagg gctgatacta tgaggctgaa acaatccttg tgatgaagta gatcatgcag
                                                                       360
tgacatacaa agaccaagga ttatgtatat ttttatatct ctgtggtttt gaaactttag
                                                                       420
tacttagaat tttggccttc tgcactactc ttttgctctt acgaacataa tggactctta
                                                                       480
agaatggaaa gggatgacat ttacctatgt gtgctgcctc attcctggtg aagcaactgc
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tacttgttct ctatgcctct aaaat
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<221> NAME/KEY: misc_feature
<222> LOCATION: (229)..(229)
<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (244) .. (244)
<223> OTHER INFORMATION: n is a, c, g, or t
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                                                                      120
ggtagaaaat caattcaatt gtcgcatcat tcatggttct ttaatattga tgctcagtgc
antggcctna gaatatccca gcctctcttc tggtttgntg agtgctntnt aagtaagcat
ggtngaattg tttggggnca natatagtga nccttggtca ctggtgtttc aaacattctg
gnaagtcaca tcnatcaaga atanttttta nttttaagaa agcataacca gcaataaa
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<211> LENGTH: 441
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<223 > OTHER INFORMATION: AffymetrixID: 213309_at
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attattcact ctagctccac tgagaaacat tttcctaagt gaaaacaatt tcttaagatg	180
gaaatggatt ggattgtcaa attattattt attggagaaa aaaacctgat ctacacattt	240
ttacttatat ggggttgcca gagtctctgg gttctagatg attttggtgg catgcttgct	300
gagccataat tactaaagag aatgtaagtg gacgggttcc ctgaatcccc ggggtccttg	360
gagagecate gaggagaatg tgeaattgga etgaagetee etggetgaag atacatgeeg	420
agtcagcaca tgggtagaga t	441
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totgtttgtt gacttattag gactttgaat tatttottta ttaaccotot gagttttngt	180
atgtattatt attaaagaaa aatgcaatca ggattttaaa catgtaaata caaattttgt	240
ataacttttg atgacttcag tgaaattttc aggtagtctg agtaatagat tgttttgcca	300
cttagaatag catttgccac ttagtatttt aaaaaataat tgttggagta tttattgtca	360
gttttgttca cttgttatct aatacaaaat tataaagcct tcagagggtt tggaccacat	420
ctctttggaa a	431
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agttotgtat aattttttgt ggtttttgtt ttgttgagtt aaagtatatt attgtgagat	120
ttatttaata ggactteett tgaaagetgt ataatagtgt tteteggget tetgteteta	180
tgagagatag cttattactc tgatactctt taatctttta caaaggcaag ttgccacttg	240
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attgatgaga gaaatcgccc actttctgat gaggaattag atgctatgtt cccagaagga
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tataaggtac ttcctcctcc agctggttat gttcctattc gaactccagc tcgaaagctg
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acagctactc caacaccttt gggtggtatg actggtttcc acatgcaaac tgaagatcga
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<223> OTHER INFORMATION: n is a, c, g, or t
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                                                                        120
aaaaagcaag ttgctccaga aaaacctgta aagaaacaaa agacaggtga gacttcgaga
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gccctgtcat cttctaaaca gagcagcagc agcagagatg ataacatgtt tcagattggg
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ccttctgtgc ctatcaaaca aatacatagc atgaanctaa ttttagaagt ttcatggggg
aattttaggg gaaagtataa acctaagagt gagtgaatgg agatgattca tggaaaaaaa
aaanaaaaan nnanatgtgc tatnaggcag agttattaac ttcttttagt tgttgtttga
gatngngttc tgctcttgtt ncccaggctg gagtgcantg gcgtgatctc gtctcnctgc
aacctccqcc tcccaqqttc aaqcqattct cctqccccaq ctactttqqa qqctqaaqtq
                                                                      420
                                                                      436
taaqaqttqc ttqaqc
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<212> TYPE: DNA
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<223> OTHER INFORMATION: AffymetrixID: 214953_s_at
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                                                                      120
catgtgaacg tgggagttca gctgcttctc ttgcctaagt attcctttcc tgatcactat
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gcattttaaa gttaaacatt tttaagtatt tcagatgctt tagagagatt tttttccat
                                                                      240
gactgcattt tactgtacag attgctgctt ctgctatatt tgtgatatag gaattaagag
                                                                      300
gatacacacg tttgtttctt cgtgcctgtt ttatgtgcac acattaggca ttgagacttc
                                                                      360
aagettttet ttttttgtee aegtatettt gggtetttga taaagaaaag aateeetgtt
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cattgtaagc acttttacgg ggcgggtg
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<223> OTHER INFORMATION: AffymetrixID: 215726_s_at
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gacagaccaa agttaaacaa gcctccggaa actcttatca ctactattga ttctagttcc
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agttggtgga ccaactgggt gatccctgcc atctctgcag tggccgtcgc cttgatgtat
                                                                     120
cgcctataca tggcagagga ctgaacacct cctcagaagt cagcgcagga agagcctgct
                                                                     180
ttggacacgg gagaaaagaa gccattgcta actacttcaa ctgacagaaa ccttcacttg
                                                                     240
aaaacaatga ttttaatata tctctttctt tttcttccga cattagaaac aaaacaaaaa
                                                                     300
gaactgtcct ttctgcgcnc aaatttttcg agtgtgcctt tttattcatc tactttattt
                                                                     360
tgatgtttcc ttaatgtgta att
                                                                     383
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<211> LENGTH: 492
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(492)
<223 > OTHER INFORMATION: AffymetrixID: 216016_at
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gccaatgcta aaaagctgca gatccagccc agccagctgg aattgttcta ctgtttgtac
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qaqatqcaqq aqqaqqactt cqtqcaaaqq qccatqqact atttccccaa qattqaqatc
                                                                     120
aatctctcca ccagaatgga ccacatggtt tcttcctttt gcattgagaa ctgtcatcgg
                                                                     180
gtggagtcac tgtccctggg gtttctccat aacatgccca aggaggaaga ggaggaggaa
                                                                     240
aaggaaggcc gacaccttga tatggtgcag tgtgtcctcc caagctcctc tcatgctgcc
                                                                     300
tgttctcatg ggtaaggaaa ctcggcttcc aggtgcttcc tcctgcttcc tcgccagctt
                                                                     360
cttcttggca cctgcctcct ctcatctctt ttcaactatc ttccaaatac tgttgccaca
                                                                     420
gctacatcat aatgccacca ctgtctgttt gagactcctt catgagcaaa gattgatgta
                                                                     480
                                                                     492
tggtaggtgg at
<210> SEQ ID NO 65
<211> LENGTH: 275
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(275)
<223> OTHER INFORMATION: AffymetrixID: 217722_s_at
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ctgcatatgg ataagccacc ttggaatagg aagaggtgtt gagcctggac tgtgggagga
aagagetgeg tggatagatt caaactteet gtggtagtge teccagtetg acctetgtag
accttcagta ctcactcttc ttgcttaggc tctctgtgtg ttgaaagcca tcccgtgttg
catgtgttgt tacaattttc tgtgatactt gcaat
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<210> SEQ ID NO 66
<211> LENGTH: 339
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<212> TYPE: DNA

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<220> FEATURE:
<221> NAME/KEY: misc_feature <222> LOCATION: (1)..(339)
<223> OTHER INFORMATION: AffymetrixID: 217753_s_at
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tggtcgtgcc aaaaagggcc gcggccacgt gcagcctatt cgctgcacta actgtgcccg
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atgcgtgccc aaggacaagg ccattaagaa attcgtcatt cgaaacatag tggaggccgc
                                                                      120
agcagtcagg gacatttctg aagcgagcgt cttcgatgcc tatgtgcttc ccaagctgta
                                                                      180
tgtgaagcta cattactgtg tgagttgtgc aattcacagc aaagtagtca ggaatcgatc
                                                                      240
tcgtgaagcc cgcaaggacc gaacaccccc accccgattt agacctgcgg gtgctgcccc
                                                                      300
agctccccca ccaaagccca tgtaaggagc tgagttctt
                                                                      339
<210> SEQ ID NO 67
<211> LENGTH: 532
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (532)
<223> OTHER INFORMATION: AffymetrixID: 217970_s_at
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tgagctggag ctggttggac taatgagact gaggaagcag cttttcctac gatctgcatt
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atgtaatcac aggtccagag agctttatgg aagcgggaga ggaggagcac ttactcatgt
                                                                      120
tgtatttgtt aatggaggat gtcatctttt catagatgct agaactagag tgcacttgtt
                                                                      180
agatgctaaa ggtttgagct ttacacaaaa tgtcttcatc tgtatttgtt attgtctaca
                                                                      240
                                                                      300
atatatttga atttggggca gcatattaag atgtaatggc ctgttatgtc ttgaaaatac
ttgttttgcc tcttccaggc atactgcatt ctgtggatca gtttgaacag cttctccacc
                                                                      360
ttatttggac agtgataaat tgaaccaaga gtgtagattt acaagtgtaa ccttcaaaag
                                                                      420
aggaagaact atttggggtc tgtaggtaat gaacagtcac accaaaatag actatgatgc
                                                                      480
ttttgttaag aaaggtttca tgttttagat attttccgtg tcctaaataa tt
                                                                      532
<210> SEQ ID NO 68
<211> LENGTH: 379
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(379)
<223> OTHER INFORMATION: AffymetrixID: 218190_s_at
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                                                                      120
acctccacct tegeceteae cateategtg ggegteatgt tettegageg egeettegat
caaggegegg acgetateta egaceacate aacgagggga agetgtggaa acacateaag
cacaagtatg agaacaagta gttccttgga ggcccccatc caggccagaa ggaccaggtc
cacccagcag ctgtttgccc agagctggag cctcagcttg aagatgatgc tcaaggtact
cttcatggac caccattcgc tgttggcaag aaacggcttt acttacaaaa cagactcttt
accttctgct gtgtttgaa
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<210> SEO ID NO 69
<211> LENGTH: 545
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (545)
<223> OTHER INFORMATION: AffymetrixID: 218345_at
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tggaacactc cagccccac tcagagtcca gaagaagtca gaaggctaca cctatgtacc
                                                                      120
tccttcatgg acatgctgaa ggccttgttc agaacccttc aggccatgct cttgggtgtt
                                                                      180
tggattctgc tgcttctggc atctctggcc cctctgtggc tgtactgctg gagaatgttc
                                                                      240
                                                                      300
ccaaccaaag ggaaaagaga ccagaaggaa atgttggaag tgagtggaat ctagccatgc
ctctcctgat tattagtgcc tggtgcttct gcaccgggcg tccctgcatc tgactgctgg
                                                                      360
aagaagaacc agactgagga aaagaggctt ttcaacagcc ccagttatcc tggccccatg
accgtggcca cagccctgct ccagcagcac ttgcccattc cttacacccc ttccccatcc
tgctccgctt catgtcccct cctgagtagt catgtgataa taaactctca tgttattgtt
cccag
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<210> SEQ ID NO 70
<211> LENGTH: 557
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<221> NAME/KEY: misc_feature
<222> LOCATION: (101) .. (101)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (557)
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gtaatgtgag tcctgccagt attctggtgg ataaggtctt ntgagtattt ggttgcttgt
                                                                      120
cacaacattc tccaagcagt gatatttcta aagaggagat acatgttgaa aacggtttta
                                                                      180
atttacactt ccatttcctg attacatttg gaaatacttt gtgtaaacca tcccccttcc
                                                                      240
acctccattt gtctgttgaa agattttaag ttggaaacag ttcctgtctg aaaactcttc
                                                                      300
tgagaaccac aaaccttgtg tatggattcg gcatggagcc ctcagctggc ggctctgggt
                                                                      360
gctgacggcc gctggagagg tgggctcccc tcgtgcactt tattgcctgg gcagttttgc
                                                                      420
ttgatctttt gtgactttga gccttttaag tagtttgaat gataagactt aaaatgtttc
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ataattatgt tttatgtaac agactttgac attatttaaa cgagcatgtg taatgtaact
                                                                      540
tttctctttg aatcata
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<210> SEQ ID NO 71
<211> LENGTH: 541
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(541)
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<213 > ORGANISM: Homo sapiens

<220> FEATURE:

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                                                                   120
180
gatctgatat atcacttaaa ctaaaggggt gtgtgtggtg tatgcttgtt tcctatttct
                                                                   240
gctctttaaa gatactttga atcaataaaa ccattagtct acaaatcaaa ttgtgaactt
                                                                   300
aatototaga aagagaatat aactoagooa titataggaa titaggitoa agtacaggat
                                                                   360
atatgaaatc ttttcccagt atttcagaat gtacttaatt cacaggcagg atgcttcaat
                                                                   420
gcaaaatcat gaatattttt aattcaaaac taaaatgtca ttaatatgta tgtatgcaaa
                                                                   480
tgttttatct tattttctga aatgcatcta ctttcatggg ctttgtacgt ttctgagatt
                                                                   540
                                                                   541
<210> SEQ ID NO 72
<211> LENGTH: 160
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(160)
<223 > OTHER INFORMATION: AffymetrixID: 218728_s_at
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atatcgatac attatggtgc cgagtggtaa catgggagtg tttgatccaa cagaaataca
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caatcgaggg cagctgaagt cacacatgaa agaagccatg atcaagcttg gtttccactt
                                                                   120
gctctgcttc ttcatgtatc tttatagtat gatcttagct
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<210> SEO ID NO 73
<211> LENGTH: 461
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(461)
<223> OTHER INFORMATION: AffymetrixID: 219269_at
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atagecetca gtteteaaat attagaetae gtgtaaaate ttgggtaeet ttagattett
                                                                   120
gtaacactag totgtactoo ottttootto occaagactg ataggatgca agotgaggto
                                                                   180
gtggcacagg aatgacagac accatttggg gagtatccac agagtcaaag gaacactaga
                                                                   240
atccccacct cagcgtgagg ataattgatt tccagctgca ataagccgtg cctcattata
                                                                   300
gccacactgt ggctagatta tacttctttg ggtgctgtgc taagaatgtc aatggaaaaa
geogatetea gattttgttt gaagttaaca tgeetgacae agacateett teeteteaca
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<211> LENGTH: 563
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<223> OTHER INFORMATION: AffymetrixID: 219410_at
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attatgcttt cattacctgg ttggttaaat ctagacttaa gaggctctgc tcctcagaag
                                                                     120
ttggacttct gaaaaatgct gaacgagaac aagaatcaga agaagaaatg tgactttgat
                                                                     180
gagettecag tttttetaga taaacetttt ettttttaca ttgttettgg ttttgtttet
                                                                     240
cgatcttttg tttggagaac agctggctaa ggatgactct aagtgtactg tttgcatttc
                                                                     300
caatttggtt aaagtatttg aatttaaata ttttcttttt agctttgaaa atattttggg
                                                                     360
tgatactttc attttgcaca tcatgcacat catggtattc aggggctaga gtgattttt
                                                                      420
tccagattat ctaaagttgg atgcccacac tatgaaagaa atatttgttt tatttgcctt
                                                                      480
atagatatgc tcaaggttac tgggcttgct actatttgta actccttgac catggaatta
                                                                      540
tacttgttta tcttgttgct gca
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<210> SEQ ID NO 75
<211> LENGTH: 472
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(472)
<223 > OTHER INFORMATION: AffymetrixID: 219862_s_at
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                                                                     120
aagacttcca agaggtcacc cttgagaaga acggagaggt ggtgttacgc tttgctgcag
cctatggctt tcgaaacatc cagaacatga tcctgaagct taagaagggc aagttcccat
                                                                     180
tccactttgt ggaggtcctc gcctgtgctg gaggatgctt aaatggcaga ggccaagccc
                                                                     240
agactccaga cggacatgcg gataaggccc tgctgcggca gatggaaggc atttacgctg
                                                                     300
acatecetgt geggegteeg gagteeagtg cacaegtgea ggagetgtae caggagtgge
                                                                     360
tggaggggat caactccccc aaggcccgag aggtgctgca taccacgtac cagagccagg
                                                                     420
agegtggcac acacageetg gacateaagt ggtgaagtea ggeeagggee tt
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<211> LENGTH: 396
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (396)
<223> OTHER INFORMATION: AffymetrixID: 219905_at
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gagtcccatg agagctgatg gtttagttcc agtctgatgg cagcaggctt gacgccaagg
aagagatgat gtttaattca agtccgaagg caaggaaaaa gctgatggtc ctgtccaaag
gctattaggc aggaagaatt ctcttagggc agagttagct cttttgttct attcaggcct
tcaactgatt cagcaaggcc cgcccacatt tgggaggaca gtctgcatta ctcagtctac
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<400> SEQUENCE: 79

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accaaatagc tgggcatctt gtgacccagt taagtg	396
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gagtgtagag cttacatgca gatgctgagg aagttgttca cagcaatccg tgccctgttc	180
ctggctgtct gtgtcttgaa ggtcattgtg tccttggttt ccttgggagt aggtcttcga	240
aacttgtgtg gccagagctc ccagcccctg aatgaggaag gatcagagaa gaggctactg	300
ggggagaatt cagtgccccc ttcgccctct agggagcaga cctccactgc cattgtcctg	360
tgagccgcca aagaccccac ggggtgcccg catgtccctg tctagggcag cccagggccc	420
ccactcctgg ctcctcacac ttgcctcccc tatggccgct ctccagaccc tcctcctttc	480
ttetececae ateegeaeet getgtteeea etetggggtt eteaagteea tga	533
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tcaattcctg tgttttggtg tcttccctta tctgctaccc tgaatcacct gtcctggtct	120
tgctgtgtga tgggaacatg cttgtaaact gcgtaacaaa tctactttgt gtatgtgtct	180
gtttatgggg gtggtttatt atttttgctg gtccctagac cactttgtat gaccgtttgc	240
agtotgagoa ggocaggggo tgacagotaa tgtcaggaco otcagoggtg gagootgotg	300
gggggaccca getgetettg gacaagtgge tgageteeta tetggeetee tettttttt	360
ttttttcaag taatttgtgt gtatttctaa ctgattgtat tgaaaaaatt cctagtattt	420
cagtaaaaat geetgttgtg agatgaaeet eetgtaaett etatetgtte ttttttgagg	480
ctcaggga	488
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cctagaagaa aatg	taacga aagaatcaat cagtagtaaa aaaaggaaa aaaggaaaca	120
tgtggaccac gtag	aaagtt cactatttgt agcaccagga agtgttcaat cctcagatga	180
cctagaagaa gaca	gtagcg actacagcat teetteeagg actagteaca gtgacteeag	240
catttacctt cgac	gacata ctcataggtc ttcggaatcg gatcatttta gctatgttca	300
gttgaggaac gcag	cagatc tggatgacag aagaaaccga atattaacca ggaaggccaa	360
cagctcagga gaag	ccatgt cactggggag ccacagcccg cagagtgact ccctgacaca	420
gcttgtccag cagc	cggata tgatgtattt tattctcttc ctgtggctcc tggtgtactg	480
cttgctgctc ttcc	cacaac tggatgttag caggctctga tacgtg	526
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tgagaagaat teet	tggact gcggcgtcga gtcagctgaa agaacacttt gcacagttcg	120
gccatgtcag aagg	tgcatt ttaccttttg acaaggagac tggctttcac agaggtttgg	180
gttgggttca gttt	tettea gaagaaggae tteggaatge actacaacag	230
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gtctgtaatt tata	gagatc totagaattc ttattgtaat tttcctactt ctttgataaa	120
agaaaaataa gtca	gattgt taactccaag attgaaaaaa aaaactcttg aaagaagatt	180
attagttgta acta	atttgg gggttctggg cacagacatc taacctggta ttgtaaggca	240
gaggeteeca ttgg	aatggt agtggtccgg gtcagttgtt catggtgtaa gctttgcaca	300
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-210, CEO ID NO 02	
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ctgncaagtc tcagaagagg ttgggcttcc atgcctgtag ctttcctggt ccctcacccc	180
catngcccca ggcccacage gtgggaacte actttccctt gtgtcaagac atttctnnnn	240
nnnnnnnnn nnnnnnnnn nnactccatg caggggtcag tgcagcagag gacagtctgg	300
agaaggtatt agcaaagcaa aaggctgaga aggaacaggg aacattggag ctgactgttc	360
ttggtaactg attacctgcc aattgctacc gagaaggttg gaggtgggga aggctttgta	420
taateecace caceteacea aaacgannnn nnnnnnnnn nnnngteett tetggaagtt	480
tctggtgcca tttc	494
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cagcagctat ctcgaattat ggacagattt aatttgcctc gtcgaagtac tgactttaca	180
agcagggact attatattaa tataagaaaa gctttggtta ctgggtattt tatgcaggtg	240
gcacatttag aacgaacagg gcattactta actgtgaaag ataaccaggt ggttcagttg	300

catcoctota otgitotiga ocacaaacot gaatgggtgo titataatga giitgiiota	360
acaacaaaga attacatccg gacatgtaca gatatcaagc cagaatggtt ggtgaaaatt	420
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totgtaatat gatacatttt ootatotttt aagttattgt taootaaagt taatooagat	240
tatatggtcc ttatatgtgt acaacattaa aatgaaaggc tttgtcttgc attgtgaggt	300
acaggeggaa gttggaatea ggttttagga ttetgtetet eattagetga ataatgtgag	360
gattaacttc tgccagct	378
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acctggcctg ctcaggcttc ccaccctgtg cggggcacac ccccaggaag ggaccctgga	240
cacggetece aegtecagge ttaaggtgga tgeaetteee geaectecag tettetgtgt	300
agcagettta acceaegttt gtetgteaeg teeagteeeg agaeggetga gtgaeeceaa	360
gaaaggette eeegacaeee agacagagge tgeagggetg gggetgggtg agggtggegg	420
gcctgcgggg acattctact gtgctaaa	448
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ctgtagaagc tgtagagata ggcttcagtt gttaattggt ttggagcctc ctatgtgtga	240
cttatgactc tctgtgttct gtgtatttgt ctgaattaat gacctgggat ataaagctat	300
gctagctttc aaacaggaga tgccttcaga aagctttgta tattttgcag ttgccagacc	360
aataaaatac c	371
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tggcttttat agtgacaggc aaagaggaat ttattgagat cactgctcat ggcatttgtt	180
gctgtaagaa gtgttgcctt tgattgttac taaccacgga tgggtaacgg tcatacatta	240
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aactttgaaa tacaaatgtt tgccctggta attagcaatg aactgctggc agtttcttca	360
gctgtgtata tacggatctg gcttttaatt gatgaatcaa cttctacaga aacttttgca	420
gggacagtgt tgatgaggca gtttagcttg ccagggtgat gataaagccc aggtccctgc	480
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aaactggagt tgttgaaatg aaagacagtg gctacaaagt ttctgaccca gagaacttgt	180
atttgaagca ggggatagca aacttatctg cagaggttgt ctcactcaag agacttatag	240
ccacacaacc aatetetget teagactetg ggtaaattae taetgagtaa gagetgggea	300
tttagaaaga tgtcatttgc aatagagcag tccattttgt attatgctga attttcactg	360
gacctgtgat gtcatttcac tgtgatgtgc acatgttgtc tgtttggtgt ctttttgtgc	420
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gaaactgagg aattttcttt gtgtagcttt gctctttggt agaaaaggct aggtacacag
                                                                      180
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actetgggee tgggeeteat catettetet ettggtgtga teagetggeg gagagetgge
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cactctagtt acactcctct tcctgggtcc aattattcag aaggatggca catttcctag
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aggcagaatc ctacaacttc cactccaagt gagaaggaga ttcaaactca atgatgctac
                                                                      300
catgcctctc caacatcttc aaccccctga cattatcttg gatcctatgg tttctccatc
                                                                      360
caattetttg aattteecag teteecetat gtaaaaetta geaaettggg ggaeeteatt
                                                                      420
cctgggacta tgctgtaacc aaattattgt ccaaggctat atttctggga tgaatataat
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tctaaaaact gaacaatggc acaattgttt gctatgtgca cccgtccagg acagaaccgt
gcataggcaa aaggagtgga gcacagcgtc cggcccagtg tgtttccggt tctgagtcag
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atgctggagg agaaaccctg ggaaggctcc tggttgtcta cccatggacc cagaggttct	180
ttgacagett tggcaacetg teetetgeet etgecateat gggcaacece aaagteaagg	240
cacatggcaa gaaggtgctg actteettgg gagatgeeat aaagcaeetg gatgatetea	300
agggcacctt tgcccagctg agtgaactgc actgtgacaa gctgcatgtg gatcctgaga	360
acttcaagct cctgggaaat gtgctggtga ccgttttggc aatccatttc ggcaaagaat	420
tcaccectga ggtgcagget teetggcaga agatggtgae tggagtggee agtgeeetgt	480
cctccagata ccactgagct cactgcc	507
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gtctatttct cccttcaatc ctgtcaatgt ttgctttatg tattttgggg aactgttgtt	180
tgatgtgtat gtgtttataa ttgttataca tttttaattg agccttttat taacatatat	240
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agggcacctt tgcccagctg agtgaactgc actgtgacaa gctgcatgtg gatcctgaga
                                                                     360
acttcaaget eetgggaaat gtgetggtga eegttttgge aatccattte ggeaaagaat
                                                                     420
tcacccctga ggtgcaggct tcctggcaga agatggtgac tgcagtggcc agtgccctgt
                                                                     480
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gaaatatgaa ggagaagetg aggaacgaaa gaaacttega caagagaatg gaaatgtaca
tgctatagca taactgaaga taaaattaca ggatatcaca ttggagtcac tgccaagtca
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tagccataaa tgatgagtcg gtcctctttc cagtggatca taagacaatg gacccttttt
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                                                                     180
aaatagcaaa gccaaagaac tgcaaacttg ggagtggata tatggcaaaa ctccaaagtt
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catagacata aagaatggaa gaattgaaat ttgtaatatt gaagcacctg atcattggtt
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gccattggaa atacgtgaca aattaaattc aagtcttatt ggcagtaagt tttgcccaac
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<212> TYPE: DNA
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<213 > ORGANISM: Homo sapiens

<220> FEATURE:

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acceaecttt caccaetteg eccatgetae agtteagttt eetegtetgt aaaatgggga
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tgataatggt acctaccttg cagtgttgtt ataaggatta aaggagacag tgcaagaaaa
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actgggatgt ccctgtctcc ccctcccctt gctccttgaa catggccaag gaaagtgaaa
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<223 > OTHER INFORMATION: AffymetrixID: 205863_at
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<212> TYPE: DNA

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cacagecetg ettetgacat aateeagtta aaataataat ttttaagaaa taaatttatt
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tagttcttac tgcttaattc aaataataat tagtaagcta gcaaatagta atctgtaagc
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ctcttccatg aattggattg ccttggtagt gatagtgccc ttggtgattc taatagtcct
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tgtgttatgg tttaagaagc actgctcata tcaggacatc ctgtgagact cttccccctg
                                                                    360
actoccccat tgtgttaaga acccagcaac ccaggagcct agtacaatat agtgatgcca
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (1)..(490)
<223> OTHER INFORMATION: AffymetrixID: 206025_s_at
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aaggagtgtg gtggcgtctt tacagatcca aagcaaattt ttaaatctcc aggcttccca
aatgagtacg aagataacca aatctgctac tggcacatta gactcaagta tggtcagcgt
                                                                    240
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attcacctga gttttttaga ttttgacctt gaagatgacc caggttgctt ggctgattat
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gttgaaatat atgacagtta cgatgatgtc catggctttg tgggaagata ctgtggagat
                                                                     360
gagettecag atgacateat cagtacagga aatgteatga eettgaagtt tetaagtgat
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gcttcagtga cagctggagg tttccaaatc aaatatgttg caatggatcc tgtatccaaa
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tccaqtcaaq
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (1) .. (479)
<223> OTHER INFORMATION: AffymetrixID: 206111_at
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caatgcaatg caggtcatta acaattatca acggcgatgc aaaaaccaaa atactttcct
tcttacaact tttgctaacg tagttaatgt ttgtggtaac ccaaatatga cctgtcctag
taacaaaact cgcaaaaatt gtcaccacag tggaagccag gtgcctttaa tccactgtaa
cctcacaact ccaagtccac agaatatttc aaactgcagg tatgcgcaga caccagcaaa
catgttctat atagttgcat gtgacaacag agatcaacga cgagaccctc cacagtatcc
ggtggttcca gttcacctgg atagaatcat ctaagctcct gtatcagcac tcctcatcat
                                                                     420
cactcatctg ccaageteet caatcatage caagateeca teteteeata taetttggg
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<210> SEQ ID NO 106
<211> LENGTH: 524
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(524)
<223> OTHER INFORMATION: AffymetrixID: 206834_at
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ggccctgggc agattactgg tggtctaccc ttggacccag aggttctttg agtcctttgg
                                                                     120
ggatctgtcc tctcctgatg ctgttatggg caaccctaag gtgaaggctc atggcaagaa
                                                                     180
ggtgctaggt gcctttagtg atggcctggc tcacctggac aacctcaagg gcactttttc
                                                                     240
tcagctgagt gagctgcact gtgacaagct gcacgtggat cctgagaact tcaggctctt
                                                                     300
gggcaatgtg ctggtgtgt tgctggcccg caactttggc aaggaattca ccccacaaat
                                                                     360
gcaggctgcc tatcagaagg tggtggctgg tgtggctaat gccctggctc acaagtacca
                                                                      420
ttgagatcct ggactgtttc ctgataacca taagaagacc ctatttccct agattctatt
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<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (1)..(560)

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gtaggtatga ataagttcga agctccgtga gtgaaccatc atataaacgt gtagtacagc
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tgtttgtcat agggcagttg gaaacggcct cctagggaaa agttcatagg gtctcttcag
                                                                     180
gttcttagtg tcacttacct agatttacag cctcacttga atgtgtcact actcacagtc
                                                                     240
tetttaatet teagttttat etttaatete etetttate ttggaetgae atttagegta
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gctaagtgaa aaggtcatag ctgagattcc tggttcgggt gttacgcaca cgtacttaaa
                                                                     360
tgaaagcatg tggcatgttc atcgtataac acaatatgaa tacagggcat gcattttgca
                                                                      420
gcagtgagtc tcttcagaaa acccttttct acagttaggg ttgagttact tcctatcaag
                                                                      480
ccagtacgtg ctaacaggct caatattcct gaatgaaata tcagactagt gacaagctcc
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<221> NAME/KEY: misc_feature
<222> LOCATION: (159) .. (159)
<223> OTHER INFORMATION: n is a, c, g, or t
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tgttaaagaa acaggggtgg gaataaaatg gatttaggna cacccagttt gaattgcagt
                                                                     180
ttttttttt ctgacacatg gccaggctgt ggtgccagct taatggagta ggctgtcctt
                                                                     240
ggcacttgca tgtgtgaaag gagggttttg cctcttcttg agcatggctt gagttggtaa
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ggaaagctgt aactcacgaa gccctgagac ctgctacccc taagatcgag cttgttttca
                                                                     360
gtgactggct tgagtcatag gaggaggagt ctggtacagc tgcaggagag cagggccatc
                                                                     420
tgaageggta geattgeeae eateteeete teatetagag eagttttett atgeettggt
                                                                     480
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<210> SEQ ID NO 109
<211> LENGTH: 494
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(494)
<223> OTHER INFORMATION: AffymetrixID: 209007_s_at
<400> SEQUENCE: 109
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tctaataatt ctgtagcaaa gccaatacaa aaatcagcta aagctgccac agaagaggca
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tetteaagat caccaaaaat agateagaaa aaaagteeat atggaetgtg gatacetate

<221> NAME/KEY: misc_feature <222> LOCATION: (1)..(535)

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                                                                     300
cacaaaaaga tgtaaatact taacactcaa atattaacat tttaggtttc tcttgcagat
                                                                     360
atgagagata gcacagatgg accaaaggtt atgcacaggt gggagtcttt tgtatatagt
                                                                     420
tgtaaatatt gtcttggtta tgtaaaaatg aaatttttta gacacagtaa ttgaactgta
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ttcctgtttt gtat
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<210> SEQ ID NO 110
<211> LENGTH: 445
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(445)
<223> OTHER INFORMATION: AffymetrixID: 209458_x_at
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ttccccacca ccaagaccta cttcccgcac ttcgacctga gccacggctc tgcccaggtt
aagggccacg gcaagaaggt ggccgacgcg ctgaccaacg ccgtggcgca cgtggacgac
atgeceaacg egetgteege eetgagegae etgeaegege acaagetteg ggtggaeeeg
                                                                     300
gtcaacttca agetectaag ccactgeetg etggtgacee tggeegeeca ecteecegee
                                                                     360
qaqttcaccc ctqcqqtqca cqcctccctq qacaaqttcc tqqcttctqt qaqcaccqtq
                                                                     420
ctgacctcca aataccgtta agctg
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<210> SEQ ID NO 111
<211> LENGTH: 432
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(432)
<223> OTHER INFORMATION: AffymetrixID: 209795_at
<400> SEOUENCE: 111
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taagatttgt aatatttctc tctttttaga gaaatttgcc aatttacttt gttatttttc
                                                                     120
cccaaaaaga atgggatgat cgtgtattta tttttttact tcctcagctg tagacaggtc
                                                                     180
cttttcgatg gtacatattt ctttgccttt ataatctttt atacagtgtc ttacagagaa
                                                                     240
aagacataag caaagactat gaggaatatt tgcaagacat agaatagtgt tggaaaatgt
                                                                     300
gcaatatgtg atgtggcaaa tototattag gaaatattot gtaatottoa gacotagaat
                                                                      360
aatactagtc ttataatagg tttgtgactt tcctaaatca attctattac gtgcaatact
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tcaatacttc at
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<212> TYPE: DNA
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tgtggagacc tcaatgtggc acatgaagaa attgaccttc gcaaccccaa ggggaacaaa
                                                                     120
aagaatgctg getteacgee acaagagege caaggetteg gggaattaet geaggetgtg
                                                                     180
ccactggctg acagetttag gcacetetae eccaacacae ectatgeeta eacettttgg
                                                                     240
acttatatga tgaatgctcg atccaagaat gttggttggc gccttgatta ctttttgttg
                                                                     300
teccaetete tgttacetge attgtgtgac ageaagatee gttecaagge eetegegagt
                                                                     360
gatcactgtc ctatcaccct atacctagca ctgtgacacc acccctaaat cactttgagc
                                                                      420
ctgggaaata agcccctca actaccattc cttctttaaa cactcttcag agaaatctgc
                                                                      480
attotattto toatgtataa aacgaggaat cotocaacca ggotootgtg ataga
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<210> SEQ ID NO 113
<211> LENGTH: 368
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (220) .. (220)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(368)
<223> OTHER INFORMATION: AffymetrixID: 210254_at
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gaccacggag gtgacagcag ccatgaacgc catcccggct ggcatgtaca ggtgcagatg
                                                                     120
gtgggattcg gtcaccccat cagacaggat gccctctgca atctcacaca ccaggacgaa
                                                                     180
gagcagcatg aaggtcagga tccaccgcag gttgtgcccn gggaaatgaa gccatgtgct
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gtggtggatg tgcaccttgg agetetgact tececateca atgaagagga tggggaaggt
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gatgaagagt aggaagacgt gcggcaccac gttgagcgcg tccacaaagc agccgttgtt
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gaggaccc
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<211> LENGTH: 414
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<222> LOCATION: (1) .. (414)
<223> OTHER INFORMATION: AffymetrixID: 210338_s_at
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gccaaactag acaagtcaca gattcatgat attgtcctgg ttggtggttc tactcgtatc
cccaagattc agaagcttct ccaagacttc ttcaatggaa aagaactgaa taagagcatc
aaccctgatg aagctgttgc ttatggtgca gctgtccagg cagccatctt gtctggagac
aagtetgaga atgtteaaga tttgetgete ttggatgtea eteetette eettggtatt
gaaactgctg gtggagtcat gactgtcctc atcaagcgta ataccaccat tcctaccaag
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agacacaga cetteactae etattetgae aaccageetg gtgtgettat teag	414
2210 > SEQ ID NO 115 2211 > LENGTH: 557 2212 > TYPE: DNA 2213 > ORGANISM: Homo sapiens 2220 > FEATURE: 2221 > NAME/KEY: misc_feature 2222 > LOCATION: (1)(557) 2223 > OTHER INFORMATION: AffymetrixID: 211038_s_at	
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ggtgtteet tgaatgeeta tetteetttt gtgeetegga aceteteaeg eetgeeacaa	60
ttactcttt tccttggtag ttctgaactt taaataaggt aatgcctgta agaatgccat	120
aatgotcaa taattgtoat otgttattat titoatoagt aacatoatot gaatoatoag	180
attgtctgc ttttaacagc tgcatttttc attgtccaaa tatagtcaca tacatttgac	240
attttataa ttattgaata ataaattogt totgotattt tacaatgaaa aataatgotg	300
agagagcat tittgcacat gtatcgtggc agatgtaggc cagaggctct tctttatcca	360
cctatggcc aacctatgaa tgtatacacg tttaatgaga ttttgccagc aatcaaagcc	420
tcagggaaa atgtccctag ctctttacta catcagatca aggactctgg ataattggca	480
aacatectg gaatagetga aacagagata ttattetetg etgteetetg ttgtetttgt	540
ttttcacgt cttaata	557
220> FEATURE: 221> NAME/KEY: misc_feature 222> LOCATION: (1)(545) 223> OTHER INFORMATION: AffymetrixID: 211458_s_at	
400> SEQUENCE: 116	
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tetetggtg etecteatet eacceetace ttggaattta ataagettea ggeattteea	120
ttgcagact aaaaccactt ctaccatctc ctctagtatt ttccatgtat caggacagag	180
tgtettatg tagggaaggg geaggtatga agtgaggtag attatetata ceteteacte	240
ttcaggatt ctcgctccca tgctgctgtc ccttcattct cacactcaca ggaatgctat	300
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agggatgac ttttagtaaa tcatggggat tttattgatt tattatcact tataggattt	420
gtggggtgg gagtggggag caggaattgc actcagacat gacatttcaa ttcatctctg	480
aaatgaaaa gggttettee tettggggga aatetgtgtg teagttetgt eagetgeaag	540
tett	545
2210 > SEQ ID NO 117 2211 > LENGTH: 441 2212 > TYPE: DNA 2213 > ORGANISM: Homo sapiens 2205 > FEATURE: 2221 > NAME/KEY: misc_feature 2222 > LOCATION: (1)(441) 2223 > OTHER INFORMATION: AffymetrixID: 211560_s_at	

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tgcgcttggc accetcecce caccacagee etcagatgat ggaagatttt gtggagaage	180
tgctgctggc ttggactgcg gtggggctgc ccctccagga tgtgtctgtg gctgcctgca	240
atttetgteg eegteetgta eactttgage teatgagtga gtgggaaegt teetaetteg	300
ggaacatggg gccccagtat gtcaccacct atgcctgaga agccagctgc ctaggattca	360
caccccacct gcgcttcact tgggtccagg cctactcctg tcttctgctt tgttgtgtgc	420
ctctagctga attgagccta a	441
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tetgegttet g	131
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ctatgttttg tgtcacattg tctgatatat attgtgtaac ctgtcaggtg agttgattta	300
gacaacatag ctgacctttt atgacaaggc agtttgaata gggactattg taataccctc	360
acacattata ggggcancag agaatggcat ggaagagaca gtctacagag agctttaaga	420
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ag	482

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<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (249) .. (249)
<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: AffymetrixID: 212224_at
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ttctatggct tatcagcagg agtgtttacc aaagacattg ataaagccat aacaatctcc
                                                                      180
tetgetetge aggeaggaac agtgtgggtg aattgetatg gegtggtaag tgeeeagtge
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ccctttggnt gggattcaag atgtctggaa atggaagaga actgggagag tacggtttcc
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atgaatatac agaggtcaaa acagtcacag tgaaaatctc tcagaagaac tcataaagaa
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<223 > OTHER INFORMATION: AffymetrixID: 212232_at
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agatggccac actetttaga gtagttetea taagttetag aactggtage teggtegttt
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cgcacactag gtggcataca ggcagcagca ggtgttcata tccttgattt tgagaatttc
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ccctcaagta tgtggcagta aatacaacaa gacactctat gtattaatgt ctccattgtc
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<220> FEATURE:
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<222> LOCATION: (209) .. (209)
<223> OTHER INFORMATION: n is a, c, g, or t
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<222> LOCATION: (1)..(427)
<223> OTHER INFORMATION: AffymetrixID: 212534_at
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acctattccc tgtggcttag gtgagcatgt gaccaggcct ggcctcctga gtcccacagc
ttcctagcca cagtgataaa agaatgggnt atataactta agccaggcta aggaaagccc
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ggaccatgta agcctgaatt tgtgccatgt ggagagagtc tgtctgagga gaaactcgga	360
tgctagcaga aatggaaaga gaactaagtt ctgatgtcat ttttctggag gccctagatc	420
cagctgt	427
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tacacgttca gacagaactg ctgtatcaca ttccaatttt gaatagccag tgagcaatca	180
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taaaaattaa atgttacata agaacactat ttggaaagag ggtcctttta aaaactgaat	420
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agggtttgtc tttgtga	497
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<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (452)..(452)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(501)
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agaggattct gatcaggaag tggacattga gggcgataaa agctatttta atgctggatg
atgaccactg gcattggcat gttcagaaaa ctggatttag gaataatgtt ttgctacaga
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ggaaacctaa aaatatttgg tgcactgctc aattaacaaa cctacatgga gaccttaatt
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                                                                      420
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ccttcttgaa cgacttttct g
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: AffymetrixID: 217478_s_at
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cttttcttac ttaaacttca caccagaacc ttctgacatt ttctcctgca ttgtgactca
                                                                      180
cgaaattgac cgctacacag caattgccta ttgggtaccc cggaacgcac tgccctcaga
                                                                      240
tetgetggag aatgtgetgt gtggegtgge etttggeetg ggtgtgetgg geateategt
                                                                      300
gggcattgtt ctcatcatct acttccggaa gccttgctca ggtgactgat tcttccagac
cagagtttga tgccagcagc ttcggccatc caaacagagg atgctcagat ttctcacatc
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ctgc
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<210> SEQ ID NO 127
<211> LENGTH: 530
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(530)
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cagtetteet geceetttea caetgeaget gaagtteatt acetgaagga egeeteatea	180
tttcattcct tggctccaaa ccttctgctg cctctaagat aaaagctcaa cttcttaaca	240
gtgtacagtg tgcaacttcc aaccttttta tctgttctct ccaccttcag tttagcgtca	300
ttccaaaacc acaccettge aaagetttgt acteegeace ecagatgate tecaggeage	360
teagatetet tteetgeett tgeeetgeae tgtteeeegg taetteetee tttattgtag	420
cactcagete eccageeaat etgtacatee etcagaggea gegatetgat gaattggttt	480
ttgaateeea gaaagggtet geeatggagt tggeagteat eaeggtagat	530
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accetggtea acctacatga teettaaget aatggegaat caegatgace ttgtagacat	120
gcacacaact atacetttgt ccaacagate ataatatate tgctatecaa etggttttae	180
ctgcctaatc ctactgattt gggcactgct tgtatagtct ctcaagttca caggaaatgt	240
tgattttcta aggtcctcat tt	262
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atcctgagat ttcttaattt catggttctt taaatattat aaacacagag tcaacataga	180
atgaaattgt atttgttaaa atacacacat tggaggacaa gagcagatga ctacttttcg	240
aagtaatget geteetteet aaaagtetgt ttteaateet ggtaatatta ggggeaetge	300
ggcacctaag aagcettaaa tgagagetaa tecaatttag agagegatgg tgtcageatt	360
teggtetgea tatetgtgtg teegtatetg egtttgtgtg egtgtaegtg tgeecetgtg	420
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<223> OTHER INFORMATION: AffymetrixID: 219228_at
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cagaatgtgg gaaggccttc aattgtggct atcacctcac tcagcacgag agaatccaca
                                                                      120
caggogaaac coogtataaa tgtaaggagt gtgggaaggo tttcatttat ggatcgagco
                                                                      180
tcgtgaaaca tgagagaatt cataccgggg tgaaacccta tgggtgtaca gaatgtggga
                                                                      240
agagetttag teaeggeeat eagettaeae aacateagaa aacgeaeagt ggggegaaat
                                                                      300
cctacgaatg taaggagtgc gggaaggcat gtaaccacct aaaccatctc cgagaacatc
                                                                      360
agaggatcca caacagttga agagcctttt gaacgcagta gcccgctcgt atctatggtt
                                                                      420
tcgctttcca cagtttgtta cctgca
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<211> LENGTH: 331
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(331)
<223 > OTHER INFORMATION: AffymetrixID: 219607_s_at
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ctcttaagtg tgctggaatt ctgcattgct gtgtccctct ctgcctttgg atgtaaagtg
                                                                      180
ctctgttgta cccctggtgg ggttgtgtta attctgccat cacattctca catggcagaa
                                                                      240
acagcatete ecacaceact taatgaggtt tgaggeeace caaagateaa cagacaaatg
                                                                      300
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (149)
<223> OTHER INFORMATION: AffymetrixID: 221748_s_at
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cttatcctgg acatgaatgt attgtacact gacgcgtccc cactcctgta cagctgcttt
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<211> LENGTH: 534
<212> TYPE: DNA
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<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
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                                                                      120
gcctctgatg aaatcaagac ccttcaaagg tatatgtgtt ccaggttttt catcgacttc
                                                                      180
tcagacattg gagagcagca gagaaaactg gagtcctatt tgcagaacca ctttgtggga
                                                                      240
ttggaagacc gcaagtatga gtatctcatg acccttcatg gagtggtaaa tgagagcaca
gtgtgccntg atgggacatg aaagaagaca gactttaaac cttatcacca tgctggctat
ccgggtgtta gctgaccaaa atgtcattcc taatgtggct aatgtcactt gctattacca
gccagccccc tatgtagcag atgccaactt tagcaattac tacattgcac aggttcagcc
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<223> OTHER INFORMATION: AffymetrixID: 221622_s_at
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ttggcatagt ttgtggtgtt ttctatccca gttctttggc ttttactaaa aatggacgcc
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tggcaaccaa gtatcatacc gttccactgc caccaaaagg aagggtttta atccattgga
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tgacgetttg tcaaacacaa atgaaattaa ttgcgattcc tctagtettt cagattatgt
                                                                      300
ttggaatatt aaatggctat accattatgc aagtatttga aagagacact tgagaaaact
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atacatgaag agtaaccaaa aaaatgaatg gttgctaact tagcaaaatg aagtttctat
                                                                      420
aaagaggact caggcattgc tgaaagagtt aaaagtaact gtgaacaaat aatttgttct
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<223> OTHER INFORMATION: AffymetrixID: 218845_at
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aaaagcaaca tagagtttaa gtatccagta gtgatttgta aacttgtttt tcatttgaag	180
ctgaatatat acgtagtcat gtttatgttg agaactaagg atattcttta gcaagagaaa	240
atattttccc cttatcccca ctgctgtgga ggtttctgta cctcgcttgg atgcctgtaa	300
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gtgaacgcct cccaaggacg agcccagtgt agttgtgtgg gcgtgaactc tgcccgtgtg	420
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tggcagcaat ggctgtattt gaagataagt ttaggccaga catggaggag gaggaagcca	180
agaatetggt gagegaagee ategeagetg geatetteaa egaeetggge teeggaagea	240
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ccaacaagaa ggggaccagg cttggccggt acaggtgtga gaaagggact actgcagtcc	360
tcactgagaa aatcactcct ctggagattg aggtgctgga agaaacagtc caaacaatgg	420
acactteetg aatggeatea gtgggtgget ggeegeggtt etggaaggtg gtgageattg	480
aggcccagta agacactcat gtgg	504
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gattgagacc atcctggcta acacagtgaa accctgtctc tactaaaaaa atacaaaaaa	180
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aatggtgtga acccaggagg cggagcttgc agtgagccaa gatcgcgcca ctgcactcca	300
gcccgggtga cagagcaaga ctccgtctca aaaaaaagaa aagaaaaaag aaagcattgt	360
tttaattgag aggggcaggg ctggagaagg agcaagttgt ggggagccag gcttccctca	420
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<223> OTHER INFORMATION: n is a, c, g, or t
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atatcgtctt tgaaaatgtt aaattgagaa acctgttaac ttacatttta tgnattggca
cattgtatta cttactgcaa gagatatttc attttcagca cagtgcaaaa gttctttaaa
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aggtetegat eceggaceag aagtteetet aggtetegta geegateeeg tteeegtagt
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cgcaaatctt acagccggtc aagaagcagg agcaggagcc ggagccggag caagtcccgt
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tctgttagta ggtctcccgt gcctgagaag agccagaaac gtggttcttc aagtagatct
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aagteteeag catetgtgga tegecagagg teeeggteee gateaaggte cagateagtt
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gacagtggca attaaactgt aaataacttg ccctgggggc ctttttttaa aaaacaaaaa
                                                                      420
ccacaaaaat tcccaaacca tacttgctaa aaattctggt aagtatgtgc ttttctgtgg
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<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (268) .. (268)
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<223> OTHER INFORMATION: n is a, c, g, or t
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cctaactgat tatgcgaaat acccaagatt catgctactg taccacagat ttgttttcac 360	
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taaacagatt gatgcacgtg gtgggaaccc tgagctagta gccttagtaa aacacttaag
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                                                                   300
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ctccatccat acaatcacag ataactatgc aaaaaatcaa cagcagaaga aataccaaga 30	00
ggaggccatt ccagccttaa gagatatttc tattagtgaa gtaaaccaaa tgttctttct 36	50
tgcagccaaa gaactttaca ccaaaaactg aactgtgtgt aaccatagta acaccaagca 42	20
cgtatttatt tataagtttt tgccattata attttgacca taaattaatt tgaccatctc 48	30
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aagtgggaat tcaggaactt ggaccacgtt ttaccttaaa attaaggtct cttcagaaag 30	00
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caagtagaag aaaattccat ttataaagta ctgagagaat gatattggat tttgctgaac
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ccatgggcgg ataacactgc tttgaaaaga cattttcatg gagtgaaaga cataaagtgg
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tctattacag tatgtcatgt ttgctgtagt gctcatattt attgttgttt ttgttttagt
                                                                      180
actcacttgt ttcataatat caagattact aaaaatgggg gaaaggactt ctaatctttt
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ataagacttg accaagaccg actgccagta atagagcctg ttagtattaa tgaagaaaat	180
gagggatttg aacataacac acaagttaga aatcaaggaa ttatagcttt gagttaccgt	240
gactgggagg agattgtgaa gacctttgag atttcagagc ctgtgattac tccaagtcag	300
aggcagcaga agccaagtgc ttgatgctag ctgaaggact caaatggata gtgaagtcca	360
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ggtgtgcaaa cttgtatctg aagacctacc agggacaagc aggtaagagc tgatgtgagt	180
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cagetgettg ttgtcaagta taaagtcagg acetggettg getttaaceg tttttcaaga	300
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agagotgoat tgactaccag atttattttt taaaccagaa aatgttttaa atttataatt	480
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gcaatgtttt gtttgccttt atgcagagag gtgctccaag tgctgtgatt gagcaccgtg
ctagaggaac tgtaatgctt cagaagttgt agcttataca aaggaaacag gtcctgctgg
cttaatttaa acagttattg catgaagtag cgtggaggcc ctggactgct gctcgttctt
taggatggac tgttctggta tctggtattg gtttagagac tgttaataag ggacatcaca
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aggtgatggg attcatttga agcactctat ttctgtttta atg
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<210> SEQ ID NO 162
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<212> TYPE: DNA
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<222> LOCATION: (1)..(499)
<223> OTHER INFORMATION: AffymetrixID: 219452_at
<400> SEQUENCE: 162
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                                                                      120
tagaggagtt gctgagtcgt ggctggagtg aggaagagct tcagggtgtc cttcgtggaa
                                                                      180
acctgctgcg ggtcttcaga caagtggaaa aggtacagga agaaaacaaa tggcaaagcc
                                                                      240
cettggagga caagtteeeg gatgageage tgageagtte etgecactee gaceteteae
                                                                      300
gtctgcgtca gagacagagt ctgacttcag gccaggaact cactgagatt cccatacact
                                                                      360
ggacagccaa gttaccagcc aagtggtcag tctcagagtc ctccccccac atggccccag
                                                                      420
teettgeagt tgtggccace tteecagtee ttattetgtg getetgatga eccagttagt
                                                                      480
cctgccagat gtcactgta
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<210> SEQ ID NO 163
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(424)
<223 > OTHER INFORMATION: AffymetrixID: 219889_at
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ccatttgcaa taacagctgc aattccctgg atagacgagt tgatttcctc cctctgcccc	180
tcccccagcc atgccagctg gcctttgtaa gtgcaggaaa ccgagtagaa aatgtgaccc	240
tccaaatgga gaagctgcca gctttgccat tgtgaaccat ggtgaagtgc ttggaacata	300
ctgttcactc actctaaagg cgctgagact gtgctgttgt tctcgttttt atagtcaatg	360
gcttgttcat catccagatg tggctactga catatctaca cttcgcaccg gagtgtctgg	420
aatt	424
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gttggatgtc cctcaggtgt ccctcatcat taactatgat ctccctaata acagagaatt	180
gtacatacac agaattggga gatcaggtcg atacggccgg aagggtgtgg ccattaactt	240
tgtaaagaat gacgacatcc gcatcctcag agatatcgag cagtactatt ccactcagat	300
tgatgagatg ccgatgaacg ttgctgatct tatctgaagc agcagatcag tgggatgagg	360
gagactgttc acctgctgtg tactcctgtt tggaagtatt tagatccaga ttctacttaa	420
tggggtttat atggactttc ttctcataaa tggcctgccg tctc	464
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ttgggaggcc gttattctgc ccaccgcacc ctccgttcat cccctgccct gccgggcacc	180
tegetetace ecaggaaaat gtgagetegt ttteetgete ggeatgtget ecceetaagg	240
ctctgctcct ccctgggcct gaaagttcct tctcagcctg agagggggcc cttcgatctc	300
aggeatgact cagecegget gatgeetetg cagtgetgag teaggatttg gggeeggete	360
tettgggtet gteccetttt eccaggtaet geettaeaaa getgtggeea ggaagtggee	420
ggtataaagg atgcccaagg tctttgtacg tgtg	454

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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(239)
<223> OTHER INFORMATION: AffymetrixID: 221923_s_at
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tagtccatac tgagtgtcat caacaatcca gactgaagtc ttctatttta atctcaatcc
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cettttetga tttgccacce atgcctette aggetggaaa caatetettg gttccctaaa
                                                                      120
gcactttctt ctgactgctg tgattcagtg aaccttgccc tttgctttct attacttgtg
                                                                      180
catttgcctc acctgacaat gttttaaatc gcctttgtat ctccttagct gctcaataa
                                                                      239
<210> SEQ ID NO 167
<211> LENGTH: 477
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(477)
<223 > OTHER INFORMATION: AffymetrixID: 201887_at
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catgaagagg atgctgtgaa attcccaaca aacattgatg ctgacagtca tgcagtctgg
qaqtqqqqaa qtqatctttt qttcccatcc tcttctttta qcaqtaaaat aqctqaqqqa
                                                                      180
aaagggaggg aaaaggaagt tatgggaata cctgtggtgg ttgtgatccc taggtcttgg
                                                                      240
gagetettgg aggtgtetgt ateagtggat tteccatece etgtgggaaa ttagtagget
                                                                      300
catttactgt tttaggtcta gcctatgtgg atttttcct aacataccta agcaaaccca
                                                                      360
qtqtcaqqat qqtaattctt attctttcqt tcaqttaaqt ttttcccttc atctqqqcac
                                                                      420
tgaagggata tgtgaaacaa tgttaacatt tttggtagtc ttcaaccagg gattgtt
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<210> SEQ ID NO 168
<211> LENGTH: 444
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (444)
<223> OTHER INFORMATION: AffymetrixID: 211582_x_at
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aagagcaagg actagagttc ctgacctcca ggccagtccc tgatccctga cctaatgtta
                                                                      120
tegeggaatg atgatatatg tatetaeggg ggeetgggge tgggeggget eetgettetg
gcagtggtcc ttctgtccgc ctgcctgtgt tggctgcatc gaagagcacc ttctgtcctg
                                                                      240
gtcccaggcc cagggctcct cagagcagga actccactat gcatctctgc agaggctgcc
agtgcccagc agtgagggac ctgacctcag gggcagagac aagagaggca ccaaggagga
tccaagagct gactatgcct gcattgctga gaacaaaccc acctgagcac cccagacacc
ttcctcaacc caggcgggtg gaca
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<211> LENGTH: 490
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (1) .. (490)
<223> OTHER INFORMATION: AffymetrixID: 219030_at
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atgtaaaaaa tgcgggagac ttgagaagaa aggccatgga aggcaccatc gatggatcac
                                                                      120
tgataaatcc tacagtgatt gttgatccat ttcagatact tgtggcagca aacaaagcag
                                                                      180
ttcacctcta caaactggga aaaatgaaga caagaactct atctactgaa attattttca
                                                                      240
acctttcccc aaataacaat atttcagagg ctttgaaaaa atttggtatc tcagcaaatg
                                                                      300
acacttcaat tctaattgtt tacattgaag agggagaaaa acaaataaat caagaatacc
                                                                      360
taatatotoa agtagaaggt catcaggttt ototgaaaaa tottootgaa ataatgaata
ttacagaagt caaaaagata tataaactct cttcacaaga agaaagtatc gggacattat
tggatgctat
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<210> SEQ ID NO 170
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(37)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (75)..(75)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(412)
<223> OTHER INFORMATION: AffymetrixID: 212706_at
<400> SEOUENCE: 170
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ttntatgagg caatnggaaa tttgaacact gatcaactat aggatgattg gaattattaa
                                                                      120
tttttaaagg tgtgataaga tactgcactt ggctgggcac agtggcacat gcctgtaatc
                                                                      180
ccagctactt ggcaggctga ggtgggagaa tcgcttgagc tcaggagttc gagaccagcc
                                                                      240
tgggcaacgt ggcgaaatcc ccgtctttac aaaaacaaac aaacaaacaa aaaagatatt
gcagttgtgt tgtaagcgtc cttatctttc agagctacat agtggaatgt ttatggaata
tttaggataa atgatatagg catttgggat ttgctgcaaa atgacccaga gg
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<210> SEQ ID NO 171
<211> LENGTH: 419
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (1)..(419)
<223> OTHER INFORMATION: AffymetrixID: 202902_s_at
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tcctgaaaga agctgtggcc aataaaggcc cagtgtctgt tggtgtagat gcgcgtcatc
                                                                     120
cttctttctt cctctacaga agtggtgtct actatgaacc atcctgtact cagaatgtga
                                                                     180
atcatggtgt acttgtggtt ggctatggtg atcttaatgg gaaagaatac tggcttgtga
                                                                     240
aaaacagctg gggccacaac tttggtgaag aaggatatat tcggatggca agaaataaag
                                                                     300
gaaatcattg tgggattgct agctttccct cttacccaga aatctagagg atctctcctt
                                                                     360
tttataacaa atcaagaaat atgaagcact ttctcttaac ttaatttttc ctgctgtat
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<210> SEQ ID NO 172
<211> LENGTH: 452
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (452)
<223 > OTHER INFORMATION: AffymetrixID: 200663_at
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gccattgctg gctatgtgtt tagagataag gtgatgtcag agtttaataa caacttccgg
                                                                     120
cagcagatgg agaattaccc gaaaaacaac cacactgctt cgatcctgga caggatgcag
                                                                     180
gcagatttta agtgctgtgg ggctgctaac tacacagatt gggagaaaat cccttccatg
                                                                     240
togaagaacc gagtccccga ctcctgctgc attaatgtta ctgtgggctg tgggattaat
                                                                     300
ttcaacgaga aggcgatcca taaggagggc tgtgtggaga agattggggg ctggctgagg
                                                                     360
aaaaatgtgc tggtggtagc tgcagcagcc cttggaattg cttttgtcga ggttttggga
                                                                     420
attgtctttg cctgctgcct cgtgaagagt at
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<210> SEQ ID NO 173
<211> LENGTH: 517
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (517)
<223> OTHER INFORMATION: AffymetrixID: 202138_x_at
<400> SEQUENCE: 173
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gtgccgaaga cgcagatgaa attcagcatc cagacgatgt gccccatcga aggcgaaggg
                                                                      120
aacattgcac gtttcttgtt ctctctgttt ggccagaagc ataatgctgt caacgcaacc
                                                                     180
cttatagata gctgggtaga tattgcgatt tttcagttaa aagagggaag cagtaaagaa
aaagccgctg ttttccgctc catgaactct gctcttggga agagcccttg gctcgctggg
aatgaactca ccgtagcaga cgtggtgctg tggtctgtac tccagcagat cggaggctgc
agtgtgacag tgccagccaa tgtgcagagg tggatgaggt cttgtgaaaa cctggctcct
tttaacacgg ccctcaagct ccttaagtga attgccgtaa ctgattttaa agggtttaga
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ttttaagaat ggtgctcttt catgcctatt atcagta	517
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<400> SEQUENCE: 174	
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gcgtgctgtt tcccttgtac cagagggcgg caccgtggaa attctgtttt ccctgtagca	120
tattgtgttg gattgcatta ctggcagaga aaggacaagg tgccattcaa gtcctagggt	180
gggcttccag ctgccttaat agaagtactc aagtcttttg ggtagtgagc tggaaagcct	240
acaggaaaag aggggtacct gttttcattt gaaaactttg attcatggaa cctttaaaac	300
taatctcaga aaaatttttg gtgcccatgc agctgtagtt gttcactgct ttcctggatg	360
gatgggactc ttatgtcata acttctgtta ctcctttggc ccatagctaa ggtcatcctt	420
ccccacaggg gtggctttgg gattggatga tacagctttt gcttctgtgt agtatacctg	480
tacatacttg tttcaggcag cctttc	506
<pre><210> SEQ ID NO 175 <211> LENGTH: 558 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (124)(124) <223> OTHER INFORMATION: n is a, c, g, or t <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (422)(422) <223> OTHER INFORMATION: n is a, c, g, or t <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (422)(422) <223> OTHER INFORMATION: n is a, c, g, or t <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (1)(558) <223> OTHER INFORMATION: AffymetrixID: 201109_s_at</pre>	
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cctngcagtg gccagaatta gggaatcaga atcaaaccag tgtaaggcag tgctggctgc	180
cattgcctgg tcacattgaa attggtggct tcattctaga tgtagcttgt gcagatgtag	240
caggaaaata ggaaaaccta ccatctcagt gagcaccagc tgcctcccaa aggaggggca	300
gccgtgctta tatttttatg gttacaatgg cacaaaatta ttatcaacct aactaaaaca	360
tteettttet etttttteet gaattateat ggagttttet aattetetet tttggaatgt	420
angatttttt ttaaatgott taogatgtaa aatatttatt ttttaottat totggaagat	480
ctggctgaag gattattcat ggaacaggaa gaagcgtaaa gactatccat gtcatctttg	540
ttgagagtet tegtgaet	558
<210> SEQ ID NO 176 <211> LENGTH: 502 <212> TYPE: DNA	

<222> LOCATION: (1)..(338)

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<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<223> OTHER INFORMATION: AffymetrixID: 202531_at
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cactggctgg ctcctagggg aacagaccag tgaccccaga aaagcataac accaatccca
                                                                       120
gggctggctc tgcactaagc gaaaattgca ctaaatgaat ctcgttccaa agaactaccc
                                                                       180
cttttcagct gagccctggg gactgttcca aagccagtga atgtgaagga aactcccctc
                                                                       240
cttcggggca atgctccctc agcctcagag gagctctacc ctgctccctg ctttggctga
                                                                       300
ggggcttggg aaaaaaactt ggcacttttt cgtgtggatc ttgccacatt tctgatcaga
                                                                       360
ggtgtacact aacatttccc ccgagctctt ggcctttgca tttatttata cagtgccttg
ctcggggccc accacccct caagccccag cagccctcaa caggcccagg gagggaagtg
                                                                       480
tgagcgcctt ggtatgactt aa
                                                                       502
<210> SEQ ID NO 177
<211> LENGTH: 513
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (378) .. (378)
<223 > OTHER INFORMATION: n is a, c, g, or t
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<222> LOCATION: (453) .. (453)
<223> OTHER INFORMATION: n is a, c, g, or t
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<222> LOCATION: (1) .. (513)
<223> OTHER INFORMATION: AffymetrixID: 216274_s_at
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gaaagtccga ttgtagtggt gctcagtggc agcatggaac ctgcatttca tagaggagat
                                                                       120
cttctctttc taacaaatcg agttgaagat cccatacgag tgggagaaat tgttgttttc
                                                                       180
aggatagaag gaagagagat tootatagtt caccgagtot tgaagattoa tgaaaagcaa
                                                                       240
aatgggcata tcaagttttt gaccaaagga gataataatg cggttgatga ccgaggcctc
                                                                       300
tataaacaag gacaacattg gctagagaaa aaagatgttg tggggagagc caggggattt
                                                                       360
gttccttata ttggaatngt gacgatcctc atgaatgact atcctaaatt tangtatgca
                                                                       420
gttctctttt tgctgggttt attcgtgctg gtncatcgtg agtaagaagc ctgccttgct
                                                                       480
gttcctggga agatgccata gttttcgtta ctg
                                                                       513
<210> SEQ ID NO 178
<211> LENGTH: 338
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: AffymetrixID: 200041_s_at	
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acctatttgg ccgaggcatg gacatcgagc gggtgaacat tgcttttaat tatgacatgc	120
ctgaggatte tgacacetae etgeateggg tggeeagage aggeeggttt ggeaceaagg	180
gcttggctat cacatttgtg tccgatgaga atgatgccaa gatcctcaat gatgtgcagg	240
ategetttga ggteaatatt agtgagetge etgatgagat agacatetee teetacattg	300
aacagacacg gtagaagact cgcccatttt ggaatgtg	338
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gaagateett ggeeaggagg gtgatgeeag etatettget tetgaaatat etaeetggga	120
tggagtgata gtaacacctt cagaaaaggc ttatgagaag ccaccagaga agaaggaagg	180
agaggaagaa gaggagaata cagaaagaac cacctcaagg agaggaagaa gaaagcatgg	240
aaactcagga gtgacattcc cttcactcct tttcctaccc aagggaaaga ctggagccta	300
agctgcctgc tactggcttt acatggtgac agacattccg tggataggaa gatagcagga	360
gaaagtaact ccatagagtg tcattccact ggttgatatt ggcttagctg ccagtctccc	420
attigigace taigecatee atetataatg gaggatacea acattiette etaatattet	480
ataatotooa actootga	498
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atggagegga teatgaaage eeaggeaett egggaeaact eeaceatggg etatatgatg	120
gccaaaaagc acctggagat caaccctgac caccccattg tggagacgct gcggcagaag	180
gctgaggccg acaagaatga taaggcagtt aaggacctgg tggtgctgct gtttgaaacc	240
gccctgctat cttctggctt ttcccttgag gatccccaga cccactccaa ccgcatctat	300
cgcatgatca agctaggtct aggtattgat gaagatgaag tggcagcaga ggaacccaat	360
gctgcagttc ctgatgagat cccccctctc gagggcgatg aggatgcgtc tcgcatggaa	420
gaagtogatt aggttaggag ttoatagttg gaaaacttgt gooottgtat agtgtooc	478

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<211> LENGTH: 508
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(508)
<223> OTHER INFORMATION: AffymetrixID: 200079_s_at
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agetgecaga aacgaacete tttgaaactg aagaaacteg caaaattett gatgatatet
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gtgtggcaaa agctgttgaa tgccctccac ctcggaccac agccaggctc cttgacaagc
                                                                     120
ttgttgggga gttcctggaa gtgacttgca tcaatcctac attcatctgt gatcacccac
                                                                     180
agataatgag ccctttggct aaatggcacc gctctaaaga gggtctgact gagcgctttg
                                                                     240
agctgtttgt catgaagaaa gagatatgca atgcgtatac tgagctgaat gatcccatgc
                                                                     300
ggcagcggca gctttttgaa gaacaggcca aggccaaggc tgcaggtgat gatgaggcca
                                                                     360
tgttcataga tgaaaacttc tgtactgccc tggaatatgg gctgcccccc acagctggct
                                                                      420
ggggcatggg cattgatcga gtcgccatgt ttctcacgga ctccaacaac atcaaggaag
tacttctgtt tcctgccatg aaacccga
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<210> SEQ ID NO 182
<211> LENGTH: 393
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(393)
<223 > OTHER INFORMATION: AffymetrixID: 200629_at
<400> SEOUENCE: 182
tccagtttac tgaactccag accatgcatg tagtccactc cagaaatcat gctcgcttcc
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cttggcacac cagtgttctc ctgccaaatg accctagacc ctctgtcctg cagagtcagg
                                                                     120
gtggcttttc ccctgactgt gtccgatgcc aaggagtcct ggcctccgca gatgcttcat
                                                                     180
tttgaccctt ggctgcagtg gaagtcagca cagagcagtg ccctggctgt gtcctggacg
                                                                     240
ggtggactta gctagggaga aagtcgaggc agcagccctc gaggccctca cagatgtcta
                                                                     300
ggcaggcctc atttcatcac gcagcatgtg caggcctgga agagcaaagc caaatctcag
                                                                     360
ggaagtcctt ggttgatgta tctgggtctc ctc
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<210> SEQ ID NO 183
<211> LENGTH: 439
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (439)
<223> OTHER INFORMATION: AffymetrixID: 200634_at
<400> SEQUENCE: 183
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aagtttttac gtgaatgggc tgacacttgg gggccagaaa tgttcggtga tccgggactc
actgctgcag gatggggaat ttagcatgga tcttcgtacc aagagcaccg gtggggcccc
caccttcaat gtcactgtca ccaagactga caagacgcta gtcctgctga tgggcaaaga
aggtgtccac ggtggtttga tcaacaagaa atgttatgaa atggcctccc accttcggcg
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ttcccaqtac tqacctcqtc tqtcccttcc ccttcaccqc tccccacaqc tttqcacccc
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tttcctcccc atacacaca aaaccatttt attttttggg ccattacccc atacccctta
                                                                      420
                                                                     439
ttgctgccaa aaccacatg
<210> SEQ ID NO 184
<211> LENGTH: 541
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(541)
<223> OTHER INFORMATION: AffymetrixID: 200802_at
<400> SEQUENCE: 184
taattgcacg gattaccagg ctcgccggct tcgaatccga tatgggcaaa ccaagaagat
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gatggacaag gtggagtttg tccatatgct caatgctacc atgtgcgcca ctacccgtac
catctgcgcc atcctggaga actaccagac agagaagggc atcactgtgc ctgagaaatt
                                                                     180
gaaggagttc atgccgccag gactgcaaga actgatcccc tttgtgaagc ctgcgcccat
tgagcaggag ccatcaaaga agcagaagaa gcaacatgag ggcagcaaaa agaaagcagc
                                                                     300
agcaagagac gtcaccctag aaaacaggct gcagaacatg gaggtcaccg atgcttgaac
attectgect cectatttge caggetttea tttetgtetg etgagatete agageetgee
caacagcagg gaagccaagc acccattcat ccccctgccc ccatctgact gcgtagctga
                                                                     480
qaqqqqaaca qtqccatqta ccacacaqat qttcctqtct cctcqcatqq qcataqqqac
                                                                     540
                                                                      541
<210> SEQ ID NO 185
<211> LENGTH: 456
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (456)
<223> OTHER INFORMATION: AffymetrixID: 200860_s_at
<400> SEQUENCE: 185
acttcagttg caccatgctg tacctttttg cagaggccaa tacggaagcc atccaagaac
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agatcacaag agttctcttg gaacggttga ttgtaaatag gccacatcct tggggtcttc
                                                                     120
ttattacctt cattgagctg attaaaaacc cagcgtttaa gttctggaac catgaatttg
                                                                     180
tacactgtgc cccagaaatc gaaaagttat tccagtcggt cgcacagtgc tgcatgggac
                                                                     240
agaagcaggc ccagcaagta atggaaggga caggtgccag ttagacgaaa ctgcatctct
                                                                     300
gttgtacgtg tcagtctaga ggtctcactg caccgagttc ataaactgac tgaagaatcc
                                                                     360
tttcagctct tcctgacttt cccagccctt tggtttgtgg gtatctgccc caactactgt
                                                                      420
tgggatcagc ctcctgtctt atgtgggcac gttcca
                                                                      456
<210> SEQ ID NO 186
<211> LENGTH: 506
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(506)
<223 > OTHER INFORMATION: AffymetrixID: 200983_x_at
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<213 > ORGANISM: Homo sapiens

<220> FEATURE:

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gtctgtcctg ttcgggctgc tgctcgtcct ggctgtcttc tgccattcag gtcatagcct
                                                                      120
gcagtgctac aactgtccta acccaactgc tgactgcaaa acagccgtca attgttcatc
                                                                      180
tgattttgat gcgtgtctca ttaccaaagc tgggttacaa gtgtataaca agtgttggaa
                                                                      240
gtttgagcat tgcaatttca acgacgtcac aacccgcttg agggaaaatg agctaacgta
                                                                      300
ctactgctgc aagaaggacc tgtgtaactt taacgaacag cttgaaaatg gtgggacatc
                                                                      360
cttatcagag aaaacagttc ttctgctggt gactccattt ctggcagcag cctggagcct
                                                                      420
tcatccctaa gtcaacacca ggagagette teccaaacte ecegtteetg egtagteege
                                                                      480
tttctcttgc tgccacattc taaagg
                                                                      506
<210> SEQ ID NO 187
<211> LENGTH: 375
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (375)
<223> OTHER INFORMATION: AffymetrixID: 200991_s_at
<400> SEQUENCE: 187
tgccacccgg gagtctatgg tcaaactctc aagtaagctg agtgccgtga gcttgcgggg
                                                                       60
aattggcagt cccagcacag atgccagtgc cagtgatgtc cacggcaatt tcgccttcga
                                                                      120
gggcattgga gatgaggatc tgtaatctcc actgcttgga tgtctgccct ctaccccaga
                                                                      180
ggaatttaca gaaacttgcc ctgtgcctgt gtcccccatg ctaggggcgg aggggtcttt
                                                                      240
teettettet tteetaeeta eccetttet ettggeeagg ggeetegtat eetaeette
                                                                      300
cttgtcccct gggctggctg cacagaggat tgccccttct cttttcagag ctggccctcg
                                                                      360
                                                                      375
atqccaaatt aqcat
<210> SEQ ID NO 188
<211> LENGTH: 312
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (312)
<223> OTHER INFORMATION: AffymetrixID: 201112_s_at
<400> SEQUENCE: 188
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                                                                       60
agtataccaa actgtggact ccattattac agtctttgat tggtcttttt gagttacccg
                                                                      120
aagatgatac cattcctgat gaggaacatt ttattgacat agaagataca ccaggatatc
agactgcctt ctcacagttg gcatttgctg ggaaaaaaaga gcatgatcct gtaggtcaaa
                                                                      240
tggtgaataa ccccaaaatt cacctggcac agtcacttca catgttgtct accgcctgtc
                                                                      312
caggaagggt tc
<210> SEQ ID NO 189
<211> LENGTH: 338
<212> TYPE: DNA
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<221> NAME/KEY: misc feature
<222> LOCATION: (1)..(338)
<223> OTHER INFORMATION: AffymetrixID: 201214_s_at
<400> SEOUENCE: 189
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gctgaaggga gccaggagcc tggagacagt gtacctggag cggaacccct tgcagaagga
                                                                   120
180
gttegteagg ttetgagtee ttettggete eteatgtggt eeeteteete ggaagaactg
                                                                   240
cccagccacg ggtttttaac ccacctgttg ctcctgaggt cgtcactata tcaacagtca
                                                                   300
caaacccaat ggcaataaag gcactgacga tagctggc
                                                                   338
<210> SEQ ID NO 190
<211> LENGTH: 385
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (385)
<223 > OTHER INFORMATION: AffymetrixID: 201241_at
<400> SEQUENCE: 190
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tgtagcagcc gtggaaaagg gtgttataac acaagactca aggaagatgg aggctgtacc
atatggtaca acqagatgca gttactatct gagatagaag aacacctgaa ctgtaccatt
                                                                   180
tctcaggttg agccggatat aaaggtacca gtggatgaat ttgatgggaa agttacctac
                                                                   240
ggtcagaaaa gggctgctgg tggtggaagc tataaaggcc atgtggatat tttggcacct
                                                                   300
actgttcaag agttggctgc ccttgaaaag gaggcgcaga catctttcct gcatcttggc
                                                                   360
taccttccta accaqctqtt caqaa
                                                                   385
<210> SEQ ID NO 191
<211> LENGTH: 371
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(371)
<223> OTHER INFORMATION: AffymetrixID: 201263_at
<400> SEOUENCE: 191
gatctggatc caggctgtac attgaataaa aagattcgaa atgcacagtt agcacagtat
                                                                    60
aacttcattt tagttgttgg tgaaaaagag aaaatcactg gcactgttaa tatccgcaca
                                                                   120
agagacaata aggtccacgg ggaacgcacc atttctgaaa ctatcgagcg gctacagcag
                                                                   180
ctcaaagagt tccgcagcaa acaggcagaa gaagaatttt aatgaaaaaa ttacccagat
                                                                   240
tggctccatg gaaaaggagg aacagcgttt ccgtaaaatt gactttgtac tcgaaaacgt
                                                                   300
caatttatat tgaacttgga ggaggagttt ggcaaagtct gaaataggtc aacctgcagg
cgtaactatt t
                                                                   371
<210> SEQ ID NO 192
<211> LENGTH: 492
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
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<221> NAME/KEY: misc feature
<222> LOCATION: (1)..(492)
<223> OTHER INFORMATION: AffymetrixID: 201386_s_at
<400> SEOUENCE: 192
ggagatcatc tgacactgct gaacgtctac catgctttta aacaaaatca tgaatcggtt
                                                                      60
cagtggtgtt atgacaactt cattaactac aggtccctga tgtccgcaga caatgtacgc
                                                                     120
cagcagctat ctcgaattat ggacagattt aatttgcctc gtcgaagtac tgactttaca
                                                                     180
agcagggact attatattaa tataagaaaa gctttggtta ctgggtattt tatgcaggtg
                                                                     240
gcacatttag aacgaacagg gcattactta actgtgaaag ataaccaggt ggttcagttg
                                                                     300
catccctcta ctgttcttga ccacaaacct gaatgggtgc tttataatga gtttgttcta
                                                                     360
                                                                      420
acaacaaaga attacatccg gacatgtaca gatatcaagc cagaatggtt ggtgaaaatt
gcccctcaat attatgacat gagcaatttc ccacagtgtg aagcaaagag acagttggac
                                                                      480
cgcatcattg cc
                                                                      492
<210> SEQ ID NO 193
<211> LENGTH: 408
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(408)
<223 > OTHER INFORMATION: AffymetrixID: 201417_at
<400> SEQUENCE: 193
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                                                                     120
atctatctaa atgccgattt gagttcgcga cactatgtac tgcgtttttc attcttgtat
ttgactattt aatcetttet acttgteget aaatataatt gttttagtet tatggeatga
                                                                     180
tgatagcata tgtgttcagg tttatagctg ttgtgtttaa aaattgaaaa aagtggaaaa
                                                                     240
catctttgta catttaagtc tgtattataa taagcaaaaa gattgtgtgt atgtatgttt
                                                                     300
aatataacat gacaggcact aggacgtctg cctttttaag gcagttccgt taagggtttt
                                                                     360
tgtttttaaa ctttttttg ccatccatcc tgtgcaatat gccgtgta
                                                                     408
<210> SEQ ID NO 194
<211> LENGTH: 422
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(422)
<223> OTHER INFORMATION: AffymetrixID: 201576_s_at
<400> SEQUENCE: 194
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                                                                      60
                                                                     120
ccccagcaca tcctgatgac ctcggcccca aacaccatca ccgtgctgga actggagtgg
gcaccetgca gcagtgatga tecagaacta tgtgetgtga egttegtgga eaggeeagtt
attggctcat ctgtgaccta cgatcatccc tccaaacctg ttgaaaaaaag actcatgccc
ccacccccgc aaaaaaacaa agattcatgg ctggaccatg tatgatgatg aaagcctgtg
tetttgaggg attetaceet gaacatacet cacagateet ceetgteatg ceacatttea
ctgattggaa tgtggaaatg gaaaaggaat ttaggatgtg cattttcacc tgaggtttcc
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<400> SEQUENCE: 197

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422
ct
<210> SEQ ID NO 195
<211> LENGTH: 551
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(551)
<223> OTHER INFORMATION: AffymetrixID: 201872_s_at
<400> SEOUENCE: 195
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aaaagaagag tggaaactac tttttcttgg atgattagac tgactctgag aatattgata
                                                                      120
agccatttat taaaaggagt atttactaga attttttgtc atataaaact tgaatcagga
                                                                      180
ttttatgccc cacatactct ggaacttgaa gtataatata cttaatataa cataaaaagc
                                                                      240
cagttgggtt ctaaattgta gttgaaacac agaaaatgcc acttttctgt tcctgaagag
                                                                      300
gctcttttgt gcataatatt ctaaaatgaa gacatttcaa gctatacaaa ttacttccaa
gttttcatga tgtatgggaa gattttcagt aggtgtatta tattcacggt accaaatgct
gaccagtgtt gctccatttt ttaaatcttg aaaagggttt ctgtacttac ctggtttgcc
aagtatgcca gtgtaatgaa actgccctta ttttaaaagc cagtcaaaga ttccactgat
tgacatttga t
                                                                      551
<210> SEQ ID NO 196
<211> LENGTH: 519
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(519)
<223> OTHER INFORMATION: AffymetrixID: 201892_s_at
<400> SEOUENCE: 196
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tgggtcatat tgcgaaagcc ttggcccttg gggcctccac agtcatgatg ggctctctcc
                                                                      120
tggctgccac cactgaggcc cctggtgaat acttcttttc cgatgggatc cggctaaaga
                                                                      180
aatatcgcgg tatgggttct ctcgatgcca tggacaagca cctcagcagc cagaacagat
                                                                      240
atttcagtga agctgacaaa atcaaagtgg cccagggagt gtctggtgct gtgcaggaca
                                                                      300
aagggtcaat ccacaaattt gtcccttacc tgattgctgg catccaacac tcatgccagg
                                                                      360
acattggtgc caagagettg acceaagtee gagecatgat gtactetggg gagettaagt
                                                                      420
ttgagaagag aacgtcctca gcccaggtgg aaggtggcgt ccatagcctc cattcgtatg
                                                                      480
agaagcggct tttctgaaaa gggatccagc acacctcct
                                                                      519
<210> SEQ ID NO 197
<211> LENGTH: 283
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(283)
<223 > OTHER INFORMATION: AffymetrixID: 202174_s_at
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<220> FEATURE:

<221> NAME/KEY: misc_feature <222> LOCATION: (106)..(106)

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caacctttaa ataqtqctqc ccataaqqaq tcacctccta ctqttqattc aactcaacaq
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cctaaccctt tgccgttacg tttacctgaa atggaaccct tagtgcctag agtcaaagaa
                                                                     120
gttaaatctg ctcaggaaac tcctgaaagc tctctggctg gaagtcctga tactgaatct
                                                                     180
ccagtgttag tgaatgacta tgaagcagaa tctggtaata taagtcaaaa gtctgatgaa
                                                                     240
gaagattttg taaaagttga agatttacca ctgaaactga caa
                                                                     283
<210> SEQ ID NO 198
<211> LENGTH: 522
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (522)
<223> OTHER INFORMATION: AffymetrixID: 202176_at
<400> SEQUENCE: 198
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gcaacagcag ctcttacaga aagtcctggc agccactgac ctggatgccg aggaggaggt
ggtggctggg gaatttggct ccagatccag ccaggcatct cggcgctttg gcaccatgag
ttctatgtct ggggccgacg acactgtgta catggagtac cactcatcgc ggagcaaggc
gcccagcaaa catgtacacc cgctcttcaa gcgctttagg aaatgatgct taggcagggt
acttegttea agaceggege ttggcacect tgttggaaag ggatttteag cataacattt
teetteeace tetttgacet teetteeage gttggeeaaa ttgtgetgag gaagatgeat
                                                                     420
caaqqqcttq qctqtqcctt cataqqtcat ctaqqqtttt ataaaqqaqq aqqaqacaat
                                                                     480
attttttcaa actttttggg gagtggggtc atttctgtat at
                                                                     522
<210> SEQ ID NO 199
<211> LENGTH: 423
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(423)
<223> OTHER INFORMATION: AffymetrixID: 202220_at
<400> SEOUENCE: 199
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cttctaagat cctgtcttca gctgggtcag agaaaacttc ttgactaaaa ctggtcagaa
                                                                     120
ctcatcacag aaatgaaata cagtggtctc tctctcccag aactggttgc agctaaaaca
                                                                     180
gagagatctg actgctggct ataggatttt ggacttaatg actgaaattg caaattgtcc
                                                                     240
tttttcttgg cattacagat tttgccaaaa taactttttg tatcaaatat tgatgtgtga
                                                                     300
aagtgaagga gctagtctgc tgaaccagga atagtttgag atattgaact gtcatttttg
                                                                      360
cacatttgaa tactttgcag gctggctttg tataaactta tcctctggtt tcctatatgt
                                                                      420
                                                                      423
tgt
<210> SEQ ID NO 200
<211> LENGTH: 344
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (108)..(113)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature <222> LOCATION: (1)..(344)
<223> OTHER INFORMATION: AffymetrixID: 202225_at
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tacttgtaga aaaaccttgt cacaactgat ttgaatgttc ctattntnnn nnnctttgac
                                                                       120
tttgatattg gcttgtaatg tctcttttca tcatatgtaa tatcagtgga acaggcagcg
                                                                       180
ctactcaagt cctaaggatt cctcagtgat cagtgatcca gggccgttca tgaaccactg
                                                                       240
ggctggattt gactgttgag tgtggcagtt aatgcccctc aagaaatcaa aggatgtctt
                                                                       300
ataagtgtct tccaaaaaaa agcaaatgct gaaatcctat tggc
                                                                       344
<210> SEQ ID NO 201
<211> LENGTH: 371
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(371)
<223 > OTHER INFORMATION: AffymetrixID: 202464_s_at
<400> SEQUENCE: 201
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ggaaccacac caatgatatt tttctttgta atacttgaaa tttattttt tattattttg
                                                                       120
atagcagatg tgctatttat ttatttaata tatgtataag gagtcctaaa caatagaaag
                                                                       180
ctgtagaagc tgtagagata ggcttcagtt gttaattggt ttggagcctc ctatgtgtga
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cttatgactc tctgtgttct gtgtatttgt ctgaattaat gacctgggat ataaagctat
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aaatttagac agggatctct tacctttgga aaataggggt taggcatgaa ggtggttgtg	540
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ttgctcccat gctgctgtcc cttcaggctc acatgcacag gaatgctaca tgatggccag	180
ctgcttccct ccttggttat catccactgc agctgctagt tagaaaggtt tggagggatg	240
acttttagta aatcatgggg attttattga tttattttca cttttgggat tttgtggggt	300
gggagtgggg agcaggaatt gcactcagac atgacatttc aattcatctc tgctaatgaa	360

aagggttett tetettgggg gaaatgtgtg tgteagttet gteagetgea agttettgta	420
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gatgggtcac cgggttgatt attttattgc ttcaaaagca gtggactgtc ttttggattc	180
aaagtgggca aaggccaaga aaggagagga agctttattt acaaccaggg agtctgtggt	240
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ggcatgaaca tgactttggt tgggattgcg gatagttagg gttacctctg aatcgtgtag	180
cttttatgag agcagctgtg caagtgaatc cacattaatg ccttgtcgtg gtgccattcc	240
cagegeetga egataegete ttetattgte ttattetgge aggttttgae gttttaaatt	360
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cettteetee tetgaettgg ggaeettttg ggggaggget gegaegettg etetgtttgt	240
ggggtgacgg gactcaggcg ggacagtgct gcagctccct ggcttctgtg gggcccctca	300

cctactta	acc caggtgggtc ccggctctgt gggtgatggg gaggggcatt gctgactgtg	360
tatatagg	gat aattatgaaa agcagttetg gatggtgtge ettecagate etetetgggg	420
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ttcagaga	agg tcagttaagt gacggattct gttgtggttt gaatgcagta ccagtgttct	180
cttcgagc	caa agtagacetg ggteaetgta ggeataggae ttggattget teagatggtt	240
tgctgtat	ca tttttcttct ttttcttttc ctggggactt gtttccatta aatgagagta	300
attaaaat	cg cttgtaaatg agggcataca agcatttgca acaaatattc aaatagaggc	360
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	gt aaagaagttg tcagcagagg agatgactat taaacttagt ccaaagccac	180
	cct ttattttctg agetttgttg gaaaacatga taccagaatt aatttgccac	240
	otg tittaacagt ggacccatgt aatactitta tocatgitta aaaagaagga	300 337
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aagaatgctg getteacgce acaagagege caaggetteg gggaattaet geaggetgtg	180
ccactggctg acagetttag gcacetetae eccaacacae ectatgeeta cacettttgg	240
acttatatga tgaatgctcg atccaagaat gttggttggc gccttgatta ctttttgttg	300
teccaetete tgttacetge attgtgtgae ageaagatee gttecaagge eetegegagt	360
gateactgte etateaceet atacetagea etgtgacace acceetaaat caetttgage	420
ctgggaaata agcccctca actaccattc cttctttaaa cactcttcag agaaatctgc	480
attotattto toatgtataa aacgaggaat ootooaacca ggotootgtg ataga	535
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aagtacagcc acccactgac atctgaattt atatacctgt tgagttttga gtgcacccaa	180
acactcgata aaccaggtga agaaatttag cttccatgtt ctacttcagc taaaacagct	240
acatacaacc tagtacactt gaagtcagac agacatttca gttgcttacc tccagtactg	300
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cgactttggt atcatctgtc agtttttgcc cagtgagttc tgcatttgca gctccttgtt	180
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gagtaagaac agtccccagt ccagcagcca cccttttcag ctgctgttca ttgccagttg	300
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gatggtttcc taggaaatca caggcttctg agcacagctg catt	164
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tggatctgcc cactgtgcac tccatcatca gcaaaatgat cattaatgag gagctgatgg	180
cctccctgga ccagccaaca cagacagtgg tgatgcaccg cactgagccc actgcccagc	240
agaacctggc tctgcagctg gccgagaagc tgggcagcct ggtggagaac aacgaacggg	300
tgtttgacca caagcaggge acctacgggg gctacttccg agaccagaag gacggctacc	360
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attgcagact aaaaccactt ctaccatctc ctctagtatt ttccatgtat caggacagag	180
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tgtggggtgg gagtggggag caggaattgc actcagacat gacatttcaa ttcatctctg
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cattgcagca gccactggct ttgtcaaaaa ggaccagttg ggcaagaatg aagaaggagc
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<223> OTHER INFORMATION: n is a, c, g, or t
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                                                                      120
gaatgtatta atgagactgc tttgcataaa actgggaaga aagagaagac agttggagat
                                                                      180
ggaagatggt tttgtatata ttttggaact ttagttcctc tgtgagacga aagaggagag
                                                                      240
ctatgttttg tgtcacattg tctgatatat attgtgtaac ctgtcaggtg agttgattta
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gacaacatag ctgacctttt atgacaaggc agtttgaata gggactattg taataccctc
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acacattata ggggcancag agaatggcat ggaagagaca gtctacagag agctttaaga
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                                                                      120
ttctatggct tatcagcagg agtgtttacc aaagacattg ataaagccat aacaatctcc
                                                                       180
tctgctctgc aggcaggaac agtgtgggtg aattgctatg gcgtggtaag tgcccagtgc
                                                                       240
ccctttggnt gggattcaag atgtctggaa atggaagaga actgggagag tacggtttcc
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atgaatatac agaggtcaaa acagtcacag tgaaaatctc tcagaagaac tcataaagaa
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<223> OTHER INFORMATION: AffymetrixID: 212388_at
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aactcaataa tgctgtgtgt tctcaagaag ctcccttagt gaggccgatc ttaagatggc
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cgattctgcc cgttgaaggc atncctggga aagaaaacaa gcatcccagc gggcatctca
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ccacgacttc tcctggagtc ctcacacggt cactgacaac tacagtcagt tttaggaact
                                                                       300
agagtgccgt atcatcagac ttaccctgtc ctgccccacc ttccctgcta acatcgaggt
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<223> OTHER INFORMATION: AffymetrixID: 212591_at
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gaagcacttt ctggactgtg gaagtatcat ggccgtgagg attgtgagag acaaaatgac
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taaagaaaaa tttaaacaac aaaattcaaa tccacgattg aagaatgtca gtaaacctaa
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                                                                      420
agaaaaagct gttctcctta aaacgaagaa gaaaggacag aagaaaagtg gacgccctaa
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gaaacagaga aaacagaaat aacaaccagg aactgctttt tcttttcctg ctgagtactg
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                                                                      546
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nagttgaaga gggcagaatc cgcagctctc atcattgtga tgtgtagcat gtctgccctc
                                                                      180
tgactggaca tcattgccat taactttctt ctgggcatca cggcaatgtc acgatgccca
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gacttggagc aaggcaacct tggagtcagt ccactcataa aatatggtaa cacccatttt
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aaaatttaag ttttgtcctt aaagacaact tcagtggtta attataaaag ttgtgttact
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tcgtcctaaa ttaaattgat agaaagattt aaaaatgtgt tttgtttcta ctattcagaa
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actgcgaact agggaaaggt tggtatgaaa aaatgtcttt cctttttca atgtacatag
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ttcaactctt tctttgttac atttaaacta tatccatgga tatcagtctg ctttggactc
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<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc feature
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<223 > OTHER INFORMATION: AffymetrixID: 212709_at
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aatgcaatta ttttggtcca gaactgacct gtattttctg tattgtacac aaaagctaat
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atattagcaa cagattotca gagtaaattg ttaacttota tgatttatga taatcaagct
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ggacttgatc atacaagtta gtctcataat gtattggacc aaaatgtaaa cttcattggt
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tgagtaaatc ctcctttgaa attcacctga ttattagata acttaaagtt tatttttaaa
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agctgacaac tttttatgaa tcttcgagtt gacagttcct aaaagcgtaa ctcagatatt
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aatgggctgt gtattaaatg gttttatttt cagttttgca gcacagaaca ctgttgaaat
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atccatatca acttgatttt tttaacctaa ttcaggtgtc ctttgcatct cttaaatgtt
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (489)
<223> OTHER INFORMATION: AffymetrixID: 212893_at
<400> SEQUENCE: 245
aattgtcctt aattaccaac agtgaagcac tacaggaggc aactgtggca ttgcttcctt
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aaccagctca tggtgtgtga atgttataaa attgtcactc agatatattt tttaaatgta
atgttatata agatgatcat gtgatgtgta caaactatgg tgaaaagtgc cagtggtagt
aactgtgtaa agtttctaat tcacaacatt aattccttta aaatacacag ccttctgcct
ctgtatttgg agttgtcagt acaactcatc aaagaaaact gcctaatata aaaatcatat
atatggtaat aatttccctc ttttgtagtc tgcacaagat ccataaaaga ttgtatttt
```

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attactattt aaacaaqtqa ttaaatttaq tctqcacaqt qaqcaaqqqt tcacatqcat
                                                                      420
tcttttatac tgctggattt tgttgtgcat catttaaaac attttgtatg tttcttctta
                                                                      480
tctqtqtat
                                                                      489
<210> SEQ ID NO 246
<211> LENGTH: 417
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (81)..(81)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (417)
<223> OTHER INFORMATION: AffymetrixID: 212989_at
<400> SEQUENCE: 246
gtcagagcct gttcacatat tgtgatcagg tagcaatgac atgtaccact taaattattt
tatcgtcgat ttggtagttc nattttaact actcaatgaa aacagccatg aatatctttt
cttaaagaga gttttgaaaa tgatcactta cctaaaactt gaaagctatg aattagttat
ccatactctc atgacaattt tgttggtgaa caacaaaaaa gagatctatt tctttaaaag
atatttgtgc agaaactgca tgtaactcta agttttactc ctaacataca tatgtttggg
gaagtattct attctatact tgccaatgtg gagaacaaaa tagtttttta agaatgaaga
                                                                      360
agtatatata tocattotgt attttacgtg cagcagaatt atottocgta ggatttt
                                                                      417
<210> SEQ ID NO 247
<211> LENGTH: 448
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (448)
<223> OTHER INFORMATION: AffymetrixID: 213410_at
<400> SEOUENCE: 247
gacaaattac ggttgagttc tgtggcttct tcacttgaag tgctaacatc agaatcaaac
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ttaaagcttc cactatttat gtctttgaga agtatgtagt acctcggtat taacagacct
                                                                      120
gctgtgatgc agttacactt tcacgtattt ttgaagtatg tcaagctaca cgggtctaag
                                                                      180
atatgattat tttggataaa atgttacttt ggtcaagaga acttttatcc agatgacatt
                                                                      240
acaggttcaa gtgggttaag gagacctcct gtacatctac agtgtttcct tttaaattgt
                                                                      300
ccagaaaaaa ggtgtgttct tcataagctt cagtgcagga tttttcaaag acgagctgtt
                                                                      360
gtgcaatttg ctgtatttaa tgcatgttct gaaaggattc acttttgact ttatatgaca
                                                                      420
gttgatcaag aacaggtact accccttt
                                                                      448
<210> SEQ ID NO 248
<211> LENGTH: 234
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (81)..(82)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(234)
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<223 > OTHER INFORMATION: AffymetrixID: 213515_x_at
<400> SEOUENCE: 248
ggatgatete aagggeacet ttgeecaget gagtgaactg cactgtgaca agetgeatgt
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ggatcctgag aacttcaagc nncctgggaa atgtgctggt gaccgttttg gcaatccatt
                                                                     120
tcggcaaaga attcaccct gaggtgcagg cttcctggca gaagatggtg actggagtgg
                                                                      180
ccagtgccct gtcctccaga taccactgag ctcactgccc atgatgcaga gctt
                                                                      234
<210> SEQ ID NO 249
<211> LENGTH: 407
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (407)
<223> OTHER INFORMATION: AffymetrixID: 213528_at
<400> SEQUENCE: 249
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tgatgaagta accttaccta atgtagtagc taactccact ttggaagatg aagaaaatga
tgtaaatgag ccagatgtga aaagatgcag gaaaccaaaa gtaacacaac tatataaatg
ccgatttttt tctggtgagt ggtctgagtt ttgtaagctt gtactaagta gtgaaaaact
ttttgtaaaa tatgatetea tteteacete agaaaceatt tacaacecag attattatag
taatttgcac cagactttcc ttagactgtt aagtaaaaat ggacgtgtac ttttggccag
                                                                      360
                                                                      407
caaaqcacat tattttqqtq taqqtqqaqq tqttcatctc tttcaqa
<210> SEQ ID NO 250
<211> LENGTH: 406
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (406)
<223> OTHER INFORMATION: AffymetrixID: 213604_at
<400> SEQUENCE: 250
gcaatgtcag tatccatttt ggcacataaa gatttttgat gagccctgtt tgcatagagc
                                                                       60
cagatgtttt cccctcccc aagagtatct acatcaggga tgtgacttgg tgcgaagagt
                                                                      120
caggggaaag aggaaaaacc caatttctaa atgacctcct tgcccagctt actaaaatgg
                                                                      180
ctgcagagca gacacaggat gaatttgaac ctgacacagg atgaatttga acctttggtc
                                                                      240
tcatttatgg aaaaacttgt gcaatttttt ttctgtgcta cactacatac aaatcaccaa
                                                                      300
attacaaatt accettttgt gatcettggt gtactgagca gtttetttgg ggetttttet
                                                                      360
ttctgggaag cgggagggaa aggagcaagg tgtcatcctg ctcttc
                                                                      406
<210> SEQ ID NO 251
<211> LENGTH: 466
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (85)..(85)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(466)
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<223> OTHER INFORMATION: AffymetrixID: 213619_at
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qtctcaaatt tttcccatta acttnaaaaa aaaaaaaaqc ttaaacttac qtqccttaca
                                                                     120
ggttattaaa tgaaactaga attaacaaac atgccaaaat gtttcacttt taatagtaga
                                                                     180
cacageteet atattgtttt acaaaaaaat aaaageatgt ettteaacat geateeaaaa
                                                                     240
cagtgttcaa tttaacgtgg caaagggcaa catttaacat aattcaactg cttttaccta
                                                                     300
aatacgetta etgettaagt acateetata actaaettga gaaaagetgg aaettaagtt
                                                                     360
taacagttat agtttactca gcttcactgt tacatcctag atgagtattg tattcaaaaa
                                                                     420
tactgggcct taagtcttca taacaatcct gatttccact tagagt
                                                                      466
<210> SEQ ID NO 252
<211> LENGTH: 474
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(474)
<223 > OTHER INFORMATION: AffymetrixID: 213655_at
<400> SEQUENCE: 252
cttcaacgct aacctgcttc agtgggagag taaagtaggc aagaatgagc agccacggat
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tgttgaactg ttaccagcac catgcttttc agcaacattt cagcggagtt ggaaacattt
                                                                     120
tttacaqcaa aaccattaca acqaaqtccc tccccaaacc acctttaacc atctcaaqct
                                                                     180
aacacccaat tacttgcaaa cactggtata aaacacagtt taaacaatta gaaaaatgaa
                                                                     240
aactgatacc acttatgcct ctatagtgtg attaacctct ctcttagatg cttgcatcac
                                                                     300
ctataagtct aatggctttc aaatgtaatt tccatttgct aatggtgatc ttgccacatc
                                                                     360
tggcacggag acgacacagt aatgctgaaa aagcctctat gtagtcctgt tagtgtctta
                                                                     420
aagaacctaa aagctgggac cagtaaaatc cacagaaatt cactcttgcc ttta
                                                                     474
<210> SEQ ID NO 253
<211> LENGTH: 302
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (302)
<223> OTHER INFORMATION: AffymetrixID: 213743_at
<400> SEQUENCE: 253
ttgtgtgagc tattcaaact cttcaacccc tgaacagggt attaagcttc caaaataatg
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atggggataa atatggaaat cctttttaag ttgtatttcc attaaacaaa aacccttata
                                                                     120
atteatacta teatgaattt getttateea teteatttge ataacagtte atetgtetgg
tcccattagg ctctaccaaa gaaagactct gatgagtgga cattattact gtgactcttg
taagtagcca taaataaacc aaaatagtat caaatttagg tatgaaattc cacatgtgca
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<210> SEQ ID NO 254

<211> LENGTH: 549

<212> TYPE: DNA

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<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature <222> LOCATION: (1)..(549)
<223> OTHER INFORMATION: AffymetrixID: 213788_s_at
<400> SEOUENCE: 254
gtttcagtca tttccggact aactgtgaca acgcgtgagc agggagcacc gtgcgagtct
                                                                     60
ccgggaggga atcctcctgg ggcccagaga ctcctccacc cctggggagg gcagacaggc
                                                                    120
tcgggagggc ctggccaggc cactggaggc tggcagggag caggcatgtc cacccgcaag
                                                                    180
cctgggaggc taactctggc attcctggcc ggagccgcca tgctcattgg tgggccagtt
                                                                    240
tgggacatcc ccgtactcaa agaccatatg gcagcctctg ggaaaacaaa accaaaacat
                                                                    300
caccttctat taaactctgt atattattat tttttacaat agaaagttaa aaatcaagac
                                                                    360
420
ccctaaattg atttctttta aaacagtctt aaagagacca gaagtgaata caaaagaact
                                                                    480
aaacaaaata aaaaattaga atgtgctgta gctgaaagct gtctatacct gtaagcctcc
aagtttcat
                                                                     549
<210> SEQ ID NO 255
<211> LENGTH: 576
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (99)..(99)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (101) .. (101)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(576)
<223> OTHER INFORMATION: AffymetrixID: 213872_at
<400> SEQUENCE: 255
aaactggtca gctagagatt ctttttctt tctaagctga gcacgtagtc tgttcagagc
                                                                     60
ttgtttcttc cgggagtttg ggtcccccat tttgaaatnc nggtggtact aaagcctttg
                                                                    120
gaaattgtca ctaaactatg ggcacttttt cttaagactc aagtacaaca gaaacaagtc
                                                                    180
attittittc ctgctaatat gattgattag cgaaaatcac gactataacc caaaaactgc
                                                                    240
accttctgtc aatattagca gactgtcata ttacagggtc aagaaacaaa agctgctgtc
                                                                    300
cagtcatgtt tggacaataa cgtttggggt cagacgggaa aaagggagga aagaaaggaa
                                                                    360
agaaagagga gaaaataact aactttctgg aaaacacatt tggcttaact gccaaaataa
                                                                     420
aggetttgeg gagaaatgaa aageetataa teaggattta ggtgtgeaat aaaacacage
                                                                     480
tgacaccaga ccaatcccta aaatccatcc ggattttccc ccctttttag aaaagggatt
                                                                    540
                                                                     576
aaggaacagg gagggggaag tgtgatcctt gctttc
<210> SEQ ID NO 256
<211> LENGTH: 380
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(380)
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<222> LOCATION: (1)..(244)

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ggacggcact ggtgcaggcg gggacgctgc caccctccac gtccccagga cagacgtcga
                                                                      120
tgggcagcgg gcacgctggg caccgcccaa gcttttcctt ttggagctgc ttcgtgatgc
                                                                      180
cgtcttcatt tggaacaagg gggggttcat gccaaaatta ggaaaaacag cctttgtttt
                                                                      240
gtttttctaa attattctaa aaataagaca agcaggtaga aaaaacaatg cactgtgtgg
                                                                      300
cataaaaaga aaaacgggaa ggattcattg tcctgagaag tttgccaact gcctcattct
                                                                      360
ggggcacgtt ccaacataca
                                                                      380
<210> SEQ ID NO 257
<211> LENGTH: 371
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(371)
<223> OTHER INFORMATION: AffymetrixID: 214257_s_at
<400> SEQUENCE: 257
attataacct gggcctgcct ttgttctcat gaagccaggg gcctctccat atcctatact
tgctcttacg ctaataacaa accaaatgct gcaaaataaa agtaataatg acccaaacta
atttaagtct tttgtttaag gagtaaatga gagaaacatt ttagcttctt aatcaaggag
                                                                      180
tgctataatt tcaaggcatc ttaatataat tcacttaccc taaagcaatt gtgcaataag
                                                                      240
caaattataa aaggaaaaca acaaaggtta actttctaca ggggccaata gacaagatct
                                                                      300
gtggagcaca gcaattaacc ttcacatact ggagtcttgt ttaaaaggcc atcaaaaact
                                                                      360
cagattactq a
                                                                      371
<210> SEQ ID NO 258
<211> LENGTH: 244
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (164) .. (169)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (171)..(172)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (176) .. (176)
<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (180) .. (181)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
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agttcaaccc ctgnggtgca cgcctccctg ganaagttcc tggcttctgt gagcaccgtg
                                                                      120
ctgacctcca aataccgtta agctggagcc tcggtagccg ttcnnnnnnc nngctnggcn
                                                                      180
ntccaacggg ccctcctcc ctccttgcac cggcccttcc tggtctttga ataaagtctg
                                                                      240
agtg
                                                                      244
<210> SEQ ID NO 259
<211> LENGTH: 519
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (118) .. (118)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (125)..(125)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (133)..(133)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (136) .. (136)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (519)
<223> OTHER INFORMATION: AffymetrixID: 214696_at
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aaagcctcca tgtcatttga cctacgaatt ctatctttgg gaatttatcc taagaaanta
                                                                      120
cttanggatt tanttngtga taagatgttc atcccagcat tgcaatggag aaaaatggga
                                                                      180
agcaatggtt tggttgggaa tttattcctt ttctgctgta acgaaagttt gcaatagggg
                                                                      240
attgcttaag taaattattg tatctccatc cagatggtgg agtaccgcgc agacattaaa
                                                                      300
agtcatgtaa aagaacatct gactgaaaga aaaatgctcc ttgaatatta aaaggttgta
                                                                      360
aaaatagtgc atgttatgtg atttcaattt tgttttttaa aatatgggtg tatgcttgta
                                                                      420
tacgtagagc agataaaaaa gacggaaggc atactaaaaa atgttgagtg gttatctttg
                                                                      480
tatggtggaa caaagtcact gtaattttca tctttggtt
                                                                      519
<210> SEQ ID NO 260
<211> LENGTH: 399
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (48)..(48)
<223 > OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (75)..(75)
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature <222> LOCATION: (1)..(399)
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aaccagaatc ccagngccct acacccacca ccagacacac tcacacccac acacgttctc
                                                                       120
agacacaca aagagtgctt gccggttata ccaaacccta ctattactgc ctgcagaaat
                                                                       180
caatttaaaa aaataataat aacaataaac aattttaaaa aggacaaaaa aattaatgat
                                                                       240
tgagaaaaga ggcatttttt tctgacattt ggtcctgctt gaaacaacaa aagaagaaga
                                                                       300
aaaacccacc atcaccaccg attcctttgc ttcttttttc cttttttcct accttgtttg
                                                                       360
aaaaccgtgg gcttgggact gtgaattatt gcatgacat
                                                                       399
<210> SEQ ID NO 261
<211> LENGTH: 202
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(202)
<223 > OTHER INFORMATION: AffymetrixID: 215043_s_at
<400> SEQUENCE: 261
caqtctttcc caqqqaactc cqatqaaqtq ttccaacaaa atqaqcqaqt qaaccaaqaa
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qaqqatqaca ttaqatccaq qaqatacaac aqaqqaqata atctccaqqa tqcctqtqaa
                                                                       120
gaaagatccc tggatcccag gatgattata ggacaagttg ttcataatcc agcaggccag
                                                                       180
                                                                       202
aagacttcca gggaaactca tt
<210> SEO ID NO 262
<211> LENGTH: 501
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (437) .. (437)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (452)..(452)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) .. (501)
<223> OTHER INFORMATION: AffymetrixID: 215933_s_at
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ggacagttcc tgtgatcaga ggcaagattt gcccagngaa cagaataaag gtgcttcttt
ggatagetet caatgttege eeteeeetge eteecaggaa gaeettgaat cagagattte
agaggattct gatcaggaag tggacattga gggcgataaa agctatttta atgctggatg
atgaccactg gcattggcat gttcagaaaa ctggatttag gaataatgtt ttgctacaga
aaatetteat agaagaactg gaaggetata taagaaaggg aateaattet etggtattet
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ggaaacctaa aaatatttgg tgcactgctc aattaacaaa cctacatgga gaccttaatt	360
ttgacttaac aaatagttta tgtactgctc ttaggttgtt ttgataaagt gacattatag	420
tgattaaatt ctttccnctt taaaaaaaaca gntagtggtt ttcactattt ataaatagga	480
ccttcttgaa cgacttttct g	501
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atgaagcota gtagaatatg gacttggaaa attotottaa toactaotgt atgtaatatt	120
tacataaaga ctgtgctgag aagcagtata agccttttta accttccaag actgaagact	180
gcacaggtga caagcgtcac ttctcctgct gctcctgttt gtctgatgtg gcaaaaggcc	240
ctctggaggg ctggtggcca cgaggttaaa gaagctgcat gttaagtgcc attactactg	300
tacacggacc atcgcctctg tctcctccgt gtctcgcgcg actgagaacc gtgacatcag	360
cgtagtgttt tgacctttct aggttcaaaa gaagttgtag tgttatcagg cgtcccatac	420
cttgttttta atctcctgtt tgttgagtgc actgactgtg aaacctttac cttttttgtt	480
gttgttggca agctgcaggt tt	502
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ggagcagatc atcaceteca tgaagtgeat catgggge	158
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agaggtgctg agcagcette tgggaggtga aggacactte teaaaggatg tgcacttgce	180
acacaattat catattgatt ttgaaatcag aatggacact aacaggaatc aagtgctacc	240

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actitictgat gtgatacaac tictgctaca gataticaaa gagtagctgt gctatgtgtt
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tecagatetg ettattgttt gggtteaage eaceceagag gatteettge tatgaaaatg
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cggcatttga atgcaatggg ttttcatgtg atcttggtca ataactggga gatggacaaa
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ggttctacta ttttcctttc ttttgcttat ttccccttaa gcacaatttg cagaccctac
ttctatttaa ctgatcatac ccttttaaat gccttgtcat catttttcat agttcctgca
                                                                      240
tcctagaaaa aataaaaaat catttaaaat attccttggt gtctagaaaa gaaaatttct
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ctaacaatag agatnatcat tttgctttct cacttaagct gatctgaatg atgatttggt
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gattctcgtg cctcagtctc ccgagtagct gggattgtag gcgcctgcca ccacgcccag
ctaatttttg tatttgtagt agnnatgggg tttcatcatg ttggcgaagc tggtcttgaa
cacctgacct caagtgatct gccttagcct cactgcttgc ccctangtgg tgggattgca
ggtgtgagcc actgtgctgg cctcaaatag tttttatcaa agctacttca attagtggtt
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agcaaggett aaagactaat teagtgettt attttgacae ttgttegeaa eatgttgett	420
tttttcctgt gtcctatggg acctagtcat ctgtatgtta ga	462
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ccgcccgtgc tgcaggtgct gcattgcggg gatgagtcca tgctggacat tggaggagag	240
cgcggctgtg ccttctgcgg gggcctgggt catcggatca ctgactgccc caaactcgag	300
gctatgcaga ccaagcaggt cagcaacatc ggtcgcaagg actacctggc ccacagctcc	360
atggaettet gageegaeag tetteeette teteeaagag geeteagtee eeaagaetge	420
caccagtota cacatacago agococotgg acagaatcag catttcagot cagotggoot	480
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ggcatcttga aacacctatt tctactcagg tactcattgt cctgttactg attcaccttt	180
ctgatccttt tcaaccagtt ttcccccaag gggggaaatt ttacttaacc tctagtattt	240
gaacaactca atatttgaat tgttgcccca tttgctttta cctgtactgt attcttggtc	300
atotoaaatg gogtotaaac ocagotaott tgoattocag aagtttocat toootocaat	360
tocacctaat titteatetg tectagitae tggetetite ticatgiett attietetig	420
ctttgggagc ttaaaagatt ttacaagacc taattttggg ttccttcctt ggagccatag	480
ttaccctgcc aa	492
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cattetteaa geageaaaag tteeeggaae aattagggaa gaegtatggt etgaatttat
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                                                                   120
actaattgac taaacaactt gaacgctagt ggtttgtcct tagacaatct gtctttgaat
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ttaaagtctt tatcgctaag accttgactt taaatttttc atcactacaa ccttgaattt
tttatcatat tattcacaga tgcatttttg aaatgtagta tgtaaaagta tgtaacgtgc
tgtttattaa caaaagattg ttcacaacat ctcatgtagt ttaaatttgt aaatactgct
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tgtaacttgt tctagtatgg tgctaaaaac tttaaccaaa ccagttacat taagtagaag
                                                                   180
caaaataaac aaaactaagg ttttaaaaaat gatttttgta catttgatca tattctgttt
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ctgttttgtt ccttacaata tcaatcttat tttatattct cttgtgagaa cacaaacatt
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tgttaattgc tcagtagtgg cagcagtaag gacaatgtac ccaatcactc tctgtattgc
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tgtttccaac tgttgttttg accctatagt ttactacttt acatcggaca caattcagaa
                                                                   420
ttcaataaaa atgaaaaact ggtctgtcag gagaagtgac ttcagattct ctgaagttca
                                                                   480
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<211> LENGTH: 500
<212> TYPE: DNA
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<223 > OTHER INFORMATION: AffymetrixID: 218604_at
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gtgcttttg tgggcacctt gtttatgaag aataaaaaat gatttgttat ctgaagagaa 180
aaattttaa attotoagtt tatgtotoag atgotaacgt gtgaaaatat aaatatatat 240
atatataaa gtaaccagtc ttcctgtatt ttatgtgcat catagtgatt tatctgagct 300
agtgacccc catcttgtaa cctgttgcaa gagtgaatgt aaaaaatagt tgtggcattt 360
aaaaggteg eetttgatge agatgeatet tittettget tetaaaaeat attteatgta 420
acattgtac atttattatt gtaatatata ctattatgca gcttatttta cctgaaactg 480
taagccgac caagatccct 500
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tttactagg gagatagacc tttacagcaa tcaagatatt tttgtccata tccaggttag 120
tggtaagag gatttttttg gagaaaaaaa atgatattta gaaagttaat ttctaattcc 180
gaatggaat aaaaacaata tgagtagtgt aatcttgtag aaaaagagtt gtataatctt 240
tagaatttc tcattctgtg gtacaaccca ggggtaaact attattccag tagtcagtac 300
cttttctag ataaatcttg agtgaaaacc agcaatttct ttttccttgt ggtctgattc 360
tttttctaa tccatgaagg ccatcttgta gattacattt atcattaatg caagaataaa 420
acaatteet eetgteagtt gegtgaattt tttttaagaa acaaeceagt gaagagttet 480
ccatagcaa ggcctaatgt tagctttagc tttagaaaat aacagtttgt gaacttactt 540
cctatattt gcagctgt 558
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gccttttaa aaaaggtgtt agtgtttatt atagctactt tcaaggaaag tttgaatatg 120
ttctagtct ctaaagttct tcacgttttc tgacattccc tggagggtga ctggggaaga 180
ttgctccag ggtagaagaa ccaggcccaa gactttacca ttctgatcta gagacaaagg 240
tactcaatg aggagetttt tteeeetett ggaacaggta aaatgetttt tettattaat 300
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gaagaaatga aagaagggac agacatgttc atcatcaagg ctgtgctgcc tgttgctgaa	180
agetttggtt ttgctgatga aatcaggaag aggacaagtg geetggeeag eecacaacta	240
gtattcagcc attgggagat cattcccagt gaccccttct gggtgccaac tactgaggag	300
gaatacttgc actttgggga gaaggctgac tetgagaacc aagcceggaa gtacatgaac	360
gcagtacgaa agcggaaggg gctttatgtg gaagaaaaga ttgtggagca tgcagaaaag	420
cagaggacac tcagcaaaaa taagtagcta cctactactg gtggattett tteettatag	480
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totgtttatt cact	554
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gcacacaact atacetttgt ccaacagate ataatatate tgetatecaa etggttttae	180
ctgcctaatc ctactgattt gggcactgct tgtatagtct ctcaagttca caggaaatgt	240
tgattttcta aggtcctcat tt	262
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atcctgagat ttcttaattt catggttctt taaatattat aaacacagag tcaacataga	180
atgaaattgt atttgttaaa atacacacat tggaggacaa gagcagatga ctacttttcg	240

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aaqtaatqct qctccttcct aaaaqtctqt tttcaatcct qqtaatatta qqqqcactqc
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ggcacctaag aagcettaaa tgagagetaa tecaatttag agagegatgg tgtcageatt
                                                                      360
teggtetgea tatetgtgtg teegtatetg egtttgtgtg egtgtaegtg tgeecetgtg
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tgtgggccca gttttcaggc atgtagaata agcatggagt catattgagg aggactcact
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cagttaaaag ccaattttta gctccagtgg aaccatagcc acataaaact ttaatggaca
accatataga attaacttat tttgtccaag tacagttggc attttccaga ataattttac
caccetgeta gatgteatet etggattgea eatggatgat gaaggaacte ageattgaaa
gttgggggat tagtaacctt gttacaacgg tttctttttc attttagcct attttaatgg
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tattccaggt taagttgggg aatcagaatg tggaaactaa acaacttctt agtgcaagct
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atgagtttca gagggagttc acacaaggag taaagcctga ctggaccatt gcacggattg
                                                                      240
aacactcaaa attattagaa taattttctt ggaaaaatca gcttatggac tttagcagtt
                                                                      300
gctgtgaaaa actaaggaag aaaaattttg gggtcatttg atcttcactt aatctaagtc
                                                                      360
tgtgaattac ttttatatta ttttgaaata ctccttgcag tatattggca tgatacagta
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ecccaaatg ctgaaaaagt gaaatacagc aattcaacag ataatagagc aatgtttagt	360
attcagct gtatctgtag aaactctttg acgaacctca atttaaccaa tttgatgaat	420
eccagttot ottottttot agagaaagat agttgcaaco toacotocot cactcaacac	480
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eccaagget getaactgga agtetggaac eegtgaagga aaatatgaag gtttategte	180
gaacttgg ttttaaacat aacgaaattc aacatatgat caccagaatc ccaaagatgt	240
actgcaaa taaaatgaaa cttaccgaga cgtttgattt tgtgcacaat gtgatgagca	300
ccccacca catcattgtc aagttcccac aggtatttaa tacaaggctg tttaaggtca	360
gaaagaca cttgtttctt acctatttag gaagagcaca gtatgatcca gcaaaaccta	420
tacatoto titggacaaa otagtatota tiootgatga aatatitigi gaagagatig	480
aaagcatc agtacaggac t	501
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atcagtgt gtgatctacc agoctcccaa ggagcctcac atgctgttcg atcgcatccg	120 180
atcagtgt gtgatctacc agcctcccaa ggagcctcac atgctgttcg atcgcatccg tggtggtg accaagggtt tttcagggac ccctggctcc aatgagaatt ctacccagaa gtgtataag attcctccta ccaccactaa ggccttgtgc ccactctata ccagccccag	120 180 240

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ttggggggtg ggggggtatt tgcaagaata ctcattttga cataataggt cctcttgtca
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gagateetet accaeagaea ttaatagetg ageaggagee acatggattg attgtateea
ctcaccattg acgatggcat tgagcgtagc tagcttattt ccatcactac gtgtttttga
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gacttgaaga actaaattta gcatattgca aaaatatttt gtgcggaatt cgatataagt
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acttttacag caagatggta tagttatgtt gcctggactg gtttttacat ttttaaaata
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tttcagctgt catttttgta ctaattataa aattggcaca taattcaaaa atatacattt
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (97)..(98)
<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (101) .. (103)
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tcaccctggt caacaagaag nacgctctca tcnnnannca nnnccngcnn cnnnnnnca
                                                                       120
tggaggagca ggacttggag cgaaggttcg agctgctgag ccgcgagctg cgggccatgc
                                                                       180
tggccatcga agactggcag aaaacgtccg ctcagcagca ccgagagcag ctcctactgg
aggagetggt gtegetggtg aaccagegeg atgagetagt cegggaeetg gaccacaagg
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                                                                       120
agaggetact gataaatett tacaagettg taaaatetca gatatetgtt tattetgage
                                                                       180
tcaacaagat tgaagtaagt tttcgggagc tacagaaatt aaatcaagaa aagaataata
                                                                       240
gaggattata ttcaattgaa gtgctggagc tcttctgata ttatcaattc tccttcatag
                                                                       300
acattttata aagctctttt atgtgaactc ttgcttcatc caggcaagaa cggtgttttg
tttgcgacca tctcagtgtc aagagaaacg tgtcagtgag tacctggacc atcacttaac
tgatgctccg gggtaggact gcaggtttca catgaacctg ttntaggctg tggacattgg
tgtggaga
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<222> LOCATION: (1)..(462)
<223> OTHER INFORMATION: AffymetrixID: 222127_s_at
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attgttccag cattgcacag tcccactaaa ccttgtgaaa gaagaaaaga taactgaatg
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aagcatttga gtataacaga cactatacca aaataccaag caactgtttt gagaacccag
                                                                      180
acttaaaatt ttatgtatta ttaaatgtta gataaatggg tagtaccata ctacaaatat
                                                                      240
ttaaatgcaa aattaccaac ctatatagca gttttatttg ccctataggt tgcatactaa
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cttaagcatt catgtcacca taaaatgcct ttagcatttc tcaatgactg gatgggaaat
tttcctttat tgcctagctg cttgtgtttg agtggttgtc ctatgagcaa tgcatttgga
gttcttcagc tttcactact tctctgttgc ttgctaatca tg
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (62)..(62)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (86)..(86)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (113) .. (113)
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<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223 > OTHER INFORMATION: AffymetrixID: 36711_at
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atentanatt tagggaaage engagagnaa caacaaaaaa tgtttaagee nnnnnnnnn
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240
300
360
420
agaatttatt tattteetga ettaeageaa gegagttate gtettetgta ttttg
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<210> SEQ ID NO 290
<211> LENGTH: 494
<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (124) .. (124)
<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<223> OTHER INFORMATION: AffymetrixID: 38037_at
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aaagcccaag gtgctgatgt caaagtgtaa cagatatcag tgtctccccg tgtcctctcc
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ctgncaagtc tcagaagagg ttgggcttcc atgcctgtag ctttcctggt ccctcacccc
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catngcccca ggcccacagc gtgggaactc actttccctt gtgtcaagac atttctnnnn
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nnnnnnnnn nnnnnnnnn nnactccatg caggggtcag tgcagcagag gacagtctgg
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agaaggtatt agcaaagcaa aaggctgaga aggaacaggg aacattggag ctgactgttc
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<223> OTHER INFORMATION: AffymetrixID: AFFX-BioB-M_at
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aacggtaaaa gatcgcgccg gattattgct gcaactggca aacctgccga cgccgccgga
                                                                      180
aagcgtgcca atcaacatgc tggtgaaggt gaaaggcacg ccgcttgccg ataacgatga
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tgtcgatgcc tttgattt
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<210> SEQ ID NO 292
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<212> TYPE: DNA
<213 > ORGANISM: E. coli
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cqcatqctaa tcqcttttta ccqccaqatq aaatcqaaca qtcqctqaac qqcqtqcatt
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atcaacatca tattcagccc atcacgctgt ggtttgatga tgcgctcagt gccatgcgtt
                                                                      180
cgctgaaagg catcggtgcc acgcatcttc atgaagggcg cgacccgcga atattaacgc
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<210> SEO ID NO 293
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<213 > ORGANISM: Homo sapiens
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<223> OTHER INFORMATION: AffymetrixID: 204018_x_at
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agaggatgtt cctgtccttc cccaccacca agacctactt cccgcacttc gacctgagcc
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acggctctgc ccaggttaag ggccacggca agaaggtggc cgacgccctg accaacgccg
                                                                      240
tggcgcacgt ggacgacatg cccaacgcgc tgtccgccct gagcgacctg cacgcgcaca
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agettegggt ggacceggte aactteaage teetaageea etgeetgetg gtgaccetgg
ccgcccacct ccccgccgag ttcacccctg cggtgcacgc ctccctggac aagttcctgg
cttctgtgag caccgtgctg acctccaaat accgttaagc tg
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<212> TYPE: DNA
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<223> OTHER INFORMATION: AffymetrixID: 222043_at
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catgccttca ttttgctatg gggggcaggc aggggggatg gaaaataagt agaaacaaaa
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aagcagtggc taagatggta tagggactgt cataccagtg aagaataaaa gggtgaagaa
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taaaagggat atgatgacaa ggttgatcca cttcaagaat tgcttgcttt caggaagaga
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<213 > ORGANISM: Homo sapiens
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<223> OTHER INFORMATION: AffymetrixID: 206026_s_at
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tgatctcact gttattatta acatttattt attattttc taaatgtgaa agaaatacat
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aatttaggga aaattggaaa atataggaaa ctttaaacga gaaaatgaaa cctctcataa
                                                                     240
teccaetgea tagaaataac aagegttaac atttteatat ttttttettt cagteatttt
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tgtatttgtg gtatatgtat atatgtacct atatgtattt gcatttgaaa ttttggaatc
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ctgctctatg tacagttttg tattatactt tttaaatctt gaactttatg aacattttct
                                                                     420
qaaatcattq attattctac aaaaacatqa ttttaaacaq ctqtaaaata ttctatqata
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<223> OTHER INFORMATION: AffymetrixID: 208894_at
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<212> TYPE: DNA
<213 > ORGANISM: Homo sapiens
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<223> OTHER INFORMATION: AffymetrixID: 222150_s_at
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cagaactgct gtatcacatt ccaattttga atagccagtg agcaatcaag tgtagagaaa	180
tgataaatgg cctaagaagg catacagtgg cataaacgat gctcttccta gtagcttaat	240
aggccacaag ctagtttctg ttgccctctg aaataaaata	300
cagtgcttag aaaagcaaaa actaggtgtg tcattgaaat aataggcata aaaattaaat	360
gttacataag acccctattt ggaaaaaggg tccttttaaa aactgaattt gtactaaatc	420
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acaatagget gtteecatgt ageceeetgg eetetgtgee ttettttgat tatgttttt	420
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ctgtcattcg ctcccacatt ctgatgagca accgcttccc tatttattta tttatttgtt	360
tgtttgtttt attcattggt ctaatttatt caaagggggc aagaagtagc agtgtctgta	420
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aaatcaagtc c		49	1
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105 110

His His Glu Cys Gly Arg Asn Met Tyr Leu Thr Gly Leu Cys Phe Leu

100

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Ile	Ala 1025		у Суя	. Lev	ı Arg	Phe 103		rg C	ys A	sp Va		ro 035	Ser	Phe :	Ser
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Lys	Tyr 1100	-	3 Val	l His	s Asn	Pro		ır P:	ro L	eu I		al 110	Gly	Ser :	Ser
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Leu	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Lys	Ala	Pro	Lys 45	Leu	. Leu	Ile
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What is claimed is:

1. A method for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, the method comprising: (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to a TNF α inhibitor in an autoimmune disorder, and (ii) predicting responsiveness of the subject to the TNF α inhibitor based on expression of the one or more biomarkers in the subject, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected

from the group consisting of SEQ ID NO: 1-10, 12-28, 30-43, 45-61, 63, 64, 66-73, and 75-82.

wherein decreased expression of the one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 12-14, 18, 20, 21, 23, 25, 26, 28, 30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 66-69, 71-73, 76-78, 80 and 81 is predictive of responsiveness of the subject to a TNFα inhibitor; and/or

- wherein increased expression of the one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43, 45-47, 49, 51, 54, 55, 57, 59, 61, 64, 70, 75, 79 and 82 is predictive of responsive of the subject to a TNFα inhibitor.
- 2. A method for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, the method comprising:
 - (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to a $TNF\alpha$ inhibitor in an autoimmune disorder, and
 - (ii) predicting responsiveness of the subject to the TNFα inhibitor based on expression of the one or more biomarkers in the subject, wherein the one or more biomarkers is selected from the group consisting of Aquaporin 3 (Genbank Accession No. NM_004925); Similar to ribosomal protein S24, clone MGC:8595 (Genbank Accession No. NM_033022); Transmembrane emp24 domain trafficking protein 2 (Genbank Accession No. NM 006815); Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (Genbank Accession No. NM_000454); Calmodulin 1 (phosphorylase kinase, delta) (Genbank Accession No. NM 006888); Guanine nucleotide binding protein (G protein), beta polypeptide 1 (Genbank Accession No. NM_002074); Prothymosin, alpha (gene sequence 28) (Genbank Accession No. NM_002823); Homo sapiens isocitrate dehydrogenase 1 (NADP+) soluble (IDH1) (Genbank Accession No. NM_005896); Tumor protein D52 (Genbank Accession Nos. NM_001025252, NM_001025253, NM_005079); Early growth response 1 (Genbank Accession No. NM_001964); Cytochrome c oxidase subunit VIIb (Genbank Accession No. NM_001866); CUG triplet repeat, RNA binding protein 2 (Genbank Accession No. NM_001025077, NM_001025076, NM_006561); Ubiquinol-cytochrome c reductase hinge protein (Genbank Accession No. NM 006004); Homo sapiens leptin receptor gene-related protein (HS0BRGRP) (Genbank Accession No. NM_017526); Wiskott-Aldrich syndrome protein interacting protein (Genbank Accession Nos. NM 001077269, NM 003387); CD97 antigen (Genbank Accession Nos. NM_001025160, NM_001784, NM_078481); Glutamate-cysteine ligase, catalytic subunit (Genbank Accession No. NM_001498); Crystallin, zeta (quinone reductase) (Genbank Accession No. NM_001889); Rap guanine nucleotide exchange factor (GEF) 2 (Genbank Accession No. NM_014247); Ataxin 1 (Genbank Accession No. NM_000332); Adaptor-related protein complex 1, sigma 2 subunit (Genbank Accession No. NM_003916); Ectonucleotide pyrophosphatase/phosphodiesterase 4 (Genbank Accession NM 014936); Desmocollin 2 (Genbank Accession Nos. NM_024422, NM_004949); MAL, T-cell differprotein entiation (Genbank Accession Nos. NM 002371, NM 022438, NM 022439, NM_022440); Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (Genbank Accession No. NM_005476); Chemokine (C—C motif) ligand 3 (Genbank Accession Nos. NM 001001437, NM_021006); Carboxypeptidase A3 (Genbank Accession No. NM_001870); NADH dehydrogenase

(ubiquinone) 1 beta subcomplex, 1, 7 kDa (Genbank Accession No. NM_004545); Interleukin 8 receptor, beta (Genbank Accession No. NM_001557); Platelet factor 4 variant 1 (Genbank Accession No. NM_002620); Poly(A) binding protein interacting protein 1 (Genbank Accession No. NM_006451); ATPbinding cassette, sub-family C (CFTR/MRP), member 3 (Genbank Accession No. NM 003786); Actinin, alpha 1 (Genbank Accession No. NM 001102); NAD kinase (Genbank Accession No. NM 023018); Platelet/endothelial cell adhesion molecule (CD31 antigen) (Genbank Accession No. NM_000442); Esterase D/formylglutathione hydrolase (Genbank Accession NM_001984); Chromosome 20 open reading frame 111 (Genbank Accession No. NM_016470); Sterol-C4methyl oxidase-like (Genbank Accession Nos. NM 001017369, NM 006745); PIM-1 oncogene (Genbank Accession No. NM_002648); GATA binding protein 2 (Genbank Accession No. NM_032638); Cathepsin Z (Genbank Accession No. NM_001336); Lectin, galactoside-binding, soluble, 8 (galectin 8) (Genbank Accession Nos. NM 006499, NM_201545); CD86 antigen (CD28 antigen ligand 2, B7-2 antigen) (Genbank Accession Nos. NM_006889, NM 175862); Interleukin 8 (Genbank Accession No. NM 000584); Fc fragment of IgE, high affinity I, receptor for alpha polypeptide (Genbank Accession No. NM_002001); Actin, gamma 1 (Genbank Accession No. NM_001614); KIAA0746 protein (Genbank Accession No. NM_015187); Glucosamine (N-acetyl)-6-sulfatase (Sanfilippo disease IIID) (Genbank Accession No. NM 002076); Transcription factor 4 (Genbank Accession Nos. BF592782, CR612521); Major histocompatibility complex, class II, DQ alpha 1 (Genbank Accession Nos. NM_002122, NM_020056); Cell division cycle 2-like 6 (CDK8-like) (Genbank Accession No. NM_015076); Major histocompatibility complex, class II, DQ beta 1 (Genbank Accession No. XM_942240); Phospholipase C-like 2 (Genbank Accession No. NM_015184); Coagulation factor II (thrombin) receptor-like 1 (Genbank Accession No. NM_005242); TM2 domain containing 1 (Genbank Accession No. NM_032027); Splicing factor 3b, subunit 1, 155 kDa (Genbank Accession No. NM 012433); SUB1 homolog (S. cerevisiae) (Genbank Accession No. NM_006713); MRNA, cDNA DKFZp564O0862 (Genbank Accession No. AI278204); Cytochrome b-5 (Genbank Accession Nos. NM 001914. NM 148923); Cold autoinflammatory syndrome 1 (Genbank Accession No. NM_183395); Ribosomal protein S26, 40S ribosomal protein (Genbank Accession No. XM_941927); CCR4-NOT transcription complex, subunit 6 (Genbank Accession No. NM 015455); Ubiquinol-cytochrome c reductase complex (7.2 kD) NM 013387, (Genbank Accession Nos. NM_001003684); Hepatocellular carcinoma-associantigen 112 (Genbank Accession No. NM 018487); Kruppel-like factor 11 (Genbank Accession No. XM_001129527); GGA binding partner (Genbank Accession No. NM_018318); Cornichon homolog 4 (Drosophila) (Genbank Accession No. NM_014184); Hypothetical protein FLJ21616 (Genbank Accession No. NM_024567); Nuclear prelamin A recognition fac-(Genbank Accession Nos. NM_012336,

- NM_001038618); Erythroblast membrane-associated protein (Genbank Accession Nos. NM_018538, NM_001017922); LR8 protein (Genbank Accession No. NM_014020); Likely ortholog of mouse limb-bud and heart gene (LBH) (Genbank Accession No. NM_030915); Calmin (calponin-like, transmembrane) (Genbank Accession No. NM_024734); Chromosome 14 open reading frame 156 (Genbank Accession No. NM_031210); Guanine nucleotide binding protein (G protein) alpha 12 (Genbank Accession No. NM_007353); and SRY (sex determining region Y)-box 18 (Genbank Accession No. NR_003287).
- 3. A method for predicting responsiveness to a TNF α inhibitor, which TNF α inhibitor is adalimumab, in a subject having an autoimmune disorder, the method comprising:
 - (i) assaying the subject for expression of one or more biomarkers predictive of responsiveness to adalimumab in an autoimmune disorder, and
 - (ii) predicting responsiveness of the subject to adalimumab based on expression of the one or more biomarkers in the subject,
 - wherein decreased expression of the one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 12-14, 18, 20, 21, 23, 25, 26, 28, 30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 66-69, 71-73, 76-78, 80 and 81 is predictive of responsiveness of the subject to a TNFα inhibitor; and/or
 - wherein increased expression of the one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43, 45-47, 49, 51, 54, 55, 57, 59, 61, 64, 70, 75, 79 and 82 is predictive of responsive of the subject to a $TNF\alpha$ inhibitor.
- **4**. The method of any of claims **1-3**, wherein a sample from the subject is assayed for expression of mRNA encoding the one or more biomarkers.
- 5. The method of any of claims 1-3, wherein a sample from the subject is assayed for protein expression of the one or more biomarkers.
- **6**. The method of any of claims **1-3**, which further comprises selecting a treatment regimen with the TNF α inhibitor based upon expression of the one or more biomarkers in the subject.
- 7. The method of claim 6, which further comprises administering the TNF α inhibitor to the subject according to the treatment regimen such that the autoimmune disorder is inhibited in the subject.
- **8**. The method of any of claims 1-3, wherein the TNF α inhibitor is an anti-tumor necrosis factor-alpha (TNF α) anti-body, or antigen-binding portion thereof.
- 9. The method of claim 8, wherein the anti-TNF α antibody, or antigen-binding portion thereof, is a human antibody, a humanized antibody, a chimeric antibody or a multivalent antibody.
- 10. The method of claim 8, wherein the anti-TNF α anti-body, or antigen-binding portion thereof, is adalimumab.
- 11. The method of claim 9, wherein the anti-TNF α anti-body, or antigen-binding portion thereof, is selected from the group consisting of
 - i) an isolated human antibody that dissociates from human TNF α with a Kd of 1×10^{-8} M or less and a Koff rate constant of 1×10^{-3} s⁻¹ or less, both determined by sur-

- face plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard in vitro L929 assay with an IC50 of 1×10^{-7} M or less;
- ii) an isolated human antibody with the following characteristics:
 - a) dissociates from human TNF α with a Koff rate constant of 1×10-3 s-1 or less, as determined by surface plasmon resonance;
 - b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 305, or modified from SEQ ID NO: 305 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;
 - c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 306, or modified from SEQ ID NO: 306 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12; and
- iii) an isolated human antibody with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 303 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 304.
- 12. The method of claim 1, wherein the TNF α inhibitor is etanercept.
- 13. The method of any one of claims 1-3, wherein the subject is a human.
- **14**. The method of any one of claims **1-3**, wherein the autoimmune disorder is rheumatoid arthritis.
- 15. A kit for predicting responsiveness to a TNF α inhibitor in a subject having an autoimmune disorder, the kit comprising:
 - a) means for isolating monocytes;
 - b) means for measuring expression in the subject of one or more biomarkers predictive of responsiveness to a $TNF\alpha$ inhibitor in an autoimmune disorder;
 - c) means for measuring expression of at least one housekeeping gene; and
 - d) instructions for use of the kit to predicting responsiveness to a TNFα inhibitor in a subject having an autoimmune disorder, wherein decreased expression of the one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-5, 8, 9, 11-14, 18, 20, 21, 23, 25, 26, 28-30, 32, 33, 40-42, 48, 50, 52, 53, 56, 58, 60, 63, 65-69, 71-74, 76-78, 80 and 81 is predictive of responsiveness of the subject to a TNF α inhibitor and/or wherein increased expression of the one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 10, 15-17, 19, 22, 24, 27, 31, 34-39, 43, 44-47, 49, 51, 54, 55, 57, 59, 61, 62, 64, 70, 75, 79 and 82 is predictive of responsive of the subject to a TNFa inhibitor.
- 16. A method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 83-133, thereby monitoring the autoimmune disorder in the subject.

- 17. A method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 134-177, 110, 112, 118, 123 and 131, thereby monitoring the autoimmune disorder in the subject.
- 18. A method of monitoring an autoimmune disorder in a subject having an autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 178-292, 91 and 97, thereby monitoring the autoimmune disorder in the subject.
- 19. A method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 87, 97, 101, 293, 92, 272, 93, 107, 108, 121 and 123, and wherein the subject is monitored prior to treatment with a TNF α inhibitor, thereby monitoring the autoimmune disorder in the subject.
- 20. A method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence

- selected from the group consisting of SEQ ID NO: 290, 209, 98, 112, 116, 121, 130, 155, 92, 289, 216 and 131, and wherein the subject is monitored after treatment with a TNF α inhibitor, thereby monitoring the autoimmune disorder in the subject.
- 21. A method of monitoring an autoimmune disorder in a subject having the autoimmune disorder, the method comprising: assaying the subject for expression of one or more biomarkers, wherein the one or more biomarkers is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 97, 102, 29, 294, 295, 91, 131, 290, 100, 134, 296, 297, 298, 299, 136, 174 and 300, thereby monitoring the autoimmune disorder in the subject.
- 22. A method of selecting an autoimmune disorder subject for a treatment with a TNF α inhibitor, the method comprising:
 - (i) identifying, in a database comprising a plurality of autoimmune disorder subjects, a subject whose database entry is associated with a biomarker expression pattern that is predictive of responsiveness to treatment with a TNFα inhibitor, and
 - (ii) selecting the subject for treatment with a TNFα inhibitor, wherein the biomarker expression pattern reports expression in the subject of one or more biomarkers encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-82.

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