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(54) **Title:** METHOD FOR EVALUATING THE RESPONSE OF AN INDIVIDUAL TO TNF BLOCKING THERAPY

(57) **Abstract:** The present invention is directed to methods to predict the responsiveness of a patient to a TNF blocking drug comprising the steps of: a) assessing in a synovial sample from said patient at least two genes or a fragment thereofs or proteins encoded by said at least two genes, wherein said genes or fragment thereof is as defined in claim 1, and b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a). The invention is also directed to kits for predicting the response to a treatment with a TNF blocking agent comprising a low density microarray comprising probes suitable for hybridizing with at least two genes or fragments thereof as defined in the claims.

Method for evaluating the response of an individual to TNF blocking therapy

Field of the invention

The present invention is directed to methods for determining the response of an individual to a treatment with TNF blocking agent, for instance individuals suffering from rheumatoid arthritis. In particular, the invention relates to methods to predict the responsiveness of a patient with rheumatoid arthritis to a TNF blocking drug.

Background of the invention

Rheumatoid arthritis (RA) is an autoimmune disease which causes chronic inflammation of the joints, particularly those of the hands and feet.

RA has a worldwide distribution and involves all ethnic groups. Although the disease can occur at any age, the prevalence increases with age and the peak incidence is between the fourth and sixth decade. The prevalence estimates for the North American population vary from 0.3% to 1.5%. Today, over 2,500,000 individuals are diagnosed with rheumatoid arthritis in the United States alone, with some statistics indicating from 6.5 to 8 million potentially afflicted with the disease. Women are affected 2-3 times more often than men.

The early symptoms of rheumatoid arthritis are mostly joint specific such as painful joints with joint swelling or tenderness, but may also include rather non-specific manifestations like stiffness, fever, subcutaneous nodules, and fatigue. Very characteristic is the symmetric involvement of joints. The joints of the hands, feet, knees and wrists are most commonly affected, with eventual involvement of the hips, elbows and shoulders. As the disease progresses, any type of motion becomes very painful and difficult leading eventually to a loss of function of the involved joints The more severe cases of rheumatoid arthritis can lead to intense pain and joint destruction. Some 300,000 bone and joint replacement surgical procedures are performed annually in an effort to alleviate the pain and mobility loss resultant from arthritis related joint destruction.

The effective treatment of rheumatoid arthritis has generally comprised a combination of medication, exercise, rest and proper joint protection therapy. The therapy for a particular patient depends on the severity of the disease and the joints that are involved. Non-steroidal anti-inflammatory drugs, corticosteroids, methotrexate and systemic immunosuppressants are widely used to reduce inflammation and joint destruction.

Over the last decade or more, it has become widely accepted that certain inflammatory cytokines are involved in the pathogenesis of RA. The most prominent of these is tumor necrosis factor (TNF). TNF levels are elevated in inflammatory joints. TNF-alpha blocking

agents are thus routinely used in the care of rheumatoid arthritis patients with severe disease who resist conventional disease modifying drug therapies. Three TNF blocking agents (etanercept, infliximab and adalimumab) are currently available and others are in development; all of them display dramatic clinical effects on the course of the disease. Unfortunately, about 25% of the patients display poor clinical responses to these drugs, which results in disease progression, joint damage and unnecessary expenses related to the high cost of these therapies. There is currently no way to distinguish these "non-responder" patient, much less to predict the degree of response to TNF blockade therapy in any particular individual, and avoid unnecessary costly treatment.

Therefore, there is a need for a means to determine whether a subject having RA is likely to respond to TNF blockade therapy.

Summary of the invention

The present inventors have identified a group of genes expressed in the synovium of RA patients that are predictive of individual responses to tumor necrosis factor ("TNF") inhibition.

One aspect of the invention relates to a method for predicting the response to a treatment with a TNF blocking agent in a patient comprising the steps of

(a) assessing in vivo or ex vivo, preferably in a synovial sample, at least one, preferably at least two genes or fragments thereof, or a protein encoded by said at least one, preferably at least two genes, wherein said genes or fragments thereof are selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1,

GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT, and

(b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a). In an embodiment, said method comprises (a) assessing ex vivo in a biological sample, preferably in a synovial sample, from said patient at least one gene or a fragment thereof, or the presence of the protein encoded by said at least one gene, preferably (a) assessing ex vivo in a biological sample, preferably in a synovial sample, from said patient at least two genes or fragments thereof, or the presence of the proteins encoded by said at least two genes, wherein said gene or fragment thereof is selected from the group listed herein and (b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a). In another embodiment, said method comprises (a) assessing in vivo at least one gene or a fragment thereof, or the presence of the protein encoded by said at least one gene, wherein said gene or fragment thereof is selected from the group listed herein and (b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a).

In an embodiment, the present method comprises assessing the expression profile of at least one, preferably at least two genes or fragments thereof, as described herein, and predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a). In an embodiment, the present method comprises assessing the expression profile of at least 5 genes or fragments thereof, preferably at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 69, 70, 80, 90, 100, 150, 200, 300, at least 352, or up to 352 genes or fragments thereof selected from the groups listed in Table 1.

In a particular embodiment, said synovial sample is a synovial tissue. In another particular embodiment, said synovial sample is a synovial fluid. In yet another embodiment said method is performed on cells from the synovial fluid.

The present inventors have designed methods based on the listed genes that are predictive of the response to TNF blocking agents in severe RA, and that are useful for determining whether an individual with rheumatoid arthritis will be a poor, moderate or good responder to TNF blocking therapy. The expression profiles of these genes are particularly useful for identifying the probability of a positive clinical response in a patient, with rheumatoid arthritis, to treatment with a TNF blocking drug.

Another aspect of the invention relates to a method to determine the probability of a positive clinical response in a patient, with rheumatoid arthritis, to treatment with a TNF blocking agent; comprising: (a) determining the levels of gene expression or protein synthesis of at least one, preferably at least two of the genes or fragments thereof listed in Table 1 in vivo or ex vivo in a synovial sample obtained from said patient, and (b) determining from the level of expression or the presence of the protein of said at least one , preferably at least two, gene or fragment thereof the probability that the patients will respond to a TNF inhibitor.

The method of the present invention is based on the comparison level of at least one gene as compared to standard values.

Another aspect of the invention relates to the use of a probe that hybridizes under stringent conditions to at least one gene or fragment thereof selected from the group of genes or fragments thereof as defined herein, or an antibody that binds to at least one protein or fragment thereof encoded by said at least one gene or fragment thereof, or a peptide that binds to at least one protein or fragment thereof encoded by said at least one gene or fragment thereof for predicting the response to a treatment with a TNF blocking agent in a patient.

Preferably, the use of probes that hybridizes under stringent conditions to at least two genes or fragment thereof selected from the group of genes or fragments thereof as defined herein, or antibodies that binds to at least two proteins or fragments thereof encoded by said at least two genes or fragments thereof, or peptides that binds to at least two proteins or fragments thereof encoded by said at least two genes or fragments thereof for predicting the response to a treatment with a TNF blocking agent in a patient.

Another aspect of the invention relates to a kit for predicting the response to a treatment with a TNF blocking agent comprising a low density microarray comprising probes suitable for hybridizing with at least one gene or fragments thereof, preferably at least two, at least 5 genes or fragments thereof, preferably at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 69, 70, 80, 90, 100, 150, 200, 300, at least 352, or up to 352 genes or fragments thereof selected from the group of genes listed herein.

Those skilled in the art will immediate recognize the many other effects and advantages of the present method and the numerous possibilities for end uses of the present invention from the detailed description and examples provided below.

Detailed description

The present invention provides several methods to predict or estimate the likelihood or probability that a patient with rheumatoid arthritis will respond with positive or favorable clinical results to treatment with a TNF blocking agent. These methods involve several forms of genomic or genetic analysis and proteomics.

In an embodiment, the invention relates to a method for predicting the response to a treatment with a TNF blocking agent in a patient comprising the steps of

(a) assessing in synovial tissue from said patient – in vivo or ex vivo – the expression of at least one gene or a fragment thereof, or the presence of the protein encoded by said at least one gene, preferably at least two genes or fragments thereof, or the presence of the proteins encoded by said at least two genes, wherein said gene or fragment thereof is selected from the group listed herein, and (b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a).

In an embodiment, the method for predicting the response to a treatment with a TNF blocking agent in a patient comprises the steps of:

(a) assessing in vivo or in a biological sample from said patient, preferably in a synovial sample from said patient, at least one gene or a fragment thereof or a protein encoded by said at least one gene, preferably at least two genes or fragments thereof, or the presence of the proteins encoded by said at least two genes, wherein said gene is selected from the group of genes as defined herein, and preferably from the group comprising MKI67,

MCM7, MAD2L1, CCNB1, CCNB2, CDC25C, PKMYT1, BUB1, BUB1B, ORC6L, CDC6, CDC2, CCNA2, CCNE2, E2F1, CDKN3, SHC1, E2F7, ZWINT, CDCA5, DBF4, AURKB, STMN1, AURKA, PBK, E2F8, TCF19, EXO1, NUSAP1, UBE2C, CKS2, CENPE, KIF11, BRRN1, CKAP2, MCM2, CEP55, SPAG5, CCNF, FANCD2, H2AFX, UBE2V1, RACGAP1, TTK, CDC20, TPX2, KIF23, GTSE1, PTTG1, KNTC2, CNAP1, E2F2, ANLN, PRC1 KIF15, RPS6KB2, KIF2C, HCAP-G, DLG7, BIRC5, IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and gp130, and

(b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a).

In an embodiment, said patient has rheumatoid arthritis, preferably severe rheumatoid arthritis.

In an embodiment, step (a) of assessing said at least one gene or a fragment thereof comprises the steps of

(i) assessing the level of expression of said at least one gene or a fragment thereof, and

(ii) determining whether the level of expression assessed in step (i) is above or below a threshold value.

In an embodiment, step (a) of assessing said at least two genes or fragments thereof comprises the steps of

(i) assessing the level of expression of said at least two gene or fragments thereof, and

(ii) determining whether the level of expression assessed in step (i) is above or below a threshold value.

In an embodiment, step (a) comprises assessing the expression profile of at least two genes or fragments thereof as described herein.

In an embodiment, the threshold value is determined before step (i) by:

(i1) assessing the level of expression of said at least one gene or fragment thereof in a plurality of biological samples, preferably a plurality of synovial samples, from patients before treatment with said TNF blocking agent,

(i2) assessing the level of expression of said at least one gene or fragment thereof in a plurality of biological samples, preferably a plurality of synovial samples, from patients after treatment with said TNF blocking agent, and

(i3) correlating the response of the patients treated with said TNF blocking agent to the level of expression of said at least one gene determined in step (a) thereby determining the threshold value.

In an embodiment, the threshold value is determined before step (i) by:

(i1) assessing the level of expression of said at least two genes or fragments thereof in a plurality of synovial samples from patients before treatment with said TNF blocking agent,

(i2) assessing the level of expression of said at least two genes or fragments thereof in a plurality of synovial samples from patients after treatment with said TNF blocking agent, and

(i3) correlating the response of the patients treated with said TNF blocking agent to the level of expression of said at least two genes determined in step (a) thereby determining the threshold value.

Preferably, the method comprises determining in vivo or in said biological sample preferably in said synovial sample, the expression level of at least one, preferably at least two to at least 352 genes or fragments thereof.

In an embodiment, said method comprises:

- providing in vivo or in said biological sample, preferably in said synovial sample, the gene expression level of at least one gene or fragment thereof as defined herein,
- providing reference level by establishing gene expression level for reference samples, preferably reference synovial samples, from reference subjects which are poor, moderate and good responder to TNF inhibition,
- comparing the subject level together with reference level, and
- determining whether said biological sample, preferably said synovial sample, is from a poor, moderate or good responder to TNF inhibition.

More preferably, said method comprises determining in said biological sample, preferably said synovial sample, the expression level of at least 1, 2, 30, 60, 100, 150, 200, 300, 352 genes or fragments thereof selected from the groups listed in Table 1.

In an embodiment, said method comprises:

- providing in vivo or in said biological sample, preferably in said synovial sample, the gene expression level of at least two genes or fragments thereof as defined herein,
- providing reference level by establishing gene expression level for reference samples, preferably reference synovial samples, from reference subjects which are poor, moderate and good responder to TNF inhibition,
- comparing the subject level together with reference level, and
- determining whether said biological sample, preferably said synovial sample, is from a poor, moderate or good responder to TNF inhibition.

As used herein the term "biological sample" refers to a sample that comprises a biomolecule that permits the expression level of a gene to be determined. Representative

biomolecules include, but are not limited to total RNA, mRNA, and polypeptides, and derivatives of these molecules such as cDNAs and ESTs. As such, a biological sample can comprise a cell or a group of cells. Preferably, said biological sample is a synovial sample, more preferably a knee synovial sample.

As used herein the term “subject" or “patient” or “individual” refers to any vertebrate species. Preferably, the term subject encompasses warm-blooded vertebrates, more preferably mammals. More particularly contemplated are mammals such as humans, as well as animals such as carnivores other than humans (such as cats and dogs), swine (pigs, hogs, and wild boars), poultry, ruminants (such as cattle, oxen, sheep, giraffes, deer, goats, bison, and camels), and horses.

When describing the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

As used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a method" means one method or more than one method.

The term "and/or" as used in the present specification and in the claims implies that the phrases before and after this term are to be considered either as alternatives or in combination.

As used herein, the term "level" refers to the expression level data that can be used to compare the expression levels of different genes among various subjects.

As used herein the term "gene" encompasses sequences including, but not limited to a coding sequence, a promoter region, a transcriptional regulatory sequence, a non-expressed DNA segment that is a specific recognition sequence for regulatory proteins, a non-expressed DNA segment that contributes to gene expression, a DNA segment designed to have desired parameters, sense and anti-sense strands of genomic DNA (i.e. including any introns occurring therein), EST, RNA generated by transcription of genomic DNA (i.e. prior to splicing), RNA generated by splicing of RNA transcribed from genomic DNA, and proteins generated by translation of spliced RNA (e. g. including proteins both before and after cleavage of normally cleaved regions such as transmembrane signal sequences), cDNA made by reverse transcription of an RNA generated by transcription of genomic DNA (including spliced RNA) and fragments thereof, or combinations thereof.

As used herein the term “fragment” shall be understood to mean a nucleic acid that is the same as part of, but not all of a nucleic acid that forms a gene. The term "fragment" also encompasses a part, but not all of an intergenic region.

The term “increased expression” and “decreased expression” refers to expression of the gene in a sample, at a greater or lesser level, respectively, than the level of expression of said gene (e. g. at least two-fold greater or lesser level) in a control (reference sample). The gene is said to be up-regulated or over-expressed or down-regulated or under-expressed if either the gene is present at a greater or lesser level, respectively, than the level in a control. Expression of a gene in a sample is "significantly" higher or lower than the level of expression of a gene in a control if the level of expression of the gene is greater or less, respectively, than the level by an amount greater than the standard error of the assay employed to assess expression, and preferably at least twice, and more preferably three, four, five or ten times that amount. Alternately, expression of the gene in the sample can be considered "significantly" higher or lower than the level of expression in a control if the level of expression is at least about two, and preferably at least about three, four, or five times, higher or lower, respectively, than the level of expression of the gene in said control.

As used herein, the term "profile" refers to a repository of the expression level data that can be used to compare the expression levels of different genes among various subjects.

The degree of gene expression of said listed genes or fragment thereof is measured. The level of gene expression of these genes is able to distinguish between those patients who will respond well and those patients who will not respond well to a TNF blocking agent.

In practice, the pattern of the expression of at least one of the listed genes or fragments thereof in a patient whose response status is unknown is compared to the pattern of the same genes in patients whose response statue is known. The mathematical similarity between the two patterns determines the probability that the unknown patient response will be similar to response of the known patient. The discovery and identification of these genes form part of the basis of this invention.

In various embodiments the gene expression pattern can be determined in a wide variety of ways including, but not limited to, measuring mRNA levels in a biological sample or measuring protein expression products in a biological sample. These can be performed either ex vivo for example in synovial tissue using low-density microarrays, or in vivo after injection of isotopic tracers allowing to identify and quantify the presence of specific markers in affected patients.

In an embodiment, the TNF blocking agents (also referred as TNF inhibitors) can be adalimumab (HUMIRA®, Abbott), infliximab (REMICADE®, Schering-Plough), etanercept (ENBREL®, Wyeth), certolizumab pegol (CIMZIA®, UCB) or Golimumab (Schering-Plough).

In particular, the following genes are significantly up-regulated in a biological sample preferably synovial samples of poor-responders : genes involved in cytokine-cytokine receptor interactions : IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and genes involved in cell proliferation and control of the cell cycle: MKI67, MCM7, MAD2L1, CCNB1, CCNB2, CDC25C, PKMYT1, BUB1, BUB1B, ORC6L, CDC6, CDC2, CCNA2, CCNE2, E2F1, CDKN3, SHC1, E2F7, ZWINT, CDCA5, DBF4, AURKB, STMN1, AURKA, PBK, E2F8, TCF19, EXO1, NUSAP1, UBE2C, CKS2, CENPE, KIF11, BRRN1, CKAP2, MCM2, CEP55, SPAG5, CCNF, FANCD2, H2AFX, UBE2V1, RACGAP1, TTK, CDC20, TPX2, KIF23, GTSE1, PTTG1, KNTC2, CNAP1, E2F2, ANLN, PRC1 KIF15, RPS6KB2, KIF2C, HCAP-G, DLG7 and BIRC5, while gp130 is down-regulated in synovial samples from poor-responders.

In an embodiment, the level of expression of said at least one gene or fragment thereof in (vivo or in) said sample, preferably synovial sample, is assessed by detecting the level of expression of a protein or a fragment thereof encoded by said at least one gene or fragment thereof. In a preferred embodiment, the level of expression of said protein or fragment thereof is detected using a reagent which specifically binds with said protein or fragment thereof.

In an embodiment, the level of expression of at least two genes or fragments thereof in said synovial sample, is assessed by detecting the level of expression of proteins or fragments thereof encoded by said at least two genes or fragments thereof.

Preferably said, reagent is selected from the group consisting of an antibody, a fragment thereof or a derivative thereof. For some in vivo applications, said reagent is a peptide that binds specifically to the protein of interest.

In an embodiment, the level of expression is determined using a method selected from the group consisting of DNA microarray, reverse transcriptase polymerase chain reaction (RT PCR), immunohistochemistry, immunoblotting, and protein microarray. Preferably, the level of expression is determined using DNA-microarray, preferably low-density DNA-spotted microarray.

In an embodiment, the level of expression of said at least one gene or fragment thereof in said biological sample, preferably in said synovial sample, is assessed by detecting the level of expression of at least one transcribed polynucleotide or fragment thereof encoded by said at least one gene or fragment thereof. Preferably, said at least one transcribed polynucleotide or fragment thereof is a cDNA, or mRNA. In an embodiment, the step of detecting further comprises amplifying the transcribed polynucleotide. The step of detecting can be done using the method of quantitative RT PCR.

n an embodiment, the level of expression of at least two genes or fragments thereof in said biological sample, preferably in said synovial sample, is assessed by detecting the level of expression of at least two transcribed polynucleotides or fragments thereof encoded by said at least two genes or fragments thereof. Preferably, said at least two transcribed polynucleotides or fragments thereof is a cDNA, or mRNA.

In an embodiment, the level of expression of said at least one gene or fragment thereof is assessed by detecting the presence of at least one transcribed polynucleotide or fragment thereof in a sample, preferably in a synovial sample, with a probe which anneals with the transcribed polynucleotide or fragment thereof under stringent hybridization conditions.

In an embodiment, the level of expression of said at least two genes or fragments thereof is assessed by detecting the presence of at least two transcribed polynucleotides or fragments thereof in a sample, preferably in a synovial sample, with probes which anneals with the transcribed polynucleotides or fragments thereof under stringent hybridization conditions.

The present invention therefore also provides arrays comprising probes for detection of polynucleotides (transcriptional state) or for detection of proteins (translational state) in order to detect differentially-expressed genes of the invention. By "array" is intended a solid support or substrate with peptide or nucleic acid probes attached to said support or substrate. Arrays typically comprise a plurality of different nucleic acid or peptide capture probes that are coupled to a surface of a substrate in different, known locations. These arrays, also described as "microarrays" or colloquially "chips" have been generally described in the art. These arrays may generally be produced using mechanical synthesis methods or light directed synthesis methods which incorporate a combination of photolithographic methods and solid phase synthesis methods.

In one embodiment of the invention, microarrays are provided and used to measure the values to be included in the expression profiles. Microarrays are particularly well suited for this purpose because of the reproducibility between different experiments. In an embodiment, the step of determination of the level of expression is performed using DNA-microarray (also referred as gene chip array), preferably low-density DNA-spotted microarray. As used herein low-density DNA-spotted microarray comprises spotting probes suitable for hybridizing from at least 1 to 5000 genes or fragments thereof, preferably from at least 1 to 3000 genes or fragments thereof, more preferably from at least 1 to 2050 genes or fragment thereof, even more preferably from at least 1 to 500 genes, even more preferably from at least 1 to 352 genes.

The skilled person is capable of designing oligonucleotide probes that can be used in methods of the present invention. Preferably, such probes are immobilized on a solid surface as to form an oligonucleotide microarray of the invention. The oligonucleotide probes useful in methods of the present invention are capable of hybridizing under stringent conditions to the at least one, at least two, at least three, at least five, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 50, at least 100, at least 120, at least 150, at least 180, at least 200, at least 220, at least 240, at least 250, at least 260, at least 264, at least 270, or at least 300 nucleic acids as described herein.

In some embodiments, each probe in the array detects a nucleic acid molecule selected from the nucleic acid molecules listed in Table 1.

Although a planar array surface is preferred, the array may be fabricated on a surface of virtually any shape or even a multiplicity of surfaces. Arrays may be peptides or nucleic acids on beads, gels, polymeric surfaces, and fibers such as fiber optics, glass or any other appropriate substrate. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of an all-inclusive device.

The methods of the present invention are particularly useful for subjects with rheumatic arthritis, preferably severe rheumatic arthritis.

The sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e. g. fixation, storage, freezing, lysis, homogenization, DNA or RNA extraction, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to determining the level of expression in the sample.

Expression of a gene according to the invention may be assessed by any of a wide variety of well known methods for detecting expression of a protein or transcribed molecule. Non-limiting examples suitable determination steps include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods. Such methods may also include physical methods such as liquid and gas chromatography, mass spectroscopy, nuclear magnetic resonance and other imaging technologies.

In a preferred embodiment, the step of determination of the level of expression is performed using microarray, preferably DNA-microarray, more preferably low-density DNA-spotted microarray. Suitable probes for said microarray are identified hereunder.

In particular, a mixture of transcribed polynucleotides obtained from the sample, preferably from the synovial sample, is contacted with a substrate having fixed thereto a

polynucleotide complementary to or homologous with at least a portion (e. g. at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 250, 296, or more nucleotide residue) of a RNA transcript encoded by a gene for use in the invention. If polynucleotides complementary to or homologous with a RNA transcript encoded by the gene for use in the invention are differentially detectable on the substrate (e. g. detectable using radioactivity, different chromophores or fluorophores), are fixed to different selected positions, then the levels of expression of a plurality of genes can be assessed simultaneously using a single substrate.

When the assay has an internal control, which can be, for example, a known quantity of a nucleic acid derived from a gene for which the expression level is either known or can be accurately determined, unknown expression levels of other genes can be compared to the known internal control. More specifically, when the assay involves hybridizing labeled total RNA to a solid support comprising a known amount of nucleic acid derived from reference genes, an appropriate internal control could be a housekeeping gene (e. g. glucose-6-phosphate dehydrogenase or elongation factor-1), a housekeeping gene being defined as a gene for which the expression level in all cell types and under all conditions is substantially the same. Use of such an internal control allows a discrete expression level for a gene to be determined (e. g. relative to the expression of the housekeeping gene) both for the nucleic acids present on the solid support and also between different experiments using the same solid support. This discrete expression level can then be normalized to a value relative to the expression level of the control gene (for example, a housekeeping gene). As used herein, the term "normalized", and grammatical derivatives thereof, refers to a manipulation of discrete expression level data wherein the expression level of a reference gene is expressed relative to the expression level of a control gene. For example, the expression level of the control gene can be set at 1, and the expression levels of all reference genes can be expressed in units relative to the expression of the control gene.

In one embodiment, nucleic acids isolated from a biological sample, preferably from a synovial sample, are hybridized to a microarray, wherein the microarray comprises nucleic acids corresponding to those genes to be tested as well as internal control genes. The genes are immobilized on a solid support, such that each position on the support identifies a particular gene. Solid supports include, but are not limited to nitrocellulose and nylon membranes. Solid supports can also be glass or silicon-based (i.e. gene "chips"). Any solid support can be used in the methods of the presently claimed subject matter, so long as the support provides a substrate for the localization of a known amount of a nucleic

acid in a specific position that can be identified subsequent to the hybridization and detection steps.

A microarray can be assembled using any suitable method known to one of skill in the art, and any one microarray configuration or method of construction is not considered to be a limitation of the disclosure.

The present invention also encompasses a method for predicting the response to a treatment with a TNF blocking agent in a patient, said method comprising:

- first obtaining a polynucleotide sample from a biological sample, preferably from a synovial sample, and

- then reacting the sample polynucleotide obtained in the first step with probes immobilized on a solid support having polynucleotide sequences corresponding to all or part of at least one gene or fragment thereof, preferably to all or part of at least two genes or fragments thereof, selected from the group listed in Table 1, and

- detecting the reaction product and comparing with a reference reaction product.

The present invention also encompasses the use of a probe that hybridizes under stringent conditions to at least one gene or fragment thereof, preferably the use of probes that hybridizes under stringent conditions to at least two genes or fragments thereof, from a biological sample, preferably from a synovial sample, said gene or fragment thereof being selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR,

HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT, or an antibody that binds to at least one protein or fragment thereof encoded by said at least one gene or fragment thereof, or antibodies that bind to at least two proteins or fragments thereof encoded by said at least two genes or fragments thereof, for predicting the response to a treatment with a TNF blocking agent in a patient.

Also provided are kits for use in practicing the subject methods. The term "kit" as used herein refers to any combination of reagents or apparatus that can be used to perform a method of the invention.

The present invention also provides kits useful for predicting the response to a treatment with a TNF blocking agent in a patient. In one embodiment, the invention provides a kit predicting the response to a treatment with a TNF blocking agent in a patient, the kit comprising a low density microarray comprising probes suitable for hybridizing with at least one gene or fragment thereof, preferably at least two genes or fragments thereof, selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1,

BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT. In one embodiment, said probes selectively hybridize to a sequence at least 95% identical to a sequence of a gene or fragment thereof listed Table 1. Preferably said probes are selected from the group of probes listed in Table 1.

In an embodiment, said microarray comprises probes suitable for hybridizing with at least 352 genes or fragments thereof selected from the group of genes or fragment thereof listed herein.

The kit may comprise a plurality of reagents, each of which is capable of binding specifically with a nucleic acid or polypeptide corresponding to a gene for use in the invention. Suitable probe for binding with a nucleic acid (e. g. a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

In an embodiment, the kit comprises a nucleic acid probe that binds specifically with a gene nucleic acid or a fragment of the nucleic acid.

The kit may further comprise means for performing PCR reactions. The kit may further comprise media and solution suitable for taking a sample, preferably a synovial sample, and for extracting RNA from said blood sample.

The kit can further comprise additional components for carrying out the method of the invention, such as RNA extraction solutions, purification column and buffers and the like. The kit of the invention can further include any additional reagents, reporter molecules, buffers, excipients, containers and/or devices as required described herein or known in the art, to practice a method of the invention.

The various components of the kit may be present in separate containers or certain compatible components may be pre-combined into a single container, as desired. In addition to the above components, the kits may further include instructions for practicing the present invention. These instructions may be present in the kits in a variety of forms, one or more of which may be present in the kit.

One form in which these instructions may be present is as printed information on a suitable medium or substrate, e. g., a piece or pieces of paper on which the information is printed, in the packaging of the kit, in a package insert, etc. Yet another means would be a computer readable medium, e. g., diskette, CD, etc., on which the information has been recorded. In an embodiment, said kit further comprises a computer-readable medium comprising one or more digitally encoded expression profiles, where each profile has one or more values representing the expression of said at least one gene as defined herein. Said digitally encoded expression profiles are preferably profiles of poor, moderate and good responder to TNF blocking therapy.

The invention also provides a computer-readable medium comprising one or more digitally encoded expression profiles, where each profile has one or more values representing the expression of said at least one gene or fragment thereof, as listed herein that are differentially-expressed in a poor, moderate or good responder to TNF blockade therapy. In some embodiments, the digitally-encoded expression profiles are comprised in a database.

The kits according to the invention may comprise a microarray as defined above and a computer readable medium as described above. The array comprises a substrate having addresses, where each address has a probe that can specifically bind a nucleic acid molecule (by using an oligonucleotide array) or a peptide (by using a peptide array) that is differentially-expressed in at least one poor, moderate or good responder, preferably in the joints of a poor, moderate or good responder, preferably in a synovial sample from a poor, moderate or good responder. The results are converted into a computer-readable medium that has digitally-encoded expression profiles containing values representing the expression level of a nucleic acid molecule detected by the array. Any other convenient means may be present in the kits.

The invention also provides for the storage and retrieval of a collection of data relating to poor, moderate or good responder to TNF blockade therapy specific gene expression data of the present invention, including sequences and expression levels in a computer data storage apparatus.

The method of the invention can also be performed in vivo on a patient after injection of isotopic tracers allowing to identify and quantify the presence of the genes or of the encoded protein thereof in affected patients.

The present invention therefore also provides a method for predicting the response to a treatment with a TNF blocking agent in a patient comprising the steps of:

(a) assessing in vivo at least one gene or a fragment thereof selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3,

CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT, and (b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a). In an embodiment, said patient has rheumatoid arthritis.

In an embodiment the method comprises the steps of (i) assessing in said patient the level of expression of at least one gene or a fragment thereof selected from the group as defined herein,

(ii) determining whether the level of expression assessed in step (i) is above or below a threshold value, and

(iii) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (ii).

In an embodiment, the level of expression of said at least one gene or fragment thereof in said patient is assessed by detecting the level of expression of a protein or a fragment thereof encoded by said at least one gene or fragment thereof.

Preferably, the level of expression of said protein or fragment thereof is detected using a reagent which specifically binds with said protein or fragment thereof. Said reagent can be selected from the group consisting of a peptide, an antibody, or a fragment thereof. Preferably, the level of expression of said protein or fragment thereof is detected by measuring or detecting joint uptake of the reagent.

Preferably, said reagent is labeled with a radioactive isotope, which can be detected by radio-imaging. Suitable radioactive isotope can be selected from the group comprising Technetium^{99m}, Carbon^{11}, Oxygen^{15}, Nitrogen^{13}, Rubidium^{82}, Gallium^{67}, Gallium^{68}, Yttrium^{90}, Molybdenum^{99}, Iodine^{123,124,131} Fluorine^{18}, Phosphorus^{32}, Copper^{62}, Thallium^{201} , Copper^{64}, Copper^{62}, Indium^{111}, and Xenon^{133}.

Suitable radio-imaging method can be selected from the group consisting of single photon emission computed tomography (SPECT), positron emission tomography (PET) and gamma cameras.

The present invention discloses at least one, at least two, at least 10, at least 50, at least 100, at least 120, at least 150, at least 180, at least 200, at least 220, at least 240, at least 250, at least 260, or at least 352 genes described herein that are differentially-expressed in poor, moderate or good responder to TNF blockade. Accordingly, these genes and their gene products are potential therapeutic targets that are useful in methods of screening test compounds to identify therapeutic compounds for the treatment of rheumatic arthritis. The differentially-expressed genes of the invention may be used in cell-based screening assays involving recombinant host cells expressing the differentially-expressed gene product. The recombinant host cells are then screened to identify compounds that can activate the product of the differentially-expressed gene (i.e. agonists) or inactivate the product of the differentially-expressed gene (i.e. antagonists).

The following Table and examples are intended to illustrate and to substantiate the present invention.

Table 1 list about 439 genes or fragments thereof used as synovial markers that are useful for predicting the response to TNF blocking agents in severe RA.

Table 1

Probe set id	Fold change	Gene name	GenBank	Description
Genes up-regulated in poor-responder patients at baseline				
218741_at	17.63	C22orf18	NM_024053	chromosome 22 open reading frame 18
239219_at	13.55	AURKB	N55457	aurora kinase B
202580_x_at	12.99	FOXM1	NM_021953	forkhead box M1
205495_s_at	10.68	GNLY	NM_006433	granulysin
209464_at	10.32	AURKB	AB011446	aurora kinase B
212949_at	8.949	BRRN1	D38553	barren homolog (Drosophila)
228361_at	7.683	E2F2	AL561296	E2F transcription factor 2
219990_at	7.548	FLJ23311	NM_024680	FLJ23311 protein. Synonym: E2F8
214461_at	7.345	LBP	NM_004139	lipopolysaccharide binding protein
202095_s_at	7.269	BIRC5	NM_001168	baculoviral IAP repeat-containing 5 (survivin)
206632_s_at	6.991	APOBEC3B	NM_004900	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B
207746_at	6.896	POLQ	NM_014125	synonyms: POLH, PRO0327; isoform 2 is encoded by transcript variant 2; polymerase (DNA-directed), theta; go_component: nucleoplasm [goid 0005654] [evidence P] [pmid 10395804]; go_function: DNA-directed DNA polymerase activity [goid 0003887] [evidence P] [pmid 10395804]; go_function: DNA repair enzyme [goid 0003686] [evidence P] [pmid 10395804]; go_process: DNA repair [goid 0006281] [evidence P] [pmid 10395804]; Homo sapiens polymerase (DNA directed), theta (POLQ), transcript variant 2, mRNA.
201890_at	6.882	RRM2	BE966236	601660172R1 NIH_MGC_71 Homo sapiens cDNA clone IMAGE:3905920 3', mRNA sequence.
203213_at	6.614	CDC2	AL524035	cell division cycle 2, G1 to S and G2 to M
215942_s_at	6.599	GTSE1	BF973178	G-2 and S-phase expressed 1
218663_at	6.566	HCAP-G	NM_022346	chromosome condensation protein G
212022_s_at	6.482	MKI67	BF001806	antigen identified by monoclonal antibody Ki-67
213008_at	6.295	FLJ10719	BG403615	hypothetical protein FLJ10719
221436_s_at	6.269	CDCA3	NM_031299	cell division cycle associated 3
205666_at	6.232	FMO1	NM_002021	flavin containing monooxygenase 1
204649_at	6.231	TROAP	NM_005480	trophinin associated protein (tastin)
210559_s_at	6.208	CDC2	D88357	cell division cycle 2, G1 to S and G2 to M
211652_s_at	6.14	LBP	M35533	lipopolysaccharide binding protein
219918_s_at	5.962	ASPM	NM_018123	synonyms: MCPH5, FLJ10517, FLJ10549; microcephaly, primary autosomal recessive 5; Homo sapiens asp (abnormal spindle)-like, microcephaly associated (Drosophila) (ASPM), mRNA.
202870_s_at	5.914	CDC20	NM_001255	CDC20 cell division cycle 20 homolog (S. cerevisiae)
238439_at	5.845	ANKRD22	AI925518	wo31e07.x1 NCI_CGAP_Gas4 Homo sapiens cDNA clone IMAGE:2456964 3' similar to contains Alu repetitive element;, mRNA sequence.
203418_at	5.613	CCNA2	NM_001237	cyclin A2
202094_at	5.575	BIRC5	AA648913	baculoviral IAP repeat-containing 5 (survivin)
210052_s_at	5.52	TPX2	AF098158	TPX2, microtubule-associated protein homolog (Xenopus laevis)
209773_s_at	5.506	RRM2	BC001886	ribonucleotide reductase M2 polypeptide

Probe set id	Fold change	Gene name	GenBank	Description
219911_s_at	5.449	SLCO4A1	NM_016354	solute carrier organic anion transporter family, member 4A1
209891_at	5.418	Spc25	AF225416	kinetochore protein Spc25
219148_at	5.277	TOPK	NM_018492	T-LAK cell-originated protein kinase (synonym: PBK)
202338_at	5.242	TK1	NM_003258	thymidine kinase 1, soluble
202705_at	5.235	CCNB2	NM_004701	cyclin B2
212021_s_at	5.159	MKI67	AU132185	antigen identified by monoclonal antibody Ki-67
222608_s_at	5.151	ANLN	AK023208	anillin, actin binding protein (scraps homolog, Drosophila)
210163_at	5.119	CXCL11	AF030514	chemokine (C-X-C motif) ligand 11
202503_s_at	5.042	KIAA0101	NM_014736	KIAA0101 gene product
220423_at	5.041	PLA2G2D	NM_012400	phospholipase A2, group IID
228868_x_at	5.03	CDT1	AW075105	DNA replication factor
212023_s_at	4.985	MKI67	AU147044	antigen identified by monoclonal antibody Ki-67
204267_x_at	4.963	PKMYT1	NM_004203	membrane-associated tyrosine- and threonine-specific cdc2-inhibitory kinase
229479_at	4.963		AI739132	Transcribed sequences
211056_s_at	4.938	SRD5A1	BC006373	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)
203214_x_at	4.733	CDC2	NM_001786	cell division cycle 2, G1 to S and G2 to M
205167_s_at	4.699	CDC25C	NM_001790	cell division cycle 25C
219493_at	4.653	SHCBP1	NM_024745	likely ortholog of mouse Shc SH2-domain binding protein 1
202589_at	4.616	TYMS	NM_001071	thymidylate synthetase
201262_s_at	4.508	BGN	NM_001711	biglycan
221658_s_at	4.488	IL21R	AF269133	interleukin 21 receptor
225687_at	4.483	C20orf129	BC001068	chromosome 20 open reading frame 129
206134_at	4.448	ADAMDEC1	NM_014479	ADAM-like, decysin 1
207165_at	4.422	HMMR	NM_012485	hyaluronan-mediated motility receptor (RHAMM)
216228_s_at	4.371	WDHD1	AK001538	WD repeat and HMG-box DNA binding protein 1
1554408_a_at	4.365	TK1	BC007986	thymidine kinase 1, soluble
222039_at	4.348	LOC146909	AA292789	hypothetical protein LOC146909
203554_x_at	4.34	PTTG1	NM_004219	pituitary tumor-transforming 1
203764_at	4.314	DLG7	NM_014750	discs, large homolog 7 (Drosophila)
205207_at	4.313	IL6	NM_000600	interleukin 6 (interferon, beta 2)
201292_at	4.274	TOP2A	AL561834	topoisomerase (DNA) II alpha 170kDa
203755_at	4.251	BUB1B	NM_001211	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)
226218_at	4.238	IL7R	BE217880	interleukin 7 receptor
218726_at	4.207	DKFZp762E1312	NM_018410	hypothetical protein DKFZp762E1312
204603_at	4.181	EXO1	NM_003686	exonuclease 1
209642_at	4.151	BUB1	AF043294	BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast)
204822_at	4.114	TTK	NM_003318	TTK protein kinase
218585_s_at	4.111	RAMP	NM_016448	RA-regulated nuclear matrix-associated protein
219555_s_at	4.1	BM039	NM_018455	uncharacterized bone marrow protein BM039
37145_at	4.052	GNLY	M85276	Homo sapiens NKG5 gene, complete cds.
211519_s_at	4.026	KIF2C	AY026505	kinesin family member 2C
222958_s_at	4.019	DEPDC1	AK000490	DEP domain containing 1

Probe set id	Fold change	Gene name	GenBank	Description
1552619_a_at	3.996	ANLN	NM_018685	anillin, actin binding protein (scraps homolog, Drosophila)
207072_at	3.987	IL18RAP	NM_003853	interleukin 18 receptor accessory protein
218755_at	3.985	KIF20A	NM_005733	kinesin family member 20A
235572_at	3.927	Spc24	AI469788	kinetochore protein Spc24
208079_s_at	3.919	STK6 (AURKA)	NM_003158	synonyms: AIK, ARK1, AURKA, AURA, BTAK, STK15, MGC34538; aurora-A; IPL1-related kinase; serine/threonine kinase 15; breast-tumor-amplified kinase; aurora/IPL1-like kinase; aurora-related kinase 1; go_component: spindle pole body [goid 0005816] [evidence E]; go_component: spindle [goid 0005819] [evidence TAS] [pmid 9153231]; go_component: nucleus [goid 0005634] [evidence TAS] [pmid 9153231]; go_function: protein kinase activity [goid 0004672] [evidence E] [pmid 9153231]; go_function: cAMP-dependent protein kinase activity [goid 0004691] [evidence IEA]; go_function: protein kinase CK2 activity [goid 0004682] [evidence IEA]; go_function: protein-tyrosine kinase activity [goid 0004713] [evidence IEA]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_function: protein serine/threonine kinase activity [goid 0004674] [evidence IEA]; go_function: transferase activity [goid 0016740] [evidence IEA]; go_process: oncogenesis [goid 0007048] [evidence E]; go_process: mitosis [goid 0007067] [evidence TAS] [pmid 9153231]; go_process: protein amino acid phosphorylation [goid 0006468] [evidence TAS] [pmid 9153231]; go_process: cell cycle [goid 0007049] [evidence IEA]; Homo sapiens serine/threonine kinase 6 (STK6), transcript variant 2, mRNA.
229490_s_at	3.911	IQGAP3	AW271106	xr49a07.x1 NCI_CGAP_Ov26 Homo sapiens cDNA clone IMAGE:2763444 3', mRNA sequence.
1554696_s_at	3.814	TYMS	AB077208	thymidylate synthetase
205118_at	3.694	FPR1	M60626	Human N-formylpeptide receptor (fMLP-R98) mRNA, complete cds.
232278_s_at	3.675	DEPDC1	AJ278112	DEP domain containing 1
221258_s_at	3.654	DKFZP434G2226	NM_031217	kinesin family member 18A
204033_at	3.615	TRIP13	NM_004237	thyroid hormone receptor interactor 13
219510_at	3.611	POLQ	NM_006596	polymerase (DNA directed), theta
214710_s_at	3.604	CCNB1	BE407516	cyclin B1
205568_at	3.6	AQP9	NM_020980	aquaporin 9
204092_s_at	3.597	STK6	NM_003600	serine/threonine kinase 6
202779_s_at	3.571	UBE2S	NM_014501	ubiquitin-conjugating enzyme E2S
229625_at	3.545	GBP5	BG545653	guanylate binding protein 5
218355_at	3.523	KIF4A	NM_012310	kinesin family member 4A
228863_at	3.493	PLA2G2D	N69091	protocadherin 17
227165_at	3.493	C13orf3	AI829603	chromosome 13 open reading frame 3
202833_s_at	3.492	SERPINA1	NM_000295	serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1
204887_s_at	3.484	PLK4	NM_014264	polo-like kinase 4 (Drosophila)
223381_at	3.478	CDCA1	AF326731	cell division cycle associated 1

Probe set id	Fold change	Gene name	GenBank	Description
218039_at	3.467	NUSAP1	NM_016359	nucleolar and spindle associated protein 1
206364_at	3.46	KIF14	NM_014875	
205656_at	3.444	PCDH17	NM_014459	protocadherin 17
228729_at	3.371	CCNB1	N90191	cyclin B1
205237_at	3.36	FCN1	NM_002003	ficolin (collagen/fibrinogen domain containing) 1
219306_at	3.344	KNSL7	NM_020242	kinesin-like 7 (KIF 15)
202208_s_at	3.329	ARL7	BC001051	ADP-ribosylation factor-like 7
209825_s_at	3.322	UMPK	BC002906	uridine monophosphate kinase
205798_at	3.311	IL7R	NM_002185	interleukin 7 receptor
223307_at	3.286	CDCA3	BC002551	cell division cycle associated 3
209408_at	3.25	KIF2C	U63743	kinesin family member 2C
227289_at	3.247	LOC144997	AU119437	protocadherin 17
218009_s_at	3.229	PRC1	NM_003981	protein regulator of cytokinesis 1
204825_at	3.222	MELK	NM_014791	maternal embryonic leucine zipper kinase
236641_at	3.201	KIF14	AW183154	kinesin family member 14
205569_at	3.195	LAMP3	NM_014398	lysosomal-associated membrane protein 3
204947_at	3.195	E2F1	NM_005225	E2F transcription factor 1
205884_at	3.192	ITGA4	NM_000885	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
205394_at	3.186	CHEK1	NM_001274	CHK1 checkpoint homolog (S. pombe)
211429_s_at	3.161		AF119873	PRO2275 mRNA, complete cds
209709_s_at	3.156	HMMR	U29343	hyaluronan-mediated motility receptor (RHAMM)
206074_s_at	3.153	HMGA1	NM_002131	high mobility group AT-hook 1
205024_s_at	3.146	RAD51	NM_002875	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
219045_at	3.135	RHOF	NM_019034	ras homolog gene family, member F (in filopodia)
207828_s_at	3.129	CENPF	NM_005196	
228323_at	3.125	AF15Q14	BF248364	AF15q14 protein
203560_at	3.106	GGH	NM_003878	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)
214847_s_at	3.098	GPSM3	BG111168	602281582F1 NIH_MGC_86 Homo sapiens cDNA clone IMAGE:4369100 5', mRNA sequence.
227609_at	3.086	EPSTI1	AA633203	epithelial stromal interaction 1 (breast)
1555758_a_at	3.084	CDKN3	AF213040	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)
204962_s_at	3.083	CENPA	NM_001809	centromere protein A, 17kDa
203362_s_at	3.068	MAD2L1	NM_002358	MAD2 mitotic arrest deficient-like 1 (yeast)
209714_s_at	3.068	CDKN3	AF213033	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)
205397_x_at	3.049	SMAD3	U76622	MAD, mothers against decapentaplegic homolog 3 (Drosophila)
228033_at	3.04	E2F7	AI341146	E2F transcription factor 7
224753_at	3.014	CDCA5	BE614410	cell division cycle associated 5
218883_s_at	3.009	KLIP1	NM_024629	KSHV latent nuclear antigen interacting protein 1
226456_at	2.991	MGC24665	AW138157	hypothetical protein MGC24665
204444_at	2.932	KIF11	NM_004523	kinesin family member 11
227212_s_at	2.925	PHF19	BE544837	PHD finger protein 19
201629_s_at	2.923	ACP1	BE872974	acid phosphatase 1, soluble
203276_at	2.904	LMNB1	NM_005573	lamin B1
205046_at	2.871	CENPE	NM_001813	centromere protein E, 312kDa
228273_at	2.869	FLJ11029	BG165011	hypothetical protein FLJ11029

Probe set id	Fold change	Gene name	GenBank	Description
218542_at	2.865	C10orf3	NM_018131	chromosome 10 open reading frame 3, synonym: CEP55
205582_s_at	2.859	GGTLA1	NM_004121	gamma-glutamyltransferase-like activity 1
204318_s_at	2.835	GTSE1	NM_016426	G-2 and S-phase expressed 1
206785_s_at	2.829	KLRC1	NM_002260	killer cell lectin-like receptor subfamily C, member 2
205180_s_at	2.822	ADAM8	NM_001109	a disintegrin and metalloproteinase domain 8
221591_s_at	2.82	FLJ10156	BC005004	hypothetical protein FLJ10156
205034_at	2.815	CCNE2	NM_004702	cyclin E2
201291_s_at	2.806	TOP2A	AU159942	topoisomerase (DNA) II alpha 170kDa
222848_at	2.794	FKSG14	BC005400	leucine zipper protein FKSG14
206214_at	2.794	PLA2G7	NM_005084	phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)
201490_s_at	2.792	PPIF	NM_005729	peptidylprolyl isomerase F (cyclophilin F)
206224_at	2.782	CST1	NM_001898	cystatin SN
201858_s_at	2.781	PRG1	J03223	proteoglycan 1, secretory granule
204026_s_at	2.778	ZWINT	NM_007057	ZW10 interactor
204162_at	2.765	KNTC2	NM_006101	kinetochore associated 2
226661_at	2.76	CDCA2	T90295	yd42f02.s1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone IMAGE:110907 3', mRNA sequence.
204768_s_at	2.727	FEN1	NM_004111	flap structure-specific endonuclease 1
229097_at	2.725		AI813331	Similar to diaphanous homolog 3 (Drosophila), clone IMAGE:5277415, mRNA
210334_x_at	2.719	BIRC5	AB028869	baculoviral IAP repeat-containing 5 (survivin)
205863_at	2.702	S100A12	NM_005621	S100 calcium binding protein A12 (calgranulin C)
204886_at	2.7	PLK4	AL043646	polo-like kinase 4 (Drosophila)
218662_s_at	2.694	HCAP-G	NM_022346	chromosome condensation protein G
212525_s_at	2.693	H2AFX	AA760862	nz14g12.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:1287814 3' similar to gb:X14850_cds1 HISTONE H2A.X (HUMAN);, mRNA sequence.
219869_s_at	2.683	SLC39A8	NM_022154	solute carrier family 39 (zinc transporter), member 8
223556_at	2.675	HELLS	AF155827	helicase, lymphoid-specific
203145_at	2.67	SPAG5	NM_006461	sperm associated antigen 5
205436_s_at	2.666	H2AFX	NM_002105	H2A histone family, member X
208189_s_at	2.651	MYO7A	NM_000260	myosin VIIA (Usher syndrome 1B (autosomal recessive, severe))
210031_at	2.644	CD3Z	J04132	CD3Z antigen, zeta polypeptide (TiT3 complex)
239205_s_at	2.641	CR1	BE552138	complement component (3b/4b) receptor 1-like
221521_s_at	2.639	Pfs2	BC003186	DNA replication complex GINS protein PSF2
211713_x_at	2.604	KIAA0101	BC005832	KIAA0101 gene product
204170_s_at	2.602	CKS2	NM_001827	CDC28 protein kinase regulatory subunit 2
220384_at	2.589	TXNDC3	NM_016616	thioredoxin domain containing 3 (spermatozoa)
204826_at	2.57	CCNF	NM_001761	cyclin F
214290_s_at	2.564	HIST2H2AA	AI313324	ta77f02.x2 NCI_CGAP_HSC2 Homo sapiens cDNA clone IMAGE:2050107 3' similar to gb:L19779 HISTONE H2A.1 (HUMAN);, mRNA sequence.
206205_at	2.556	MPHOSPH9	NM_022782	M-phase phosphoprotein 9
205119_s_at	2.555	FPR1	NM_002029	formyl peptide receptor 1
204146_at	2.552	PIR51	BE966146	601660074R1 NIH_MGC_71 Homo sapiens cDNA clone IMAGE:3905635 3', mRNA sequence.

Probe set id	Fold change	Gene name	GenBank	Description
210514_x_at	2.55	HLA-C	AF226990	HLA-G histocompatibility antigen, class I, G
214450_at	2.537	CTSW	NM_001335	cathepsin W (lymphopain)
222077_s_at	2.5	RACGAP1	AU153848	Rac GTPase activating protein 1
218308_at	2.495	TACC3	NM_006342	transforming, acidic coiled-coil containing protein 3
204709_s_at	2.491	KIF23	NM_004856	kinesin family member 23
204317_at	2.483	GTSE1	BF305380	G-2 and S-phase expressed 1
209636_at	2.472	NFKB2	BC002844	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)
204767_s_at	2.449	FEN1	BC000323	flap structure-specific endonuclease 1
203236_s_at	2.408	LGALS9	NM_009587	lectin, galactoside-binding, soluble, 9 (galectin 9)
213733_at	2.401	MYO1F	BF740152	myosin IF
230537_at	2.389		AA401256	Transcribed sequences
219259_at	2.387	SEMA4A	NM_022367	hypothetical protein FLJ12287 similar to semaphorins
230165_at	2.386	SGOL2	N31731	tripin
229305_at	2.378	KLIP1	AA460299	KSHV latent nuclear antigen interacting protein 1
227211_at	2.372	PHF19	BE544837	PHD finger protein 19
219490_s_at	2.372	DCLRE1B	NM_022836	DNA cross-link repair 1B (PSO2 homolog, S. cerevisiae)
201663_s_at	2.366	SMC4L1	NM_005496	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)
1556347_at	2.354		W72151	Full length insert cDNA clone ZD70G04
242560_at	2.352	FANCD2	AA579890	Fanconi anemia, complementation group D2
202145_at	2.343	LY6E	NM_002346	lymphocyte antigen 6 complex, locus E
229055_at	2.333		AI805006	Transcribed sequences
203234_at	2.329	UPP1	NM_003364	uridine phosphorylase 1
213226_at	2.324	PMSCL1	AI346350	polymyositis/scleroderma autoantigen 1, 75kDa
210029_at	2.322	INDO	M34455	indoleamine-pyrrole 2,3 dioxygenase
202307_s_at	2.319	TAP1	NM_000593	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)
200853_at	2.306	H2AFZ	NM_002106	H2A histone family, member Z
223274_at	2.303	TCF19	BC002493	transcription factor 19 (SC1)
222740_at	2.301	ATAD2	AI925583	PRO2000 protein
239196_at	2.299	ANKRD22	AI097229	hypothetical protein MGC22805
230494_at	2.293	SLC20A1	AI671885	solute carrier family 20 (phosphate transporter), member 1
223809_at	2.292	RGS18	AF076642	regulator of G-protein signalling 18
216841_s_at	2.289	SOD2	X15132	superoxide dismutase 2, mitochondrial
213599_at	2.283	OIP5	BE045993	Opa-interacting protein 5
200943_at	2.275	HMGN1	NM_004965	high-mobility group nucleosome binding domain 1
211040_x_at	2.274	GTSE1	BC006325	G-2 and S-phase expressed 1
205290_s_at	2.274	BMP2	NM_001200	bone morphogenetic protein 2
202151_s_at	2.255	UBADC1	NM_016172	ubiquitin associated domain containing 1
219787_s_at	2.251	ECT2	NM_018098	epithelial cell transforming sequence 2 oncogene
205241_at	2.248	SCO2	NM_005138	SCO cytochrome oxidase deficient homolog 2 (yeast)
202107_s_at	2.245	MCM2	NM_004526	MCM2 minichromosome maintenance deficient 2, mitotin (S. cerevisiae)
209231_s_at	2.235	MGC3248	AI038068	dynactin 4
218782_s_at	2.222	ATAD2	NM_014109	PRO2000 protein
228069_at	2.219	DUFD1	AL138828	

Probe set id	Fold change	Gene name	GenBank	Description
204116_at	2.219	IL2RG	NM_000206	interleukin 2 receptor, gamma (severe combined immunodeficiency)
202688_at	2.218	TNFSF10	NM_003810	tumor necrosis factor (ligand) superfamily, member 10, (synonym: TRAIL)
202819_s_at	2.217	TCEB3	NM_003198	transcription elongation factor B (SIII), polypeptide 3 (110kDa, elongin A)
211343_s_at	2.217	COL13A1	M33653	collagen, type XIII, alpha 1
223658_at	2.217	KCNK6	AF134149	potassium channel, subfamily K, member 6
204959_at	2.216	MNDA	NM_002432	myeloid cell nuclear differentiation antigen
230711_at	2.212		AA777349	CDNA FLJ13510 fis, clone PLACE1005146
218350_s_at	2.206	GMNN	NM_015895	geminin, DNA replication inhibitor
210222_s_at	2.203	RTN1	BC000314	reticulon 1
203358_s_at	2.202	EZH2	NM_004456	enhancer of zeste homolog 2 (Drosophila)
244239_at	2.202		AI887306	Full length insert cDNA YN63H06
239979_at	2.193		BE645480	Transcribed sequences
210951_x_at	2.193	RAB27A	AF125393	RAB27A, member RAS oncogene family
203968_s_at	2.193	CDC6	NM_001254	CDC6 cell division cycle 6 homolog (S. cerevisiae)
203773_x_at	2.191	BLVRA	NM_000712	biliverdin reductase A
210136_at	2.175		AW070431	myelin basic protein
226264_at	2.17	SUSD1	AL137432	sushi domain containing 1
222062_at	2.169	IL27RA	AI983115	wu18b02.x1 NCI_CGAP_GC6 Homo sapiens cDNA clone IMAGE:2517291 3' similar to contains Alu repetitive element;, mRNA sequence.
203047_at	2.165	STK10	NM_005990	serine/threonine kinase 10
1554624_a_at	2.154	SIRPB1	BC025286	signal-regulatory protein beta 1
217028_at	2.145	CXCR4	AJ224869	Homo sapiens CXCR4 gene encoding receptor CXCR4.
207850_at	2.138	CXCL3	NM_002090	chemokine (C-X-C motif) ligand 3
1562289_at	2.135		AL834519	MRNA; cDNA DKFZp434N0220 (from clone DKFZp434N0220)
202087_s_at	2.132	CTSL	NM_001912	cathepsin L
240440_at	2.131	NPL	AI368358	N-acetylneuraminate pyruvate lyase (dihydrodipicolinate synthase)
226906_s_at	2.128	ARHGAP9	AL548053	Rho GTPase activating protein 9
202954_at	2.126	UBE2C	NM_007019	ubiquitin-conjugating enzyme E2C
205789_at	2.125	CD1D	NM_001766	CD1D antigen, d polypeptide
209514_s_at	2.123	RAB27A	BE502030	RAB27A, member RAS oncogene family
201489_at	2.122	PPIF	BC005020	peptidylprolyl isomerase F (cyclophilin F)
206296_x_at	2.115	MAP4K1	NM_007181	mitogen-activated protein kinase kinase kinase kinase 1
205090_s_at	2.113	NAGPA	NM_016256	N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase
1555355_a_at	2.11	ETS1	BC017314	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)
224428_s_at	2.109	CDCA7	AY029179	cell division cycle associated 7
205483_s_at	2.106	G1P2	NM_005101	interferon, alpha-inducible protein (clone IFI-15K)
205567_at	2.095	CHST1	NM_003654	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1
203645_s_at	2.092	CD163	NM_004244	CD163 antigen
201896_s_at	2.084	DDA3	BC001425	
217436_x_at	2.08		M80469	heavy chain; Human MHC class I HLA-J gene, exons 1-8 and complete cds.

Probe set id	Fold change	Gene name	GenBank	Description
213911_s_at	2.077	H2AFZ	BF718636	H2A histone family, member Z
1552701_a_at	2.076	COP	NM_052889	CARD only protein
225418_at	2.074	PVRL2	AI520949	poliovirus receptor-related 2 (herpesvirus entry mediator B)
218252_at	2.073	CKAP2	NM_018204	cytoskeleton associated protein 2
226436_at	2.07	RASSF4	N49935	Ras association (RalGDS/AF-6) domain family 4
210046_s_at	2.069	IDH2	U52144	isocitrate dehydrogenase 2 (NADP+), mitochondrial
218600_at	2.066	MGC10986	NM_030576	hypothetical protein MGC10986
204425_at	2.066	ARHGAP4	NM_001666	Rho GTPase activating protein 4
205105_at	2.066	MAN2A1	NM_002372	mannosidase, alpha, class 2A, member 1
209172_s_at	2.06	CENPF	U30872	centromere protein F, 350/400ka (mitosin)
201920_at	2.059	SLC20A1	NM_005415	solute carrier family 20 (phosphate transporter), member 1
204806_x_at	2.05	HLA-F	NM_018950	major histocompatibility complex, class I, F
226437_at	2.048	LOC90522	AI079540	similar to putative transmembrane protein; homolog of yeast Golgi membrane protein Yif1p (Yip1p-interacting factor)
212322_at	2.047	SGPL1	BE999972	sphingosine-1-phosphate lyase 1
209179_s_at	2.046	LENG4	BC003164	leukocyte receptor cluster (LRC) member 4
218818_at	2.033	FHL3	NM_004468	four and a half LIM domains 3
205695_at	2.033	SDS	NM_006843	serine dehydratase
210058_at	2.032	MAPK13	BC000433	mitogen-activated protein kinase 13
204924_at	2.02	TLR2	NM_003264	toll-like receptor 2
234863_x_at	2.015	FBXO5	AK026197	F-box only protein 5
219105_x_at	2.013	ORC6L	NM_014321	origin recognition complex, subunit 6 homolog-like (yeast)
210732_s_at	2.01	LGALS8	AF342816	lectin, galactoside-binding, soluble, 8 (galectin 8)
219978_s_at	2.008	NUSAP1	NM_018454	nucleolar and spindle associated protein 1
217497_at	2.001	ECGF1	AW613387	endothelial cell growth factor 1 (platelet-derived)
211529_x_at	1.999	HLA-G	M90684	HLA-G histocompatibility antigen, class I, G
214329_x_at	1.992	TNFSF10	AW474434	xs95h07.x1 NCI_CGAP_Ut4 Homo sapiens cDNA clone IMAGE:2777437 3' similar to contains Alu repetitive element; contains element HGR repetitive element ;, mRNA sequence.
209753_s_at	1.99	TMPO	BG391171	thymopoietin
219690_at	1.987	FLJ22573	NM_024660	hypothetical protein FLJ22573
234068_s_at	1.983	AP2A1	AC006942	
41037_at	1.983	TEAD4	U63824	TEA domain family member 4
203817_at	1.972	GUCY1B3	W93728	guanylate cyclase 1, soluble, beta 3
1554553_s_at	1.972	LOC90522	BC014974	similar to putative transmembrane protein; homolog of yeast Golgi membrane protein Yif1p (Yip1p-interacting factor)
216262_s_at	1.966	TGIF2	AL050318	
235609_at	1.963	BRIP1	BF056791	BRCA1 interacting protein C-terminal helicase 1
207740_s_at	1.962	NUP62	NM_012346	nucleoporin 62kDa
211047_x_at	1.958	AP2S1	BC006337	adaptor-related protein complex 2, sigma 1 subunit
218384_at	1.957	CARHSP1	NM_014316	calcium regulated heat stable protein 1, 24kDa
211762_s_at	1.957	KPNA2	BC005978	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)

Probe set id	Fold change	Gene name	GenBank	Description
200889_s_at	1.951	SSR1	AI016620	signal sequence receptor, alpha (translocon-associated protein alpha)
215049_x_at	1.951	CD163	Z22969	CD163 antigen
218681_s_at	1.948	SDF2L1	NM_022044	stromal cell-derived factor 2-like 1
223172_s_at	1.946	HSPC242	AF060924	hypothetical protein HSPC242
202697_at	1.946	CPSF5	NM_007006	cleavage and polyadenylation specific factor 5, 25 kDa
227818_at	1.932	DKFZP434L0117	AL133609	hypothetical protein DKFZp434L0117
224846_at	1.924	LOC92799	AI348000	hypothetical protein BC007653
212279_at	1.918	MAC30	BE779865	hypothetical protein MAC30
219863_at	1.917	CEB1	NM_016323	cyclin-E binding protein 1
227350_at	1.915		AI889959	wm65f08.x1 NCI_CGAP_Ut2 Homo sapiens cDNA clone IMAGE:2440839 3', mRNA sequence.
210069_at	1.913	CPT1B	U62733	carnitine palmitoyltransferase 1B (muscle)
240247_at	1.912		AI653240	Transcribed sequences
226936_at	1.912		BG492359	CDNA clone IMAGE:4448513, partial cds
1553968_a_at	1.909	LOC113179	BI524128	secretory carrier membrane protein 4
201888_s_at	1.907	IL13RA1	U81379	interleukin 13 receptor, alpha 1
218383_at	1.903	C14orf94	NM_017815	chromosome 14 open reading frame 94
214032_at	1.9	ZAP70	AI817942	zeta-chain (TCR) associated protein kinase 70kDa
205249_at	1.899	EGR2	NM_000399	early growth response 2 (Krox-20 homolog, Drosophila)
213088_s_at	1.895	DNAJC9	BE551340	DnaJ (Hsp40) homolog, subfamily C, member 9
210225_x_at	1.894	LILRB3	AF009635	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 3
223303_at	1.892	URP2	BC004347	UNC-112 related protein 2
239555_at	1.891		W87626	Transcribed sequences
221581_s_at	1.884	WBSCR5	AF257135	Williams-Beuren syndrome chromosome region 5
204844_at	1.884	ENPEP	L12468	glutamyl aminopeptidase (aminopeptidase A)
236667_at	1.882		BE218186	Clone IMAGE:5538723, mRNA
212020_s_at	1.88	MKI67	AU152107	antigen identified by monoclonal antibody Ki-67
202957_at	1.876	HCLS1	NM_005335	hematopoietic cell-specific Lyn substrate 1
203777_s_at	1.872	RPS6KB2	NM_003952	ribosomal protein S6 kinase, 70kDa, polypeptide 2
203454_s_at	1.872	ATOX1	NM_004045	ATX1 antioxidant protein 1 homolog (yeast)
202120_x_at	1.87	AP2S1	NM_004069	adaptor-related protein complex 2, sigma 1 subunit
212242_at	1.87	TUBA1	AL565074	tubulin, alpha 1 (testis specific)
49306_at	1.87	RASSF4	AI890191	Ras association (RalGDS/AF-6) domain family 4
224783_at	1.868	MGC29814	AA831661	hypothetical protein MGC29814
201422_at	1.854	IFI30	NM_006332	interferon, gamma-inducible protein 30
205339_at	1.851	SIL	NM_003035	TAL1 (SCL) interrupting locus
206715_at	1.85	TFEC	NM_012252	transcription factor EC
203778_at	1.849	MANBA	NM_005908	mannosidase, beta A, lysosomal
222206_s_at	1.846	LOC56926	AA781143	hypothetical protein from EUROIMAGE 2021883
229860_x_at	1.845		AI341602	Clone IMAGE:5200861, mRNA
201251_at	1.844	PKM2	NM_002654	pyruvate kinase, muscle
223461_at	1.842	TBC1D7	AF151073	TBC1 domain family, member 7
205205_at	1.841	RELB	NM_006509	v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian)
215623_x_at	1.837	SMC4L1	AK002200	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)

Probe set id	Fold change	Gene name	GenBank	Description
209948_at	1.835	KCNMB1	U61536	potassium large conductance calcium-activated channel, subfamily M, beta member 1
225235_at	1.827	FBXO23	AW007710	MRNA for FLJ00016 protein, partial cds
210983_s_at	1.827	MCM7	AF279900	MCM7 minichromosome maintenance deficient 7 (S. cerevisiae)
236243_at	1.82	ZCCHC6	AW070776	zinc finger, CCHC domain containing 6
207224_s_at	1.817	SIGLEC7	NM_016543	sialic acid binding Ig-like lectin 7
203228_at	1.813	PAFAH1B3	NM_002573	platelet-activating factor acetylhydrolase, isoform Ib, gamma subunit 29kDa
1552977_a_at	1.812	TNRC5	NM_006586	trinucleotide repeat containing 5
202487_s_at	1.809	H2AFV	NM_012412	H2A histone family, member V
201157_s_at	1.805	NMT1	AF020500	N-myristoyltransferase 1
226804_at	1.805	FAM20A	AI632223	family with sequence similarity 20, member A
222483_at	1.805	EFHD2	AW664179	EF hand domain containing 2
243352_at	1.801	LAK	AA521086	lymphocyte alpha-kinase
227012_at	1.797	MCFP	AI823986	mitochondrial carrier family protein
204023_at	1.796	RFC4	NM_002916	replication factor C (activator 1) 4, 37kDa
221882_s_at	1.778	TMEM8	AI636233	transmembrane protein 8 (five membrane-spanning domains)
211729_x_at	1.778	BLVRA	BC005902	biliverdin reductase A
1555812_a_at	1.767	ARHGDIB	AF498927	Rho GDP dissociation inhibitor (GDI) beta
228559_at	1.766		BF111626	CDNA clone IMAGE:6043059, partial cds
209201_x_at	1.76	CXCR4	L01639	chemokine (C-X-C motif) receptor 4
201469_s_at	1.759	SHC1	AI809967	SHC (Src homology 2 domain containing) transforming protein 1
201261_x_at	1.751	BGN	BC002416	biglycan
222537_s_at	1.751	SPEC1	W44413	small protein effector 1 of Cdc42
223451_s_at	1.748	CKLF	AF096895	chemokine-like factor
217714_x_at	1.746	STMN1	AV756729	stathmin 1/oncoprotein 18
218979_at	1.744	C9orf76	NM_024945	chromosome 9 open reading frame 76
205574_x_at	1.736	BMP1	NM_001199	bone morphogenetic protein 1
225655_at	1.735	UHRF1	AK025578	ubiquitin-like, containing PHD and RING finger domains, 1
200615_s_at	1.726	AP2B1	AL567295	adaptor-related protein complex 2, beta 1 subunit
226828_s_at	1.722	HEYL	AL040198	hairy/enhancer-of-split related with YRPW motif-like
203046_s_at	1.717	TIMELESS	NM_003920	timeless homolog (Drosophila)
210776_x_at	1.71	TCF3	M31222	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)
217960_s_at	1.709	TOMM22	NM_020243	chromosome 22 open reading frame 2
208918_s_at	1.7	FLJ13052	AI334128	NAD kinase
235081_x_at	1.695	LOC201292	AI739057	wi34g07.x1 NCI_CGAP_Co16 Homo sapiens cDNA clone IMAGE:2392188 3', mRNA sequence.
208795_s_at	1.691	MCM7	D55716	MCM7 minichromosome maintenance deficient 7 (S. cerevisiae)
202655_at	1.689	ARMET	NM_006010	arginine-rich, mutated in early stage tumors
206102_at	1.682	KIAA0186	NM_021067	
211005_at	1.681	LAT	AF036906	linker for activation of T cells

Probe set id	Fold change	Gene name	GenBank	Description
209584_x_at	1.681	APOBEC3C	AF165520	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C
201774_s_at	1.674	CNAP1	AK022511	chromosome condensation-related SMC-associated protein 1
204244_s_at	1.672	ASK	NM_006716	activator of S phase kinase. Synonym DBF4
204531_s_at	1.668	BRCA1	NM_007295	breast cancer 1, early onset
206295_at	1.665	IL18	NM_001562	interleukin 18 (interferon-gamma-inducing factor)
226405_s_at	1.661	ARRDC1	AK001822	chromosome 9 open reading frame 37
203432_at	1.654	TMPO	AW272611	thymopoietin
209546_s_at	1.647	APOL1	AF323540	apolipoprotein L, 1
218815_s_at	1.634	FLJ10199	NM_018022	hypothetical protein FLJ10199
210070_s_at	1.629	CPT1B	U62733	carnitine palmitoyltransferase 1B (muscle)
239269_at	1.625		AW449577	CDNA FLJ26120 fis, clone SYN00419
201584_s_at	1.625	DDX39	NM_005804	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39
214059_at	1.625	IFI44	BE049439	interferon-induced protein 44
201666_at	1.623	TIMP1	NM_003254	tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor)
206298_at	1.611	ARHGAP22	NM_021226	Rho GTPase activating protein 22
208436_s_at	1.609	IRF7	NM_004030	interferon regulatory factor 7
207714_s_at	1.604	SERPINH1	NM_004353	synonyms: CBP1, CBP2, gp46, HSP47, RA-A47, SERPINH2; collagen-binding protein 1; colligin-1; collagen-binding protein 2; colligin-2; heat shock protein 47; rheumatoid arthritis antigen A-47; go_component: endoplasmic reticulum [goid 0005783] [evidence TAS] [pmid 7656593]; go_function: collagen binding [goid 0005518] [evidence NR]; go_function: serine protease inhibitor activity [goid 0004867] [evidence P] [pmid 1309665]; go_function: heat shock protein activity [goid 0003773] [evidence TAS] [pmid 1309665]; go_function: serpin [goid 0004868] [evidence IEA]; go_process: response to stress [goid 0006950] [evidence TAS] [pmid 1309665]; go_process: heat shock response [goid 0006951] [evidence P]; Homo sapiens serine (or cysteine) proteinase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1) (SERPINH1), mRNA.
228286_at	1.601	FLJ40869	AK025489	hypothetical protein FLJ40869
201664_at	1.597	SMC4L1	AL136877	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)
208808_s_at	1.592	HMGB2	BC000903	high-mobility group box 2
223186_at	1.591	Kua	AB044550	ubiquitin-conjugating enzyme E2 variant 1 (synonym: UBE2V1)
1555745_a_at	1.587	LYZ	U25677	lysozyme (renal amyloidosis)
213534_s_at	1.586	PASK	D50925	PAS domain containing serine/threonine kinase
201415_at	1.586	GSS	NM_000178	glutathione synthetase
201697_s_at	1.585	DNMT1	NM_001379	DNA (cytosine-5-)-methyltransferase 1
203374_s_at	1.572	TPP2	AW612376	tripeptidyl peptidase II
212316_at	1.567	NUP210	AA502912	nucleoporin 210
205546_s_at	1.554	TYK2	NM_003331	tyrosine kinase 2

Probe set id	Fold change	Gene name	GenBank	Description
222036_s_at	1.546	MCM4	AI859865	wm21f03.x1 NCI_CGAP_Ut4 Homo sapiens cDNA clone IMAGE:2436605 3' similar to contains Alu repetitive element;, mRNA sequence.
218844_at	1.538	FLJ20920	NM_025149	hypothetical protein FLJ20920
244869_at	1.535		AA677459	zj70a12.s1 Soares_fetal_liver_spleen_1NFLS_S1 Homo sapiens cDNA clone IMAGE:460222 3' similar to contains Alu repetitive element;, mRNA sequence.
204255_s_at	1.527	VDR	AA772285	vitamin D (1,25- dihydroxyvitamin D3) receptor
Genes down-regulated in poor-responder patients at baseline				
Probe set Id	**Fold change**	**Gene name**	**GenBank**	**Description**
243041_s_at	0.653	RBMS3	AI217028	RNA binding motif, single stranded interacting protein
213765_at	0.635	MFAP5	AW665892	Microfibril-associated glycoprotein-2
226558_at	0.552		BE856637	LOC389834 (LOC389834), mRNA
213176_s_at	0.522	LTBP4	AI910869	latent transforming growth factor beta binding protein 4
239183_at	0.474	ANGPTL1	W67461	angiopoietin-like 1
224918_x_at	0.421	MGST1	AI220117	microsomal glutathione S-transferase 1
242972_at	0.408		AI022648	MRNA; cDNA DKFZp564D193 (from clone DKFZp564D193)
210172_at	0.395	SF1	D26121	splicing factor 1
231736_x_at	0.394	MGST1	NM_020300	microsomal glutathione S-transferase 1
213764_s_at	0.382	MFAP5	AW665892	Microfibril-associated glycoprotein-2
212713_at	0.376	MFAP4	R72286	microfibrillar-associated protein 4
1565162_s_at	0.374	MGST1	D16947	microsomal glutathione S-transferase 1
205809_s_at	0.354	WASL	BE504979	Wiskott-Aldrich syndrome-like
204863_s_at	0.344	IL6ST	BE856546	interleukin 6 signal transducer (gp130, oncostatin M receptor)
231235_at	0.333	NKTR	AA732581	natural killer-tumor recognition sequence
206726_at	0.311	PGDS	NM_014485	prostaglandin D2 synthase, hematopoietic
1556935_at	0.311		AF085839	Full length insert cDNA clone YI44E03
219064_at	0.309	ITIH5	NM_030569	inter-alpha (globulin) inhibitor H5
239385_at	0.299	TFG	AI150613	TRK-fused gene
38037_at	0.262	DTR	M60278	diphtheria toxin receptor (heparin-binding epidermal growth factor-like growth factor)
233261_at	0.226	EBF	AU145682	early B-cell factor
203821_at	0.222	DTR	NM_001945	diphtheria toxin receptor (heparin-binding epidermal growth factor-like growth factor)
232434_at	0.211		AA160945	CDNA FLJ14199 fis, clone NT2RP3002713
207336_at	0.199	SOX5	NM_006940	SRY (sex determining region Y)-box 5
209763_at	0.145	CHRDL1	AL049176	continued from bA814C6.1.1 in Em:AL591489 match: proteins: Tr:O57472 Sw:Q24025 Tr:O57465 Sw:Q91713; Human DNA sequence from clone RP6-141H5 on chromosome Xq22.1-23 Contains the 3' end of the gene for a novel protein with von Willebrand factor type C domains, complete sequence.
209613_s_at	0.0741	ADH1B	M21692	alcohol dehydrogenase IB (class I), beta polypeptide
209612_s_at	0.0465	ADH1B	M24317	alcohol dehydrogenase IB (class I), beta polypeptide
205913_at	0.0214	PLIN	NM_002666	perilipin

Previous studies cited by the reviewer were conducted in PBMC of patients and not in their synovial tissue. It is a very significant difference in the course of rheumatoid arthritis. The pathophysiological mechanisms at work in rheumatoid arthritis are active in the synovium. The drugs administered are active on synoviocytes. The present invention provides the advantages of providing relevant information for predicting the response to a treatment with a TNF blocking agent in an patient with RA. Predicting such response using blood cells is not as effective because the gene expression profiles in these cell populations are not related to the mechanisms studied. The present inventors have shown there was no correlation between the expression profiles obtained from synovial biopsies and the expression profiles in PBMC.

Examples

Identification of genes associated with response to TNF blockade in patients with severe rheumatoid arthritis

Patients and synovial biopsies:

All patients met the American College of Rheumatology (ACR) criteria for the diagnosis of rheumatoid arthritis (Felson et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995; 38: 727-35). They were 18 females and 7 males. They were average 55.2 year-old (range 18-83). Average disease duration was 10 years (range 1-36 years). They all had active disease at the time of tissue sampling that was resistant to conventional therapy. All patients were treated with disease modifying anti-rheumatic drugs (DMARD's) (23 with methotrexate and 2 with leflunomide) and 18 of them with low-dose steroids. All of them had a swollen knee at the time of the baseline needle-arthroscopic procedure. The study was approved by the ethical committee of the Université catholique de Louvain, and informed consent was obtained from all patients.

Synovial biopsies were obtained by needle-arthroscopy from the knee of all patients before (T0) and 12 weeks (T12) after initiation of adalimumab therapy. For each procedure, 4 to 8 synovial samples were snap frozen in liquid nitrogen and stored at –80° for later RNA extraction. The same amount of tissue was also kept at –80° for immunostaining experiments on frozen sections. The remaining material was stored in formaldehyde and paraffin embedded for conventional optical evaluation and immunostaining of selected cell markers. Disease activity at T0 and T12 was evaluated using standard disease activity scores (DAS) such as DAS-28 CRP (Prevoo ML, et al. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis

Rheum 1995; 38: 44-8), and response to therapy (good responders versus moderate responders versus poor responders) was assessed based on changes in DAS according to the EULAR (European League Against Rheumatism) response criteria (van Gestel et al., Arthritis Rheum; 39: 34-40). Table 2 shows the EULAR response criteria using the DAS and DAS-28.

Table 2

DAS28 at Endpoint	**Improvement in DAS or DAS28 from Baseline**		
	> 1.2	**> 0.6 and ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good		
> 3.2 and ≤ 5.1		Moderate	
> 5.1			None

Microarray hybridization and statistical interpretation

Total RNA was extracted from the synovial biopsies using the Nucleospin® RNA II extraction kit (Macherey-Nagel GmbH & Co, Düren, Germany), including DNase treatment of the samples. 1 µg or more total RNA could be extracted from 12 samples at T0 and 12 samples at T12 for further processing. Labeling of RNA (cRNA synthesis) was performed according to a standard Affymetrix® procedure (One-Cycle Target Labeling kit, Affymetrix UK Ltd, High Wycombe, United Kingdom); briefly total RNA was first reverse transcribed into single-stranded cDNA using a T7-Oligo(dT) Promoter Primer and Superscript II reverse transcriptase. Next, RNase H was added together with E. Coli DNA polymerase I and E. Coli DNA ligase, followed by a short incubation with T4 DNA polymerase in order to achieve synthesis of the second-strand cDNA. The double-stranded cDNA was purified and served as a template for the overnight in vitro transcription reaction, carried out in the presence of T7 RNA polymerase and a biotinylated nucleotide analog/ribonucleotide mix. At the end of this procedure, the biotinylated complementary RNA (cRNA) was cleaned, and fragmented by a 35 minute incubation at 95°c.

GeneChip® Human genome U133 Plus 2.0 Arrays (Affymetrix UK Ltd, High Wycombe, UK) were hybridized overnight at 45°c in monoplicates with 10 µg cRNA. The slides were then washed and stained using the EukGE-WS2v5 Fluidics protocol on the Genechip® Fluidics Station (Affymetrix) before being scanned on a Genechip® Scanner 3000. Statistical and pathway analyses were performed using TMEV, Genespring, FatiGO and GOStat. Data were retrieved on GCOS software for the initial normalization and analysis steps. The number of positive genes was between 49 and 55% on each slide. After scaling on all probe set (to a value of 100), the amplification scale was reported between 1.1 and 2.5 for all the slides. The signals given by the poly-A RNA controls, hybridization

controls and housekeeping/control genes (GAPDH 3'/5' ratio < 2) were indicative of the good quality of the amplification and hybridization procedures. Further statistical analyses were performed using the Genespring® software (Agilent Technologies Inc). For each slide, scaled data were normalized to the 50th percentile per chip and to the median per gene. The data were analyzed by ANOVA for identification of differential gene expression at T0 and T12 between good-, moderate- and poor-responders, with further restriction of the number of genes based on a minimal fold change between good- and moderate- versus poor-responders set at 1.5. Pathway analyses were performed using Gostat (http://gostat.wehi.edu.au), an application that finds statistically overrepresented Gene Ontology (GO) terms within a group of genes. Around 439 genes displayed differences in expression patterns (Table 1) and can be used as synovial markers that are useful for predicting the response to TNF blocking agents in severe RA.

Results

According to EULAR response criteria (Table 2), 13 patients were good-, 7 moderate- and 5 poor-responders at week 12 of TNF-blocking therapy with adalimumab. RNA was extracted from 12 biopsies at baseline (5 good-, 4 moderate- and 3 poor-responders), labeled and hybridized in monoplicates on Genechip® Human Genome U133 Plus 2.0 slides. The genes differentially expressed among the three groups based on ANOVA analyses are listed in Table 1. 411 out of the 54,675 transcripts present on the slides were up-regulated and 28 down-regulated in the synovial biopsies from the poor-responders to TNF blocking therapy as compared to the two other groups. Pathway analyses indicated that these genes are enriched in genes belonging to two different GO (Gene Ontology) families: cell cycle and cytokine – cytokine receptor interactions. In particular, the following genes, involved in the regulation of cell cycle and cell proliferation, are up-regulated in synovial tissue from poor-responders : MKI67, MCM7, MAD2L1, CCNB1, CCNB2, CDC25C, PKMYT1, BUB1, BUB1B, ORC6L, CDC6, E2F2, CDC2, CCNA2, CCNE2, E2F1, CDKN3, SHC1, E2F7, ZWINT, CDCA5, DBF4, AURKB, STMN1, AURKA, PBK, E2F8, TCF19, EXO1, NUSAP1, UBE2C, CKS2, CENPE, KIF11, BRRN1, CKAP2, MCM2, CEP55, SPAG5, CCNF, FANCD2, H2AFX, UBE2V1, RACGAP1, TTK, CDC20, TPX2, KIF23, GTSE1, PTTG1, KNTC2, CNAP1, E2F2, ANLN, PRC1 KIF15, RPS6KB2, KIF2C, HCAP-G, DLG7 and BIRC5. Similarly, IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL were found to be up-regulated while gp130 is down-regulated in synovial biopsies from poor-responders.

Immunohistochemistry on frozen sections

After initial blocking of endogenous peroxidases (Peroxydase blocking reagent, DakoCytomation), frozen sections of the synovial biopsy samples were stained with the following antibodies: IL-7R (Sigma-Aldrich) and CXCL11 (Abcam). After incubation with the primary antibody, slides were sequentially incubated with HRP Envision rabbit or mouse secondary antibody conjugated to a HRP labeled polymer (DAKO EnVision™+ System, DakoCytomation) and DAB+ chromagen (DakoCytomation). The slides were finally counterstained with hematoxylin and eosin for further analyses. Semi-quantitative analyses were performed using a semi-quantitative scale from 0 to 3. Quantitative analyses were performed using ImageJ. Six digitalized pictures (400X magnification) were obtained for each slide. The surface of the staining (S) and the surface of the nuclei (N) were calculated for each picture and the normalized staining surface was calculated as the S/N ratio.

Quantitative evaluation of IL-7R, IL18rap and CXCL11 immunostaining showed that these molecules are significantly up-regulated in the synovium of poor-responders as compared to good- and moderate-responders.

Example

A 47-year-old woman suffers from severe rheumatoid arthritis. Despite adequate therapy with several disease-modifying anti-rheumatic drugs (DMARD's) including salazopyrine, leflunomide and methotrexate, she still has active disease with involvement of many joints at clinical examination and X-ray evidence of progression of bone erosions and joint damage. General physical evaluation is indicative of a severe deterioration of her general health. Therefore, her physician considers the possibility of treating her with TNF blocking agents. Because the patient needs efficient therapy, and also because the cost of the therapy is very high, her physician wants to evaluate the probability that she will respond to therapy using one of the following method according to embodiments of the present invention:

Microarray evaluation of gene expression in the synovial biopsies of the patient.

Synovial biopsies and/or synovial fluid is obtained by needle aspiration or by needle arthroscopy from one joint (preferentially the knee) of the patient. RNA is extracted from the synovial biopsies, labeled and hybridized on a low-density microarray spotted with oligonucleotides or cDNA fragments selected from Table 1, or preferably encoding at least one gene selected from : MKI67, MCM7, MAD2L1, CCNB1, CCNB2, CDC25C, PKMYT1, BUB1, BUB1B, ORC6L, CDC6, CDC2, CCNA2, CCNE2, E2F1, CDKN3, SHC1, E2F7, ZWINT, CDCA5, DBF4, AURKB, STMN1, AURKA, PBK, E2F8, TCF19, EXO1, NUSAP1,

UBE2C, CKS2, CENPE, KIF11, BRRN1, CKAP2, MCM2, CEP55, SPAG5, CCNF, FANCD2, H2AFX, UBE2V1, RACGAP1, TTK, CDC20, TPX2, KIF23, GTSE1, PTTG1, KNTC2, CNAP1, E2F2, ANLN, PRC1 KIF15, RPS6KB2, KIF2C, HCAP-G, DLG7, BIRC5, IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and gp130. The levels of gene expression are compared to standard values associated with response to therapy. Based on these results, the patient is categorized as poor responder, moderate or good responder to TNF blocking therapy. The physician decides to start therapy in the patient; alternatively the physician considers the prescription of another kind of therapy.

Evaluation of gene expression in the synovial biopsies of the patient by real-time PCR.

Synovial biopsies and/or synovial fluid is obtained by needle aspiration or by needle arthroscopy from one joint (preferentially the knee) of the patient. RNA is extracted from the synovial biopsies and cDNA is synthesized using a standard procedure. Evaluation of the expression of one, or two or more of the genes as listed in table 1 is performed by real-time PCR. The levels of gene expression are compared to standard values associated with response to therapy. Based on these results, the patient is categorized as poor responder, moderate or good responder to TNF blocking therapy.

Evaluation of the concentration of specific proteins in the biopsies or synovial fluid of the patient.

Crude synovial fluid, or crude cell lysate from the synovial fluid, or crude cell lysate from the synovial biopsies are obtained from the patient. Determination of the concentration of one or more of the following molecules selected from the group comprising MKI67, MCM7, MAD2L1, CCNB1, CCNB2, CDC25C, PKMYT1, BUB1, BUB1B, ORC6L, CDC6, E2F2, CDC2, CCNA2, CCNE2, E2F1, CDKN3, SHC1, E2F7, ZWINT, CDCA5, DBF4, AURKB, STMN1, AURKA, PBK, E2F8, TCF19, EXO1, NUSAP1, UBE2C, CKS2, CENPE, KIF11, BRRN1, CKAP2, MCM2, CEP55, SPAG5, CCNF, FANCD2, H2AFX, UBE2V1, RACGAP1, TTK, CDC20, TPX2, KIF23, GTSE1, PTTG1, KNTC2, CNAP1, E2F2, ANLN, PRC1 KIF15, RPS6KB2, KIF2C, HCAP-G, DLG7, BIRC5, IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and gp130, is performed by sandwich ELISA, Western Blot or by protein arrays using specific antibodies directed against them. Based on the results, the patient is categorized as poor responder, moderate or good responder to TNF blocking therapy.

Isotope-scan or SPECT (Single Photon Emission Computed Tomography)

The patient is injected with a Technetium-99m labeled antibody directed against one of the following markers (cell surface markers) : IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and gp130. (Non-limiting examples of suitable cell surface

markers can be selected from Table 1). After the injection, joint uptake of the tracer is evaluated by planar scintigraphy or by SPECT and the total intensity of radiation is quantified. The results of the quantification are compared to standard values associated with response to therapy. Based on these results, the patient is categorized as poor responder, moderate or good responder to TNF blocking therapy. The physician decides to start therapy in the patient; alternatively the physician considers the prescription of another kind of therapy.

PET-Scan (Positron-Emission Tomography)

The patient is injected with peptides that bind specifically to one of the following markers (cell surface markers): IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and gp130. (Non-limiting examples of suitable cell surface markers can be selected from Table 1). For example, a peptide can be designed based on the protein sequence of IL-7 that will bind specifically to the IL-7R. Conversely, a peptide can be designed based on the sequence of the IL-18 receptor that will bind specifically to IL-18. These peptides are stably chelated to positron emitting metals (Copper-64 or other metals). The patient can be injected with peptides recognizing one single target but can also be injected in one session with peptides recognizing different targets that are labeled with different tracers. After the injection, joint uptake of the tracer(s) is evaluated by positron-emission tomography and the total intensity of radiation is quantified. The results of the quantification are compared to standard values associated with response to therapy. Based on these results, the patient is categorized as poor responder, moderate or good responder to TNF blocking therapy. The physician decides to start therapy in the patient; alternatively the physician considers the prescription of another kind of therapy.

Gene expression profiles in the peripheral blood and in synovial tissue of patients with rheumatoid arthritis

This example shows the lack of concordance between the gene expression profiles in the peripheral blood and in synovial tissue of patients with rheumatoid arthritis. These data indicate that the synovial tissue provides a distinct and unique profile of gene expression, for which blood cell circulating are not informative, hence the need to investigate directly, in synovial samples.

Global analyses of gene expression were performed in sorted CD4 T and B cells from RA patients with active disease before initiation of therapy and compared them with systemic lupus (SLE) or osteoarthritis (OA) patients. None of the genes differentially expressed in RA cells matched those found to be differentially expressed in RA synovial tissue compared to SLE and OA synovial biopsies (see Table 3), neither did they match the

genes differentially expressed in RA synovial tissue of poor-responders to adalimumab therapy. This difference in gene expression between circulating elements of the immune system and synovial tissue from RA patients can be explained by the fact that in synovial tissue, the cell population that is actively involved in the pathophysiological process and is responsible for a great part of the differential patterns of gene expression, is made of synovial fibroblasts. These cells are also the main target of adalimumab therapy in RA. These cells are not present in the circulation and, therefore, cannot influence gene expression profiles in PBMC or sorted CD4 T and B cells from RA patients.

Table 3

Genes up-regulated in RA CD4 T cells as compared to OA and SLE CD4 T cells			
215336_at	AKAP11	AK002166	A kinase (PRKA) anchor protein 11
236153_at		BF447323	7p47g03.x1 NCI_CGAP_Pr28 Homo sapiens cDNA clone IMAGE:3648965 3' similar to contains Alu repetitive element;contains element PTR5 repetitive element ;, mRNA sequence.
228694_at		BE670036	Clone IMAGE:3352913, mRNA
212702_s_at	BICD2	N45111	bicaudal D homolog 2 (Drosophila)
240759_at		AW593931	Transcribed sequences
210742_at	CDC14A	AF064103	CDC14 cell division cycle 14 homolog A (S. cerevisiae)
232369_at		AF339768	Clone IMAGE:119716, mRNA sequence
226850_at	SUMF1	AA683501	sulfatase modifying factor 1
200848_at	AHCYL1	AA479488	S-adenosylhomocysteine hydrolase-like 1
223763_at	DTNBP1	AL136637	dystrobrevin binding protein 1
235531_at	IL17RB	AA928257	interleukin 17 receptor B
224368_s_at	NDRG3	AF251054	Homo sapiens NDR3 mRNA, complete cds.
219380_x_at	POLH	NM_006502	polymerase (DNA directed), eta
212345_s_at	CREB3L2	BE675139	cAMP responsive element binding protein 3-like 2
209508_x_at	CFLAR	AF005774	CASP8 and FADD-like apoptosis regulator
223243_s_at	C1orf22	BF439488	chromosome 1 open reading frame 22
244547_at	FLJ25006	AW081561	hypothetical protein FLJ25006
222683_at	RNF20	AK022532	ring finger protein 20
211316_x_at	CFLAR	AF009616	CASP8 and FADD-like apoptosis regulator
244354_at		BE677844	ELISC-1 mRNA, partial cds
218242_s_at	CGI-85	NM_017635	CGI-85 protein
230292_at		AA868809	CDNA FLJ43180 fis, clone FCBBF3013846
Genes down-regulated in RA CD4 T cells as compared to OA and SLE CD4 T cells			
205409_at	FOSL2	NM_005253	FOS-like antigen 2
205330_at	MN1	NM_002430	meningioma (disrupted in balanced translocation) 1
217264_s_at	SCNN1A	U81961	
204541_at	SEC14L2	NM_012429	SEC14-like 2 (S. cerevisiae)
Genes up-regulated in RA B cells as compared to OA and SLE B cells			
206978_at	CCR2	NM_000647	chemokine (C-C motif) receptor 2
1552691_at	ARL11	NM_138450	ADP-ribosylation factor-like 11
202688_at	TNFSF10	NM_003810	tumor necrosis factor (ligand) superfamily, member 10

209276_s_at	GLRX	AF162769	glutaredoxin (thioltransferase)
222980_at	RAB10	AL136650	RAB10, member RAS oncogene family
202687_s_at	TNFSF10	U57059	tumor necrosis factor (ligand) superfamily, member 10
Genes down-regulated in RA B cells as compared to OA and SLE B cells			
1552562_at	ZNF570	NM_144694	zinc finger protein 570
1558050_at	EIF2B5	BG112612	dishevelled, dsh homolog 3 (Drosophila)
200772_x_at	PTMA	BF686442	602143234F1 NIH_MGC_46 Homo sapiens cDNA clone IMAGE:4304193 5', mRNA sequence.
201608_s_at	PWP1	NM_007062	nuclear phosphoprotein similar to S. cerevisiae PWP1
201736_s_at	TEB4	BF000409	similar to S. cerevisiae SSM4
201881_s_at	ARIH1	NM_005744	ariadne homolog, ubiquitin-conjugating enzyme E2 binding protein, 1 (Drosophila)
203394_s_at	HES1	BE973687	hairy and enhancer of split 1, (Drosophila)
204014_at	DUSP4	NM_001394	dual specificity phosphatase 4
204015_s_at	DUSP4	BC002671	dual specificity phosphatase 4
204435_at	NUPL1	NM_014778	
204621_s_at	NR4A2	AI935096	nuclear receptor subfamily 4, group A, member 2
206683_at	ZNF165	NM_003447	zinc finger protein 165
206905_s_at	MATN1	NM_002379	matrilin 1, cartilage matrix protein
208706_s_at	EIF5	AK026933	eukaryotic translation initiation factor 5
209317_at	POLR1C	AF008442	polymerase (RNA) I polypeptide C, 30kDa
216350_s_at	ZNF10	X52332	zinc finger protein 10 (KOX 1)
219177_at	BRIX	NM_018321	BRIX
220576_at	PGAP1	NM_024989	GPI deacylase
222343_at	BCL2L11	AA629050	BCL2-like 11 (apoptosis facilitator)
222408_s_at	CGI-127	BC000836	yippee protein
222728_s_at	MGC5306	AF275800	NB4 apoptosis / differentiation related protein; Homo sapiens PNAS-104 mRNA, complete cds.
223096_at	NOP5/NOP58	AF161469	nucleolar protein NOP5/NOP58
223773_s_at	LOC85028	AF277181	PNAS-123
226758_at	LUC7L2	AA043552	LUC7-like 2 (S. cerevisiae)
227337_at	Lrp2bp	AA886870	low density lipoprotein receptor-related protein binding protein
230505_at	LOC145474	AU158212	CDNA FLJ13656 fis, clone PLACE1011520
230511_at	CREM	AI800640	cAMP responsive element modulator
Genes up-regulated in RA synovial tissue as compared to OA and SLE synovial tissue			
219463_at	C20orf103	NM_012261	chromosome 20 open reading frame 103
215565_at	DTNB	AK022277	CDNA FLJ12215 fis, clone MAMMA1001021
227224_at	RALGPS2	AW003297	Ral-A exchange factor RalGPS2
224404_s_at	IRTA2	AF343662	immunoglobulin superfamily receptor translocation associated 2
237625_s_at		BG548679	Immunoglobulin kappa light chain mRNA, partial cds
205242_at	CXCL13	NM_006419	chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)
227030_at		BG231773	CDNA FLJ46579 fis, clone THYMU3042758
205267_at	POU2AF1	NM_006235	POU domain, class 2, associating factor 1
226218_at	IL7R	BE217880	interleukin 7 receptor
242020_s_at	ZBP1	AI925506	Z-DNA binding protein 1
217235_x_at		D84140	Immunoglobulin light chain lambda variable region [Homo sapiens], mRNA sequence
221601_s_at	TOSO	AI084226	regulator of Fas-induced apoptosis
1405_i_at	CCL5	M21121	chemokine (C-C motif) ligand 5
236280_at		AI225238	Transcribed sequences

205901_at	PNOC	NM_006228	prepronociceptin
216984_x_at		D84143	immunoglobulin lambda joining 3
216430_x_at		AF043586	immunoglobulin lambda joining 3
206641_at	TNFRSF17	NM_001192	tumor necrosis factor receptor superfamily, member 17
234366_x_at		AF103591	Clone H3 anti-mucin1 light chain variable region mRNA, partial cds
236341_at	CTLA4	AI733018	cytotoxic T-lymphocyte-associated protein 4
217258_x_at		AF043583	Immunoglobulin lambda light chain variable and constant region mRNA, partial cds
227533_at		AA732944	zg78d04.s1 Soares_fetal_heart_NbHH19W Homo sapiens cDNA clone IMAGE:399463 3', mRNA sequence.
221286_s_at	PACAP	NM_016459	proapoptotic caspase adaptor protein
1555613_a_at	ZAP70	AB083211	zeta-chain (TCR) associated protein kinase 70kDa
220423_at	PLA2G2D	NM_012400	phospholipase A2, group IID
215946_x_at	LOC91316	AL022324	Human DNA sequence from clone CTA-246H3 on chromosome 22, complete sequence.
216412_x_at		AF043584	Immunoglobulin lambda light chain variable and constant region mRNA, partial cds
217179_x_at	IGLJ3	X79782	H.sapiens (T1.1) mRNA for IG lambda light chain
39318_at	TCL1A	X82240	T-cell leukemia/lymphoma 1A
211643_x_at		L14457	Clone P2-32 anti-oxidized LDL immunoglobulin light chain Fab mRNA, partial cds
211650_x_at		L34164	Partial mRNA for IgM immunoglobulin heavy chain variable region (IGHV gene), clone LIBPM376
207339_s_at	LTB	NM_002341	lymphotoxin beta (TNF superfamily, member 3)
205049_s_at	CD79A	NM_001783	CD79A antigen (immunoglobulin-associated alpha)
229629_at		AI923633	Transcribed sequences
223565_at	PACAP	AF151024	proapoptotic caspase adaptor protein
219971_at	IL21R	NM_021798	interleukin 21 receptor
205255_x_at	TCF7	NM_003202	transcription factor 7 (T-cell specific, HMG-box)
211908_x_at	IGHG1	M87268	Partial mRNA for IgM immunoglobulin heavy chain variable region (IGHV gene), clone LIBPM376
206134_at	ADAMDEC1	NM_014479	ADAM-like, decysin 1
216573_at		X84340	H.sapiens mRNA for Ig light chain, variable region (ID:CLL001VL)
217148_x_at	IGLJ3	AJ249377	immunoglobulin lambda joining 3
204655_at	CCL5	NM_002985	chemokine (C-C motif) ligand 5
205798_at	IL7R	NM_002185	interleukin 7 receptor
216401_x_at	IGKC	AJ408433	Homo sapiens partial IGKV gene for immunoglobulin kappa chain variable region, clone 38.
203413_at	NELL2	NM_006159	NEL-like 2 (chicken)
231647_s_at	IRTA2	AW241983	xn77f04.x1 Soares_NFL_T_GBC_S1 Homo sapiens cDNA clone IMAGE:2700511 3', mRNA sequence.
Genes down-regulated in RA synovial tissue as compared to OA and SLE synovial tissue			
206385_s_at	ANK3	NM_020987	ankyrin 3, node of Ranvier (ankyrin G)
205931_s_at	CREB5	NM_004904	cAMP responsive element binding protein 5
202862_at	FAH	NM_000137	fumarylacetoacetate hydrolase (fumarylacetoacetase)
223667_at	FKBP7	AF092137	FK506 binding protein 7
1567706_at		AF009316	Homo sapiens clone TUB2 Cri-du-chat region mRNA.
221841_s_at	KLF4	BF514079	Kruppel-like factor 4 (gut)
223094_s_at	ANKH	AF274753	ankylosis, progressive homolog (mouse)
223315_at	NTN4	AF278532	netrin 4

204776_at	THBS4	NM_003248	thrombospondin 4
223843_at	SCARA3	AB007830	scavenger receptor class A, member 3
223842_s_at	SCARA3	AB007830	scavenger receptor class A, member 3
205765_at	CYP3A5	NM_000777	cytochrome P450, family 3, subfamily A, polypeptide 5
238481_at	MGP	AW512787	xt77g05.x1 NCI_CGAP_Ut1 Homo sapiens cDNA clone IMAGE:2792504 3' similar to gb:X53331 MATRIX GLA-PROTEIN PRECURSOR (HUMAN);, mRNA sequence.
1563792_at	AMN	AK092824	amnionless homolog (mouse)
210571_s_at	CMAH	AF074480	MRNA for CMP-N-acetylneuraminic acid hydroxylase, complete cds.
214702_at	FN1	AJ276395	fibronectin 1
233437_at	GABRA4	AF238869	gamma-aminobutyric acid (GABA) A receptor, alpha 4
214033_at	ABCC6	AI084637	ATP-binding cassette, sub-family C (CFTR/MRP), member 6
1565641_at		BE503823	hv83e07.x1 NCI_CGAP_Lu24 Homo sapiens cDNA clone IMAGE:3180036 3' similar to contains element LTR1 repetitive element ;, mRNA sequence.
222727_s_at	SLC24A6	AI339568	solute carrier family 24 (sodium/potassium/calcium exchanger), member 6

Claims

1. Method for predicting the response to a treatment with a TNF blocking agent in a patient comprising the steps of

(a) assessing in a synovial sample from said patient at least two genes or fragments thereof or proteins encoded by said at least two genes, wherein said genes or fragments thereof are selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4,

RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT, and

(b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a).

2. Method according to claim 1, wherein step (a) of assessing said at least two genes or fragments thereof comprises the steps of

(i) assessing the level of expression of said at least two genes or fragments thereof, and

(ii) determining whether the level of expression assessed in step (i) is above or below a threshold value.

3. Method according to claim 2, wherein the threshold value is determined before step (i) by

(i1) assessing the level of expression of said at least two genes or fragments thereof in a plurality of synovial samples from patients before treatment with said TNF blocking agent,

(i2) assessing the level of expression of said at least two genes or fragments thereof in a plurality of synovial samples from patients after treatment with said TNF blocking agent, and

(i3) correlating the response of the patients treated with said TNF blocking agent to the level of expression of said at least two genes determined in step (a) thereby determining the threshold value.

4. Method according to any of claims 1 to 3 wherein said TNF blocking agent is selected from the group comprising adalimumab, infliximab, etanercept, certolizumab pegol, and Golimumab.

5. Method according to any of claims 1 to 4, wherein said patient has rheumatoid arthritis, preferably severe rheumatoid arthritis.

6. Method according to any of the claims 1 to 5, wherein said at least two genes are selected from MKI67, MCM7, MAD2L1, CCNB1, CCNB2, CDC25C, PKMYT1, BUB1, BUB1B, ORC6L, CDC6, CDC2, CCNA2, CCNE2, E2F1, CDKN3, SHC1, E2F7, ZWINT, CDCA5, DBF4, AURKB, STMN1, AURKA, PBK, E2F8, TCF19, EXO1, NUSAP1, UBE2C, CKS2, CENPE, KIF11, BRRN1, CKAP2, MCM2, CEP55, SPAG5, CCNF, FANCD2, H2AFX, UBE2V1, RACGAP1, TTK, CDC20, TPX2, KIF23, GTSE1, PTTG1, KNTC2, CNAP1, E2F2, ANLN, PRC1 KIF15, RPS6KB2, KIF2C, HCAP-G, DLG7, BIRC5, IL7R, IL18, IL18RAP, IL21R, CXCL11, CXCR4, IL13RA1, TRAIL and gp130.
7. Method according to any of the claims 1 to 6, wherein the level of expression of said at least two genes or fragments thereof in said sample is assessed by detecting the level of expression of proteins or fragments thereof encoded by said at least two genes or fragment thereof.
8. Method according to claim 7, wherein the level of expression of said proteins or fragments thereof is detected using a reagent which specifically binds with said proteins or fragments thereof.
9. Method according to claim 8, wherein the reagent is selected from the group consisting of a peptide, an antibody, a fragment thereof or a derivative thereof.
10. Method according to any of the claims 2 to 9 wherein the level of expression is determined using a method selected from the group consisting of DNA microarray, RT PCR, immunohistochemistry , immunoblotting, and protein microarray.
11. Method according to any of claims 2 to 10, wherein the level of expression is determined using DNA-microarray, preferably low-density DNA-spotted microarray.
12. Method according to any of the claims 2 to 10, wherein the level of expression of said at least two genes or fragments thereof in said synovial sample is assessed by detecting the level of expression of at least two transcribed polynucleotides or fragments thereof encoded by said at least two genes or fragments thereof.
13. Method according to claim 12 wherein said at least two transcribed polynucleotides or fragments thereof is a cDNA, or mRNA.
14. Method according to any of the claims 12 to 13, wherein the step of detecting further comprises amplifying the transcribed polynucleotide.
15. Method according to claim 14, wherein the step of detecting is using the method of quantitative reverse transcriptase polymerase chain reaction.

16. Method according to any of the claims 2 to 15, wherein the level of expression of said at least two genes or fragment thereof is assessed by detecting the presence of at least two transcribed polynucleotides or fragment thereof in a synovial sample with probes which anneals with the transcribed polynucleotides or fragments thereof under stringent hybridization conditions.

17. Use of probes that hybridizes under stringent conditions to at least two genes or fragments thereof, from a synovial sample, said genes or fragment thereofs being selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51,

RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT, or an antibody that binds to at least one protein or fragment thereof encoded by said at least one gene or fragment thereof, or a peptide that binds to at least one protein or fragment thereof encoded by said at least one gene or fragment thereof, for predicting the response to a treatment with a TNF blocking agent in a patient .

18. Kit for predicting the response to a treatment with a TNF blocking agent comprising a low density microarray comprising probes suitable for hybridizing with at least two genes or fragments thereof selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129, C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1,

KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT.

19. Kit according to claim 18, wherein said microarray comprises probes suitable for hybridizing with at least 352 genes or fragments thereof selected from the group as listed in claim 18.

20. Kit according to any of claims 18 to 19, further comprising a computer-readable medium comprising one or more digitally encoded expression profiles, where each profile has one or more values representing the expression of said at least two genes as defined in claim 18.

21. Kit according to claim 20, wherein said digitally encoded expression profiles are profiles of poor, moderate and good responder to TNF blocking therapy.

22. Method for predicting the response to a treatment with a TNF blocking agent in a patient comprising the steps of

(a) assessing in vivo at least one gene or a fragment thereof selected from the group comprising ACP1, ADAM8, ADAMDEC1, ADH1B, AF15Q14, ANGPTL1, ANKRD22, ANLN, AP2A1, AP2B1, AP2S1, APOBEC3B, APOBEC3C, APOL1, AQP9, ARHGAP22, ARHGAP4, ARHGAP9, ARHGDIB, ARL7, ARMET, ARRDC1, ASK, ASPM, ATAD2, ATOX1, AURKB, BGN, BIRC5, BLVRA, BM039, BMP1, BMP2, BRCA1, BRIP1, BRRN1, BUB1, BUB1B, C10orf3, C13orf3, C14orf94, C20orf129,

C22orf18, C9orf76, CARHSP1, CCNA2, CCNB1, CCNB2, CCNE2, CCNF, CD163, CD1D, CD3Z, CDC2, CDC20, CDC25C, CDC6, CDCA1, CDCA2, CDCA3, CDCA5, CDCA7, CDKN3, CDT1, CEB1, CENPA, CENPE, CENPF, CENPF, CHEK1, CHRDL1, CHST1, CKAP2, CKLF, CKS2, CNAP1, COL13A1, COP, CPSF5, CPT1B, CR1, CST1, CTSL, CTSW, CXCL11, CXCL3, CXCR4, DCLRE1B, DDA3, DDX39, DEPDC1, DKFZP434G2226, DKFZP434L0117, DKFZp762E1312, DLG7, DNAJC9, DNMT1, DTR, DUFD1, E2F1, E2F2, E2F7, EBF, ECGF1, ECT2, EFHD2, EGR2, ENPEP, EPSTI1, ETS1, EXO1, EZH2, FAM20A, FANCD2, FBXO23, FBXO5, FCN1, FEN1, FHL3, FKSG14, FLJ10156, FLJ10199, FLJ10719, FLJ11029, FLJ13052, FLJ20920, FLJ22573, FLJ23311, FLJ40869, FMO1, FOXM1, FPR1, G1P2, GBP5, GGH, GGTLA1, GMNN, GNLY, GPSM3, GSS, GTSE1, GUCY1B3, H2AFV, H2AFX, H2AFZ, HCAP-G, HCLS1, HELLS, HEYL, HIST2H2AA, HLA-C, HLA-F, HLA-G, HMGA1, HMGB2, HMGN1, HMMR, HSPC242, IDH2, IFI30, IFI44, IL13RA1, IL18, IL18RAP, IL21R, IL27RA, IL2RG, IL6, IL6ST, IL7R, INDO, IQGAP3, IRF7, ITGA4, ITIH5, KCNK6, KCNMB1, KIAA0101, KIAA0186, KIF11, KIF14, KIF20A, KIF23, KIF2C, KIF4A, KLIP1, KLRC1, KNSL7, KNTC2, KPNA2, Kua, LAK, LAMP3, LAT, LBP, LENG4, LGALS8, LGALS9, LILRB3, LMNB1, LOC113179, LOC144997, LOC146909, LOC201292, LOC56926, LOC90522, LOC92799, LTBP4, LY6E, LYZ, MAC30, MAD2L1, MAN2A1, MANBA, MAP4K1, MAPK13, MCFP, MCM2, MCM4, MCM7, MELK, MFAP4, MFAP5, MGC10986, MGC24665, MGC29814, MGC3248, MGST1, MKI67, MNDA, MPHOSPH9, MYO1F, MYO7A, NAGPA, NFKB2, NKTR, NMT1, NPL, NUP210, NUP62, NUSAP1, OIP5, ORC6L, PAFAH1B3, PASK, PCDH17, Pfs2, PGDS, PHF19, PIR51, PKM2, PKMYT1, PLA2G2D, PLA2G7, PLIN, PLK4, PMSCL1, POLQ, PPIF, PRC1, PRG1, PTTG1, PVRL2, RAB27A, RACGAP1, RAD51, RAMP, RASSF4, RBMS3, RELB, RFC4, RGS18, RHOF, RPS6KB2, RRM2, RTN1, S100A12, SCO2, SDF2L1, SDS, SEMA4A, SERPINA1, SERPINH1, SF1, SGOL2, SGPL1, SHC1, SHCBP1, SIGLEC7, SIL, SIRPB1, SLC20A1, SLC39A8, SLCO4A1, SMAD3, SMC4L1, SOD2, SOX5, SPAG5, Spc24, Spc25, SPEC1, SRD5A1, SSR1, STK10, STK6, STMN1, SUSD1, TACC3, TAP1, TBC1D7, TCEB3, TCF19, TCF3, TEAD4, TFEC, TFG, TGIF2, TIMELESS, TIMP1, TK1, TLR2, TMEM8, TMPO, TNFSF10, TNRC5, TOMM22, TOP2A, TOPK, TPP2, TPX2, TRIP13, TROAP, TTK, TUBA1, TXNDC3, TYK2, TYMS, UBADC1, UBE2C, UBE2S, UHRF1, UMPK, UPP1, URP2, VDR, WASL, WBSCR5, WDHD1, ZAP70, ZCCHC6, and ZWINT, and

(b) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (a).

23. Method according to claim 22, wherein said patient has rheumatoid arthritis.

24. Method according to claim 22 or 23, comprising the steps of

(i) assessing in said patient the level of expression of at least one gene or a fragment thereof selected from the group as defined in claim 22,

(ii) determining whether the level of expression assessed in step (i) is above or below a threshold value, and

(iii) predicting the response to the treatment with the TNF blocking agent in said patient by evaluating the results of step (ii).

25. Method according to any of claims 22 to 24, wherein said TNF blocking agent is selected from the group comprising adalimumab, infliximab, etanercept, certolizumab pegol, and Golimumab.

26. Method according to claim 24 or 25, wherein the level of expression of said at least one gene or fragment thereof in said patient is assessed by detecting the level of expression of a protein or a fragment thereof encoded by said at least one gene or fragment thereof.

27. Method according to claim 26, wherein the level of expression of said protein or fragment thereof is detected using a reagent which specifically binds with said protein or fragment thereof.

28. Method according to claim 27, wherein the reagent is selected from the group consisting of a peptide, an antibody, or a fragment thereof.

29. Method according to claim 27 or 28, wherein said reagent is labeled with a radioactive isotope.

30. Method according to claim 29, wherein said radioactive isotope can be detected by radio-imaging.

31. Method according to claim 29 or 30, wherein said radioactive isotope is selected from the group comprising Technetium^{99m}, Carbon^{11}, Oxygen^{15}, Nitrogen^{13}, Rubidium^{82}, Gallium^{67}, Gallium^{68}, Yttrium^{90}, Molybdenum^{99}, Iodine^{123,124,131} Fluorine^{18}, Phosphorus^{32}, Copper^{62}, Thallium^{201}, Copper^{64}, Copper^{62}, Indium^{111}, and Xenon^{133}.

32. Method according to claim 30 or 31, wherein said radio-imaging is selected from the group consisting of single photon emission computed tomography (SPECT), positron emission tomography (PET) and gamma cameras.