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(54) **Title:** A METHOD FOR PREDICTING THE RESPONSIVENESS A PATIENT TO A TREATMENT WITH AN IL-6 ANT-  
AGONIST

(57) **Abstract:** The present invention relates to a method for predicting the responsiveness of a patient to a treatment with an IL-6 antagonist, said method comprising measuring in a blood sample obtained from said patient the level of at least one subpopulation of blood monocytes selected from the group consisting of classical monocytes, intermediate monocytes and non classical patrolling monocytes.



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## A METHOD FOR PREDICTING THE RESPONSIVENESS A PATIENT TO A TREATMENT WITH AN IL-6 ANTAGONIST

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### FIELD OF THE INVENTION:

5           The present invention relates to a method for predicting the responsiveness of a patient to a treatment with an IL-6 antagonist such as tocilizumab.

### BACKGROUND OF THE INVENTION:

10           Rheumatoid arthritis (RA) is an autoimmune arthropathy associated with systemic inflammatory manifestations. In RA, the synovium, the inner lining of synovial joints, is abnormal. There is infiltration of acute inflammatory cells in the synovium, which undergoes hypertrophy, resulting in effusion of the joint. Hyperplastic synovium may also lead to erosion of the adjacent cartilage and bone, causing joint destruction. The end result is joint inflammation, effusion, joint and adjacent ligament destruction, joint deformity and, finally,  
15           loss of function.

          The pathogenesis of RA is complex and has not been fully defined. However, a number of cytokines, including interleukin IL-6, IL-15, IL-17, and tumor necrosis factor, have been implicated in causing joint and systemic inflammation (Tamer, et al., Nat. Clin. Pract. Rheumatol., 3:336-45 (2007)). Accordingly targeting one of these cytokines has been  
20           proposes as a potential therapeutic strategy of RA (Choy, et al., N. Engl. J. Med., 344:907-16 (2001)). For example, treatment with tocilizumab, an antibody against the IL-6 receptor (IL-6R), leads to significant control of symptoms in RA patients (Smolen, et al., Lancet, 371:987-97 (2008)). Although a major breakthrough has emerged in the management of RA patients with the above mentioned biotherapies, it is not curative and its effects are only partial, non  
25           responses common and loss of effect are observed. As consequences, molecular discrimination of responders versus non responders to said biotherapies becomes a major clinical interest, and there is a permanent need in the art for prognostic biomarkers that could assist physicians in providing patients optimized care management with said biotherapies.

### SUMMARY OF THE INVENTION:

30           The present invention relates to a method for predicting the responsiveness of a patient to a treatment with an IL-6 antagonist, said method comprising measuring in a blood sample obtained from said patient the level of at least one subpopulation of blood monocytes selected

from the group consisting of classical monocytes, intermediate monocytes and non classical patrolling monocytes.

### DETAILED DESCRIPTION OF THE INVENTION:

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The present invention relates to a method for predicting the responsiveness of a patient to a treatment with an IL-6 antagonist, said method comprising measuring in a blood sample obtained from said patient the level of at least one subpopulation of blood monocytes selected from the group consisting of classical monocytes, intermediate monocytes and non classical patrolling monocytes.

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As used herein, the term "IL-6 antagonist" refers to any compound that prevents, inhibits, or lessens the effect(s) of IL-6 signalling. Typically, the IL-6 antagonist according to the invention is an anti-IL-6 antibody or an anti-IL-6 receptor antibody. An "anti-IL-6 antibody" is an antibody that specifically binds an IL-6 polypeptide. An "anti-IL-6-receptor antibody" is an antibody that specifically binds the extracellular domain of an IL-6 receptor polypeptide. In a preferred embodiment the IL-6 antagonist according to the invention is tocilizumab.

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The term "patient" refers to any subject (preferably human) afflicted with a disease likely to benefit from a treatment with an IL-6 antagonist. According to a preferred embodiment, the method of the invention is particularly useful to predict the response to a treatment by a IL-6 antagonist, preferably tocilizumab, in a patient affected with rheumatoid arthritis. The rheumatoid arthritis can be moderate or active. The disease activity can be measured according to the standards recognized in the art. The "Disease Activity Score" (DAS) is a measure of the activity of rheumatoid arthritis. In Europe the DAS is the recognized standard in research and clinical practice. The following parameters are included in the calculation (Van Gestel AM, Prevoo MLL, van't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996; 39:34-40): number of joints tender to the touch (TEN), number of swollen joints (SW); erythrocyte sedimentation rate (ESR), patient assessment of disease activity (VAS; mm). Patients with a disease activity score 28 (DAS28)  $\geq 3.2$  are a preferred group of patients. Patients who are resistant to methotrexate (MTX) are a preferred group of patients for whom the method of the invention can be particularly useful. More

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generally, patients who already receive a basic treatment, e.g. with MTX, azathioprine or leflunomide, are particularly good candidates for the test method of the invention. More preferably, patients who are also resistant to a TNF blocking agent treatment are particularly good candidates for the method of the invention.

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A “responder” patient refers to a patient who shows a clinically significant relief in the disease when treated with the IL-6 antagonist. When the disease is RA, a preferred responder group of patients that provides for the control values is a group that shows a decrease of DAS28  $\geq 1.2$  after three months of treatment with the IL-6 antagonist, preferably tocilizumab.

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According to the invention, the method is performed before the treatment of the patient with the IL-6 antagonist.

In one embodiment, the blood sample is a serum sample. More preferably, the blood sample is a sample obtained from the blood of the patient that contains the non-adherent cell fraction, and more preferably the monocyte fraction.

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As used herein the term “blood monocyte” has its general meaning in the art and refers to a large mononuclear phagocyte of the peripheral blood. Monocytes vary considerably, ranging in size from 10 to 30  $\mu\text{m}$  in diameter. The nucleus to cytoplasm ratio ranges from 2:1 to 1:1. The nucleus is often band shaped (horseshoe), or reniform (kidney-shaped). It may fold over on top of itself, thus showing brainlike convolutions. No nucleoli are visible. The chromatin pattern is fine, and arranged in skein-like strands. The cytoplasm is abundant and appears blue gray with many fine azurophilic granules, giving a ground glass appearance in Giemsa staining. Vacuoles may be present. Typically human blood monocytes can be distinguished from other blood cell types by the expression of specific surface markers. Human blood monocyte are contained within CD115+ cells or DR+ cells that do not express B cell (CD19-), T cell (CD2-), NK cell (NKp46-) or granulocyte marker (CD15-). The main surface markers of human monocyte cells are therefore: CD11b, CD11c, CD33 and CD115. Upon contact with sensitive target cells, monocyte cells also produce a number of cytokines, including IFNs, TNF, GM-CSF, G-CSF, M-CSF, and IL-1.

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Human blood monocytes can be divided in three subpopulations: classical monocytes, intermediate monocytes and non classical patrolling monocytes (Cros J, Cagnard N, Woollard

K, Patey N, Zhang SY, Senechal B, Puel A, Biswas SK, Moshous D, Picard C, Jais JP, D'Cruz D, Casanova JL, Trouillet C, Geissmann F. Human CD14<sup>dim</sup> monocytes patrol and sense nucleic acids and viruses via TLR7 and TLR8 receptors. *Immunity*. 2010 Sep 24;33(3):375-86. Epub 2010 Sep 9.).

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As used herein the term “classical monocytes” has its general meaning in the art and refers to by the CD14<sup>+</sup> blood monocytes subpopulation that can include a subpopulation of cells with higher expression of CD16 and HLA-DR corresponding to activated monocytes. Typically classical monocytes are CD14<sup>++</sup>CD16<sup>+</sup>CD33<sup>++</sup>HLA-DR<sup>+</sup> monocytes with a subpopulation CD16<sup>+</sup>HLA-DR<sup>high</sup>.

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As used herein the term “intermediate monocytes” has its general meaning in the art and refers to the CD14<sup>+</sup> blood monocytes subpopulation having a higher expression of CD16<sup>+</sup> than the classical monocytes. Typically, intermediate monocytes are CD14<sup>++</sup>CD16<sup>++</sup> monocytes.

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As used herein the term “non classical patrolling monocytes” has its general meaning in the art and refers to subpopulation of monocytes with a lower expression of CD14. Typically, non classical patrolling monocytes are CD14<sup>dim</sup>CD16<sup>++</sup>HLA-DR<sup>+++</sup>.

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Accordingly, said subpopulation of monocytes may be easily isolated and quantified in the blood sample obtained from the patient by detecting the presence of specific surface markers (“positive selection”) and/or by detecting the absence of specific surface markers (“negative selection”). Standard methods for detecting the presence or absence of specific surface marker at cell surface (e.g. monocyte surface) are well known in the art. Typically cells of the blood sample are contacting with a set of binding partners specific for surface markers.

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As used herein, the term “binding partner directed against a surface marker” refers to any molecule (natural or not) that is able to bind said surface marker with high affinity.

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The binding partners may be antibodies that may be polyclonal or monoclonal, preferably monoclonal. In another embodiment, the binding partners may be a set of aptamers.

Polyclonal antibodies of the invention or a fragment thereof can be raised according to known methods by administering the appropriate antigen or epitope to a host animal selected, e.g., from pigs, cows, horses, rabbits, goats, sheep, and mice, among others. Various adjuvants known in the art can be used to enhance antibody production. Although antibodies  
5 useful in practicing the invention can be polyclonal, monoclonal antibodies are preferred. Monoclonal antibodies of the invention or a fragment thereof can be prepared and isolated using any technique that provides for the production of antibody molecules by continuous cell lines in culture. Techniques for production and isolation include but are not limited to the hybridoma technique originally; the human B-cell hybridoma technique; and the EBV-  
10 hybridoma technique.

In another embodiment, the binding partners may be aptamers. Aptamers are a class of molecule that represents an alternative to antibodies in term of molecular recognition. Aptamers are oligonucleotide or oligopeptide sequences with the capacity to recognize  
15 virtually any class of target molecules with high affinity and specificity. Such ligands may be isolated through Systematic Evolution of Ligands by EXponential enrichment (SELEX) of a random sequence library, as described in Tuerk C. 1997. The random sequence library is obtainable by combinatorial chemical synthesis of DNA. In this library, each member is a linear oligomer, eventually chemically modified, of a unique sequence. Possible  
20 modifications, uses and advantages of this class of molecules have been reviewed in Jayasena S.D., 1999. Peptide aptamers consist of conformationally constrained antibody variable regions displayed by a platform protein, such as E. coli Thioredoxin A that are selected from combinatorial libraries by two hybrid methods.

The binding partners of the invention such as antibodies or aptamers may be labelled  
25 with a detectable molecule or substance, such as preferentially a fluorescent molecule, or a radioactive molecule or any others labels known in the art. Labels are known in the art that generally provide (either directly or indirectly) a signal.

As used herein, the term "labelled", with regard to the antibody or aptamer, is intended to encompass direct labelling of the antibody or aptamer by coupling (i.e., physically linking)  
30 a detectable substance, such as a fluorophore [e.g. fluorescein isothiocyanate (FITC) or phycoerythrin (PE) or Indocyanine (Cy5)] or a radioactive agent to the antibody or aptamer, as well as indirect labelling of the probe or antibody by reactivity with a detectable substance. An antibody or aptamer of the invention may be labelled with a radioactive molecule by any

method known in the art. For example radioactive molecules include but are not limited radioactive atom for scintigraphic studies such as I123, I124, In111, Re186, Re188.

Preferably, the antibodies against a surface marker are already conjugated to a fluorophore (e.g. FITC-conjugated and/or PE-conjugated).

5       The aforementioned assays may involve the binding of the binding partners (ie. antibodies or aptamers) to a solid surface. Typically the solid surfaces may be beads, such as activated beads, magnetically responsive beads. Beads may be made of different materials, including but not limited to glass, plastic, polystyrene, and acrylic. In addition, the beads are preferably fluorescently labelled. In a preferred embodiment, fluorescent beads are those  
10       contained in TruCount(TM) tubes, available from Becton Dickinson Biosciences, (San Jose, California).

      According to the invention, methods of flow cytometry are preferred methods for isolating and quantifying the subpopulation of monocytes in the blood sample. Said methods are well known in the art. For example, fluorescence activated cell sorting (FACS) may be  
15       therefore used. Typically, a FACS method such as described in Example here below may be used.

      According to the invention, the level a subpopulation of monocytes could be expressed in percentage of the total population of monocytes contained in the blood sample of the  
20       patient.

      In a particular embodiment, the levels of the three subpopulation of monocytes are determined in the blood sample obtained from the patient.

25       The method of the invention may further comprise a step of comparing the level of the subpopulation of monocytes with reference values obtained from responder and non-responder group of patients, wherein detecting differential in the level between the biological sample and the reference values is indicative whether the patient will be a responder or not to the treatment with the IL-6 antagonist. Typically, as described in the EXAMPLE, a lower  
30       level of classical monocytes, associated with higher levels for intermediate monocytes and non classical patrolling monocytes are indicative that the patient will not respond to the treatment.

After being considered as responder to the treatment, the patients may be prescribed with said IL-6 antagonist.

A further aspect of the invention related to kits for performing the methods the present invention comprising means for measuring the level of the subpopulation of monocytes. The kit may include a set of binding partners as above described. In a particular embodiment, the binding partners are labelled as above described. The kit may also contain other suitably packaged reagents and materials needed for the particular detection protocol, including solid supports, if applicable, and standards.

The invention will be further illustrated by the following figures and examples. However, these examples and figures should not be interpreted in any way as limiting the scope of the present invention.

#### **FIGURES:**

**Figure 1 shows the DAS of the patients (responders and non responders)**

**Figure 2 shows the CRP of the patients (responders and non responders)**

**Figure 3 shows the 3 subpopulations of monocytes**

**Figure 4 shows the monitoring of the monitoring of the three subpopulations of monocytes**

#### **EXAMPLE:**

##### **Methods:**

**Patients:** 19 patients with severe and active Rheumatoid Arthritis fulfilling the revised criteria from ACR, refractory to methotrexate or anti-TNF therapies were recruited. Patients are 20 to 80 years old with only 3 male include in the study. The presence of at least one susceptible allele (HLA-DRB1\*01 or DRB1\*04) is 84% in the non responders versus 73% in the responders. Patients were treated with 8mg/kg of tocilizumab monthly. Peripheral blood

was recovered for each patient at day 0, as well as 1 and 3 month after informed consents. Patients were classified in 2 groups according to the clinical response

-non responders (labelled N on Figures 1 and 2) with a decrease of the DAS 28 lower than 1.2 (EULAR criteria)

5                    -responders (labelled R Figures 1 and 2) with a remarkable decrease of the DAS 28.

**Antibodies:** The antibodies used for the staining of monocytes are the following: FITC-conjugated CD64, PE-conjugated CD33, PE-conjugated CD314, PerCP-Cy5.5-  
10 conjugated HLA-DR, PE-Cy7-conjugated CD56, PE-Cy7-conjugated CD14, CD32 APC-conjugated CD32, APC-H7 conjugated CD4, APC-H7 conjugated CD16, V450-conjugated CD3 and V500-conjugated CD45. Staining was performed on whole blood. The data were acquired on a FACS Canto II (3 fixed alignment lasers, 405,488 and 635 nm) and analyzed using DIVA software.

15                    The viable population was gated according to FSC and SSC, excluding the doublets. The monocytes were gated based on the SSC and CD45 staining. The 3 populations of monocytes were defined according to the intensities of CD14 and CD16 staining (Figure 3):

-                    The classical monocytes CD14+ with a subpopulation of cells with higher expression of CD16 and HLA-DR corresponding to activated monocytes.

20                    -                    A population with higher expression of CD16+ than the classical monocytes

-                    A third population with a lower expression of CD14 called the Non-classical patrolling monocytes.

### **Results:**

25                    As shown in Figure 4, a lower percentage of classical monocytes, associated with higher frequencies of the CD14+CD16+ and patrolling CD14dimCD16+ monocytes were found in non responders compared with responders, before initiation of the treatment. These results suggest that the frequencies of the subpopulations of monocytes might have a  
30                    predictive value for the Tocilizumab treatment.

### **REFERENCES:**

Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.

**CLAIMS:**

- 5 1. A method for predicting the responsiveness of a patient to a treatment with an IL-6 antagonist, said method comprising measuring in a blood sample obtained from said patient the level of at least one subpopulation of blood monocytes selected from the group consisting of classical monocytes, intermediate monocytes and non classical patrolling monocytes.

1/3

# DAS of patients

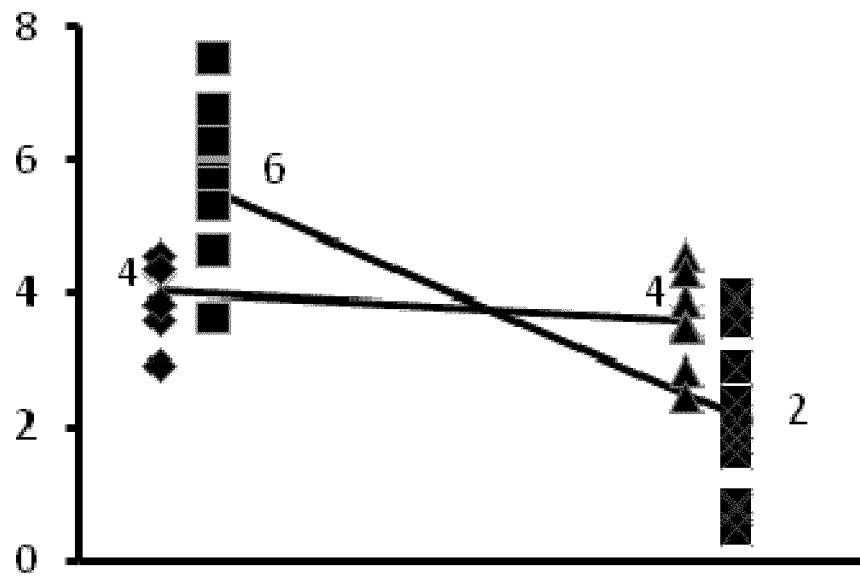


Figure 1

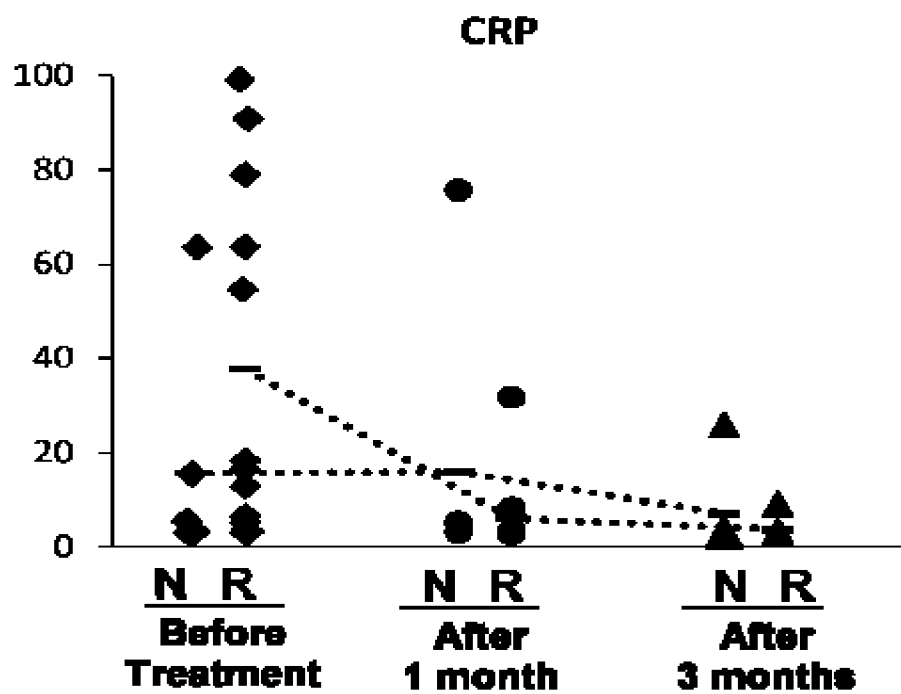


Figure 2

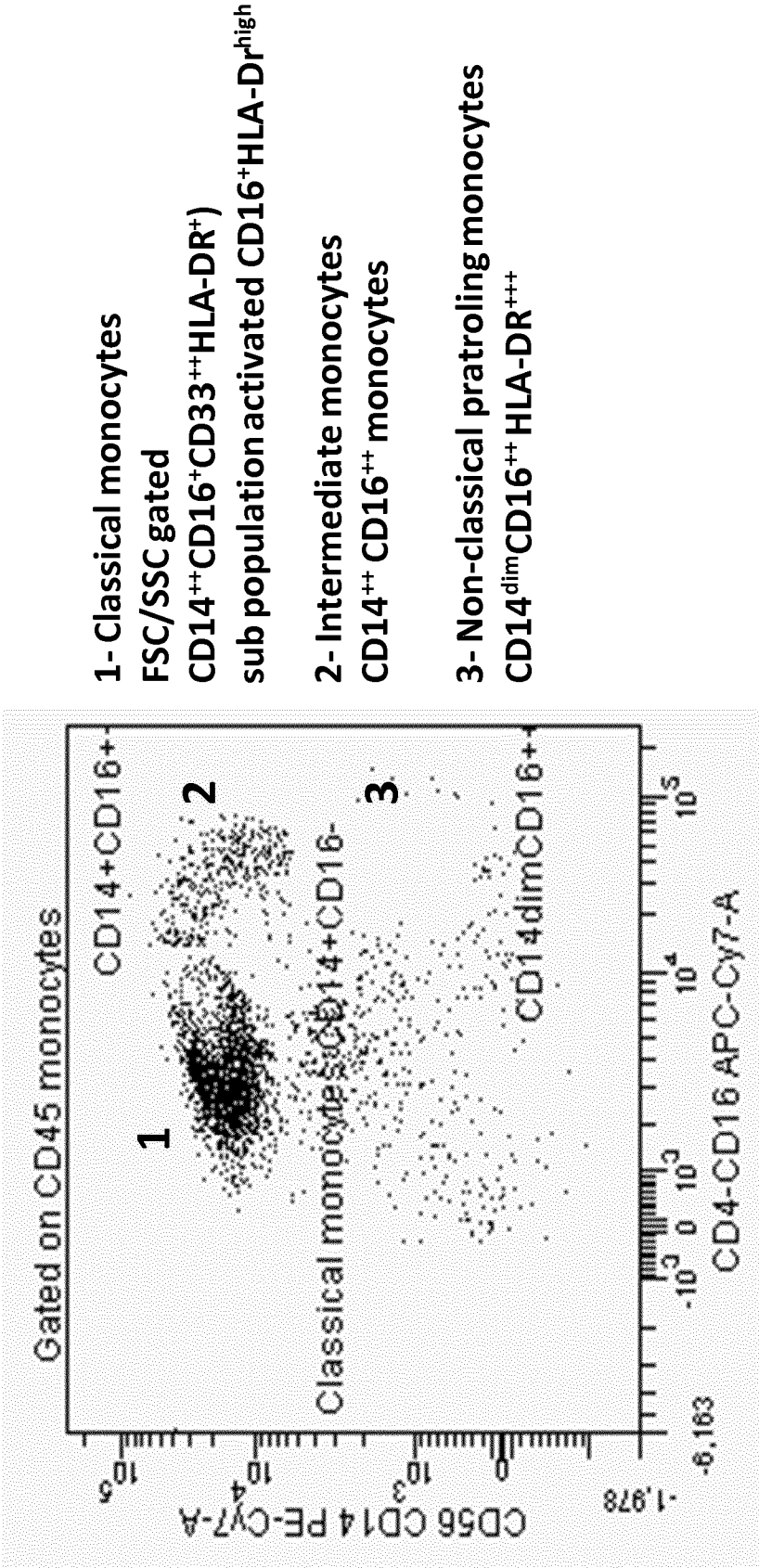


Figure 3

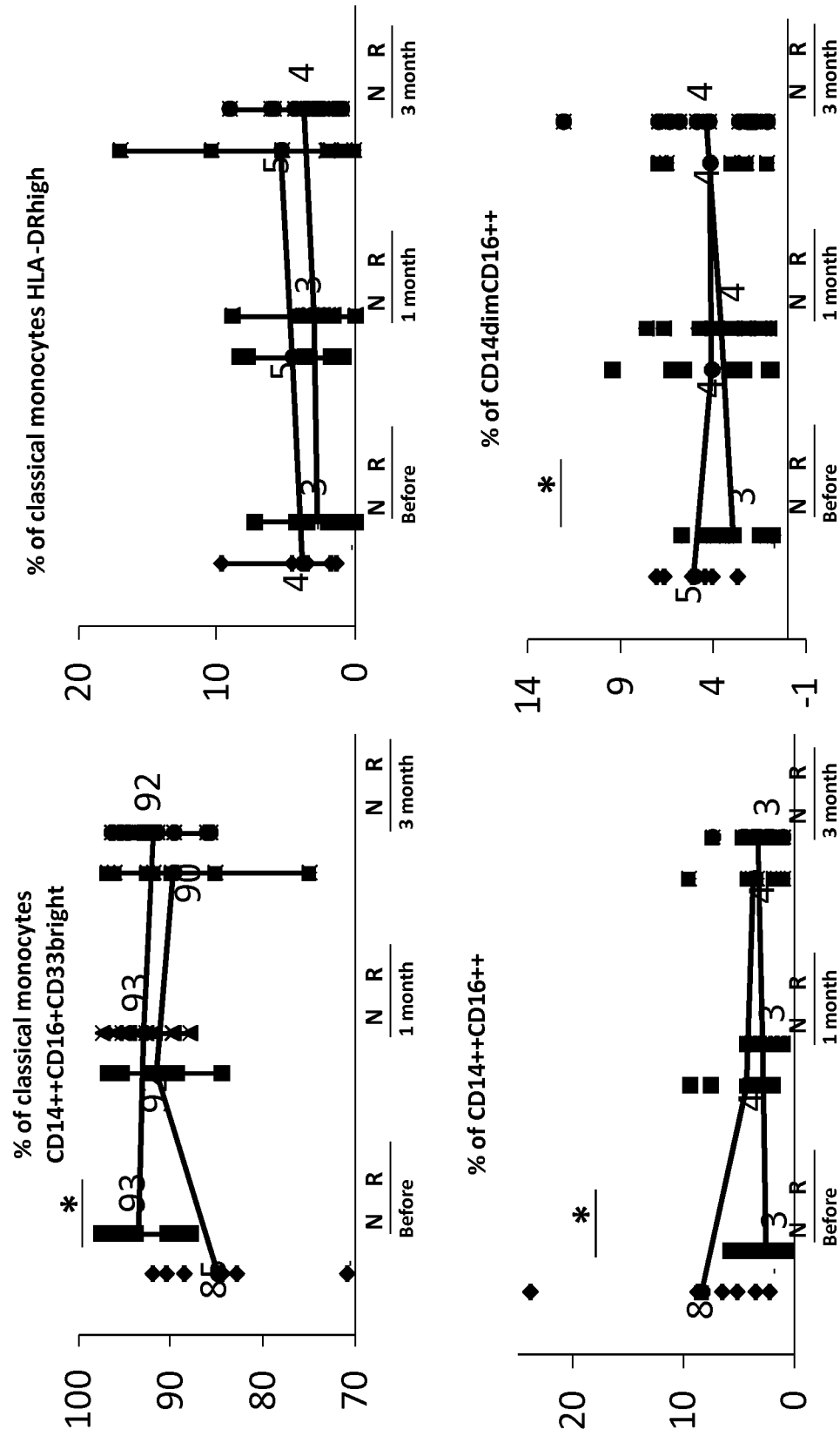


Figure 4

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2012/069279A. CLASSIFICATION OF SUBJECT MATTER  
INV. G01N33/50 G01N33/564  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                  | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A,P       | WO 2012/041332 A2 (RIGSHOSPITALET [DK];<br>NIELSEN CLAUS HENRIK [DK]; ENEVOLD<br>CHRISTIAN [DK]) 5 April 2012 (2012-04-05)<br>claim 1, Table 1      | 1                     |
| A,P       | WO 2011/154139 A2 (ROCHE DIAGNOSTICS GMBH<br>[DE]; HOFFMANN LA ROCHE [CH])<br>15 December 2011 (2011-12-15)<br>claim 1, tables 1 -3<br>-----<br>-/- | 1                     |



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

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09/01/2013

Name and mailing address of the ISA/

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Authorized officer

Hoesel, Heidi

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2012/069279

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                |                       |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                             | Relevant to claim No. |
| A                                                    | KAWADA Y ET AL: "Predicting effectiveness of anti-interleukin-6 receptor antibody e.g. tocilizumab against rheumatism and other IL-6 associated diseases e.g. cachexia, involves measuring expression level of specific human gene or its complement",<br>WPI / THOMSON,,<br>vol. 2009, no. 47,<br>30 April 2009 (2009-04-30), XP002661658,<br>the whole document<br>-----     | 1                     |
| A                                                    | WO 2008/156867 A1 (UNIV LELAND STANFORD JUNIOR [US]; US GOV VETERANS AFFAIRS [US]; UNIV C) 24 December 2008 (2008-12-24)<br>par. 88, claims 1 - 7<br>-----                                                                                                                                                                                                                     | 1                     |
| A                                                    | KAMISHIMA TAMOTSU ET AL: "Monitoring anti-interleukin 6 receptor antibody treatment for rheumatoid arthritis by quantitative magnetic resonance imaging of the hand and power Doppler ultrasonography of the finger.",<br>SKELETAL RADIOLOGY JUN 2011,<br>vol. 40, no. 6, June 2011 (2011-06), pages 745-755, XP002687177,<br>ISSN: 1432-2161<br>abstract, discussion<br>----- | 1                     |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/069279

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                            | Publication<br>date                    |
|-------------------------------------------|---------------------|-------------------------------------------------------|----------------------------------------|
| WO 2012041332 A2                          | 05-04-2012          | NONE                                                  |                                        |
| WO 2011154139 A2                          | 15-12-2011          | US 2012009177 A1<br>WO 2011154139 A2                  | 12-01-2012<br>15-12-2011               |
| WO 2008156867 A1                          | 24-12-2008          | EP 2158326 A1<br>US 2009142792 A1<br>WO 2008156867 A1 | 03-03-2010<br>04-06-2009<br>24-12-2008 |