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(54) **Title**: METHODS RELATED TO TREATMENT OF INFLAMMATORY DISEASES AND DISORDERS

(57) **Abstract**: The present invention relates to gene markers associated with a method for predicting the clinical response in a patient suffering from an inflammatory diseases or disorders to an anti-inflammatory treatment.

METHODS RELATED TO TREATMENT OF INFLAMMATORY DISEASES AND DISORDERS

TECHNICAL FIELD

The present invention concerns methods within the field of diagnosis, prognosis and treatment optimization of inflammatory diseases and disorders aiming to improve the treatment options and regiments for patients by providing methods for predicting responsiveness to a therapeutic agent.

BACKGROUND

Inflammatory diseases and disorders and in particular auto-immune disease and severely impact patient's well-being and treatments options are unsatisfactory for a large group of patients.

Rheumatoid arthritis (RA) is a clinically important, chronic systemic autoimmune RA is an autoimmune disorder of unknown etiology. Most RA patients suffer a chronic course of disease that, even with currently available therapies, may result in progressive joint destruction, deformity, disability and even premature death. Diagnosis of RA typically relies on clinical and laboratory evaluation of a patient's signs and symptoms. Generally, laboratory evaluation of a patient suspected of having RA may include determination of the level of certain antibodies in serum known as rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (anti-CCP). While these antibodies are often found in the serum of RA patients, not all RA patients have them. An additional blood test known as the erythrocyte sedimentation rate (ESR) may also be used. An elevated ESR indicates the general presence of an inflammatory process, although not necessarily RA. Further blood tests may be used to assess the level of other factors, such as C-reactive protein (CRP) that has been associated with RA. In addition, radiographic analysis of affected joints may be performed. In sum, such currently available laboratory tests to diagnose RA are imprecise and imperfect.

The American College of Rheumatology (ACR) criteria are frequently used for diagnosis and determination of severity (http://www.rheumatology.org)

Attempts has been made to improve diagnosis and prognosis based on biomarkers (See e.g., Rioja et al., Arthritis and Rheum. 58(8):2257-2267 (2008); Pyrpasopoulou et al,

Mol. Diagn. Ther. 14(l):43-48 (2010); WO 2004/0009479; WO 2007/0105133; WO 2007/038501; WO 2007/135568; WO 2008/104608; WO 2008/056198; WO 2008/132176; and WO 2008/154423). Recently, methods for subgrouping RA patients and identification of patients groups which demonstrate a higher responsiveness to anti-CD20 therapy based on particular molecular profiles has been presented (WO2011028945). However, no clinically validated diagnostic or prognostic markers, have been identified that enable clinicians or others to accurately define pathophysiological aspects of rheumatoid arthritis, clinical activity, response to therapy, prognosis, or risk of developing the disease.

Accordingly, as RA patients seek treatment, there is considerable trial and error involved in the search for therapeutic agent(s) effective for a particular patient. Such trial and error often involves considerable risk and discomfort the patient in order to find the most effective therapy. Thus, there is a need for more effective means for determining which patients will respond to which treatment and for incorporating such determinations into more effective treatment regimens for RA patients.

It would therefore be highly advantageous to have additional methods for objectively identify the presence of the disease in a patient, define pathophysiologic aspects of rheumatoid arthritis, clinical activity, response to therapy, including response to treatment with various RA therapeutic agents, prognosis, and/or risk of developing rheumatoid arthritis.

Thus, there is a continuing need to identify new molecular diagnostic or prognostic markers associated with rheumatoid arthritis as well as other autoimmune disorders.

SUMMARY

As described herein the inventor provides a number of methods useful for improving therapy of inflammatory diseases or disorder, auto-immune diseases and in particular RA.

An aspect of the invention concerns a method for predicting the response of a subject to an anti-inflammatory agent comprising; obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient, wherein altered expression of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

A further aspect of the invention relates to a method for predicting the response of a patient to an anti-inflammatory agent comprising;

a) measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient and
b) comparing said level with a reference level of said gene(s)

wherein altered expression of one or more of said gene(s) compared to said reference level,
5 is predictive of a response of the patient to the anti-inflammatory agent.

The invention further describes a method for identification of a subject with an increase probability of responding to anti-inflammatory agent comprising; obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological
10 sample from said subject, wherein altered expression of one or more of said gene(s) compared to a reference level of said gene(s) indicates that a subject with an increased probability of responding to an anti-inflammatory agent has been identified.

In an aspect the invention relates to a method for identification of a patient with an
15 increase probability of responding to anti-inflammatory agent comprising;

a. measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient
b. comparing said level with a reference level of said gene(s),

wherein altered expression of one or more of said gene(s) compared to the reference level of
20 said gene(s), indicates that a patient with an increased probability of responding to an anti-inflammatory agent has been identified.

The methods of the invention may concern situations where the altered expression is an increased expression of a gene of Figure 1A compared to the reference level and/or
25 where the altered expression is a decreased expression of a gene of Figure 1B compared to the reference level.

The methods further describes that the level of expression may be determined in a blood sample based on mRNA using qRT-PCR or using micro array chip. In specific
30 embodiments of the invention the level of expression of complement factor D (CFD) is determined and found to be above a reference level, which may be differently defined depending on the method applied for detection of said transcript.

An aspect of the invention relates to an anti-inflammatory agent for treatment of an auto-immune disease or disorder, wherein the patient has an altered expression of one or more of the genes of Figure 1, compared to the reference level of said gene(s).

5 A further aspect of the invention relates to method of treatment of a subject suffering from an inflammatory disease or where the expression levels of one or more of the genes of Figure 1 is altered compared to a reference level, comprising administering a therapeutic amount of an anti-inflammatory agent to said subject.

10 The method may include a further step comprising; considering if the expression level(s) of one or more of the genes of Figure 1, in said patient is altered compared to a reference level.

An aspect of the invention relates to a method for treating an inflammatory disease
15 or disorder in a patient comprising;

a. measuring the levels of expression of one or more gene(s) of Figure 1 in a biological sample from said patient
b. comparing said levels with a reference level of said genes,
c. determine if the expression levels of one or more of the genes of Figure 1, is altered
20 compared to said reference level
d. administering a therapeutic amount of an anti-inflammatory agent to said patient.

In some cases the information on gene expression with be used to determine if the patient is actually to be dosage with the anti-inflammatory agent and the methods described
25 above may thus include the evaluation of the expression data e.g. concluding that the level of expression one or more of the genes of Figure 1, is altered in said biological sample compared to said reference level. It is considered relevant to consider if the expression level of one or more gene(s) of Table 1A is increased compared to the reference level and/or if the expression level of one or more gene(s) of Table 1B are decreased compared to the
30 reference level

In a further aspect the invention relates to an article of manufacture comprising, packaged together, a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a label stating that the pharmaceutical

composition is useful for treating a patient suffering from an auto-immune disease or disorder with an altered expression of one or more of the genes of Figure 1.

An aspect of the invention concerns a kit comprising

5 a) one or more composition comprising at least one detecting agent for determining the expression level of one or more gene(s) from Table 1A and/or Table 1B and

b) instructions for use of the kit including how to correlate expression level(s) with response probability of a subject.

10 Based on the present data an improved treatment can be suggested to patients and the impact of trial and error can be minimized. It is clear to the skilled person that the invention may be performed with certain variation in addition to the specific examples herein.

15 **SEQENCE LISTING**

The present application includes a sequence listing including the following sequences

SEQ ID NO 1: CFD mRNA probe: CCTGCTGCTACAGCTGTCGGAGAAG

20 SEQ ID NO 2: 18S rRNA control probe: TGGAGGGCAAGTCTGGTGCCAGCAG

SEQ ID NO 3: rs1683565:

AGAGCCCAAAGCTCATGGAAAAGAG**X**ATATAAAGGAGTCCCTGCAGTAGA

wherein X at position 26 is A or G

SEQ ID NO 4: rs1683591:

25 TCTGTCCACAGGCGGGGGTGGAGGG**X**ATGGCCGGCCTCACACCATCTGCCA

wherein X at position 26 is A or G

SEQ ID NO 5: rs1683590:

AATATCTGAAATTTTCCCAGTTTAC**X**AGCCTCTGACGTAACCGTCCTCTCT

wherein X at position 26 is A or G

30 SEQ ID NO 6: ACTB probe:

CCTTTGCCGATCCGCCGCCCGTCCA

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows a list of positively (Table 1a) and a list negatively (Table 1b) correlated
5 transcripts to Disease Activity Score of 28 joints – C-reactive protein (DAS28-CRP) changes (at week 8) in anti-IL20 RA trials. Transcripts showing significant correlation (False Discovery Rate (FDR) = 5%) in dosed patients (excluding placebo controls) are included in the lists (ranked order with most significant correlation in the top of each list). The genes listed in Table 1A have been identified as relevant for use in methods of the invention where a
10 relative high level of expression is of interest.
The genes listed in Table 1B have been identified as relevant for use in methods of the invention where a relative low level expression is of interest.

FIG. 2 shows Table 2 including a selection of genes from Table 1A and 1B which are
15 considered relevant for use in methods of the invention and in particularly in methods applying multi-variate analysis. The selected transcript/genes are relevant for a multivariate based prediction of DAS28-CRP.

FIG. 3 shows the distribution of transcript level of the CFD (complement factor D) transcripts
20 in PaxGene whole blood samples from RA-patients in anti-IL20 trials. Robust Multichip Average (RMA) normalized values are shown on the Y-axis (log2 scale). Samples from individual patients are presented in alternating colours (black or white) and individual patients are arbitrarily numbered 1-82

25 **FIG. 4** shows a Receiver Operating Characteristic (ROC) curve of CFD mRNA and American College of Rheumatology 50 % composite criteria (ACR50) responses in the phase-2a anti-IL20 trial. The threshold value of 10.32 (RMA normalized expression value) is indicated by the X on the ROC curve.

30 **FIG. 5** shows a ROC curve of CFD mRNA and American College of Rheumatology 70 % composite criteria (ACR70) responses in the phase-2a anti-IL20 trial.

FIG. 6 shows correlation of quantitative RT-PCR (qRT-PCR) detection of CFD mRNA in pre-dosage (Day 1) samples with the data from microarray based detection at more time points.

Microarray signals on a linear scale (Back transformed RMA data (Y-axis)) are compared to 18S normalized CFD levels from the qRT-PCR analysis.

Fig. 7 shows the ACR20, ACR50 and ACR70 response rates in the anti-IL20 phase-2a trial (clinicaltrials.gov identifier NCT01282255) with two alternative tresholds of CFD based stratification. If a stratification of the patients based on the CFD mRNA levels from the ROC curve of Fig. 4 is applied (e.g. a threshold value of >10.32 (RMA normalized expression value) is used), a high responding patient population is obtained (bottom of chart A). The upper part of chart A displays the responses if only individuals with CFD levels below the threshold are included. When applying an alternative threshold for CFD (based on absolute quantification of CFD and beta actin (ACTB)) a similar enrichment in responding patients is obtained (lower part of chart B).

Fig. 8 shows the levels of Bb in synovial fluid from RA patients exhibiting either high or low CFD expression levels in PaxGene samples as evaluated by qPCR.

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DESCRIPTION

The present invention is associated with a method for predicting therapeutic effect of an anti-inflammatory compound. As described in the background section the treatment presently available have, at least to some extent, a low success rate and treatment frequently involves some degree of trial and error. This invention provides a method for identification of a patient subgroup that have a high treatment success rate whereby a large number of patients can avoid the risk an discomfort associated with the difficulties in finding an effective therapy.

Definitions

For the purpose of interpretation of this application the following definitions is to be used on less otherwise explained herein.

The term "polynucleotide" or "nucleic acid," as used interchangeably herein, refers to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their

analogues, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogues. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be
5 interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labelling component and other types of modifications known in the art.

The term "oligonucleotide," as used herein, refers to short, single stranded polynucleotides that are at least about seven nucleotides in length and less than about 250
10 nucleotides in length. Oligonucleotides may be synthetic. The terms "oligonucleotide" and "polynucleotide" are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides.

The term "primer" refers to a single stranded polynucleotide that is capable of hybridizing to a nucleic acid and allowing the polymerization of a complementary nucleic
15 acid, generally by providing a free 3' -OH group.

The term "array" or "microarray" refers to an ordered arrangement of hybridisable array elements, preferably polynucleotide probes (e.g., oligonucleotides), on a substrate. The substrate can be a solid substrate, such as a glass slide, or a semi-solid substrate, such as nitrocellulose membrane.

20 The term "amplification" refers to the process of producing one or more copies of a reference nucleic acid sequence or its complement. Amplification may be linear or exponential (e.g., PCR). A "copy" does not necessarily mean perfect sequence complementarity or identity relative to the template sequence. For example, copies can include nucleotide analogues such as deoxyinosine, intentional sequence alterations (such
25 as sequence alterations introduced through a primer comprising a sequence that is hybridisable, but not fully complementary, to the template), and/or sequence errors that occur during amplification.

The term "multiplex-PCR" refers to a single PCR reaction carried out on nucleic acid obtained from a single sample (e.g., one patient) using more than one primer set for the
30 purpose of amplifying two or more DNA sequences in a single reaction.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally
5 depends on the ability of denatured DNA to re-anneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridisable sequence, the higher the relative temperature should be. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details
10 and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, can be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1 procent sodium dodecyl
15 sulfate at 50 °C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50 percent (v/v) formamide with 0.1 percent bovine serum albumin/0.1 percent Ficoll/0.1 percent polyvinylpyrrolidone/5 OmM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42C; or (3) overnight hybridization in a solution that employs 50 percent formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM
20 sodium phosphate (pH 6.8), 0.1 percent sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 micro g/ml), 0.1 percent SDS, and 10 percent dextran sulfate at 42C, with a 10 minute wash at 42C in 0.2 x SSC (sodium chloride/sodium citrate) followed by a 10 minute high- stringency wash consisting of 0.1 x SSC containing EDTA at 55C.

25 "Moderately stringent conditions" can be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and percent SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37 degrees centigrade in a solution
30 comprising: 20 percent formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10 percent dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "detection" includes any means of detecting, including direct and indirect detection.

The terms "level of expression" or "expression level" is generally used interchangeably and refer to the amount of a polynucleotide or an amino acid product or protein in a biological sample. "Expression" generally refers to the process by which gene-encoded information is converted into the structures present and operating in the cell. Therefore, as used herein, "expression" of a gene may refer to transcription into a polynucleotide, translation into a protein, or even posttranslational modification of the protein. Fragments of the transcribed polynucleotide, the translated protein, or the post-translationally modified protein shall also be regarded as expressed whether they originate from a transcript generated by alternative splicing or a degraded transcript, or from a posttranslational processing of the protein, e.g., by proteolysis. "Expressed genes" include those that are transcribed into a polynucleotide as mRNA and then translated into a protein, and also those that are transcribed into RNA but not translated into a protein (for example, transfer and ribosomal RNAs).

The term “expression profile” can be used to define the level of expression of a group of genes providing a more composite picture of the transcriptional activity in the sample.

The term "biomarker" as used herein refers to an indicator of a state of a patient; as such biomarker can be useful for evaluating the disease state of a patient including diagnosis and evaluating response of treatment in an individual). A biomarker is a molecular entity, which can be detected in a biological sample from the patient. Biomarkers include, but are not limited to, DNA, RNA, protein, carbohydrate, and other biochemical entities or moieties, including combinations thereof, for example a glycolipid or a glycoprotein-based molecular marker. “Diagnostic marker” and “prognostic marker” is a specification of “biomarkers” that indicates that the presence or absence or level of a molecular entity can provide information on diagnosis and/or prognosis, including such as the response to one or more types of therapy. Some biomarkers may be suited for diagnostics, some are suited for following disease development and treatment response, whereas other are suited for predictions of a clinical response to a therapy.

The "amount" or "level" of a “prognostic marker” associated with an increased clinical benefit to a patient is the detectable level in a biological sample from said patient. The

expression level can be measured by methods known to one skilled in the art and also disclosed herein. The expression level or amount of biomarker assessed can be used to determine or predict the response of treatment.

The term “altered expression” refers to an increased or decreased expression level of a gene, usually measured at the mRNA or protein level. . The expression level is considered altered relative to a reference level, e.g. the level of expression is “higher” or “lower compared to a predetermined level of relevance. Altered expression level of a gene, may represent a gene which expression is “high” or “low” compared to other genes and/or relative to the level of expression in other individuals.

The term "increased expression" or "increased levels" refers to an elevated or increased expression level of a gene, usually measured at the mRNA or protein level. The expression level is considered increased relative to a reference level, e.g. the level of expression is “higher” than a predetermined level of relevance. Increased expression level of a gene, may represent a gene which is expressed at “a high” level in an individual, relative to other genes and/or relative to the level of expression in other individuals.

The term "decreased expression" or "decrease levels" refers to a reduced or decreased expression level of a gene, usually measured at the mRNA or protein level. The expression level is considered decreased relative to a reference level, e.g. the level of expression is “lower” that a predetermined level of relevance. Decreased expression level of a gene, may represent a gene which is expressed at “a low” level in an individual, relative to other genes and/or relative to the level of expression in other individuals.

The term "rheumatoid factor," or "RF," refers to IgM, IgG, or IgA isotypes, singly or in any combination, of antibodies detected in patient serum and directed to antigenic determinants present on human and animal IgG.

The term "positive for RF" refers to a result of an assay for RF, e.g., an ELISA assay, where the result is above a threshold or cut-off value for that assay for samples that are considered to reproducibly contain detectable levels of RF.

The term "negative for RF" refers to a result of an assay for RF, e.g., an ELISA assay, where the result is at or below a threshold or cut-off value for that assay for samples that are considered to reproducibly contain undetectable levels of RF.

The term "sample" or “biological sample” as used herein refers to a composition that is obtained or derived from a subject of interest that contains one or more molecular entities that is/are detected, measured or identified. For example, the phrase "patient sample", “subject sample” and variations thereof refers to any sample obtained from a patient or subject of interest that would be expected or is known to contain the cellular and/or molecular entity that is to be characterized, including but not limited to a tissue sample, a cell sample or a blood sample.

The terms "tissue sample" or "cell sample" or “blood sample” are meant for samples including one or more cells obtained from a subject. The source of the tissue or cell sample may be solid tissue as from a fresh, frozen or preserved organ or tissue sample or biopsy or aspirate; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid, interstitial fluid, or blood or any blood constituents. The tissue sample or cell sample may also be primary or cultured cells or cell lines. Optionally, the tissue or cell sample is obtained from a diseased tissue/organ (e.g., demonstrating a pathological characteristic). The tissue sample may contain compounds which are not naturally intermixed with the tissue in nature such as preservatives, anticoagulants, buffers, fixatives, nutrients, antibiotics, or the like.

The term "serum sample" refers to any serum sample obtained from an individual. Methods for obtaining sera from mammals are well known in the art.

A "control sample", "control cell", or "control tissue", as used herein, refers to a biological sample, cell or tissue obtained from a source known, or believed, not to be afflicted with the disease or condition for which a method or composition of the invention is being used to identify. In one embodiment, a control sample, control cell, or control tissue is obtained from a seemingly unaffected part of the body of the same subject or patient in whom a disease or condition is being identified using a composition or method of the invention. In one embodiment, control sample, control cell, or control tissue is obtained from a part of the body of an individual who is not the subject or patient in whom a disease or condition is being identified using a composition or method of the invention.

The term "diagnosis" is used herein to refer to the identification or classification of a molecular or pathological state, disease or condition. For example, "diagnosis" may refer to identification of a particular type of inflammatory disease or disorder or a specific autoimmune disease, such as RA.

The term "prediction", “predicting” or variations hereof are used to refer to the likelihood that a patient will respond either favourably or unfavourably to a drug or set of drugs. In one embodiment, the prediction relates to the extent of those responses. In one embodiment, the prediction relates to the probability that a patient will improve following treatment, for example treatment with a particular therapeutic agent, and for a certain period of time without disease recurrence. The predictive methods of the invention can be used clinically to make treatment decisions by choosing the appropriate treatment modalities for any particular patient. The predictive methods of the present invention are valuable tools in determining if a patient is likely to respond favourably to a treatment regimen, such as a given therapeutic regimen, including for example, administration of a given medicament or therapeutic agent or combinations hereof.

The term “indication”, “indicative” or variations hereof are used to refer to the guidance obtained; as an “indication” based on an altered expression level of a gene as described herein provide information that the subject or patient is likely to respond to an anti-inflammatory treatment. Based on such guidance the methods of the invention can be used clinically to make treatment decisions by choosing the appropriate treatment modalities for any particular patient.

As used herein, "treatment" refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed before or during the course of clinical pathology. Desirable effects of treatment include preventing the occurrence or recurrence of a disease or a condition or symptom thereof, alleviating a condition or symptom of the disease, diminishing any direct or indirect pathological consequences of the disease, decreasing the rate of disease progression, ameliorating or palliating the disease state, and/or achieving remission or improved prognosis. In some embodiments, methods and compositions of the invention are useful in attempts to delay development of a disease or disorder.

An "effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result. A "therapeutically effective amount" of a therapeutic agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the therapeutic agent are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and

for periods of time necessary, to achieve the desired prophylactic result. Typically but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

5 The terms "individual," "subject" or "patient", as used herein, can be used interchangeably and generally refers to a vertebrate. In certain embodiments, the vertebrate is a mammal. Mammals include, but are not limited to, primates (including human and non-human primates) and rodents (e.g., mice and rats). In certain embodiments, the mammal is a human. The term “patient” further indicates that the subject is not a healthy subject. In one 10 embodiment a “patient” is an individual diagnosed or suffering from sign(s) or symptom(s) associated with inflammatory diseases or disorders. In one embodiment the “patient” is suffering from an autoimmune disease or disorders, such as RA.

A "control subject" refers to a seemingly healthy subject who has not been diagnosed and/or who does not suffer from any sign or symptom associated with 15 inflammatory diseases or disorders.

By "correlate" or "correlating" is meant comparing, in any way, the performance and/or results of a first analysis or protocol with the performance and/or results of a second analysis or protocol. For example, one may use the results of a first analysis or protocol in carrying out a second protocols and/or one may use the results of a first analysis or protocol 20 to determine whether a second analysis or protocol should be performed. With respect to the embodiment of gene expression analysis or protocol, one may use the results of the gene expression analysis or protocol to determine whether a specific therapeutic regimen should be performed.

The term "patient response" or "response" can be assessed using any endpoint 25 indicating a benefit to the patient, including, without limitation hereto, a) inhibition of disease progression, b) reduction in the number of disease episodes and/or symptoms; c) reduction in lesional size; d) inhibition of disease cell infiltration into adjacent peripheral organs and/or tissues; e) inhibition of disease spread; f) decrease of auto-immune response, which may, but does not have to, result in the regression or ablation of the disease lesion; g) relief, to 30 some extent, of one or more symptoms associated with the disorder; h) increase in the length of disease-free presentation following treatment; and/or i) decreased mortality at a

given point of time following treatment. For the purpose of patient response, inhibition is meant to cover; reduction, slowing down or complete arrest or symptom(s) of relevance.

The expression "not responsive to," as it relates to the reaction of subjects or patients to one or more of the medicaments that were previously administered to them, describes those subjects or patients who, upon administration of such medicament(s), did not exhibit any or adequate signs of treatment of the disorder for which they were being treated, or they exhibited a clinically unacceptably high degree of toxicity to the medicament(s), or they did not maintain the signs of treatment after first being administered such medicament(s), with the word treatment being used in this context as defined herein. The phrase "not responsive" includes a description of those subjects who are resistant and/or refractory to the previously administered medication(s), and includes the situations in which a subject or patient has progressed while receiving the medicament(s) that he or she is being given, and in which a subject or patient has progressed within 12 months (for example, within six months) after completing a regimen involving the medicament(s) to which he or she is no longer responsive. The non-responsiveness to one or more medicaments thus includes subjects who continue to have active disease following previous or current treatment therewith. For instance, a patient may have active disease activity after about one to three months of therapy with the medicament(s) to which they are non-responsive. Such responsiveness may be assessed by a clinician skilled in treating the disorder in question. For purposes of non-response to medicament(s), a subject who experiences "a clinically unacceptably high level of toxicity" from previous or current treatment with one or more medicaments experiences one or more negative side-effects or adverse events associated therewith that are considered by an experienced clinician to be significant, such as, for example, serious infections, congestive heart failure, demyelination (leading to multiple sclerosis), significant hypersensitivity, neuropathological events, high degrees of autoimmunity, a cancer such as endometrial cancer, non-Hodgkin's lymphoma, breast cancer, prostate cancer, lung cancer, ovarian cancer, or melanoma, tuberculosis (TB), and the like.

The term “inadequate response” or “an inadequate responder” is used to describe patients that experience an unsatisfactory effect of a given treatment. This may be characterized by a low therapeutic effect and/or by substantial side effects. The criteria is considered equivalent to none-responsiveness. The “term inadequate response” is used in connection with therapeutics for where a given response is expected or aimed at based on previous trials. If after a certain period no “adequate response“is obtained, the treatment is

usually discontinued and the patient is considered “an inadequate responder”. It may also be that the patient continues the treatment, but in combination with further treatment in order to improve treatment response.

The term “adequate response” is used to describe the effect of a treatment in a patient when expectations to treatment efficacy are fulfilled.

A "medicament" is an active drug to treat a disease, disorder, and/or condition. In one embodiment, the disease, disorder, and/or condition is RA or its symptoms or side effects.

An “anti-inflammatory agent” is a compound, medicament or agent, which can, or is expected to; decrease an inflammatory response or symptom(s) of inflammatory diseases or disorders.

A "RA therapeutic agent," a "therapeutic agent effective to treat RA," and grammatical variations thereof, as used herein, refer to an agent that when provided in an effective amount is known, clinically shown, or expected by clinicians to provide a therapeutic response in a subject who has RA.

An "antagonist" refers to a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing or interfering with the activities of a particular or specified protein, including its binding to one or more receptors in the case of a ligand or binding to one or more ligands in case of a receptor. Antagonists include antibodies and antigen-binding fragments thereof, proteins, peptides, glycoproteins, glycopeptides, glycolipids, polysaccharides, oligosaccharides, nucleic acids, bioorganic molecules, peptidomimetics, pharmacological agents and their metabolites, transcriptional and translation control sequences, and the like. Antagonists also include small molecule inhibitors of the protein, and fusion proteins, receptor molecules and derivatives which bind specifically to the protein thereby sequestering its binding to its target, antagonist variants of the protein, antisense molecules directed to the protein, RNA aptamers, and ribozymes against the protein.

DETAILED DESCRIPTION

The inventors of the present inventions have found that patients with a high probability of a successful treatment can be identified based on examination of the

expression profile of certain genes. The present invention is based on data obtained as described in the examples. The patient according to the invention typically suffers from an inflammatory diseases or disorder and in particular an auto-immune disease or disorder. Based on the obtained data the information can be used in various methods, as patients with an enhanced probability of responding to therapy can be selected.

One aspect of the invention relates to a method for predicting the response of a subject to an anti-inflammatory agent comprising obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject, wherein altered expression of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

Different wording may be used to explain the context of evaluating gene expression of the one or more genes of Figure 1. It is equally useful to obtain information on the level of expression, assess the level or expression or to consider the level of expression. All of these methods need not including obtaining the blood sample as that may have occurred previously and the methods thus specifies that information on gene expression from a biological sample for the purpose of prediction the clinical response or the likelihood of a clinical response, in a given patient, is used. This further indicates that information regarding the level of gene expression that has also been obtained previously may be used in the methods according to the invention.

One aspect of the invention relates to a method for identification of a subject with an increased probability of responding to an anti-inflammatory agent comprising obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject, wherein altered expression of one or more of said gene(s) compared to a reference level of said gene(s) in said sample, identifies a subject with an increased probability of responding to an anti-inflammatory agent.

As above alternative wording, such as assessing the level of expression or consider the level of expression may be used according to the methods of the invention and furthermore, as also described above, the methods do not necessarily include the step of obtaining the blood sample and assaying the level of expression in the blood sample.

In further aspects of the invention the methods do include a step of measuring the levels of expression of one or more gene(s) of Figure 1 in a biological sample from said patient and comparing said levels with a reference level of said genes.

One aspect of the invention thus covers a method for predicting the response of a subject to an anti-inflammatory agent comprising;

a) measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject and
b) comparing said level with a reference level of said gene(s)

wherein altered expression of one or more of said gene(s) compared to said reference level, is predictive of a response of the subject to the anti-inflammatory agent.

A further aspect relates to a method for identification of a subject with an increased probability of responding to anti-inflammatory agent comprising;

a) measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject,
b) comparing said level with a reference level of said gene(s),

wherein altered expression of one or more of said gene(s) compared to the reference level of said gene(s), indicates that a subject with an increased probability of responding to an anti-inflammatory agent has been identified.

Gene Expression

The molecular background of many inflammatory diseases or disorders, including auto-immune diseases or disorders is not well understood and therefore diagnosis is complicated and is prone to inaccuracies. The currently available therapies are useful for some patient but not for others, and the reason here fore has not yet been clarified. In order to increase the treatment success, attempts are made to subgroup patients depending on various parameters.

One option is to characterize the gene expression profile of patients and group patients based hereon. Usually gene expression is measured at the RNA level or at the protein level, as the level of a given mRNA or alternatively the translational product is determined. . Alternatively gene expression may be measured or determined indirectly, such as by correlation to other genes or makers, also including markers of polymorphism such as SNPs. SNPs are usually bi-allelic and easily assayed. Gene expression can thus be measured at various levels by multiple methods known by the person skilled in the art.

The test used to measured gene expression by mRNA level may be based on PCR technology, such as multiplex-PCR, where more than two primer sets are used for the purpose of amplifying two or more DNA sequence in a single reaction carried out on nucleic acid isolated from a biological sample, such as a blood sample from a patient. The method may be a two-step method also including a step of cDNA synthesis ahead of the amplification. Microarray chips are also useful for analysing a large group of genes, such microarray chips can be specifically designed to include probes of relevance or information

from standard chips on genes of interest can be collected to evaluate the gene expression profile for genes considered relevant.

The specificity of PCR and array technology is dependent on the hybridization of primers and probes to mRNA molecules in the sample analysed and the stringency can be adjusted by the parameters known to a person skilled in the art.

Measuring gene expression by correlation to other genes or markers may be performed when there is evidence that the detection of said other genes or said markers correlates with the level of expression of the gene of interest. As described in Example 4 herein the skilled person may perform expression quantitative trait loci (eQTL) analyses for a gene of interest and identify SNP correlations or associations to the expression level of that gene. In a further alternative the level of expression may thereby be determined by correlation with another gene(s) or marker(s).

Measuring gene expression at the protein level is also contemplated in so far as the translational product is a protein that is detectable in the sample obtained from the patient.

Proteins may be detected using suitable techniques, which are frequently antibody based as an antibody with specificity for a given protein may be generated and used based on technologies known in the art. Antibody-based technologies are most usable when gene expression data from a low number of genes are used. More complex analysis of gene expression at the protein level can be made using proteome analysis.

For certain gene products a functional assay could equally well be applied with the purpose of determining expression level. A functional assay could be an assay testing for biological or enzymatic activity, depending on the functionality of the protein and the knowledge in the art about such a proteins activity.

As described above one embodiment of the invention relates to a method for identification of a patient with an increased probability of responding to an anti-inflammatory agent comprising;

a) measuring the levels of expression of one or more gene(s) of Figure 1 in a biological sample from said patient
b) comparing said levels with a reference level of said genes,

wherein altered expression of one or more of said gene(s) compared to the reference level of said gene(s), is predictive of a response of the patient to the anti-inflammatory agent.

The same criteria may be applied for identifying or selecting a patient for treatment using said anti-inflammatory agent based on the wish to identify patients that have an increased probability of responding to treatment using said inflammatory agent.

As can be seen in the example disclosed herein an altered expression level of one more genes of Figure 1 is indicative for a clinical response to the anti-inflammatory agent. It is furthermore attractive to focus on one or more gene(s) that are increased compared to the reference level. Alternatively emphasis could be on one or more gene(s) that are decreased compared to the reference level. Genes, for which, either of these characteristics, have been correlated with an improved response rate in patients are listed in Figure 1A and Figure 1B, respectively. In a further embodiment the methods described herein concerns the situation where the altered expression of a gene of Figure 1A is an increase compared to the reference level. In a further embodiment the methods described herein relates to the case where the altered expression of a gene of Figure 1B is decreased compared to the reference level. In further embodiments more genes may be included, such as one or more gene(s) of Figure 1A with an expression level above the reference level in combination with one or more gene(s) of Figure 1B with an expression level below the references level, whereby expression information on multiple genes is used. In one embodiment the expression level of at least two genes are compared with the individual reference levels. It is further possible to combine information that an altered expression of a gene of Figure 1A is increased compared to the reference level with information that an altered expression of a gene of Figure 1B is decreased compared to the reference level.

A combination of genes useful for multivariate based methods according to the invention is exemplified in Table 2, in such methods information of expression levels for one or more genes may be used, such as at least two, at least three, at least four.

As will be described further below the reference level is gene specific and will depend on the specific aim of the method.

Reference level

The reference level may be the expression level in an unaffected or healthy subject, which is most likely the case for genes where an altered expression of a gene is characteristic for an inflammatory disease or disorder, and such genes may be useful as diagnostic markers. In one embodiment the reference level may be the level of expression in an unaffected or healthy l individual.

As is apparent from the data herein, other biomarkers do not necessarily display a different expression in unaffected or healthy individuals compared to patients. In one embodiment the reference level may be an average of expression levels determined in a population of either healthy individuals or patients or a mixture thereof. In other situations, the level of gene expression of certain genes may provide information predictive of the

treatability of a patient using an anti-inflammatory agent although the expression profile cannot be correlated with disease state or diagnostic criteria. This may be due to the fact that the disease diagnostic is not accurate as the tools for diagnosis do not reflect the variability of diseases. Such biomarkers may none the less have great value as they can be used according to methods herein for directing treatment to the individual patents that are more likely to respond to a given treatment.

Based on such information the reference level may be a pre-determined level, an arbitrarily level of expression useful for screening patients that response to an anti-inflammatory drug. In on embodiment according to the invention the reference level is a predetermined level.

The examples herein demonstrate that the level of expression of a single gene can be used according to the methods of the invention. This predetermined level may thus be an expression level that is indicative a given response, such as a response measured by DAS28-CRP, an ACR20, an ACR50 and/or an ACR70 response. The reference level or predetermined level may considered a threshold and said threshold may be selected aiming for a certain response level in a patient group. The threshold selected will then be indicative of the probability of reaching an ACR20, an ACR50 and/or an ACR70 response in a fraction of patients. Likewise the threshold may be selected based on DAS28-CRP scores aiming for a certain score in a patient group. The level may thus be set to deselect non-responders for each criteria, or to increase the fraction of patients that reaches one or more or the criteria for a positive response. The biomarkers are thus predictive for a treatment response and even useful for predicting the degree of response if aiming for only high responders.

In one embodiment the predetermined reference level may be based on a ROC curve set to select an expression level that reaches a ACR50 response in at least 40% or the patients, such as 45%, such as 50 %, such as 55 %, such as 60 %, such as 65 % or such at least 70 % of patients treated with the anti-inflammatory agent.

In one embodiment the predetermined reference level may be based on a ROC curve set to select an expression level that reaches a ACR70 response in at least 25% or the patients, such as 30%, such as 35 %, such as 40 %, such as, such as 45 %, such as 50 % of patients treated with the anti-inflammatory agent.

In one embodiment according to the invention the expression level of complement factor D (CFD), also known as adiposin, is used for selecting, identifying and/or determining if a patient has a higher probability of responding to an anti-inflammatory drug. The gene is listed in Figure 1A (and Figure 2), and exemplifies how a gene with an increased expression level can be used in the methods of the invention. In the examples herein the expression

level is determined using microarray technology and qRT-PCR, but it is also relevant according to the present invention to consider alternative methods for measuring the mRNA level of CFD and methods in general for measuring the protein level or activity of CFD.

Accordingly a method of the present invention may include that the level of
5 expression of complement factor D (CFD) is above 9.5 on a log2-scale of normalized expression values when determined by microarray technology. Based on the ROC data presented herein increasing the threshold to such as 9.8, 10.0, 10.2, 10.3, 10.4 or even 10.5 provides methods with higher specificity but also less sensitivity.

The level of expression may also be determined based on PCR measurements,
10 such as RT-PCR, either as qRT-PCR performed using internal controls or using multiplex PCR were more than one transcript can be assayed at a time, also frequently including internal controls.

Accordingly a method of the present invention may include methods wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the
15 transcript is detected with a Cycle Threshold Value (Ct) of 30 (using Assay ID: Hs00157263_m1(Applied Biosystems by Life technologies). In further such embodiments the CFD transcript may be detected within PCR cycle 28 or even 26. It is further preferred that at the same time, 18S RNA is detected with a Cycle Threshold Value (Ct) of 12.5 on the same cDNA sample confirming that the quality of the PCR analysis.

20 The efficiency of the amplification reaction can also be measured and should be above 95 %, where 100 % indicates the theoretical doubling of amplicons per cycle. Alternatively the efficiency of the PCR amplification should be at least 1.9 or preferably at least 1.93, where 2.0 represents the theoretical doubling of amplicons per cycle.

In further embodiments the methods of the present invention include methods
25 wherein the level of expression of complement factor D (CFD) is measured indirectly by SNP detection. In such method one or more SNPs may be evaluated. Contrary to gene expression, SNP detection provides a yes/yes, yes/no (=no/yes) or no/no response and not a relative scale of high or low expression and the evaluation must thus focus on the genotype corresponding to the altered expression of interest.

30 Depending on the selected SNP's the reference level may be "no/no"" and to correlate with altered expression at least one allele should provide a "yes". In alternative embodiment the reference level may be "yes/yes" or even "yes/no".

In the example of CFD, increased CFD expression would be correlated with specific "reference levels for each SNPs. Such method will thus include a method where the level of
35 expression of complement factor D (CFD) is measured indirectly by detection of one or more

of rs1683565, rs1683591, rs1683590, rs1683569, rs1683574, rs1651888, rs2930894, rs2930891, rs4417648, rs1651891, rs1651890 and rs2930898.

As these SNPs all concerns a single nucleotide which is either A or G the reference level will be AA, AG, or GG.

5 For the SNP rs1683591 described in the example the reference level would be the AA genotype (low CFD expression and the AG and GG genotypes would indicate an altered expression of CFD (high CFD expression).

Methods according to the invention thus include methods where the level of CFD is measured indirectly by the presence of the AG or GG genotypes of SNP rs1683591.

10 As seen from the method using microarray data and RT-PCR data the specificity of the method can be increased by lowering the threshold although thereby losing some sensitivity.

If an increased expression of a gene is relevant for the method according to the invention, as for CFD, increasing the threshold will provide methods with higher specificity
15 but also less sensitivity.

Vice versa, if a decreased expression of a gene is relevant for the method according to the invention decreasing the expression level threshold will provide a method with higher specificity but also less sensitivity. It is also clear that to fulfil the threshold criteria in this case the expression level to be below the threshold.

20 It is clear from the above, that other genes, as identified herein, may likewise alone or in combination, be used in methods for predicting the likelihood of a clinical response in a patient and thereby selection of patients for a given treatment base on a high probability that the selected patients will response to said treatment.

25 **Biological sample**

The starting point for any subgrouping or characterizing of an individual patient, beyond the initial diagnosis, is a biological sample or information based on a biological sample that has been obtained prior. The biological sample can according to the invention be any sample that is obtained from a patient prior to or in the cause of using the present
30 invention. The sample is preferably a blood sample that can be easily obtained by routine methods but also other types of samples may be used. The sample may also be a serum sample. In some cases a tissue sample such as a synovial sample may be used. The person skilled in the art will understand how to treat a given sample prior to measuring the level of expression of given set of genes. Full blood sample may be collected as PaxGene samples.

If the gene of interest is expressed in specific cell types this may reflect the sample used for expression studies. The biological sample may thus be a sample of peripheral blood mononuclear cell from a blood sample, also called a PBMC fraction, or even sub-fractions hereof including monocytes only, such as one or more of CD14+, CD4+ and/or CD8+ positive cells.

In case the gene encodes a soluble protein marker the expression studies may be performed on a serum sample and the presence of the protein, not the transcript, may be evaluated. Soluble proteins in serum may be detected using a specific antibody, such as by an ELISA know in the art. If more proteins are evaluated more complex analysis of gene expression at the protein level can be made using proteome analysis may be considered.

Apart from the expression level and alterations hereof, the biological sample may also be used to determine rheumatoid factor (RF) status of the patient.

Patient and patient status

In one embodiment the subject is patient e.g. an individual diagnosed or suffering from sign(s) or symptom(s) associated with inflammatory diseases or disorders as described herein. In one embodiment the patient is suffering from an autoimmune disease or disorders. In a specific embodiment the patient is an RA patient or suffering from symptoms of RA.

The sample may be obtained from a patient that is naive for treatment of the inflammatory disease or disorder, meaning that no treatment for the inflammatory disease or disorder has been previously administered to said patient. For patients suffering from auto-inflammatory a disease that is likely to be a rare occasion as various treatments are usually considered before the anti-inflammatory agents described herein are considered, particularly with regards to the class of biological drugs. In some cases gene expression information may be obtained from a sample obtained previously, thus the sample maybe considered naive whereas the patient is no longer naïve to a given therapy. The sample may in some situations be obtained from a patient currently being treated for the inflammatory disease or disorder. The patient may be in treatment using basically any drug not limited to the anti-inflammatory agents mentioned herein.

Drugs that are used as first line drugs for treatment of the inflammatory disease or disorder will usually be administered to the patient before it is evaluated if a therapy according to the present invention has a high probability of success.

Drugs that a patient is being treated with or has previously been treated with may include one or more of the following: non-steroidal anti-inflammatory drugs (NSAIDs) like Asprin™, Ibuprofen™ etc, Corticosteroids, disease-modifying ant-irheumatic drugs

(DMARDs) like Plaquenil™, Azulfidine™, Methotrexate™, etc, Copaxone™ (glatirimer acetate), Gilneya™ (fingolimod), antibiotics like Flagyl™, Cipro™, Topical (skin applied) medications including topical corticosteroids, vitamin D analogue creams (Dovonex™), topical retinoids (Tazorac™), moisturizers, topical immunomodulators (tacrolimus and pimecrolimus), coal tar, anthralin, and others, Raptiva™, Ustekimumab™, light therapy like PUVA, UVB and CellCept™ (mycophenolate mofetil). Also including biological anti-inflammatory agents including, but are not limited to, IFN-beta, Orencia™ (CTLA4-Ig), Humira™ (anti-TNF), Cimzia™ (anti-TNF, PEG Fab), Tysabri™ (a4-integrin mAb), Simponi™, Rituxan/MabThera™, Actemra/RoActemra™ and Kineret™.

If a sample obtained prior to treatment is not used, the patient may be treated using one or more of a broad range of anti-inflammatory drugs including NSAIDs, DMARDs and TNF-alfa inhibitors as mentioned above. Frequently the patient will be treated with methotrexate (MTX).

It may also be that the treatment applied previously did not provide an adequate response in the patient, and thus the patient is no longer naïve to said treatment but is considered an inadequate responder. As for the diagnosis and clinical response the criteria applied to determine if a given patient is an inadequate responder will depend on the disease or disorder to be treated as described below.

The patient may thus be an inadequate responder to MTX treatment and/or to TNF-alfa inhibitor treatment, where TNF-alfa inhibitor treatment is meant to be one or more of the drugs recognised as TNF-alfa inhibitors including both antibody drugs and soluble receptor drugs.

It is preferred that the expression of the genes selected for the identification method described herein are not affected by prior or concurrent treatment with any anti-inflammatory drug, before or at the time where the biological sample is obtained.

As mentioned above it may also be relevant to consider rheumatoid factor (RF) status and anti-cyclic citrullinated protein antibodies (anti-CCP) status of the patient. Assays for determining RF and anti-CCP status is known in the art and the skilled person can apply any such assay without difficulties following the instructions from the manufacture. Patients positive for RF have a level of rheumatoid factor above a certain threshold indicative of the presence of RF in a sample. If negative, the level of rheumatoid factor is below said threshold, indicative of the absence of RF in said sample.

In one embodiment the patient RF status is positive or negative. In further specific embodiments the patient RF status is either positive or negative.

In one embodiment the patient anti-CCP status is positive or negative. In further specific embodiments the patient anti-CCP status is either positive or negative.

Indications

5 As described herein above, the present invention relates to treatment of a variety of diseases, particular including auto-immune and inflammatory diseases or disorders.

The conditions or disorders of to be treated with the anti-inflammatory agent are rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Sjogren's syndrome, multiple sclerosis, inflammatory bowel diseases such as
10 ulcerative colitis and Crohn's disease, systemic lupus erythematosus, or lupus nephritis, and any combination thereof, as well as co-morbidities associated with these diseases, with cardiovascular disease being a non-limiting example of said comorbidities. In a further aspect, other exemplary conditions include, but are not limited to, juvenile chronic arthritis, osteoarthritis, other spondyloarthropathies than ankylosing spondylitis, systemic sclerosis
15 (scleroderma), idiopathic inflammatory myopathies (dermatomyositis, polymyositis), vasculitis, systemic vasculitis, temporal arteritis, atherosclerosis, sarcoidosis, myasthenia gravis, autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria), pernicious anemia, autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia), thyroiditis (Grave's
20 disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis), diabetes mellitus, Type 2 diabetes, immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis, autoimmune oophiritis), pancreatitis, autoimmune orchitis, autoimmune uveitis, anti- phospholipid syndrome, demyelinating diseases of the central and peripheral nervous systems in addition to multiple sclerosis, idiopathic demyelinating
25 polyneuropathy or Guillain- Barre syndrome, and chronic inflammatory demyelinating polyneuropathy, hepatobiliary diseases such as infectious hepatitis (hepatitis A, B. C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, viral hepatitis, primary biliary cirrhosis, granulomatous hepatitis, Wegener's granulomatosis, Behcet's disease, and sclerosing cholangitis, inflammatory bowel diseases such as celiac disease,
30 gluten-sensitive enteropathy, and Whipple's disease, autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, atopic dermatitis, dermitis herpetiformis, pemphigus vulgaris, vitiligo (leukoderma), allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria, sepsis, endotoxemia, immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic
35 pulmonary fibrosis and hypersensitivity pneumonitis, chronic obstructive pulmonary disease,

and organ or bone marrow transplantation associated diseases including graft rejection and graft-versus-host disease.

The causes of inflammatory diseases are multiple and multiple pathways and components are involved. Inflammation is a cascade of events involving multiple components, including the vasculature (e.g., endothelial cells, pericytes, smooth muscle cells), cells of the immune system (e.g., T and B lymphocytes; polymorphonuclear leukocytes or granulocytes, such as monocytes and neutrophils; dendritic cells, macrophages, and NK cells), cell-derived soluble mediators (cytokines, chemokines) and also resident cells in the targeted tissue (e.g., epithelial cells, synovial fibroblasts, neuronal cells). Each of these elements including regulators hereof may have role in disease development and may subsequently also be a target of therapy for the above mentioned diseases and disorders. Inflammatory diseases may thus also be characterized by the pathway affected, e.g. as a B or T- cell mediated disease or disorder, as a cytokine mediated disorder or a receptor mediated disorder etc. etc.

For the present invention the indication may thus be any disorder meliorated by treatment of an anti-inflammatory agent, such as a disorder mediated by down-regulation of signaling/activity of the IL-10 family e.g. receptors and ligands as described herein below.

Indication which may be treated using modulators of the IL-10 family of cytokines and receptors include auto-immune diseases and disorders, such as Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Multiple sclerosis (MS), Inflammatory Bowel Disease (IBD), psoriasis or Psoriatic Arthritis (PSA).

Anti-inflammatory agent

As described herein above multiple pathways are involved in inflammation and each pathway may be targeted at multiple levels. Inhibition of receptor signalling may be obtained by blocking a receptor, by providing a soluble receptor fragment or by preventing the ligand from binding or signalling through the receptor as exemplified by targeted biological therapeutics for treatment of certain autoimmune diseases and/or cancer. For example, patients with cancer may be treated with an antibody against CD20 (anti-CD20); patients with rheumatoid arthritis may be treated with anti-CD20, a TNF antagonist (soluble TNFR or anti-TNF-α); patients with psoriasis may be treated with anti-CD11a; patients with multiple sclerosis may be treated with INF-beta; patients with ulcerative colitis may be treated with anti-TNF-α and patients with Crohn’s disease may be treated with anti-TNF-α or anti-α4 integrin. Unfortunately these treatments are not fully effective.

It has previously been described that member of the IL-10 family are useful targets for treatment of inflammatory diseases or disorders (WO 2001/46261).

The IL-10 family include IL-10, IL19, IL-20, IL-22, IL-24 and IL-26, which binds to the following receptor heterodimers:

IL-10: Binds to IL-10R1 / IL-10R2

IL-19: Binds to IL-20R1 / IL-20R2

IL-20: Binds to IL-20R1 / IL-20R2 and IL-22R / IL-20R2

IL-22: Binds to IL-22R / IL-10R2

IL-24: Binds to IL-20R1 / IL-20R2 and IL-22R / IL-20R2

IL-26: No known receptor

This receptor overlap suggests that, although some functionalities are specific for each family member there is also some shared effects. The exact role of each ligand and receptor in inflammatory diseases is not yet established but several have been linked to diseases. Examples include IL-20, that may be targeted by antibodies or receptor fragments, for treatment of certain inflammatory diseases (WO 2001/45261), IL-22 and IL- 19, IL-17 (WO10025369, WO2010102251), that are all members of the IL-10 family of cytokines.

Interleukin-19 (IL-19), IL-20, and interleukin-24 (IL-24) are members of the interleukin-10 (IL-10) cytokine family. As seen from the above these three interleukins bind and signal through the IL-20R1/IL-20R2 heterodimeric receptor. IL-20 and IL-24 (but not IL-19) are also ligands for the receptor complex composed of IL-20R2 and IL-22R1 (Parrish-Novak et al., J Biol Chem 2002; 277: 47517- 47523; Dumoutier et al., J Immunol 2001; 167:3545-3549). It has been proposed that IL-19 and IL-20, along with other IL-10 family members, form a distinct subfamily of helical cytokines where at least IL-19 and IL-20 have similar three-dimensional structures (Chang et al., J Biol Chem 2003; 278: 3308-13).

Antagonizing IL-20 activity using receptor fragments or monoclonal antibodies has therefore been described as a promising approach for treatment of various inflammatory conditions. Antigenic epitopes of human IL-20 (hIL-20), as well as rat or murine monoclonal antibodies binding huIL-20, have also been described (e.g., WO2005052000, US20060142550, and WO2007081465). Anti-IL-20 monoclonal antibodies that can reduce IL-20-mediated activation of IL-20R1/IL-20R2 and IL-22R1/IL-20R2 receptor complexes in one or more species, including humans, have been described in WO 2010/000721.

The anti-inflammatory agent may accordingly be an antagonist of IL-20 capable of reducing IL-20 mediated activation of both the IL-20R1 / IL-20R2 and the IL-22R / IL-20 receptor. The anti-inflammatory agent may be specific by not reducing receptor activation through the IL-19 or IL-24 receptor.

Based on an at least shared mode of action targeting of each ligand and receptor may provide a similar biological effect. An anti-inflammatory agent according to the invention may thus be an antagonist of IL-10 family members and their receptors e.g. a compound that regulates signalling of the above mentioned receptors by binding either ligand or receptor, whereby the biological activity of the ligand or the receptor is decreased. Assays for determining antagonistic activity of IL-10 family members are known in the art and also described in WO 2010/000721.

The anti-inflammatory agent according to the invention may be in a pharmaceutical composition e.g. a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a label. The anti-inflammatory agent or pharmaceutical composition may be suitable for oral, i.v. and/or s.c. administration. The anti-inflammatory agent or pharmaceutical composition may be for repeated administration such as once monthly or once weekly.

The methods herein may also take account of the administration route or regime, as the response may be dependent on the treatment regime applied. In one embodiment, the response prediction or indication is based on that an anti-IL-20 antibody is administered, once weekly. In one embodiment said antibody is administered subcutaneously.

Clinical response

Depending on the indication, diagnosis and clinical response may be determined by a variety of methods. Patients that do not, upon administration of given anti-inflammatory agent, exhibit any or adequate signs of treatment of the disorder for which they are being treated are considered non responsive. Patients that on the contrary do, upon administration of given anti-inflammatory agent, respond by exhibiting adequate signs of treatment of the disorder for which they are being treated, are considered responsive. Adequate signs of treatment vary from disease to disease and from patient to patient and do not imply that the patient experiences “full” treatment but solely that amelioration of one or more clinical parameters is observed. The responsiveness may be considered a different time point after dosage of the anti-inflammatory agent and patients may respond after one or more dosage, for a short period or for longer periods, but as long as a positive result is obtained, that patient is considered responsive.

The success rate (e.g. the frequency of administering an anti-inflammatory agent to a patient that will respond) may be increased based on the present invention, furthermore the frequency of reaching not only a high success rate but also a strong response in the patient administered by be obtained using the present invention.

The clinical response may be determined by methods known in the art. Official disease scores as approved by governmental authorities are preferably to be used. It is to be said that such disease scores evolve over time, so also future methods for obtaining a clinical score is considered relevant for the present invention.

5 It is contemplated that a persons skilled in the art is able to identify relevant clinical parameters for a given disease or disorder and only few key clinical parameters are therefore included herein. Auto-immune diseases are diagnosed based on variety of criteria.

The methods herein are concerned with indications and predictions of a response of a patient to an anti-inflammatory agent, depending on the indication and symptoms, the 10 expected response may be projected at different time points. In individual embodiment the indication and prediction relates to a response to be obtained within 12 months, within 10 months, within 8 months, within 6 months, within 5 months, within 4 months, within 3 months, or within 2 months.

15 **Rheumatoid arthritis (RA)**

Rheumatoid arthritis may be diagnosed based on the criteria defined by the America college of Rheumatology (ACR) or the like. The responsiveness to a treatment may be based on degrease score when applying such criteria. Prevention or retardation of radiographic damage is also a goal for RA treatment. The America College of Rheumatology (ACR) 20 % 20 composite criteria for improvement describes patents as “improved” if there is 20 % improvement in the tender and swollen joint counts and 20 % improvement in at least three of five additional measures (pain, physical function, patient global health assessment, physician global health assessment and acute phase reactant levels). Similarly, the ACR50 and ACR70 represent even higher degrees of improvement for the patient.

25 The effectiveness of an anti-inflammatory agent as a therapeutic for RA may thus be quantified based on the number of patients or the fraction of patients that obtains ACR20, ACR50 and/or ACR70.

Alternative to the ACR scores, progression of rheumatoid arthritis can also be followed using a Disease Activity Score of 28 joints (DAS28). It is a combined index that has 30 been developed in Nijmegen in the 1980’s and has been widely used as an indicator of RA disease activity and response to treatment also in combination with the DAS based European League Against Rheumatism (EULAR) response criteria. The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2). When looking at these joints, 35 both the number of joints with tenderness upon touching (TJC28) and swelling (SJC28) are

counted. Measurements of the level of C-reactive protein (CRP) (in mg/l) may be included and the patient also makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". Based herein DAS28 is calculated.

5 Using the DAS, several thresholds have been developed for high disease activity, low disease activity or even remission. The score can also be used as response criteria, when the DAS of a patient is measured at two time points (e.g. before the start of a treatment and after treatment), the clinical response in the patients can be assessed.

The present invention is concerned with improving the effectiveness of RA
10 treatment. Although several compound have been approved and are used for treatment of RA treatment outcome is rarely optimal for all patients and involves some aspects of trial and arrow as no method for predicting the effectiveness of an RA treatment is been applied.

Recently, methods for increasing the effectiveness of RA treatment with antibody therapy against CD20 (Rituximab) have been described (WO2011/028945, Owczarczyk et al.
15 2011, Science translational medicine). In WO2011/028945 different subgroups of RA patients are defined based on expression profiles of the patients and some correlation with clinical responses is also included by identifying a subgroup of RA patients that are unlikely to respond to anti-CD20 therapy. A high (above threshold) mRNA level of one or more of FcRH5 and CXCL13 increases the ARC50 rate of RA patients. A further subgrouping
20 depending on RF status allowed further refinement, whereby the ARC50 criteria is obtained for about 40 % of the patients, which may reflect a subgroup dependent on the B-cell pathway which is the hallmark of the lymphoid subset and the target of Rituximab.

The present invention demonstrates that an altered expression level of the genes of Figure 1 and 2, are indicative for a clinical response that is higher than the average clinical
25 response in RA patients.

Systemic Lupus Erythematous (SLE)

As for RA, SLE treatment effect may be based on the basis of the American College of Rheumatology (ACR) classification criteria. These criteria were established mainly for use
30 in scientific research and in clinical trial and not for diagnostic purposes, so not all SLE patients pass the full criteria.

Multiple sclerosis (MS)

Several subtypes of the disease exist and different prognosis and progression is observed.

The United States National Multiple Sclerosis Society in 1996 standardized four subtype definitions: as 1) relapsing remitting, 2) secondary progressive, 3) primary progressive, and 4) progressive relapsing. Various criteria for diagnosing and evaluation are used which severely complicates testing of drugs potentially effective in treatment of MS. Based on MS being an auto-immune disease immune-modulators including anti-inflammatory agents may be useful for treatment or management of MS.

Psoriatic arthritis (PSA).

Psoriatic arthritis may be diagnosed based on the criteria defined by the America college of Rheumatology (ACR) or the like. The responsiveness to a treatment may be based on degrease score when applying such criteria. Prevention or retardation of radiographic damage is also a goal for PSA treatment. The America college of Rheumatology (ACR) 20 % composite criteria for improvement describes patents as “improved” if there is 20 % improvement in the tender and swollen joint counts and 20 % improvement in at least three of five additional measures (pain, physical function, patient global health assessment, physician global health assessment and acute phase reactant levels). Similarly, the ACR50 and ACR70 represent even higher degrees of improvement for the patient.

The effectiveness of an anti-inflammatory agent as a therapeutic for PSA may thus be quantified based on the number of patients or the fraction of patients that obtains ACR20, ACR50 and/or ACR70.

Alternative to the ACR scores, progression of psoriatic arthritis can also be followed using a Disease Activity Score of 28 joints (DAS28). It is a combined index that has been developed in Nijmegen in the eighties and is has been widely used as an indicator of PSA disease activity and response to treatment also in combination with the EULAR response criteria. The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2). When looking at these joints, both the number of joints with tenderness upon touching (TJC28) and swelling (SJC28) are counted.

Measurements of the level of C-reactive protein (CRP) (in mg/l) may be included and the patient also makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible". Based herein DAS28 is calculated.

Using the DAS, several thresholds have been developed for high disease activity, low disease activity or even remission. The score can also be used as response criteria,

when the DAS of a patient is measured at two time points (e.g. before the start of a treatment and after treatment), the clinical response in the patients can be assessed.

Skin psoriasis is a major aspect of PsA, although the extent of activity in the skin does not necessarily correlate with joint activity. A number of instruments to assess skin
5 psoriasis have been developed. A widely used instrument is the psoriasis area and severity index (PASI). The PASI assesses individual psoriatic lesions for erythema, thickness/induration, and scale, and then uses a formula to account for the overall extent of the body surface area of skin involved, with scores ranging from 0-72.

The Psoriatic Arthritis Response Criteria (PsARC) was specifically developed for
10 PSA clinical trials. The PsARC is composed of four measures: 1) patient global assessment of disease activity (improvement of 1 on a 5 point Likert scale is required for a response), 2) physician global assessment of disease activity (improvement of 1 on a 5 point Likert scale is required for a response), 3) joint pain (reduction of 30% or more in total score, assessing either 68 or 78 joints, using a 4 point scale is required for a response), and 4) joint swelling
15 (reduction of 30% or more in total score, assessing either 66 or 76 joints using a 4 point scoring scale, is required for a response). In order to be a ‘PsARC responder’, patients must achieve improvement in 2 of 4 measures, one of which must be joint pain or swelling, without worsening in any measure.

20 **Treatment**

One aspect of the invention relates to methods of treatment based on the information derived from the examples herein. The method for predicting clinical success of an anti-inflammatory agent, subsequently provides a method of treatment of patients identified with said method. As the method of identifying patients fulfilling certain predefined
25 criteria can easily be performed separately from the actually treatment of the patient the method applied does not necessarily include a step of determining that the patient fulfils a certain predefined criteria, although it is a preferred embodiment of the invention. When applying the method of treatment according to the invention it is expected that the patient will respond with a high degree of certainty, which would not be the case without the prior
30 knowledge of the fact that the patient fulfils certain predefined criteria.

One embodiment according to the invention relates to a method for treating an inflammatory disease or disorder in a patient where the expression levels of one or more of the genes of Figure 1, is altered compared to a reference level, comprising administering a therapeutic amount of an anti-inflammatory agent to said patient.

One further embodiment relates to a method for treating an inflammatory disease or disorder in a patient

a. considering if the expression levels of one or more of the genes of Figure 1, in said patient is altered compared to a reference level,

5 b. comprising administering a therapeutic amount of an anti-inflammatory agent to said patient.

Furthermore the invention in one embodiment relates to a method for treating an inflammatory disease or disorder in a patient

a. measuring if the expression levels of one or more of the genes of Figure 1, in a
10 biological sample from said patient is altered compared to a reference level,

b. comprising administering a therapeutic amount of an anti-inflammatory agent to said patient.

Even further the invention in one embodiment relates to a method for treating an inflammatory disease or disorder in a patient comprising;

15 a. measuring the levels of expression of one or more gene(s) of Figure 1 in a biological sample from said patient

b. comparing said levels with a reference level of said genes,

c. determine if the expression levels of one or more of the genes of Figure 1, is altered compared to said reference level

20 d. administering a therapeutic amount of an anti-inflammatory agent to said patient.

In alternative to the above methods, the reference level may be a predetermined level.

In further embodiments each of the methods may include that the level of expression one or more of the genes of Figure 1, is altered in said biological sample compared to said reference level.

25 Reference is made to the description herein above, including further detailed information of the method of prediction which is relevant to the method of treatment of the present invention.

An aspect of the invention relates to an anti-inflammatory agent for treatment of an
30 inflammatory disease or disorder in a subject, wherein said subject display an altered expression of one or more of the genes of Figure 1, compared to a reference level of said genes.

As for the method of treatment reference is made to the description herein above, including further detailed information of the methods of prediction or identification which is

obviously equally relevant to define the characteristics of the anti-inflammatory agent and the medical use hereof.

Article of manufacture

5 The present invention in a further aspect relates to an article of manufacture comprising, packaged together, a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a label stating that the pharmaceutical composition is for treating a patient suffering from an auto-immune disease or disorder with an altered expression of one or more of the genes of Figure 1.

10

Reference is made to the description herein above, including further detailed information of the method of prediction which is relevant to the article of manufacture of the present invention.

15 **Detecting agents and kits**

The present invention further relates to a composition comprising at least one detecting agent for determining the expression level of one or more gene(s) from figure 1, in particular one or more genes of figure 2 and specifically CFD. The detection agent(s) may be an antibody, a probe or a primer specific for each gene including mRNA and protein encoded 20 thereby.

A further aspect of the invention relates to a kit comprising a detecting agent or a composition comprising said detecting agent, as described above, and instructions for use. A kit, may further comprise a reference gene composition, in case an internal control is useful. The kit may also include a detecting agent for expression normalization such a detecting 25 agent for detecting a globulin gene. It is further part of the invention to include a description on how to correlate expression level(s) with response probability to an anti-inflammatory agent as described herein. In particular a kit, for determine the expression level of complement factor D (CFD) and evaluation hereof is contemplated.

30 **Therapeutic targets**

Anti-inflammatory agents are modulators of pathways essential for the phenotype of the inflammatory disease or disorder. As is apparent from the data herein the selected genes may individually be considered new therapeutic targets for treatment of inflammatory diseases or disorders, in so far, as they have not previously been described in relation to 35 autoimmune diseases and in particular RA.

Embodiments

The invention as described herein is summarized, but not limited, in the following embodiments.

5

1. A method for predicting the response of a subject to an anti-inflammatory agent comprising; obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject, wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

10

2. A method for predicting the response of a patient to an anti-inflammatory agent comprising
    a. measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient and
    b. comparing said level with a reference level of said gene(s)

    wherein altered expression of one or more of said gene(s) compared to said reference level, is predictive of a response of the patient to the anti-inflammatory agent.

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3. A method for identification of a subject with an increased probability of responding to anti-inflammatory agent comprising; obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject, wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s) indicates that a subject with an increased probability of responding to an anti-inflammatory agent has been identified.

25

4. A method for identification of a patient with an increased probability of responding to anti-inflammatory agent comprising;
    a. measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient
    b. comparing said level of expression with a reference level of said gene(s),

    wherein altered expression of one or more of said gene(s) compared to the reference level of said gene(s), indicates that a patient with an increased probability of responding to an anti-inflammatory agent has been identified.

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5. A method according to any of the previous embodiments, wherein the expression of complement factor D (CFD) is measured in a biological sample.

6. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and serpin peptidase inhibitor, clade B, member 9 (SERPINB9) is measured in a biological sample.

7. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or serpin peptidase inhibitor, clade B, member 9 (SERPINB9) and/or zinc finger, CCHC domain containing 24 (ZCCHC24) is measured in a biological sample.

8. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or fructosamine 3 kinase related protein (FN3KRP) and/or mesenchyme homeobox 1 (MEOX1) is measured in a biological sample.

9. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or serpin peptidase inhibitor, clade B, member 9 (SERPINB9) and/or zinc finger, CCHC domain containing 24 (ZCCHC24) and/or fructosamine 3 kinase related protein (FN3KRP) is measured in a biological sample.

10. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or serpin peptidase inhibitor, clade B, member 9 (SERPINB9) and/or zinc finger, CCHC domain containing 24 (ZCCHC24) and/or fructosamine 3 kinase related protein (FN3KRP) and/or mesenchyme homeobox 1 (MEOX1) is measured in a biological sample.

11. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or fibroblast growth factor 13 (FGF13) and/or tubulin, beta 2A (TUBB2A) and/or solute carrier family 39 (metal ion transporter, member 11) (SLC39A11) and/or transmembrane channel-like 4 (TMC4) is measured in a biological sample.

12. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or nuclear pore complex interacting protein-like 2 (NPIPL2) and/or zinc finger protein 880 (ZNF880) and/or aldehyde dehydrogenase 5 family, member A1 (ALDH5A1) is measured in a biological sample.

13. A method according to any of embodiments 1-4, wherein the expression of complement factor D (CFD) and/or fibroblast growth factor 13 (FGF13) and/or tubulin, beta 2A (TUBB2A) and/or solute carrier family 39 (metal ion transporter, member 11) (SLC39A11)
5 and/or transmembrane channel-like 4 (TMC4) and/or nuclear pore complex interacting protein-like 2 (NPIPL2) and/or zinc finger protein 880 (ZNF880) and/or aldehyde dehydrogenase 5 family, member A1 (ALDH5A1) is measured in a biological sample.

14. A method according to any of embodiments 1-4, wherein the expression of complement
10 factor D (CFD) and/or serpin peptidase inhibitor, clade B, member 9 (SERPINB9) and/or zinc finger, CCHC domain containing 24 (ZCCHC24) and/or fructosamine 3 kinase related protein (FN3KRP) and/or mesenchyme homeobox 1 (MEOX1) and/or fibroblast growth factor 13 (FGF13) and/or tubulin, beta 2A (TUBB2A) and/or solute carrier family 39 (metal ion transporter, member 11) (SLC39A11) and/or transmembrane channel-like 4
15 (TMC4) and/or nuclear pore complex interacting protein-like 2 (NPIPL2) and/or zinc finger protein 880 (ZNF880) and/or aldehyde dehydrogenase 5 family, member A1 (ALDH5A1) is measured in a biological sample.

15. The method according to any of the previous embodiments, wherein the altered
20 expression of a gene of Figure 1A is an increase compared to the reference level.

16. The method according to any of the previous embodiments, wherein the altered expression of a gene of Figure 1B is a decreased compared to the reference level.

25 17. The method according to any of the previous embodiments, wherein the expression level of at least two genes are compared with the individual reference levels of the at least two genes.

18. The method according to any of the previous embodiments, wherein the expression level
30 of at least two genes are compared with the individual reference levels of the at least two genes and wherein altered expression of a gene of Figure 1A is increased compared to the reference level and wherein altered expression of a gene of Figure 1B is decreased compared to the reference level.

19. The methods according to any of the previous embodiments, wherein the reference level is a predetermined level.

20. The methods according to any of the previous embodiments, wherein the predetermined level is a threshold indicative for a response measured using DAS28-CRP, ACR20, ACR50 and/or ACR70.

21. The method according to any of the previous embodiments, wherein the biological sample is a blood sample or serum sample.

22. The method according to any of the previous embodiments, wherein the biological sample is a Paxgene full blood sample.

23. The method according to any of the previous embodiments, wherein the biological sample is the PBMC fraction from a blood sample.

24. The method according to any of the previous embodiments, wherein the biological sample is a subset of cells from a blood sample.

25. The method according to any of the previous embodiments, wherein the biological sample is a subset of cells from a blood sample, wherein in the subset maybe one or more of CD14+, CD4+ and CD8+ positive cells.

26. The method according to any of the above embodiments, wherein the level of expression is measured based on mRNA.

27. The method according to any of the above embodiments, wherein the level of expression is measured using PCR.

28. The method according to any of the above embodiments, wherein the PCR is selected from the group consisting of multi-plex PCR and qRT-PCR.

29. The method according to any of the above embodiments, wherein the level of expression is measured using microarray chip.

30. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript is detected with a Cycle Threshold Value (Ct) of 30 using Assay ID: Hs00157263_m1 (Applied Biosystems).

31. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript is detected at absolute numbers of at least 0.03 copies of CFD pr. copy of beta-actin mRNA (gene symbol ACTB) using Assay ID: Hs00157263_m1 for CFD (Applied Biosystems/ Invitrogen).and Hs99999903_m1 for ACTB (Applied Biosystems/ Invitrogen).

32. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript is detected at absolute numbers of at least 0.04 copies of CFD pr. copy of beta-actin mRNA (gene symbol ACTB) using Assay ID: Hs00157263_m1 for CFD (Applied Biosystems/ Invitrogen).and Hs99999903_m1 for ACTB (Applied Biosystems/ Invitrogen).

33. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript is detected at absolute numbers of at least 0.05 copies of CFD pr. copy of beta-actin mRNA (gene symbol ACTB) using Assay ID: Hs00157263_m1 for CFD (Applied Biosystems/ Invitrogen).and Hs99999903_m1 for ACTB (Applied Biosystems/ Invitrogen).

34. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript is detected at absolute numbers of at least 0.06 copies of CFD pr. copy of beta-actin mRNA (gene symbol ACTB) using Assay ID: Hs00157263_m1 for CFD (Applied Biosystems/ Invitrogen).and Hs99999903_m1 for ACTB (Applied Biosystems/ Invitrogen).

35. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is above 9.5 on a log2 scale of RMA or GC-RMA normalized expression values when measured using micro array chip.

36. The method according to any of the above embodiments, wherein the level of expression is measured indirectly based on one or more SNPs.

37. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more CFD expression correlated SNPs.

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38. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more SNPs in the CFD haploblock.

10 39. The method according to any of the above embodiments, wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more SNP's selected from the group of; rs1683565, rs1683591, rs1683590, rs1683569, rs1683574, rs1651888, rs2930894, rs2930891, rs4417648, rs1651891, rs1651890 and rs2930898.

15 40. The methods according to any of the above embodiments, wherein the level of expression of CFD is measured indirectly by the presence of the AG or the GG genotype of SNP rs1683591.

41. The method according to any of the above embodiments 1-25, wherein the level of
20 expression is measured on protein level.

42. The method according to embodiment 41, wherein the level of expression is measured using antibody.

25 43. The method according to embodiment 41, wherein the level of expression is measured using a proteome analysis.

44. The method according to any of the above embodiments, wherein the subject or patient is a patient suffering from an inflammatory disease or disorder.

30

45. The method according to any of the above embodiments, wherein the patient is suffering from an auto-immune disease or disorder.

46. The method according to embodiment 44 or 45, wherein the patient is suffering from Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Multiple sclerosis (MS), Inflammatory Bowel Disease (IBD), Psoriatic Arthritis (PSA) or Psoriatic arthritis.

5 47. The method according to 46, wherein the patient is suffering from RA.

48. The method according to embodiments 44-47, wherein the patient is being treated or has been treated with MTX.

10 49. The method according to embodiments 44-48, wherein the patient is an inadequate responder to MTX treatment.

50. The method according to any of the above embodiments 44-49, wherein the patient is being treated with a TNF-alfa inhibitor.

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51. The method according to embodiments 44-50, wherein the patient is naive to TNF-alfa inhibitor treatment.

52. The method according to embodiments 44-51, wherein the patient is an inadequate
20 responder to TNF-alfa inhibitor treatment.

53. The method according to embodiments 44-52, wherein the patient is an inadequate responder to one or more therapies applicable for said inflammatory disease or disorder.

25 54. The method according to embodiments 44-53, wherein the patient is an inadequate responder to MTX and TNF-alfa inhibitor treatment.

55. The method according to embodiments 44-54, wherein the patient is RF positive.

30 56. The method according to embodiments 44-55, wherein the patient is RF negative.

57. The method according to any of the above embodiments, wherein the anti-inflammatory agent is an antibody.

58. The method according to any of the above embodiments, wherein the anti-inflammatory agent is a receptor antagonist.

59. The method according to any of the above embodiments wherein the anti-inflammatory agent is an antagonist of one or more members of the IL-10 family.

60. The method according to any of the above embodiments wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL19, IL-20, IL-22, IL-24 and IL-26.

61. The method according to any of the above embodiments wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

62. The method according to any of the above embodiments wherein the anti-inflammatory agent is an antagonist of IL-20.

63. The method according to any of the above embodiments wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors.

64. The method according to any of the above embodiments wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 medicate receptor activation.

65. The method according to any of the above embodiments wherein the anti-inflammatory agent is and anti-human IL-20 antibody.

66. A method for treating an inflammatory disease or disorder in a subject where the expression level of one or more of the genes of Figure 1 is altered compared to a reference level, comprising administering a therapeutic amount of an anti-inflammatory agent to said subject.

67. A method for treating an inflammatory disease or disorder in a patient comprising;
    a. considering if the expression levels of one or more of the genes of Figure 1, in said patient is altered compared to a reference level,

b. administering a therapeutic amount of an anti-inflammatory agent to said patient.

68. A method for treating an inflammatory disease or disorder in a patient comprising
    a. measuring if the expression levels of one or more of the genes of Figure 1, in a
5   biological sample from said patient is altered compared to a reference level,
    b. administering a therapeutic amount of an anti-inflammatory agent to said patient.

69. A method for treating an inflammatory disease or disorder in a patient comprising;
    a. measuring the levels of expression of one or more gene(s) of Figure 1 in a
10   biological sample from said patient.
    b. comparing said levels with a reference level of said genes,
    c. determine if the expression levels of one or more of the genes of Figure 1, is altered compared to said reference level and
    d. administering a therapeutic amount of an anti-inflammatory agent to said patient.

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70. The method according to any of the previous embodiments 68-69, wherein the level of expression one or more of the genes of Figure 1, is altered in said biological sample compared to said reference level.

20 71. The method according to any of the previous embodiments 68-70, wherein the method is characterized by any one or more of the features of previous embodiments 15-65.

72. An article of manufacture comprising , packaged together, a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a
25 label stating that the pharmaceutical composition is for treating a patient suffering from an auto-immune disease or disorder with an altered expression of one or more of the genes of Figure 1.

73. The article of manufacture according to embodiment 72, wherein the article is
30 characterized by any one or more of the features of previous embodiments 5-46.

74. An anti-inflammatory agent for treatment of an inflammatory disease or disorder in a subject, wherein said subject display an altered expression level of one or more of the genes of Figure 1, compared to a reference level of said genes.

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75. The anti-inflammatory agent according to embodiment 74, characterized by any one or more of the features of previous embodiments 15-65.

76. A composition comprising at least on detecting agent for determining the expression level of one or more gene(s) from Table 1.

77. The composition of embodiment 76, wherein the detecting agent is for determining expression of complement factor D (CFD).

78. The composition of embodiment 76, wherein the detecting agent is a CFD probe.

79. The composition of embodiment 76, wherein the detecting agent is a CFD primer.

80. The composition of embodiment 76, wherein the detecting agent is a primer for detecting a CFD expression correlated SNP's.

81. The composition of embodiment 76, wherein the detecting agent is one or more primer for detecting a CFD expression correlated SNP's, selected from rs1683565, rs1683591, rs1683590, rs1683569, rs1683574, rs1651888, rs2930894, rs2930891, rs4417648, rs1651891, rs1651890, and rs2930898

82. A kit comprising a composition according to any of embodiments 76-81 and instruction for use.

83. The kit of embodiment 82, further comprising a reference sample.

84. The kit of embodiment 82-83, further comprising a detecting agent for normalization.

85. The kit of embodiment 82-84, wherein the instructions for use include a description on how to correlate expression level(s) with response probability.

86. The kit of embodiment 82-85, wherein the kit is for determining the probability that a patient will respond to an anti-inflammatory agent.

87. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level.

88. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

89. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, it has been determined that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level.

90. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, it has been determined that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

91. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test, according to any of embodiments 1-43, has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level.

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93. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test, according to any of embodiments 1-43, has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

94. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, it has been determined, according to any of embodiments 1-43, that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level.

95. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, it has been determined, according to any of embodiments 1-43, that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

96. The method according to embodiments 87-94, wherein the subject or patient is a patient suffering from an inflammatory disease or disorder.

97. The method according to embodiments 87-94, wherein the patient is suffering from an auto-immune disease or disorder.

98. The method according to embodiment 87-96, wherein the patient is suffering from Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Multiple sclerosis (MS), Inflammatory Bowel Disease (IBD), Psoriatic Arthritis (PSA) or Psoriatic arthritis.

99. The method according to 97, wherein the patient is suffering from RA.

100. The method according to embodiments 87-98, wherein the patient is being treated or has been treated with MTX.

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101. The method according to embodiments 87-99, wherein the patient is an inadequate responder to MTX treatment.

102. The method according to any of the above embodiments 87-100, wherein the

10 patient is being treated with a TNF-alfa inhibitor.

103. The method according to embodiments 87-101, wherein the patient is naive to TNF-alfa inhibitor treatment.

15 104. The method according to embodiments 87-103, wherein the patient is an inadequate responder to TNF-alfa inhibitor treatment.

105. The method according to embodiments 87-103, wherein the patient is an inadequate responder to one or more therapies applicable for said inflammatory disease or disorder.

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106. The method according to embodiments 87-104, wherein the patient is an inadequate responder to MTX and TNF-alfa inhibitor treatment.

107. The method according to embodiments 87-105, wherein the patient is RF positive.

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108. The method according to embodiments 87-106, wherein the patient is RF negative.

109. The method according to embodiments 87-107, wherein the anti-inflammatory agent is an antibody.

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110. The method according to embodiments 87-108, wherein the anti-inflammatory agent is a receptor antagonist.

111. The method according to embodiments 87-109, wherein the anti-inflammatory agent

35 is an antagonist of one or more members of the IL-10 family.

112. The method according to embodiments 87-110, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL19, IL-20, IL-22, IL-24 and IL-26.

5 113. The method according to embodiments 87-111, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

114. The method according to embodiments 87-112, wherein the anti-inflammatory agent is an antagonist of IL-20.

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115. The method according to embodiments 87-113, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors.

15 116. The method according to embodiments 87-114, wherein the anti-inflammatory agent is an antagonist of IL-20, reducing IL-20 medicated activation of both the IL-20R1 / IL-20R2 and IL-22R / IL-20R2 receptors, but not the IL19 or IL24 medicate receptor activation.

20 117. The method according to embodiments 87-115, wherein the anti-inflammatory agent is an anti-human IL-20 antibody.

118. A method of treating an inflammatory disease comprising administering a pharmaceutically effective amount of an anti-inflammatory agent to a patient with an
25 inflammatory disease that has an expression profile in which expression of a first biomarker is increased relative to expression of the first biomarker in a person that does not respond to the anti-inflammatory agent, wherein the first biomarker is complement factor D (CFD).

30 119. The method of embodiment 118, wherein expression of CFD of in the patient with the inflammatory disease is at least one standard deviation higher than expression of CFD in the person that does not respond to the anti-inflammatory agent.

120. The method of embodiment 118, wherein the inflammatory disease is an
35 autoimmune disease or disorder.

121. The method of embodiment 120, wherein the autoimmune disease or disorder is selected from the group consisting of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), and psoriatic arthritis (PSA).

122. The method according to embodiment 121, wherein the autoimmune disease is RA.

123. The method of embodiment 118, wherein the patient with an inflammatory disease has an expression profile in which expression of a second biomarker is increased relative to expression of the second biomarker in a person that does not respond to the anti-inflammatory agent, wherein the second biomarker is SERPINB9 (serpin peptidase inhibitor and clade B (ovalbumin), member 9).

124. The method of embodiment 118, wherein the patient with an inflammatory disease has an expression profile in which expression of a second biomarker is increased relative to expression of the second biomarker in a person that does not respond to the anti-inflammatory agent, wherein the second biomarker is selected from one or more of the group consisting of SERPINB9 (serpin peptidase inhibitor, clade B (ovalbumin) member 9) and ZCCHC24 (zinc finger, CCHC domain containing 24).

125. The method of embodiment 118, wherein the patient with an inflammatory disease has an expression profile in which expression of a second biomarker is increased relative to expression of the second biomarker in a person that does not respond to the anti-inflammatory agent, wherein the second biomarker is selected from one or more of the group consisting of SERPINB9 (serpin peptidase inhibitor, clade B (ovalbumin) member 9), ZCCHC24 (zinc finger, CCHC domain containing 24), FN3KRP (fructosamine 3 kinase related protein), FN3KRP (fructosamine 3 kinase related protein), MEOX1 (mesenchyme homeobox 1), FGF13 (fibroblast growth factor 13), TUBB2A (tubulin, beta 2A), SLC39A11 (solute carrier family 39 (metal ion transporter), member 11), TMC4 (transmembrane channel-like 4), NPIPL2 (nuclear pore complex interacting protein-like 2), ZNF880 (zinc finger protein 880), and ALDH5A1 (aldehyde dehydrogenase 5 family, member A1).

126. The method according to embodiments 118-125, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26.

127. The method according to embodiments 118-126, wherein the anti-inflammatory
5 agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

128. The method according to a embodiments 118-127, wherein the anti-inflammatory agent is an antagonist of IL-20.

10 129. A method of treating an autoimmune disease comprising:
identifying a patient with an autoimmune disease;
determining that the patient expresses a first biomarker, wherein the first biomarker is complement factor D (CFD);
selecting an anti-inflammatory agent as a treatment for the patient based on a
15 recognition that the anti-inflammatory agent is effective in patients with the autoimmune disease in which an expression profile of the first biomarker is increased relative to expression of the first biomarker in a subject that does not respond to the anti-inflammatory agent; and
administering the anti-inflammatory agent to the patient.

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130. The method of embodiment 129, wherein the autoimmune disease or disorder is selected from the group consisting of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), and psoriatic arthritis (PSA).

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131. The method according to embodiment 130, wherein the autoimmune disease is RA.

132. The method of embodiment 129, wherein the selecting an anti-inflammatory agent as a treatment for the patient further comprises a recognition that the anti-inflammatory
30 agent is effective in patients with the autoimmune disease in which an expression profile of a second biomarker is increased relative to expression of the second biomarker in a subject that does not respond to the anti-inflammatory agent; and wherein the second biomarker is selected from one or more of the group consisting of SERPINB9 (serpin peptidase inhibitor, clade B (ovalbumin) member 9), ZCCHC24 (zinc finger, CCHC
35 domain containing 24), FN3KRP (fructosamine 3 kinase related protein), FN3KRP

(fructosamine 3 kinase related protein), MEOX1 (mesenchyme homeobox 1), FGF13 (fibroblast growth factor 13), TUBB2A (tubulin, beta 2A), SLC39A11 (solute carrier family 39 (metal ion transporter), member 11), TMC4 (transmembrane channel-like 4), NPIPL2 (nuclear pore complex interacting protein-like 2), ZNF880 (zinc finger protein 880), and ALDH5A1 (aldehyde dehydrogenase 5 family, member A1).

133. The method according to any of embodiments 129-132, wherein the anti-inflammatory agent is an antagonist of one or more of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26.

134. The method according to any of embodiments 129-133, wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

135. The method according to any of embodiments 129-134, wherein the anti-inflammatory agent is an antagonist of IL-20.

136. The method of embodiment 129, wherein the determining that the patient expresses a first biomarker comprises measurement of mRNA.

137. The method of embodiment 136, wherein the measurement of mRNA involves multi-plex PCR and qRT-PCR.

138. The method of embodiment 129, wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more CFD expression correlated SNPs.

139. The method of embodiment 129, wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more SNPs in the CFD haploblock.

140. The method of embodiments 138-139, wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more SNP's selected from the group of; rs1683565, rs1683591, rs1683590, rs1683569, rs1683574, rs1651888, rs2930894, rs2930891, rs4417648, rs1651891, rs1651890 and rs2930898.

141. The methods of embodiment 140, wherein the level of expression of CFD is measured indirectly by the presence of the AG or the GG genotype of SNP rs1683591.

142. A method for treating an inflammatory disease or disorder in a patient comprising
5 administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level.

10 143. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered
15 expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

144. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient,
20 wherein, prior to administration of said anti-inflammatory agent, it has been determined that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level.

145. A method for treating an inflammatory disease or disorder in a patient comprising
25 administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, it has been determined that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is
30 predictive of a response of the subject to the anti-inflammatory agent.

35 **General Methods**

Total RNA purification

Total RNA may be obtained from any type of biological sample by various methods known by the person skilled in the art.

The Examples herein are based on data obtained using the PaxGene blood RNA KIT IVD (QIAGEN), which are particularly suited for samples that are collected overtime and to be analysed subsequently. The PaxGene blood samples were handled following the instructions of the manufacturer (Qiagen) and total RNA was isolated following the protocol for the PaxGene PAXgene Blood RNA Kit (QIAGEN).

Globin mRNA reduction

A reduction of Globin mRNA in a total RNA sample can be obtained using the GLOBINClear kit (Applied Biosystems, Foster City, CA, USA) following the instructions of the manufacturer.

RNA integrity confirmation

It is advisable to confirm the integrity of RNA samples before further analyses are performed.

The Agilent 2100 Bioanalyzer and total RNA Nano chips (Agilent Technologies, Santa Clara, CA, USA) can be used following the manufacturer's instructions. Generally a sample giving an RNA integrity number (RIN-score) above 7 is considered acceptable for further analysis.

AffyMetrix GeneChip hybridization, scanning and analysis

Using a total RNA sample, labelled cRNA (targets) is/are prepared from fifty nanograms of total RNA by 3' IVT Express Kit (Affymetrix, Santa Clara, Ca, USA) following the instructions of the manufacturer. Hybridization cocktails are prepared as described by the

manufacturer and hybridised onto Human Genome U133 Plus 2.0 GeneChips® (Affymetrix) at 45° C for 17h (60 RPM) in a Hybridization Oven 640 (Affymetrix). After hybridization, the GeneChips are washed and stained in a GeneChip® fluidics station 450 using the fluidics protocol “EukGE-WS2v5_450” (Affymetrix). The GeneChips® are scanned in a GeneChip® scanner 3000 (Affymetrix). The out-put, the “*.cel files” are used for RMA (Robust Multiarray Average) normalization of GeneChip data by using the R environment and the Bioconductor package “Affy” which can be found at the URL: cran.r-project.org & bioconductor.org.

Statistical analysis of the microarray data is performed with the open-source tools available in the statistical programming environment, R (available at the URL: cran.r-project.org) as well as with QluCore Omics explorer 2.2 (QluCore AB, Sweden). Microarrays are normalized by RMA (Robust Multiarray Average) using the Affy package (available at the URL: cran.r-project.org) and the custom Chip Definition File (HGU133Plus2_Hs_ENSG) available at the URL: brainarray.mbni.med.umich.edu)

Multivariate predictions are carried out using the Simca-P +11 software (Umetrics, Umeå, Sweden), and the Partial Least Squares (PLS) tool.

ROC (receiver operating characteristic) curves are prepared using GraphPad Prism 5 (GraphPad Software, CA, USA).

Quantitative RT-PCR

Quantative RT-PCR analysis is performed by preparing 25 microliters of cDNA from 200 ng total RNA using random primers and TaqMan Reverse Transcription reagents (Applied Biosystems, Foster City, CA, USA) according to the manufacturer’s instructions.

The qPCR analysis is perfomed in a total volume of 25 microliters in duplicates on each sample (6,95 microliters of a 10-fold dilution of cDNA), using TaqMan PCR core reagents (Applied Biosystems) and the ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems).

Expression levels of CFD mRNA, ACTB mRNA, and 18S rRNA is determined using primers and FAM-labelled-probes for CFD mRNA and 18S rRNA. The primers and probes were ordered as Assays-on-Demand (Applied Biosystems). Probe sequences for these assays were as follows: CFD (CCTGCTGCTACAGCTGTCGGAGAAG (Assay ID: Hs00157263_m1)), ACTB (CCTTTGCCGATCCGCCGCCCGTCCA (Assay ID: Hs Hs99999903_m1), and 18S rRNA (TGGAGGGCAAGTCTGGTGCCAGCAG; assay Hs99999901_s1). Data were analysed using ABI Prism SDS 2.2 software (Applied Biosystems), and expression levels were normalized to 18S rRNA or ACTB mRNA.

A reliable assay the PCR product should be detectable within cycle (Ct-value) 26 in the CFD assay (ID: Hs00157263_m1), and detection of 18S rRNA (assay ID Hs99999901_s1) should be obtained at Ct=12,5. Normalization could also be done by calculating a delta-Ct value, or by using standard curves of diluted plasmid encoding CFD, ACTB, and 18S, and relating quantitated number of CFD copies to number of quantitated number of ACTB or 18S copies.

In the above, the official Gene Symbol identifiers are used for the analysed transcripts.

Examples

Example 1 - Identification of predictive transcripts

Blood samples from a phase-1b and phase-2a trial examining the safety, tolerability, and efficacy of anti-IL-20 in patients with rheumatoid arthritis (RA) (clinicaltrials.org identifiers: NCT01038674 and NCT01282255) were collected from patients at following time points: pre-dose (day 1) and after dosage at day 8, 15, 29, 43, and day 99 in the phase-1b trial and at predose (day 1) and after dosage at day 15, 36 in the phase-2a trial. Patients were dose once weekly during a 6 week period (in total 7 doses) and during an 11 week period (in total 12 doses) , respectively.

Total RNA was obtained as described above. After Globin mRNA reduction and confirmation of RNA integrity the RNA samples were analysed by AffyMetrix GeneChip hybridizations following the above described procedure.

To identify transcripts in full blood PaxGene samples that correlate to changes in DAS28-CRP and other disease score measures like ACR20, ACR50, and ACR 70, we performed regression analyses of expression profiles from individual patients enrolled in the Phase-1b and Phase-2a trials examining the effect of anti-IL20 antibody in RA patients.

Based on samples primarily obtained at pre-dose (base-line) and at day 8, 15, 29, 36, and 43, transcripts exhibiting relative stability over time, and thus suitable as pre-dosing stratification markers, were selected.

A multivariate approach for correlating the obtained microarray data points to the clinical efficacy, was also pursued. By using Partial Least Squares (PLS) projection to latent structures the best combination of transcripts for predicting clinical effect in individual patients dosed with anti-IL20 were identified. The identified PLS model was cross validated by a permutation test (reducing the R^2-coefficients for the correlation between the observed and predicted data from 0.8 to 0.1). This indicated that the PLS model was valid and not over-fitted. A PLS based prediction can be done with any multivariate analyses software tool (Like Simca-P +11 (Umetrics) or Unscrambler (CAMO software AS, Oslo, Norway). Initially the multivariate prediction was done using 18954 data points from the AffyMetrix microarrays. An example of a set of 14 predictive transcripts is shown in figure 2.

A gene of interest in the multivariate based prediction model was Complement Factor D (CFD) also known as Adipsin. The level of the CFD transcript among the RA patients is shown in figure 3. The mRNA expression level in individual patients is stable over time, but with a pronounced variation between patients. The difference between the patient with the lowest level of CFD mRNA to the patient with the highest level was approximately 8-fold.

As shown in figure 1, CFD was also among the positively correlated transcripts in the univariate regression analysis. Together, these findings prompted examination of the usefulness of CFD as a high response predictor in anti-IL20 antibody dosed RA-patients. This was done by preparing Receiver Operating Characteristics (ROC)-curves as shown in Figure 4 (ACR50 response), and Figure 5 (ACR70 response). The area under curve (AUC) for ACR50 response, was found to be 0,81 (p=0,00068) indicative of a good prediction of ACR50 responses based on CFD mRNA levels.

For testing whether CFD mRNA could be a predictor of high responses in the anti-IL20 RA-trials, the thresholds for an optimal classification of the patients were defined in either ACR50 responders and non-responders, as well as for ACR70 responders and non-responders. This was done with an average CFD-mRNA level obtained from the four samples collected at day 1 (pre-dose), and after dosing at day 15 and 36. As previously described the CFD mRNA level was found to be stable over time at these visits. For ACR50 classification a CFD mRNA threshold of 10.32 (log2 scale of RMA normalized AffyMetrix microarray levels) was found (indicated by the X in Figure 4).

When applying this threshold (10.32 or above) in the RA patients dosed with anti-IL20 antibody in the phase 2a trial data, the ACR50 response rate was found to be significantly increased from 37% to 65% (Figure 7). Approximately half of the patients enrolled in the phase 2a trial would be included when applying an inclusion threshold of 10.32 or above. Likewise for ACR70 responses, a threshold of 10.32 in the dosed RA patients was found to increase the response rate from 25% to 45%. The enrichment of response rates when applying a threshold of 10.32 is visualized in Figure 7.

In placebo dosed individuals from the phase2a trial the ACR50 response rate in patients having a CFD mRNA level of 10.32 or above was 17% compared to 11 in patients with a CFD mRNA level below 10.32. For ACR70 the response rates in placebo dosed patients having a CFD mRNA level of 10.32 or above was 8 % compared to 0 % in patients with a CFD mRNA level below 10.32

Based on the above analysis it was concluded the CFD mRNA level was a good predictor of high response to anti-IL-20 in RA patients, and that significant increases in especially ACR50 and ACR70 responses could be obtained if only including RA patients with a CFD mRNA level of 10.32 or above.

Example 2 - Correlation of qRT-PCR with array data

To examine if the CFD mRNA baseline (pre-dose) measurement alone correlates with the CFD mRNA levels from the different time points evaluated in the microarray analysis, qRT-PCR was performed on CFD mRNA on available pre-dose samples and correlated these to the recorded CFD levels from the microarrays. Quantitative RT-PCR analyses were performed as described herein above and data obtained from duplicate analysis of each of the cDNA samples. The CFD mRNA levels from the qRT-PCR platform were normalised to 18S rRNA levels which were also determined by qRT-PCR. For correlating the microarray levels to the qRT-PCR levels the RNA normalized microarray levels were transformed to a linear scale. As shown in Figure 6, a high degree of correlation (R^2 =0,86) was found between the qRT-PCR measurements at base-line and the microarray measurements from several visits. This indicates that a CFD based stratification of RA-patients at base-line (before dosing) is feasible, Since the other predictive transcripts described in Figure 1 and Figure 2 like CFD were identified not only by correlating to base-line samples but to several time points in the phase 2a trial, these have also been selected to display stability over time (as exemplified by the CFD correlations in Figure 6). The

transcripts described herein are therefore especially suited for a pre-dose predictive stratification of highly responding patients.

To obtain a stratification based on qRT-PCR data resembling the stratification obtained with a threshold of 10.32 using the micro array data, the PCR product should be detected within cycle (Ct-value) 26 in the CFD assay (ID: Hs00157263_m1)), and detection of 18S rRNA (assay Hs99999901_s1) should be obtained with a Ct=12,5. These values correspond to approximately 10.25 on the RMA scale of microarray values as estimated based on samples from an individual patient for which two array detections are close to 10.32, with an average of 10.24. Using the qRT-PCR assay, detection of CFD in this patient is obtained with a Ct-value of 26 and with the 18S control having a Ct value of 12.5).

It is also possible to measure the level of expression of complement factor D (CFD) level by qRT-PCR, wherein absolute numbers of at least 0.04 copies for CFD pr. copy of beta-acting mRNA (gene symbol ACTB) using Assay ID: Hs00157263_m1 for CFD (Applied Biosystems/ Invitrogen).and Hs99999903_m1 for ACTB (Applied Biosystems/ Invitrogen) is the threshold value for improved response.

Example 3 – Disease relevance of CFD mRNA levels in PaxGene samples

To evaluate whether the CFD levels in peripheral blood from RA patients could correlate to relevant activity markers in the local joint, paired PaxGene (full blood) and synovial fluid samples were collected. Complement factor D is the initiating serine protease in the alternative complement pathway activation, and cleaves C3b complexed with factor B into C3bBb and Ba. C3bBb is a C3 convertase which will cleave additional C3 molecules into C3a and C3b. Since the Bb molecule is unique to the alternative complement activation, Bb protein levels serve as an activity marker of this pathway. There is strong evidence supporting both the classical and alternative complement activation to be involved in the pathophysiology of rheumatoid arthritis.

A Bb plus EIA (MicroVue cat# A027) assay (an assay that measures the amount of complement fragment Bb in human plasma or serum) was prepared according to kit protocol.

A wash buffer (x20) was diluted in deionized water. 1% HBR1 (A Heterophilic Blocking Reagent (HBR1) 18,42mg/ml from Scantibodies Lab. Part 3KC533) was added to

the hydrating reagent and 1% HBR was added to the complement specimen diluent (80µl HBR1 + 7,92ml). Reconstitute std and controls were diluted in 1ml of Hydrating Reagent /HBR1 and let sit for 15min. Samples were diluted 10 (45µl+405µl) and 20 times (22µl+418µl) in Complement Specimen Diluent +1% HBR1.

5 The samples were pre-washed 3 times and incubated with 100µl std for 30 min, washed 5 times, incubated for 30 min with 50µl conjugate, washed 5 times, incubated 15 min with 100µl substrate and finally stopped with 100µl stop solution.

The absorbance was determined by an ELISA reader set at reader set at 450 nm
10 (ref at 600-690nm) with linear curve fit.

By using the MicroVue Bb Plus EIA assay and HBR1, we were able to measure the levels of Bb in synovial fluid from RA patients. When plotting these levels against the CFD mRNA levels in paired PaxGene samples from the same patients, a significant
15 correlation was found, as shown in figure 8.

This finding shows that the CFD mRNA levels in full blood from RA patients, are indicative of the activation state of the alternative complement pathway in the local joint.

20 Since CFD mRNA levels in full blood from RA patients correlates to the activation state of the alternative complement pathway in the local joint (correlation between CFD mRNA in PaxGene samples and Bb levels in paired synovial fluid levels), it is tempting to speculate that CFD mRNA levels in PaxGene samples from RA patients could also be a predictor of therapies targeting the complement activation.

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Example 4 – Analysis using single nucleotide polymorphisms (SNPs)

As an alternative to measure CFD mRNA levels in PaxGene samples, the analyses of certain single nucleotide polymorphisms (SNPs) in the CFD haploblock could provide a
30 convenient method of predicting response. The bimodal distribution of CFD mRNA in PaxGene and other samples clearly indicate that genetic polymorphisms could be an underlying explanation for the CFD mRNA expression pattern. A person skilled in the art can perform expression quantitative trait loci (eQTL) analyses for CFD, and identify SNP correlations or associations to CFD expression levels. An example of a SNP showing strong
35 associations to CFD mRNA expression levels in the haploblock of CFD and its neighbour

genes has the identity rs1683565. Measurement of this SNP, or other SNPs showing strong linkage disequilibrium to rs1683565 can be done by a number of different methods including, but not limited to, hybridization based methods (e.g. SNP microarrays) and enzyme based methods (e.g. PCR and restriction fragment length polymorphism methods). Other SNPs which show strong linkage disequilirium to rs1683565 include, but are not limited to, SNPs with identities: rs1683591, rs1683590, rs1683569, rs1683574, rs1651888, rs2930894, rs2930891, rs4417648, rs1651891, rs1651890, and rs2930898.

As an example the SNP rs1683591 provides the AA, AG, or GG genotypes. Based on the correlation with CFD expression the AA genotype corresponding to low CFD expression (with a rather low response rates), while the AG and GG genotypes corresponds to a higher level of CFD expression and thus a high probability of responding to anti-inflammatory agents.

The above mentioned SNPs, combinations of them, or other SNPs showing strong linkage to the mentioned SNPs (rs1683565, rs1683591, rs1683590, rs1683569, rs1683574, rs1651888, rs2930894, rs2930891, rs4417648, rs1651891, rs1651890, and rs2930898) can be detected by a number of well described methodologies including, but not limited to, hybridization based methods (e.g. SNP microarrays) and enzyme based methods (e.g. PCR and restriction fragment length polymorphism methods).

In one example, a blood sample is drawn from a patient, and genomic DNA is isolated by the reagent DNAzol® (Becton Dickinson) following the instructions by the manufacturer. Briefly, mix 1 ml of DNAzol® with 0.5 ml of whole blood by vortexing or hand mixing. Precipitate DNA from the sample by adding 0.4 ml of isopropanol to the DNAzol® BD-blood lysate. Vortex or the resulting mixture and store it for 5 min at room temperature. Spin down the precipitated DNA by centrifugation at 6,000 × g for 6 min. Remove the supernatant and add 0.5 ml of DNAzol to the DNA pellet. Vortex or shake the DNA pellet until it is completely dissolved. Centrifuge the resulting mixture at 6,000 × g for 5 min. Next, remove supernatant and wash the DNA pellet by mixing with 1 ml of 75% ethanol and centrifuge at 6,000 × g for 5 min. Remove the ethanol and without drying, add to the DNA pellet 200 µl of 8 mM NaOH and solubilize DNA by incubation at room temperature for 3-5 min followed by vortexing. Neutralize the alkaline DNA solution with 0.1 M HEPES. From the isolated DNA, prepare a quantitative polymerase chain reaction (qPCR) with a specific assay for the desired SNP. The qPCR setup could be based on TaqMan probes designed to specifically detect the desired SNP. As an example the SNP with identity rs1683565 would be detected by any probe and/or primer combination which can discriminate the sequence: AGAGCCCAAAGCTCATGGAAAAGAG[A/G]ATATGAAAGGAGTCCCTGCAGTAGA. This

could be done by the commercially available assay from Invitrogen (Catalog #: 4351379 ID: C___9612061_10). In another example the SNP with identity rs1683591 would be detected by any probe and/or primer combination which can discriminate the sequence TCTGTCCACAGGCGGGGGTGGAGGG[A/G]ATGGCCGGCCTCACACCATCTG
5 CCA. This could be done by the commercially availabe assay from Invitrogen (Catalog #: 4351379 ID: C___9612100_10). In a third example the SNP with identity rs1683590 would be detected by any probe and/or primer combination which can discriminate the sequence AATATCTGAAATTTTCCCAGTTTAC[A/G]AGCCTCTGACGTAACCGTCCTCTCT. This could be done by the commercially availabe assay from Invitrogen (Catalog #4351379
10 ID: C___3153459_10). For a TaqMan® genotyping assay, you must add the equivalent of 1 to 10 ng of DNA template per reaction well. To quantitate genomic DNA, use a reliable method such as A260 measurements. Thoroughly mix TaqMan® GTXpress™ Master Mix (Invitrogen (Catalog #4403311)) by swirling the bottle and mix with the TaqMan® genotyping assay and genomic DNA template as described by the manufacturer. Run the
15 PCR in a compatible PCR instrument (e.g. ABI PRISM® 7900HT Sequence Detection System with a FAST block) for 40 cycles (first 95 °C for 20 sec, and then 40 cycles with primer annealing and extend at 60 °C for 20 seconds and subsequently denaturation at 95 °C for 3 seconds. After PCR amplification, you perform an endpoint plate read on a real-time PCR. With the SDS software from Invitrogen which uses the fluorescence measurements
20 from each well made during the plate read, then plot signal values. The software determines which alleles are in each sample for later allelic discrimination analysis.

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CLAIMS

1. A method for predicting the response of a subject to an anti-inflammatory agent comprising; obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient, wherein altered expression of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

2. A method for predicting the response of a patient to an anti-inflammatory agent comprising
    a. measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient and
    b. comparing said level with a reference level of said gene(s)

   wherein altered expression of one or more of said gene(s) compared to said reference level, is predictive of a response of the patient to the anti-inflammatory agent.

3. A method for identification of a subject with an increased probability of responding to anti-inflammatory agent comprising; obtaining information on the level of expression of one or more gene(s) of Figure 1 in a biological sample from said subject, wherein altered expression of one or more of said gene(s) compared to a reference level of said gene(s) indicates that a subject with an increased probability of responding to an anti-inflammatory agent has been identified.

4. A method for identification of a patient with an increased probability of responding to anti-inflammatory agent comprising;
    a. measuring the level of expression of one or more gene(s) of Figure 1 in a biological sample from said patient
    b. comparing said level with a reference level of said gene(s),

   wherein altered expression of one or more of said gene(s) compared to the reference level of said gene(s), indicates that a patient with an increased probability of responding to an anti-inflammatory agent has been identified.

5. The method according to any of the previous claims,
    a. wherein the altered expression of a gene of Figure 1A is an increase compared to the reference level and/or

b. wherein the altered expression of a gene of Figure 1B is a decrease compared to the reference level.

6. The method according to any of the above claims, wherein the level of expression is measured in a blood sample based on mRNA using PCR, such as multi-plex PCR or qRT-PCR, or micro array chip.

7. The method according to any of the above claims, wherein the level of expression of complement factor D (CFD) is above a reference level.

8. The method according to any of the above claims,
   a. wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript detected with a Cycle Threshold Value (Ct) of 30 using Assay ID: Hs00157263_m1 (Applied Biosystems) or
   b. wherein the level of expression of complement factor D (CFD) is measured using micro array chip and wherein the level of expression is above 9,5 on a log2 scale of RMA or GC-RMA normalized expression values or
   c. wherein the level of expression of complement factor D (CFD) is measured by qRT-PCR and wherein the transcript is detected at absolute numbers of at least 0.04 copies of CFD pr. copy of beta-actin mRNA using Assay ID: Hs00157263_m1 for CFD (Applied Biosystems/ Invitrogen) or
   d. wherein the level of expression of complement factor D (CFD) is measured indirectly based on one or more CFD expression correlated SNPs.

9. A method for treating an inflammatory disease or disorder in a patient comprising administering a therapeutic amount of an anti-inflammatory agent to said patient, wherein, prior to administration of said anti-inflammatory agent, at least one test, according to any of claims 1-8, has shown that the expression levels of one or more of the genes of Figure 1, in a biological sample from said patient is altered compared to a reference level and wherein altered expression level of one or more of said gene(s) compared to a reference level of said gene(s), is predictive of a response of the subject to the anti-inflammatory agent.

10. The method according to any of the above claims, wherein the subject or patient is suffering from an auto-immune disease or disorder, such as Rheumatoid Arthritis (RA),

Systemic Lupus Erythematosus (SLE), Multiple Sclerosis (MS), Inflammatory Bowel Disease (IBD), Psoriatic Arthritis (PSA) or psoriasis.

11. The method according to any of the above claims wherein the anti-inflammatory agent is an antagonist of one or more of IL-19, IL-20 and IL-24.

12. The method according to any of the above claims wherein the anti-inflammatory agent is an anti-human IL-20 antibody.

13. An anti-inflammatory agent for treatment of an auto-immune disease or disorder, wherein the patient has an altered expression of one or more of the genes of Figure 1, compared to the reference level of said gene(s).

14. An article of manufacture comprising, packaged together, a pharmaceutical composition comprising an anti-inflammatory agent and a pharmaceutically acceptable carrier and a label stating that the pharmaceutical composition is useful for treating a patient suffering from an auto-immune disease or disorder with an altered expression of one or more of the genes of Figure 1.

15. A kit comprising
    a. one or more composition comprising at least one detecting agent for determining the expression level of one or more gene(s) from Table 1A and/or Table 1B and
    b. instructions for use of the kit including how to correlate expression level(s) with response probability of a subject.

16. The kit of claim 15, wherein the detecting agent is for determining expression of complement factor D (CFD).

FIG. 1

TABLE 1A

Ensembl ID	Genetitle	Gene
ENSG00000197766	complement factor D (adipsin)	CFD
ENSG00000165424	zinc finger, CCHC domain containing 24	ZCCHC24
ENSG00000170542	serpin peptidase inhibitor, clade B (ovalbumin), member 9	SERPINB9
ENSG00000167608	transmembrane channel-like 4	TMC4
ENSG00000142733	mitogen-activated protein kinase kinase kinase 6	MAP3K6
ENSG00000162924	v-relreticuloendotheliosis viral oncogene homolog (avian)	REL
ENSG00000156414	tudor domain containing 9	TDRD9
ENSG00000011454	RAB GTPase activating protein 1	RABGAP1
ENSG00000100106	TRIO and F-actin binding protein	TRIOBP
ENSG00000153094	BCL2-like 11 (apoptosis facilitator)	BCL2L11
ENSG00000133195	solute carrier family 39 (metal ion transporter), member 11	SLC39A11
ENSG00000226747	NA	NA
ENSG00000137267	tubulin, beta 2A	TUBB2A
ENSG00000122692	smu-1 suppressor of mec-8 and unc-52 homolog (C. elegans)	SMU1
ENSG00000147526	transforming, acidic coiled-coil containing protein 1	TACC1
ENSG00000183570	poly(rC) binding protein 3	PCBP3
ENSG00000171853	tetratricopeptide repeat domain 15	TTC15
ENSG00000053254	forkheadbox N3	FOXN3
ENSG00000106012	IQ motif containing E	IQCE
ENSG00000198624	coiled-coil domain containing 69	CCDC69
ENSG00000168038	unc-51-like kinase 4 (C. elegans)	ULK4
ENSG00000171812	collagen, type VIII, alpha 2	COL8A2
ENSG00000131187	coagulation factor XII (Hageman factor)	F12
ENSG00000130304	solute carrier family 27 (fatty acid transporter), member 1	SLC27A1
ENSG00000196436	nuclear pore complex interacting protein-like 2	NPIPL2
ENSG00000139218	splicing factor, arginine/serine-rich 2, interacting protein	SFRS2IP
ENSG00000181982	coiled-coil domain containing 149	CCDC149
ENSG00000100014	cytospin A	CYTSA
ENSG00000008083	jumonji, AT rich interactive domain 2	JARID2
ENSG00000169919	glucuronidase, beta	GUSB
ENSG00000112367	FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae)	FIG4
ENSG00000071246	vasohibin 1	VASH1

FIG. 1 (continued)

TABLE 1B

Ensembl ID	Genetitle	Gene
ENSG00000141560	fructosamine 3 kinase related protein	FN3KRP
ENSG00000005102	mesenchyme homeobox 1	MEOX1
ENSG00000161980	polymerase (RNA) III (DNA directed) polypeptide K, 12.3 kDa	POLR3K
ENSG00000129682	fibroblast growth factor 13	FGF13
ENSG00000204856	Uncharacterized protein C12orf24	C12orf24
ENSG00000127995	CAS1 domain containing 1	CASD1
ENSG00000183172	UPF0466 protein C22orf32, mitochondrial Precursor	C22orf32
ENSG00000101255	tribbles homolog 3 (Drosophila)	TRIB3
ENSG00000172687	zinc finger protein 738	ZNF738
ENSG00000143353	lysophospholipase-like 1	LYPLAL1
ENSG00000186462	nucleosome assembly protein 1-like 2	NAP1L2
ENSG00000174136	RGM domain family, member B	RGMB
ENSG00000103995	centrosomal protein 152kDa	CEP152
ENSG00000221923	zinc finger protein 880	ZNF880
ENSG00000164930	frizzled homolog 6 (Drosophila)	FZD6
ENSG00000106341	G-substrate	C7orf16
ENSG00000231369	NA	NA
ENSG00000115446	unc-50 homolog (C. elegans)	UNC50
ENSG00000179941	Bardet-Biedl syndrome 10	BBS10
ENSG00000133731	inositol(myo)-1(or 4)-monophosphatase 1	IMPA1
ENSG00000117748	replication protein A2, 32kDa	RPA2
ENSG00000106460	transmembrane protein 106B	TMEM106B
ENSG00000155970	NA	NA
ENSG00000173041	zinc finger protein 680	ZNF680
ENSG00000197776	kelch domain containing 1	KLHDC1
ENSG00000147138	G protein-coupled receptor 174	GPR174
ENSG00000169507	solute carrier family 38, member 11	SLC38A11
ENSG00000163811	WD repeat domain 43	WDR43
ENSG00000155100	OTU domain containing 6B	OTUD6B
ENSG00000145331	RNA (guanine-9-) methyltransferase domain containing 2	RG9MTD2
ENSG00000107669	arginyltransferase 1	ATE1
ENSG00000106392	core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1	C1GALT1
ENSG00000074935	tubulin, epsilon 1	TUBE1
ENSG00000111328	cyclin-dependent kinase 2 associated protein 1	CDK2AP1
ENSG00000134884	arginine and glutamate rich 1	ARGLU1
ENSG00000101751	polymerase (DNA directed) iota	POLI
ENSG00000197056	zinc finger, MYM-type 1	ZMYM1
ENSG00000198039	zinc finger protein 273	ZNF273
ENSG00000117155	synovial sarcoma, X breakpoint 2 interacting protein	SSX2IP
ENSG00000197888	UDP glucuronosyltransferase 2 family, polypeptide B17	UGT2B17
ENSG00000069712	KIAA1107	KIAA1107
ENSG00000143674	Mitogen-activated protein kinase kinase kinase (EC	RP5-

	2.7.11.25)(Mixed lineage kinase 4)	862P8.2

FIG. 2

Table 2

Ensembl ID	Genetitle	Genesymbol
ENSG00000011028	mannose receptor, C type 2	MRC2
ENSG00000103502	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	CDIPT
ENSG00000112294	aldehyde dehydrogenase 5 family, member A1	ALDH5A1
ENSG00000115758	ornithine decarboxylase 1	ODC1
ENSG00000118777	ATP-binding cassette, sub-family G (WHITE), member 2	ABCG2
ENSG00000133808	MICAL C-terminal like	MICALCL
ENSG00000140403	DnaJ (Hsp40) homolog, subfamily A, member 4	DNAJA4
ENSG00000143164	DDB1 and CUL4 associated factor 6	DCAF6
ENSG00000161980	polymerase (RNA) III (DNA directed) polypeptide K, 12.3 kDa	POLR3K
ENSG00000167608	transmembrane channel-like 4	TMC4
ENSG00000170542	serpin peptidase inhibitor, clade B (ovalbumin), member 9	SERPINB9
ENSG00000171657	G protein-coupled receptor 82	GPR82
ENSG00000197766	complement factor D (adipsin)	CFD
ENSG00000204613	Tripartite motif-containing protein 10 (RING finger protein 9)(B30-RING finger protein)	TRIM10

FIG. 3

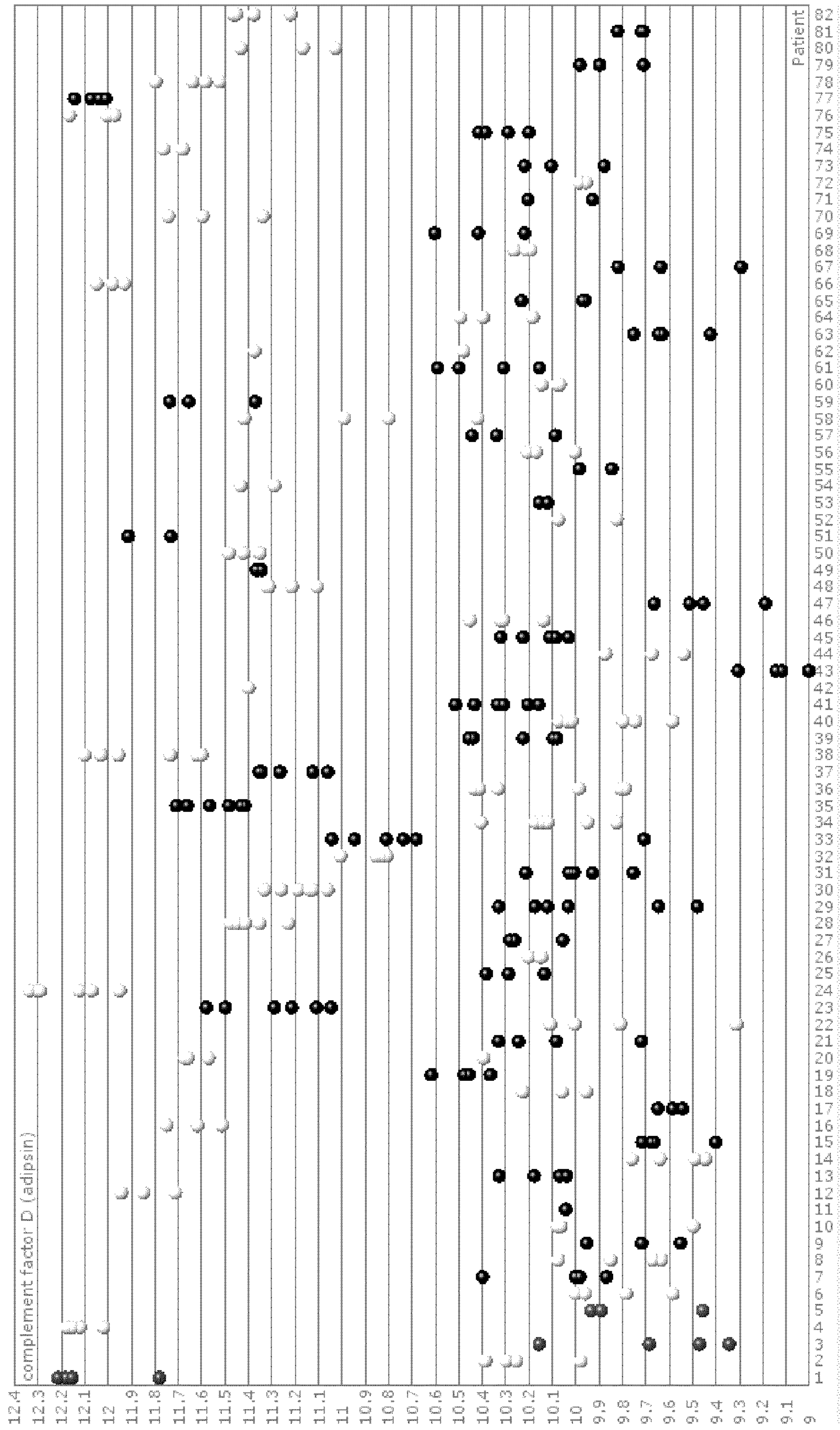


FIG. 4

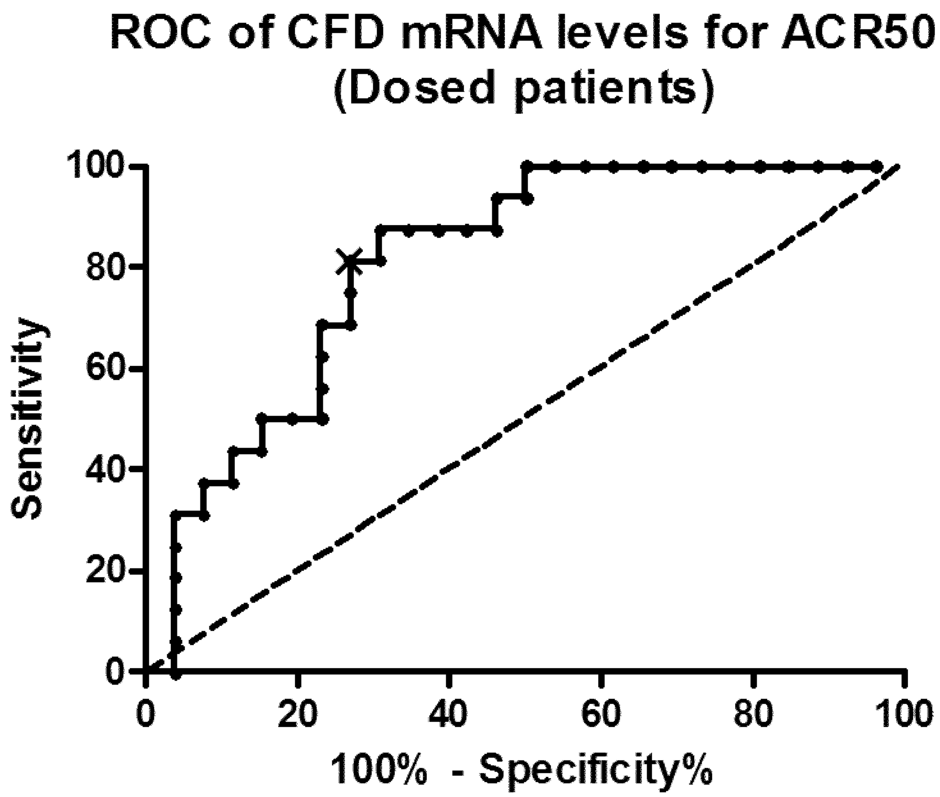


FIG. 5

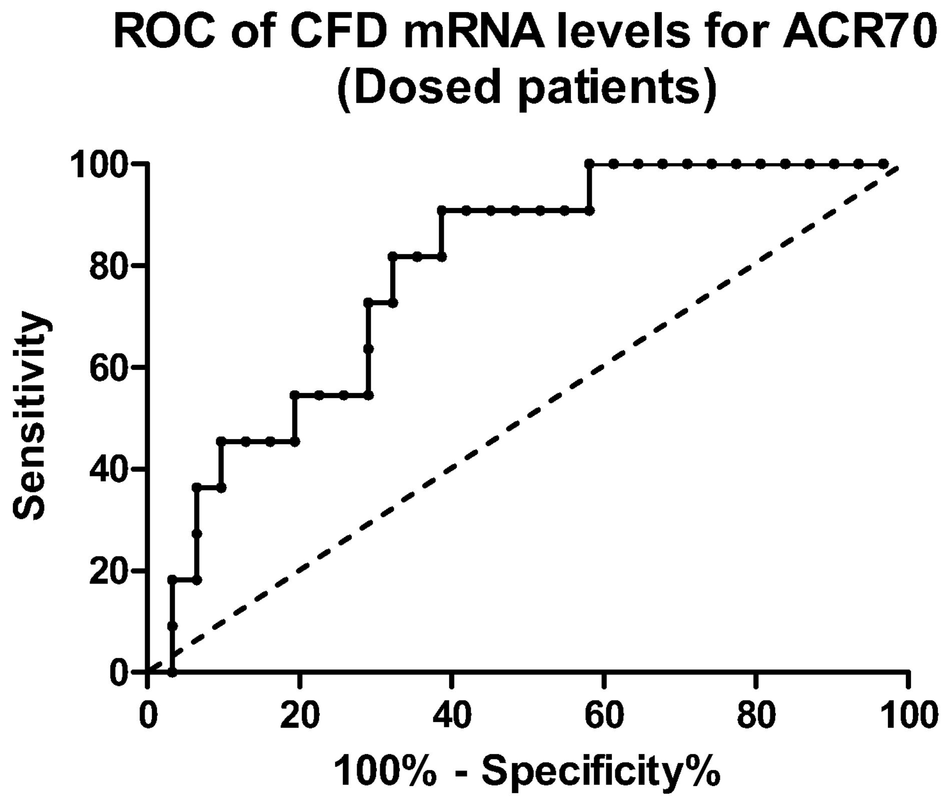


FIG. 6

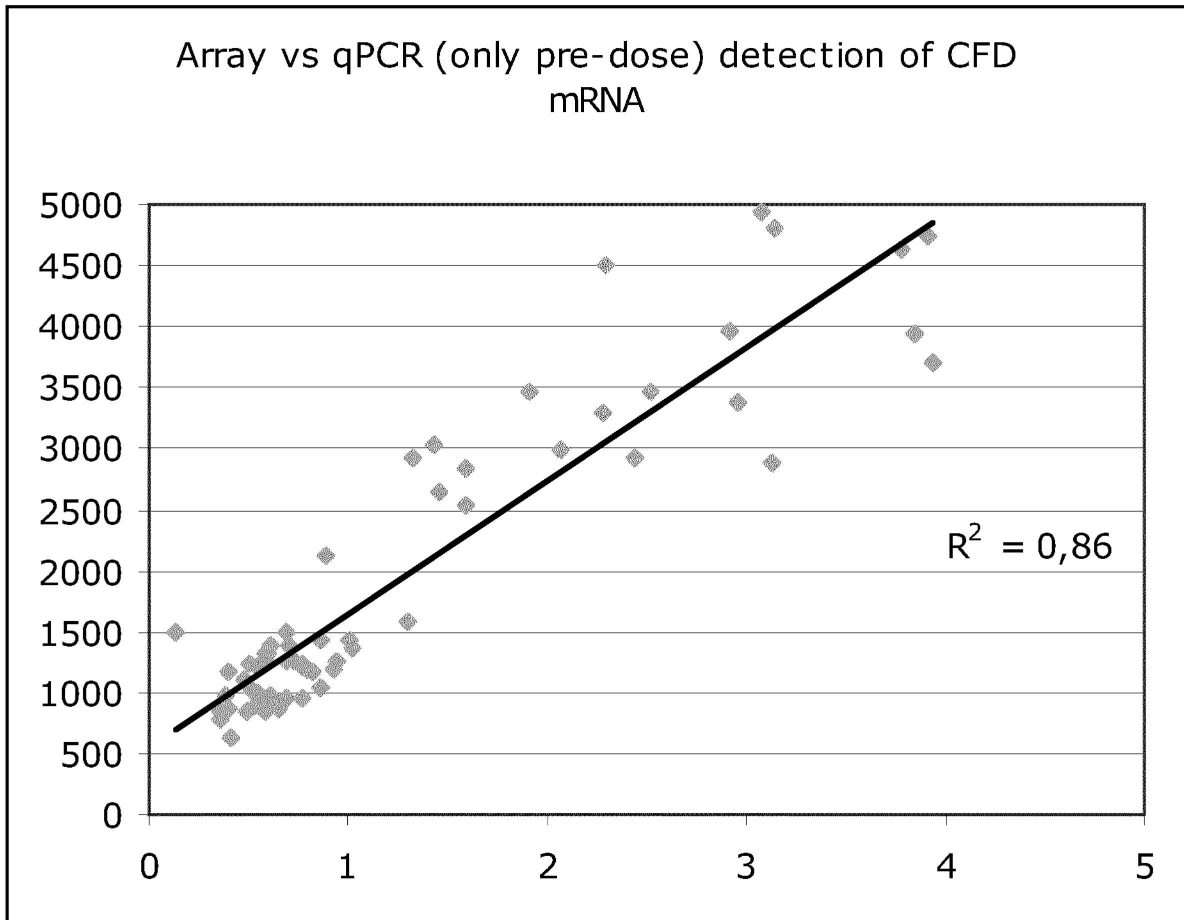


FIG. 7

FIG. 7A

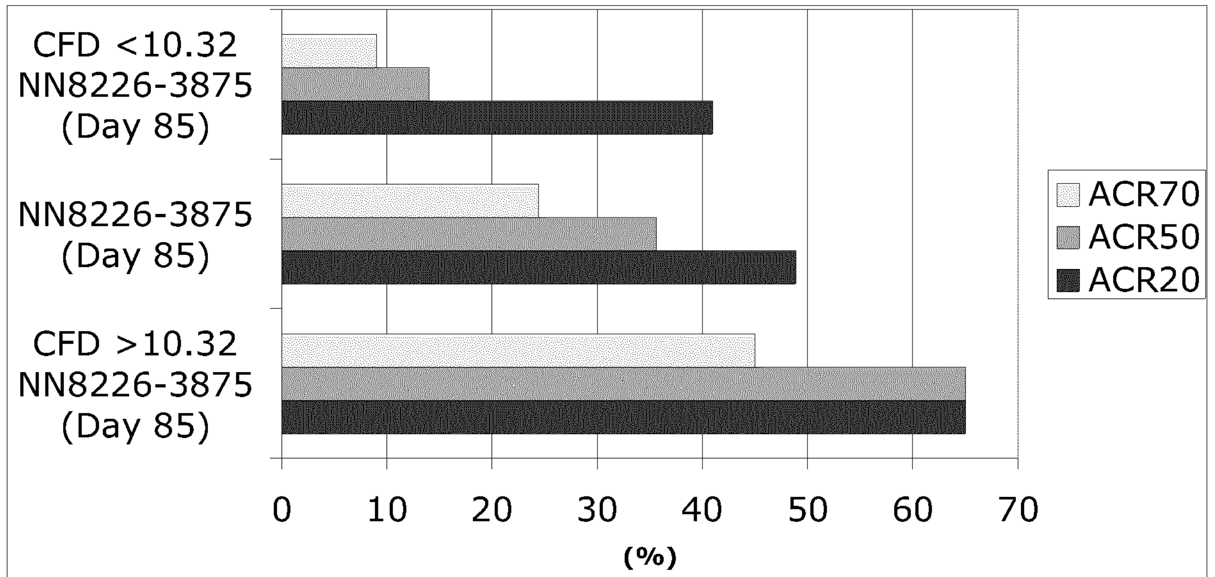


FIG. 7B

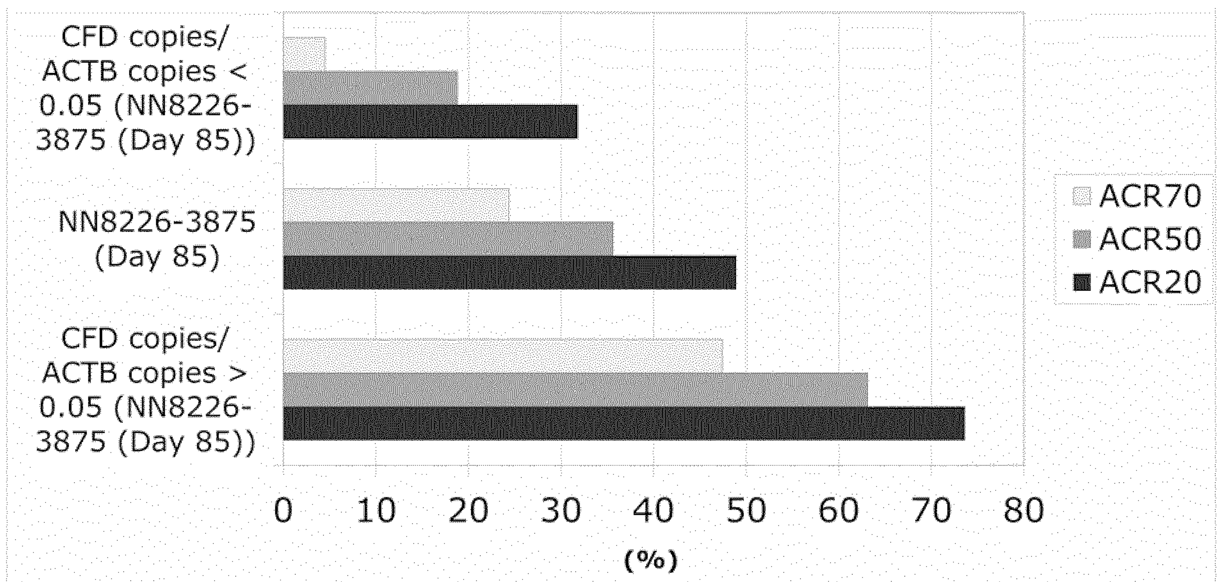
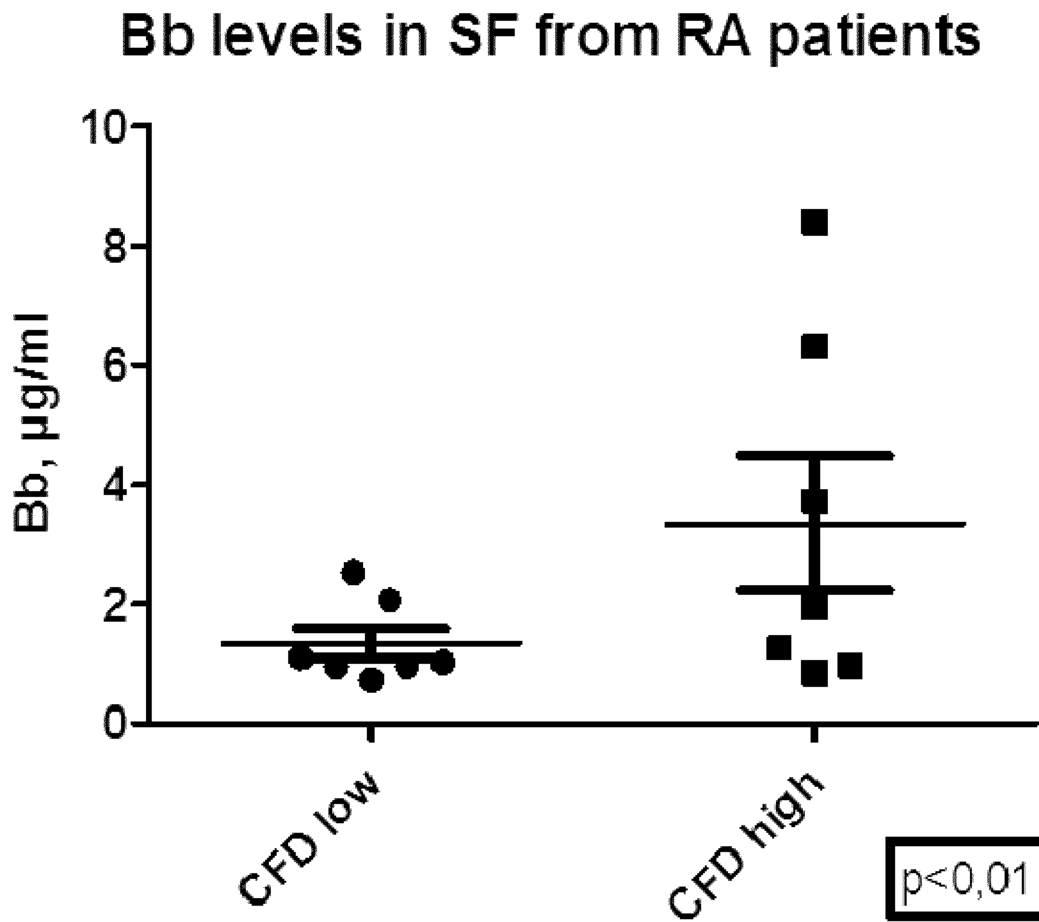


FIG. 8



patsnap

专利名称(译)	与治疗炎性疾病和病症有关的方法		
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摘要(译)

本发明涉及与用于预测患有炎性疾病或病症的患者的抗炎治疗的临床反应的方法相关的基因标记。