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(54) **Title**: CELLULAR MARKERS FOR DIAGNOSIS OF ALZHEIMER'S DISEASE AND FOR ALZHEIMER'S DISEASE PROGRESSION

(57) **Abstract**: The present invention provides methods for early diagnosis of Alzheimer's disease and for determining the efficacy of a treatment for Alzheimer's disease in an Alzheimer's patient, i.e., monitoring Alzheimer's disease progression, utilizing cellular blood markers; as well as kits for carrying out these methods.

CELLULAR MARKERS FOR DIAGNOSIS OF ALZHEIMER'S DISEASE AND FOR ALZHEIMER'S DISEASE PROGRESSION

TECHNICAL FIELD

[0001] The present invention relates to methods for early diagnosis of Alzheimer's disease and for monitoring Alzheimer's disease progression.

BACKGROUND ART

[0002] Neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease or amyotrophic lateral sclerosis (ALS) share a chronic progressive course that leads to neurodegeneration, including neuroaxonal damage, apoptosis and gliosis. The pathogenesis and pathophysiology of neurodegenerative diseases are extremely complex and only partially understood. Regardless of the differences, age is a common risk factor that plays a significant role in the pathophysiology of neurodegenerative diseases. In addition, there is substantial evidence that excitotoxicity, oxidative stress, protein aggregation, inflammation and apoptosis, among others, are common pathological events that have a role in disease progression. After more than two decades of intensive efforts by scientific and pharmaceutical communities throughout the world and despite of the accumulating knowledge, neurodegenerative diseases are still unpreventable, incurable and largely untreatable. Furthermore, no objective test is available for definitive diagnosis. Diagnosis is typically done using clinical assessments at advanced stages of the disease when damage is significant and potential for delaying disease progression is low.

[0003] The immune system, by employing an array of cellular network, is the body’s natural mechanism for host defense against foreign entities as well as for tissue maintenance, healing, regeneration and surveillance against aberrant cell growth, i.e., the recognition of tumors or transformed cells. Yet any activity of the peripheral immune cells in the central nervous system (CNS) was long considered to be undesirable. The CNS of vertebrate animals is uniquely protected from toxins, invading pathogens, inflammatory cells and macromolecules through a protective mechanism called the "blood-brain barrier", a system of tight junctions at capillaries within the CNS that provides a protective physical barricade. Under normal non-pathological conditions, blood-borne immune cells can barely be detected in the brain using standard histological methods. The scarcity of blood-borne immune cells in healthy CNS parenchyma, in combination with the concept of the

CNS being an "immune privileged site", contributed to the common view that, under normal conditions, the CNS functions most effectively in the absence of any immune cell activity.

[0004] In contrast to the common consideration, it has recently become evident that the nervous and immune systems are engaged in an intense bidirectional communication. Immune cells were also found to have a role in the different steps of neurogenesis including progenitor proliferation, survival, migration and differentiation (Ziv and Schwartz, 2008; Ekdahl *et al.*, 2008).

[0005] Active T cells were shown to patrol the CNS at all times under both normal and pathological conditions, while animals deprived of activated T cells show reduced memory capabilities which can be reversed by replenishment with T cells (Butovsky *et al.*, 2006a; Kipnis *et al.*, 2004; Ziv *et al.*, 2006).

[0006] The positive role of auto-reactive T cells in maintaining the normal activity of the brain in normal and pathological conditions was described in various publications (Schwartz, 2001; Schori *et al.*, 2001; Mizrahi *et al.*, 2002; Nevo *et al.*, 2003; Nevo *et al.*, 2004). In non-pathological conditions, it is suggested that brain activity, such as intensive learning activity, involves continuing support from autoreactive T cells needed for restoration of homeostasis. Such T cells are located at the borders of the brain. At "the borders of the CNS", CNS-specific T cells become activated, secret cytokines and growth factors and also directly affect the microglia to become supportive to neuronal survival and growth.

[0007] In the injured CNS, an emerging understanding of the role of the immune system in regulating neurotoxicity by the secretion of growth factors, removal of dying neurons and detoxification of the environment, has suggested that the situation is complex, with a balance between beneficial and detrimental effects of the immune system (Shaked *et al.*, 2005; Shaked *et al.*, 2004; Ziv *et al.*, 2006; Kipnis *et al.*, 2004; Ron-Harel and Schwartz, 2009).

[0008] As further shown, in response to acute injury, effector T-cells (T-eff) directed to self-antigens (autoimmune T-cells) are needed as part of a reparative response (Rapalino *et al.*, 1998; Hauben *et al.*, 2000; Hauben *et al.*, 2003; Schwartz and Hauben, 2002; Moalem *et al.*, 1999; Yoles *et al.*, 2001; Kipnis *et al.*, 2001; Schwartz *et al.*, 2003), yet this activity should be tightly regulated by regulatory T cells (T-reg) (Taams and Akbar, 2005) as part of a mechanism to control autoimmune disease (Kipnis *et al.*, 2002; Schwartz and Kipnis,

2002; Schwartz and Kipnis, 2004; Kipnis and Schwartz, 2005). Accordingly, boosting autoimmunity was shown to be beneficial in animal models of acute or chronic neurodegenerative disorders.

[0009] Age-dependent decline in immunity, known as immunosenescence, is associated with reduced host defense, manifested by an increased susceptibility to infection diseases, as well as reduced ability to develop immunity after vaccination (Aw *et al.*, 2007). The decline in immunity in the elderly has largely been attributed to changes in hematopoietic stem cells function and their ability to differentiate into different immune cell lineages. This goes in line with the fact that the thymus involutes with age, so that the number of naïve cells available to respond to new foreign antigens also declines. However, much less attention has been devoted to the role of the immune system in tissue maintenance, healing and regeneration. This is particularly important for understanding the link between brain aging, memory deterioration and immune senescence.

[0010] AD is an age related disease. In an animal model of AD, augmenting the adaptive immune response using glatiramer acetate vaccination resulted in decreased plaque formation and induction of neurogenesis (Butovsky *et al.*, 2006b). This treatment induced the recruitment of blood-borne monocytes to the diseased brain. Depletion of these blood-borne monocytes from the blood resulted in a significantly increased formation of amyloid plaques (Butovsky *et al.*, 2007). Furthermore, using the same animal model, exercises were shown to induce T-cell response which coincides with a decrease in amyloid plaques in advanced pathological states (Nichol *et al.*, 2008). Another subset of immune-cells shown to be involved with plaque formation are the naturally occurring $CD4^{+}CD25^{+}$ regulatory T cells. Neuronal loss caused by intraocular injection of aggregated beta-amyloid was significantly greater in immunodeficient mice than in normal mice. The neurodegeneration was attenuated or augmented by elimination or addition, respectively, of naturally occurring $CD4^{+}CD25^{+}$ regulatory T cells (Treg) (Avidan *et al.*, 2004).

[0011] It is suggested that immunity recognizing self-proteins residing in the brain provides a mechanism that can sense and respond to various deviations from CNS homeostasis and maintain tissue integrity (Schwartz and Ziv, 2008a; Schwartz and Ziv, 2008b). Accordingly, during old age, when the need for maintenance increases, the senescent immune system fails to provide the support required. Neurodegenerative diseases might emerge when the levels/potency of key immunological components, involved with anti-self response, reach threshold levels.

[0012] WO 2011/111043 discloses methods for early diagnosis of ALS and for monitoring ALS progression, utilizing cellular blood markers. In a particular method disclosed, the levels of gamma-delta T-cells, $CD11b^{+}/CD14^{-}$ cells, $Lin^{-}/DR^{-}/CD33^{+}$ cells and $CD14^{+}/CD16^{+}$ cells in a peripheral blood sample of a tested individual are measured and compared with the range levels of each one of these cell types in blood samples of age-matched controls, wherein no change in the level of $CD14^{+}/CD16^{+}$ cells and increase in the levels of each one of the other cell types indicate that said individual has a higher likelihood of having ALS than said age-matched controls.

SUMMARY OF INVENTION

[0013] It has been found, in accordance with the present invention, that while no differences were observed in the amount of lymphocytes and monocytes in the blood of Alzheimer's patients, ALS patients and healthy volunteers, significant differences in sub-population of lymphocytes and monocytes typically involved with regulation of the adaptive immune response were observed in Alzheimer's patients. Particular such differences were found in the level of gamma-delta ($\gamma\delta$)-T cells, which were significantly elevated in Alzheimer's patients (although less than in ALS patients) in comparison to healthy controls, and the pro-inflammatory sub-set of monocytes $CD14^{+}/CD16^{+}$, which were remarkably elevated in Alzheimer's patients but not in ALS patients. Furthermore, while a dramatic elevation was found in the percentage of monocytes having the markers $CD14^{-}/CD11b^{+}/CD15^{+}$, a phenotype associated with myeloid-derived suppressor cells (MDSCs), in the blood of ALS patients, no difference in the percentage of these cells was found between Alzheimer's patients and healthy controls.

[0014] In one aspect, the present invention thus relates to a method for diagnosing the likelihood of AD in a tested individual, said method comprising:

(i) measuring the levels of $\gamma\delta$ T-cells and at least one cell type of MDSCs in a peripheral blood sample obtained from said individual; and

(ii) comparing the levels measured in (i) with reference levels representing range levels of $\gamma\delta$ T-cells and said at least one cell type of MDSCs, respectively, in blood samples of age-matched controls, thus obtaining a profile expressing the levels measured in (i) relative to said reference levels, respectively,

wherein an increase in the level of γδ T-cells; and no change in the level of each one of said at least one cell type of MDSCs indicate that said individual has a higher likelihood of having AD than said age-matched controls.

[0015] In certain embodiments, this method further comprises measuring in step (i) the level of at least one cell type of pro-inflammatory monocytes in said blood sample; and comparing in step (ii) the level of said at least one cell type of pro-inflammatory monocytes with a reference level representing a range level of said at least one cell type of pro-inflammatory monocytes in blood samples of age-matched controls, wherein an increase in the level of γδ T-cells; no change in the level of each one of said at least one cell type of MDSCs; and an increase in the level of at least one of said at least one cell type of pro-inflammatory monocytes indicate that said individual has a higher likelihood of having AD than said age-matched controls.

[0016] In another aspect, the present invention relates to a method for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, said method comprising:

(i) measuring the levels of γδ T-cells in a peripheral blood sample obtained from said patient at two consecutive instants, the earlier of said instants is prior to or during said treatment and the later of said instants is during said treatment; and

(ii) comparing the levels measured for γδ T-cells at said two instants,

wherein a decrease in the level measured for γδ T-cells at said later instant compared with the level measured for γδ T-cells at said earlier instant towards a reference level representing a range level of γδ T-cells in blood samples of age-matched controls is correlated with the efficacy of said treatment.

[0017] In certain embodiments, this method further comprises measuring in step (i) the level of at least one cell type of pro-inflammatory monocytes in said blood sample at said two instants; and comparing in step (ii) the level measured for said at least one cell type of pro-inflammatory monocytes at said two instants, wherein a decrease in the level measured for γδ T-cells and/or at least one of said at least one cell type of pro-inflammatory monocytes at said later instant compared with the level measured for γδ T-cells and/or at least one of said at least one cell type of pro-inflammatory monocytes, respectively, at said earlier instant towards a reference level representing range levels of γδ T-cells and said at

least one of said at least one cell type of pro-inflammatory monocytes, respectively, in blood samples of age-matched controls is correlated with the efficacy of said treatment.

[0018] In a further aspect, the present invention provides a kit for diagnosing the likelihood of AD in a tested individual; or for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, said kit comprising:

(i) a list of cell types including γδ T-cells and at least one cell type of MDSCs;

(ii) antibodies against each one of said cell types;

(iii) reagents for detecting said antibodies;

(iv) a list of reference levels representing range levels of said cell types in blood samples of age-matched controls; and

(v) instructions for use.

[0019] In certain embodiments, the list of cell types comprised within the kit of the invention further includes at least one cell type of pro-inflammatory monocytes.

BRIEF DESCRIPTION OF DRAWINGS

[0020] **Figs. 1A-1B** show distribution of single markers on total live PBMC. Freshly isolated PBMC of healthy volunteers were stained with FITC, PE or APC-labeled mononuclear antibodies against CD3, CD14, CD19, CD15, CD11c and CD34. The proportion (% of positive cells; **1A**) and level of expression (mean intensity of fluorescence; **1B**) of each marker was analyzed by FACS. Data shown are mean ± standard error (SE) from 4-6 different blood samples.

[0021] **Figs. 2A-2B** show lymphocyte sub-population. Freshly isolated PBMC of healthy volunteers were double stained with APC-labeled mononuclear antibodies against CD3 and one of the following FITC- or PE-labeled mononuclear antibodies against CD4, CD8, CTLA4 or TCRgd. Bars represents mean ± standard error (SE) of percentage of cells that express each of the markers out of the CD3 positive cell population (**2A**) and the intensity of expression (**2B**). Data shown are from 4 different experiments.

[0022] **Fig. 3** shows the receiver operator characteristic (ROC) curve for γδ T-cells analyzed based on the results obtained in the study described in Example 2, suggesting that the percentage of γδ T-cells out of total lymphocytes and monocytes appears to be highly sensitive and accurate for AD diagnosis.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention provides a new approach identifying the age-related peripheral immune changes as primary risk factors for development of AD.

[0024] Preliminary studies conducted in accordance with the present invention and described hereinafter have shown specific and consistent changes, more particularly increase, in the levels of γδ T-cells and the pro-inflammatory monocytes $CD14^+/CD16^+$ cells in peripheral blood samples of Alzheimer's patients, compared with those measured in peripheral blood samples of age-matched controls, whereas no alteration has been observed in the level of the MDSCs $CD11b^+/CD14^-/CD15^+$. This pattern of alterations is substantially different than that disclosed in the aforesaid WO 2011/111043 as indicative for ALS, wherein no change in the level of $CD14^+/CD16^+$ cells and increase in the levels of various MDSCs were clearly observed in peripheral blood samples of ALS patients. These findings indicate that specific changes in the level of certain T-cell or monocyte subsets such as those mentioned above can be used, either separately or in combination with each other or with other markers, as blood markers for diagnosis of AD and for monitoring AD progression and treatment efficacy.

[0025] In one aspect, the present invention thus relates to a method for diagnosing the likelihood of AD in a tested individual, said method comprising:

(i) measuring the levels of γδ T-cells and at least one cell type of MDSCs in a peripheral blood sample obtained from said individual; and

(ii) comparing the levels measured in (i) with reference levels representing range levels of γδ T-cells and said at least one cell type of MDSCs, respectively, in blood samples of age-matched controls, thus obtaining a profile expressing the levels measured in (i) relative to said reference levels, respectively,

wherein an increase in the level of γδ T-cells; and no change in the level of each one of said at least one cell type of MDSCs indicate that said individual has a higher likelihood of having AD than said age-matched controls.

[0026] The term "gamma-delta T-cells" (γδ T-cells), as used herein, refers to a small subset of T cells possessing a distinct T cell receptor (TCR) on their surface. In contrast to a majority of T cells in which the TCR is composed of two glycoprotein chains designated α- and β- TCR chains, the TCR in γδ T cells is made up of a γ-chain and a δ-chain. These cells were shown to play a role in immunosurveillance and immunoregulation (Girardi,

2006), and were found to be an important source of IL-17 (Roark *et al.*, 2008) and to induce robust $CD8^+$ cytotoxic T cell response (Brandes *et al.*, 2009).

[0027] The term "myeloid derived suppressor cells" (MDSCs), as used herein, refers to a heterogeneous population of cells consisting of myeloid progenitor cells and immature myeloid cells (IMCs). In healthy individuals, IMCs that are quickly generated in the bone marrow differentiate into mature granulocytes, macrophages or dendritic cells (DCs). Interference with the differentiation of IMCs into mature myeloid cells results in the expansion of MDSC population. Accumulating evidence has shown that MDSCs contribute to the negative regulation of immune responses during cancer and other diseases. In human cancer, a subset of myeloid cells was found to have significantly increased arginase activity, which down-regulates expression of the T cell receptor CD3-ζ chain; and to suppress T cell proliferation, suggesting that these cells may mediate tumor-related immune suppression (Ochoa *et al.*, 2007; Zea *et al.*, 2005). Moreover, since it was shown that IL-13 plays a crucial role in MDSC suppressive activity (Beers *et al.*, 2008), our suggestion that MDSC activity is involved in disease progression is consistent with a report showing that the percentages of both $CD4^+$IL-13^+ and $CD8^+$IL-13^+ T cells in the blood of ALS patients are significantly higher than in healthy controls. The proportion of $CD4^+$IL-13^+ T cells was shown to have a significant negative correlation with the ALS functional rating scale scores, and a significant positive correlation with the rate of disease progression (Chiu *et al.*, 2008).

[0028] Non-limiting examples of MDSCs include $CD11b^+/CD14^-$, $CD11b^+/CD14^-/CD15^+$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$, $CD14^+$/HLA-DR^-/low, and Lin^-/HLA-DR^-/low/$CD11b^+/CD33^+$ cell types.

[0029] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any one of $CD11b^+/CD14^-$, $CD11b^+/CD14^-/CD15^+$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$, $CD14^+$/HLA-DR^-/low, or Lin^-/HLA-DR^-/low/$CD11b^+/CD33^+$.

[0030] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any two cell types of the MDSCs listed, i.e., $CD11b^+/CD14^-$ and $CD11b^+/CD14^-/CD15^+$; $CD11b^+/CD14^-$ and $CD11b^+/CD14^+/CD15^+$; $CD11b^+/CD14^-$ and Lin^-/DR^-; $CD11b^+/CD14^-$ and $Lin^-/DR^-/CD33^+$; $CD11b^+/CD14^-$ and

CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+} and CD11b^{+}/CD14^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+} and Lin^{-}/DR^{-}; CD11b^{+}/CD14^{-}/CD15^{+} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}/CD15^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}/CD15^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/DR^{-}; CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{+}/CD15^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{+}/CD15^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{+}/CD15^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; Lin^{-}/DR^{-} and Lin^{-}/DR^{-}/CD33^{+}; Lin^{-}/DR^{-} and CD34^{+}/CD33^{+}/CD13^{+}; Lin^{-}/DR^{-} and ARG^{+}/CD14^{+}; Lin^{-}/DR^{-} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; Lin^{-}/DR^{-} and CD14^{+}/HLA-DR^{-}/low; Lin^{-}/DR^{-} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; Lin^{-}/DR^{-}/CD33^{+} and CD34^{+}/CD33^{+}/CD13^{+}; Lin^{-}/DR^{-}/CD33^{+} and ARG^{+}/CD14^{+}; Lin^{-}/DR^{-}/CD33^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; Lin^{-}/DR^{-}/CD33^{+} and CD14^{+}/HLA-DR^{-}/low; Lin^{-}/DR^{-}/CD33^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD34^{+}/CD33^{+}/CD13^{+} and ARG^{+}/CD14^{+}; CD34^{+}/CD33^{+}/CD13^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD34^{+}/CD33^{+}/CD13^{+} and CD14^{+}/HLA-DR^{-}/low; CD34^{+}/CD33^{+}/CD13^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; or CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}.

[0031] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any three cell types of the MDSCs listed, i.e., CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and CD11b^{+}/CD14^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and Lin^{-}/DR^{-}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}

/DR^{-}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/DR^{-}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-} and Lin^{-}/DR^{-}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+} and

CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/DR$^-$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$

/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$/CD33$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$/CD33$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; or CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$.

[0032] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any four cell types of the MDSCs listed, i.e., CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and Lin$^-$/DR$^-$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and Lin$^-$/DR$^-$/CD33$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$,

CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/DR$^-$/CD33$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/DR$^-$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and

ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$/CD15$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$/CD15$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$

/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$/CD33$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD34$^+$/CD33$^+$/CD13$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; or ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$.

[0033] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are $\gamma\delta$ T-cells and any five cell types of the MDSCs listed, i.e., CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/DR$^-$/CD33$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$

and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD34^{+}/CD33^{+}/CD13^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and

ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$/CD33$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; or CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$.

[0034] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any six cell types of the MDSCs listed, i.e., CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and CD34$^+$/CD33$^+$/CD13$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$ and

CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; or CD11b^{+}/CD14^{-}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and ARG^{+}/CD14^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD34^{+}/CD33^{+}/CD13^{+},

ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^+$/CD15$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and CD14$^+$/HLA-DR$^-$/low; Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; Lin$^-$/DR$^-$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; or Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$, CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$, CD14$^+$/HLA-DR$^-$/low and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$.

[0035] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any seven cell types of the MDSCs listed, i.e., CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and ARG$^+$/CD14$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^-$/CD15$^+$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD34$^+$/Lin$^-$/DR$^-$/CD11b$^+$/CD15$^+$; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and CD14$^+$/HLA-DR$^-$/low; CD11b$^+$/CD14$^-$, CD11b$^+$/CD14$^+$/CD15$^+$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$ and Lin$^-$/HLA-DR$^-$/low/CD11b$^+$/CD33$^+$; CD11b$^+$/CD14$^-$, Lin$^-$/DR$^-$, Lin$^-$/DR$^-$/CD33$^+$, CD34$^+$/CD33$^+$/CD13$^+$, ARG$^+$/CD14$^+$,

CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; or Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+}, CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}, CD14^{+}/HLA-DR^{-}/low and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}.

[0036] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any eight cell types of the MDSCs listed, i.e., CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD34^{+}/Lin^{-}/DR^{-}/CD11b^{+}/CD15^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and CD14^{+}/HLA-DR^{-}/low; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{-}/CD15^{+}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+}, CD34^{+}/CD33^{+}/CD13^{+}, ARG^{+}/CD14^{+} and Lin^{-}/HLA-DR^{-}/low/CD11b^{+}/CD33^{+}; CD11b^{+}/CD14^{-}, CD11b^{+}/CD14^{+}/CD15^{+}, Lin^{-}/DR^{-}, Lin^{-}/DR^{-}/CD33^{+},

$CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$ and $CD14^+/HLA\text{-}DR^-/low$; $CD11b^+/CD14^-$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$ and $Lin^-/HLA\text{-}DR^-/low/CD11b^+/CD33^+$; or $CD11b^+/CD14^-$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$, $CD14^+/HLA\text{-}DR^-/low$ and $Lin^-/HLA\text{-}DR^-/low/CD11b^+/CD33^+$.

[0037] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and any nine cell types of the MDSCs listed, i.e., $CD11b^+/CD14^-$, $CD11b^+/CD14^-/CD15^+$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$ and $CD14^+/HLA\text{-}DR^-/low$; $CD11b^+/CD14^-$, $CD11b^+/CD14^-/CD15^+$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$ and $Lin^-/HLA\text{-}DR^-/low/CD11b^+/CD33^+$; or $CD11b^+/CD14^-$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$, $CD14^+/HLA\text{-}DR^-/low$ and $Lin^-/HLA\text{-}DR^-/low/CD11b^+/CD33^+$.

[0038] In certain embodiments, the cells whose levels are measured in step (i) of the method of the invention are γδ T-cells and all the ten cell types of the MDSCs listed, i.e., $CD11b^+/CD14^-$, $CD11b^+/CD14^-/CD15^+$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$, $CD14^+/HLA\text{-}DR^-/low$ and $Lin^-/HLA\text{-}DR^-/low/CD11b^+/CD33^+$.

[0039] In a particular embodiment, the cells whose levels are measured in step (i) of the method of the present invention are γδ T-cells and $CD11b^+/CD14^-/CD15^+$.

[0040] In certain embodiments, the present invention relates to a method for diagnosing the likelihood of AD in a tested individual as defined above, when further comprising measuring in step (i) the level of at least one cell type of pro-inflammatory monocytes in said blood sample; and comparing in step (ii) the level of said at least one cell type of pro-inflammatory monocytes with a reference level representing a range level of said at least one cell type of pro-inflammatory monocytes in blood samples of age-matched controls, wherein an increase in the level of γδ T-cells; no change in the level of each one of said at least one cell type of MDSCs; and an increase in the level of at least one of said at least one cell type of pro-inflammatory monocytes indicate that said individual has a higher likelihood of having AD than said age-matched controls.

[0041] The term "pro-inflammatory monocytes", as used herein, refers to a non-classical type of monocytes characterized by low-level expression of CD14 and additional co-expression of the CD16 receptor ($CD14^{+}/CD16^{+}$ monocytes), which develop from the $CD14^{++}$ monocytes.

[0042] In particular such embodiments, the cells whose levels are measured in step (i) of the method of the invention are thus γδ T-cells; at least one cell type of the MDSCs listed above; and $CD14^{+}/CD16^{+}$ cells. More particular such embodiments are those wherein a sole cell type of MDSCs is measured, or those wherein any combination of two, three, four, five, six, or more cell types of MDCSs as defined above are measured.

[0043] In one particular embodiment exemplified herein, the cells whose levels are measured in step (i) of the method of the present invention are γδ T-cells, $CD11b^{+}/CD14^{-}/CD15^{+}$ cells and $CD14^{+}/CD16^{+}$ cells, wherein an increase in the level of γδ T-cells; no change in the level of $CD11b^{+}/CD14^{-}/CD15^{+}$ cells; and an increase in the level of $CD14^{+}/CD16^{+}$ cells indicate that said individual has a higher likelihood of having AD than said age-matched controls.

[0044] In a particular such aspect, the present invention thus relates to a method for diagnosing the likelihood of AD in a tested individual, said method comprising:

(i) measuring the levels of γδ T-cells, $CD11b^{+}/CD14^{-}/CD15^{+}$ cells and $CD14^{+}/CD16^{+}$ cells in a peripheral blood sample obtained from said individual; and

(ii) comparing the levels measured in (i) with reference levels representing range levels of γδ T-cells, $CD11b^{+}/CD14^{-}/CD15^{+}$ cells and $CD14^{+}/CD16^{+}$ cells, respectively, in blood samples of age-matched controls, thus obtaining a profile expressing the levels measured in (i) relative to said reference levels, respectively,

wherein an increase in the level of γδ T-cells; no change in the level of $CD11b^{+}/CD14^{-}/CD15^{+}$ cells; and an increase in the level of $CD14^{+}/CD16^{+}$ cells indicate that said individual has a higher likelihood of having AD than said age-matched controls.

[0045] In certain embodiments, the present invention relates to a method as defined above, wherein the cell types whose levels are measured in step (i) are γδ T-cells, $CD11b^{+}/CD14^{-}/CD15^{+}$ cells and $CD14^{+}/CD16^{+}$ cells, and the profile obtained in step (ii), expressing the level measured in step (i) for each one of the cell types and indicating a higher likelihood of AD for the tested individual, includes increase of at least 50%, at least

60%, at least 70%, at least 80%, at least 90%, about 100%, or more, preferably about 100%, in the level of γδ T-cells in the blood sample analyzed, i.e., the blood sample obtained from the tested individual, compared with a reference level representing a range level of γδ T-cells in blood samples of age-matched controls; and increase of at least 30%, at least 35%, at least 40%, at least 45%, about 50%, or more, preferably about 50%, in the level of $CD14^+/CD16^+$ cells in the blood sample analyzed compared with a reference level representing a range level of $CD14^+/CD16^+$ cells in blood samples of age-matched controls.

[0046] The peripheral blood sample analyzed in step (i) of the method of the present invention is obtained by taking blood sample from the individual being diagnosed for the likelihood of AD; and contacting said blood sample with various types of antibodies each directed to one of the cell types or subsets whose levels are measured, i.e., γδ T-cells, at least one cell type of MDSCs as defined above, and optionally at least one cell type of pro-inflammatory monocytes as defined above, wherein each type of the antibodies used is either directly or indirectly labeled with, e.g., a fluorescent marker. The level of each one of the cell types or subsets is then measured in said blood sample utilizing any suitable technique known in the art, preferably by FACS as described in the Examples section hereinafter.

[0047] The level measured for each one of the cell types or subsets tested, according to step (i) of the diagnosing method of the invention, is compared with a reference level representing a range level of said cell type or subset in blood samples of age-matched controls, i.e., a group of healthy individuals in the same age-group as the tested individual. This range level, also termed herein "the normal range level", is derived from the available medical knowledge and represents the normal range level for the specific cell type or subset tested in blood samples of age-matched controls.

[0048] According to step (ii) of this method, after comparing the level measured for each one of the cell types or subsets tested with the reference level, i.e., the normal range level, thereof, a profile is obtained, expressing the level of each one of the cell types of subsets tested in the blood sample obtained from the tested individual relative to the level of each one of these cell types or subsets, respectively, in blood samples of age-matched controls.

[0049] The profile obtained in step (ii) of the diagnosing method of the invention is a relative profile, showing the level of each one of the cell types or subsets measured according to this method in the blood sample obtained from the tested individual relative to the reference level of said cell type or subset in blood samples of age-matched controls.

Since the reference level to which the measured level is compared represents, in fact, a range level of said cell type or subset in blood samples of healthy individuals in the same age-group as the tested individual, each one of the levels measured in the blood sample tested can be compared with either the median value or the upper level value, but preferably with the upper level value, of the normal reference.

[0050] According to step (i) of this method as defined above, the level of γδ T-cells, at least one cell type of MDSCs, and optionally at least one cell type of a pro-inflammatory monocytes, are measured, and therefore, the profile obtained in step (ii) expresses the level of at least two, i.e., two, three, four, five, six, seven, eight, or more, but preferably three or more cell types or subsets, as defined above.

[0051] The relative level of each one of the cell types or subsets measured is represented in the profile by "increase", indicating that the level of said cell type or subset in the blood sample tested is increased compared with the upper limit of the normal range level thereof, i.e., the range level of said cell type or subset in blood samples of age-matched controls, by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or more; "decrease", indicating that the level of said cell type or subset in the blood sample tested is decreased compared with the lower limit of the normal range level thereof by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, or more; or "no change", indicating that the level of said cell type or subset in the blood sample tested is neither increased nor decreased as defined above, i.e., within or close to the normal range level thereof.

[0052] AD develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years. Moreover, early symptoms of AD are often mistakenly thought to be "age-related" concerns, or manifestations of stress. AD is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alterbative conditions. The method discussed above is aimed at diagnosing, more specifically early diagnosing, the likelihood of AD in a tested individual, wherein the individuals subjected to this method are those exhibiting certain signs that might be associated with AD, particularly difficulty in remembering recent events (rather than older memories of the person's life, also called "episodic memory", facts learned, i.e., semantic memory, and implicit memory, i.e., the

memory of the body on how to do things, which are affected to a lesser degree), which is the most common symptom in early stages of the disease.

[0053] Individuals diagnosed according to the method of the present invention as having a higher likelihood of AD, can be directed to subsequent confirmatory diagnosis steps, or may start receiving a therapeutic treatment aimed at treating the cognitive manifestations of AD, e.g., an acetylcholineesterase inhibitor such as tacrine, rivastigmine, galantamine and donepezil, or an N-methyl d-aspartate (NMDA) receptor antagonist such as memantine, or psychosocial intervention. When AD is suspected, the diagnosis is usually confirmed with tests that evaluate behaviour and thinking abilities, often followed by a brain scan, also called neuroimaging, if available. Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to exclude other cerebral pathology or subtypes of dementia. The decision whether subsequent confirmatory diagnosis steps are required, or a treatment can be provided, will be determined as deemed appropriate by the practitioner.

[0054] It is expected that alterations observed in the level of certain cell types or subsets measured in a blood sample of a patient suffering from progressive AD at a first instant will be weaker, i.e., less pronounced than those measured in a blood sample taken from the same patient, at a second instant that is about 1, 2, 3, 4, 5, 6 months or more later than the first one. In other words, it is postulated that a progression of the disease would be reflected in the levels measured for one or more of the cell types or subsets tested, wherein the differences between the levels measured at the later instant for at least one of the cell types or subsets tested and the normal range levels of said cell type or subset will be significantly greater than those obtained for said cell types or subsets at the earlier instant. Similarly, it may be expected that a moderation in at least some of the alterations observed in the first instant will be noticed at the later instant in case an effective therapeutic treatment for AD is given to said patient.

[0055] In another aspect, the present invention thus relates to a method for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, said method comprising:

(i) measuring the levels of γδ T-cells in a peripheral blood sample obtained from said patient at two consecutive instants, the earlier of said instants is

prior to or during said treatment and the later of said instants is during said treatment; and

(ii) comparing the levels measured for γδ T-cells at said two instants,

wherein a decrease in the level measured for γδ T-cells at said later instant compared with the level measured for γδ T-cells at said earlier instant towards a reference level representing a range level of γδ T-cells in blood samples of age-matched controls is correlated with the efficacy of said treatment.

[0056] In certain embodiments, the present invention relates to a method for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, as defined above, when further comprising measuring in step (i) the level of at least one cell type of pro-inflammatory monocytes in said blood sample at said two instants; and comparing in step (ii) the level measured for said at least one cell type of pro-inflammatory monocytes at said two instants, wherein a decrease in the level measured for γδ T-cells and/or at least one of said at least one cell type of pro-inflammatory monocytes at said later instant compared with the level measured for γδ T-cells and/or at least one of said at least one cell type of pro-inflammatory monocytes, respectively, at said earlier instant towards a reference level representing range levels of γδ T-cells and said at least one of said at least one cell type of pro-inflammatory monocytes, respectively, in blood samples of age-matched controls is correlated with the efficacy of said treatment.

[0057] In a particular such embodiment, the method of the invention comprises measuring in step (i) the levels of γδ T-cells and $CD14^+/CD16^+$ cells in a peripheral blood sample obtained from said patient at two consecutive instants, the earlier of said instants is prior to or during said treatment and the later of said instants is during said treatment; and comparing in step (ii) the levels measured for γδ T-cells and $CD14^+/CD16^+$ cells at said two instants, wherein a decrease in the level measured for γδ T-cells and/or $CD14^+/CD16^+$ cells, i.e., for either one or both of these cell types, at said later instant compared with the level measured for γδ T-cells and/or $CD14^+/CD16^+$ cells, respectively, at said earlier instant towards a reference level representing range levels of γδ T-cells and $CD14^+/CD16^+$ cells, respectively, in blood samples of age-matched controls is correlated with the efficacy of said treatment.

[0058] In contrast to the diagnosing method described above, in which the levels of certain cell types or subsets in a blood sample obtained from a tested individual is compared with the levels of those cell types or subsets in blood samples of age-matched

controls, in this method, in which the efficacy of a treatment for AD in an Alzheimer's patient is determined, the levels of such cell types or subsets in a peripheral blood sample obtained from an AD patient are measured at two consecutive instants and are then compared so as to evaluate the progression of the disease or, alternatively, the efficacy of an AD treatment given to said patient.

[0059] The phrase "a range level", as used herein with respect to a particular cell type or subset in blood samples of age-matched controls, refers to the normal range level for a specific cell type or subset in blood samples of age-matched controls, as defined above.

[0060] The phrase "a decrease in the level measured for a particular cell type or subset at said later instant compared with the level measured for said cell type or subset at said earlier instant towards a reference level representing a range level of said cell type in blood sample of age-matched controls" refers to any case in which the difference between the level measured at the earlier instant for said cell type or subset and the normal range level of said cell type or subset is significantly greater than that obtained for said cell type or subset at the later instant when compared with the normal range level thereof. A decrease in the level measured for a certain cell type or subset at said later instant compared with the level measured for said cell type or subset at said earlier instant towards the normal range level of said cell type or subset may thus be defined as a significantly less pronounced increase in cases wherein the relative level of said cell type or subset at the earlier instant is initially increased, as defined above.

[0061] According to this method, the earlier of said instants is prior to or during said treatment and the later of said instants is during said treatment. Thus, in certain embodiments, the earlier of said two consecutive instants is prior to said treatment and the later of said instants is following about 1, 2, 3, 4, 5, 6 months or more of said treatment. In other embodiments, the earlier of said two consecutive instants is at any point in time during said treatment and the later of said instants is about 1, 2, 3, 4, 5, 6 months or more after the earlier of said two instants.

[0062] As described above, in contrast to certain neurodegenerative diseases such as ALS, no alteration was observed in the level of the MDSCs $CD11b^+/CD14^-/CD15^+$ in peripheral blood samples of Alzheimer's patients compared with the normal range level of these cells. Therefore, while the level of these monocytes can be used, in combinations with the level of other cell types or subsets as defined above, for diagnosing the likelihood of AD in a tested individual, the level of these specific monocytes has no importance in

monitoring the progression of said disease or in determining the efficacy of a treatment for AD in an Alzheimer's patient.

[0063] Nevertheless, when carrying out this method and in order to guarantee that the levels measured for the various cell types or subsets tested at each one of the two consecutive instants are not influenced by an external factor such as inflammation and can thus be relied upon, it is recommended that the level of at least one cell type or subset whose level in Alzheimer's patients is within the normal range level thereof, i.e., within the range level of said cell type or subset in blood samples of age-matched controls, e.g., any cell type of the MDSCs defined above such as $CD11b^{+}/CD14^{-}/CD15^{+}$, is further measured in step (i) of the method and serves as a control, wherein the levels measured for each one of said at least one cell type or subset at both instants should be within the normal range thereof.

[0064] The method of the invention, in which the efficacy of a treatment for AD in an Alzheimer's patient is determined, enables to evaluate the progression of the disease or, alternatively, whether there is an improvement in the patient's condition resulting from said treatment. It is assumed that an indication for significant improvement in the patient's condition, provided by utilizing this method, will be accompanied by improvement to a certain degree in the clinical symptoms observed. Nevertheless, it may be expected that in certain cases, wherein an indication for a less significant improvement in the patient's condition is provided, no improvement will be observed in the clinical symptoms. In any case, i.e., no matter what indication is provided by the method of the invention and how significant said indication is, the outcome of this method is analyzed by the practitioner and any decision regarding maintaining or changing the treatment for AD given to said patient is taken by said practitioner.

[0065] In a further aspect, the present invention provides a kit for diagnosing the likelihood of AD in a tested individual; or for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, said kit comprising:

(i) a list of cell types including γδ T-cells and at least one, i.e., 1, 2, 3, 4, 5, 6, or more cell type of M

(ii) DSCs as defined above;

(iii) antibodies against each one of said cell types;

(iv) reagents for detecting said antibodies;

(v) a list of reference levels representing range levels of said cell types in blood samples of age-matched controls; and

(vi) instructions for use.

[0066] The kit of the present invention can be used for carrying out both of the non-therapeutic methods described above, i.e., both the method in which the likelihood of AD in a tested individual is diagnosed, and the method in which the efficacy of a treatment for AD in an Alzheimer's patient is determined.

[0067] In certain embodiments, the kit of the present invention is used for diagnosing the likelihood of AD in a tested individual; or for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, as defined above, wherein said list of cell types further includes at least one cell type of pro-inflammatory monocytes as defined above. In particular such embodiments, said pro-inflammatory monocytes are $CD14^{+}/CD16^{+}$ cells.

[0068] The kit of the invention further comprises antibodies against each one of said cell types, as well as reagents required for the detection of those antibodies. The antibodies may be either monoclonal or polyclonal, but they are preferably monoclonal antibodies. Both the antibodies and the reagents provided are used for measuring the levels of the cell types listed, in said blood sample.

[0069] As defined by both of the non-therapeutic methods of the invention, the level measured for each one of the cell types listed is compared with a range level of said cell type in blood samples of age-matched controls so as to evaluate whether the level measured is higher than, or within, the normal range level of said cell type, i.e., the range level of said cell type in blood samples of age-matched controls. These data are compared with reference levels, further included in the kit, expressing range levels of said cell types in blood samples of age-matched controls, so as to determine whether said individual has a higher likelihood of having AD than said age-matched controls. Alternatively, i.e., in case a blood sample taken from an Alzheimer's patient is tested, these data may be compared with data obtained from the same patient at a previous or later instant, so as to determine whether the treatment for AD given to said patient is efficient.

[0070] The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

Materials and Methods

[0071] ***Patients***: The patient's group included individuals, both males and females, which have been clinically diagnosed as suffering from AD and agreed to sign on the informed consent. The control group included male and female volunteers without clinical symptoms of AD, who agreed to sign on the informed consent. Alzheimer's patients and controls that were included into the study have been examined for their cognitive skills using the mini-mental test. A blood sample of up to 20 ml was taken and delivered to the lab to be analyzed for the different cellular components after excluding the presence of the following viruses: HCV, HBSAG, HIV, HTLV and TPHA. Blood analysis was performed between 18-24 hours from the time it was taken.

[0072] ***Whole blood FACS staining***: 50 μl of whole blood samples were incubated with 5 μl of each of the designated mAb for 45 minutes at 4°C. Two ml of FACSlyse (Becton Dickinson, San Jose, CA) was added to each tube, and the tubes were then incubated at room temperature for 12 minutes, followed by wash with 2 ml PBS. From each sample, 10^5 events were acquired by FACSCalibur (Becton Dickinson, San Jose, CA) and analyzed by the FCS Express V3 software.

[0073] ***The designated mAb's***: CD3, CD4, CD8, CD14, CD15, CD11b, CD16, Lin, HLA-DR, CD33, TCRgd - Becton Dickinson, San Jose, CA. TLR4 eBioscience San Diego, CA.

Example 1. Accuracy and robustness of results in healthy volunteers

[0074] In this study, the distribution of single markers on total live peripheral blood mononuclear cells (PBMC) was tested, first using blood from young, healthy volunteers, so as to examine the accuracy and robustness of our measurements, and then in a controlled study comparing Alzheimer's patients and matched age controls.

[0075] Freshly isolated PBMC of healthy volunteers were stained with fluorescein isothiocyanate (FITC), phycoerythrin (PE) or allophycocyanin (APC)-labeled mononuclear antibodies against CD3, CD14, CD19, CD11c, CD34 and CD15, and the proportion and level of expression of each one of these markers were analyzed by fluorescence-activated cell sorting (FACS) (**Figs. 1A-1B**).

[0076] Freshly isolated PBMC of healthy volunteers were double stained with APC-labeled mononuclear antibodies against CD3 and either FITC- or PE-labeled mononuclear

antibodies against CD4, CD8, CTLA4 or TCRgd, and the percentage of cells expressing each one of these markers out of the CD3 positive cell population, as well as the intensity of expression, were measured (**Table 1**; **Figs. 2A-2B**).

[0077] The results shown in **Figs. 1-2** indicate that the markers with relatively small deviations between the different blood samples can be monitored. The results presented in **Table 1** show that the distribution of CD14 and CD16 on peripheral blood monocytes can be separated into three distinct subpopulations: high, dim and negative expression of CD14, each represent a different cellular phenotype.

Table 1: Monocyte's sub-population

	$CD14^+$ $CD40^+$	CD14high $CD16^-$	CD14high $CD16^+$	CD14dim $CD16^+$	$CD14^-CD15^+$ $CD11b^+$
% of positive cells	40.27 (4.72) n=4	75.23 (4.16) n=4	10.38 (3.71) n=4	4.44 (0.62) n=4	15.82 (2.81) n=4
Mean fluorescence intensity	213.38 (17.45)	247.29 (44.64)	167.42 (27.99)	32.64 (1.78)	78.05 (20.97)

Example 2. Alzheimer's patients show elevated level of both γδ-T cells and $CD14^+$/$CD16^+$ cells in PBMC compared with healthy controls

[0078] The studies described herein were conducted using about 32 blood samples, about half of them obtained from Alzheimer's patients and half of them obtained from age-matched healthy volunteers. In addition, 7 blood samples of amyotrophic lateral sclerosis (ALS) patients, another neurodegenerative disease, were analyzed. All blood samples were encoded, and analysis of the results was done blindly.

Table 2: Differential count of peripheral mononuclear cells (% of total PBMC)

		Average	SD	Min	Median	Max	n
Monocytes CD14	**Healthy**	16.6	6.28	9.1	16.2	29.8	14
	AD	19.1	4.95	11.6	18.5	29.9	15
	ALS	18.9	4.3	13.4	17.3	25.7	7
T-cells CD3	**Healthy**	53.9	11.95	27.7	57.6	69.7	14
	AD	57.5	9.39	40.4	56.5	73.2	16
	ALS	49.4	8.4	38.3	48	63.1	7
B-cells CD19	**Healthy**	8.2	3.42	2.8	8.0	17.0	14
	AD	7.2	3.44	2.9	5.7	13.0	16
	ALS	ND	ND	ND	ND	ND	ND

[0079] The proportion of PBMC population as measured by flow cytometry (monocytes-CD14, T-cells-CD3 and B-cells-CD19) are presented in **Table 2**, indicating no significant difference between the patients and the healthy controls.

[0080] The percentage of T-helper (CD4 positive cells) and cytotoxic-T cells (CD8 positive cells) out of total T-cells (CD3 positive cells), as well as the ratio between these two cell-populations, were measured using flow cytometey method in the blood of the patients and healthy controls. No difference was found between the two groups (**Table 3**).

Table 3: Leukocyte sub-populations

		Average	SD	Min	Median	Max	n
Monocytes CD14	**Healthy**	64.3	17.13	20.9	68.4	86.9	14
	AD	63.5	16.37	33.6	66.1	87.1	16
	ALS	65.5	5.2	59.3	65.2	75.4	7
T-cells CD3	**Healthy**	31.7	16.47	11.7	29.3	78.2	14
	AD	30.5	14.59	11.3	29.7	56.6	16
	ALS	27.9	7.8	16.1	31.5	34.9	7
B-cells CD19	**Healthy**	2.8	1.96	0.3	2.3	8.1	14
	AD	3.0	2.15	0.6	2.2	7.7	16
	ALS	2.6	1.1	1.7	2.0	4.3	7

[0081] While no differences were found in the amount of lymphocytes and monocytes in the blood of AD patients, ALS and healthy volunteers, as shown above, significant differences in sub-population of lymphocytes and monocytes were found, as shown in **Table 4**. These cell types are typically involved with regulation of the adaptive immune response as described below.

Table 4: Percentage of sub-populations out of total lymphocytes and monocytes respectively

		Average	SD	Min	Median	Max	n
γδ-T-cells	**Healthy**	2.6	1.96	0.7	1.9	7.3	14
	AD	6.0	2.87	2.3	5.0	12.8	16
	ALS	12.9	8.1	1.8	11.8	26.8	7
$CD14^+/CD16^+$	**Healthy**	10.5	5.78	2.4	9.7	20.4	14
	AD	16.3	8.70	3.2	17.4	34.9	16
	ALS	7.8	3.9	2.5	8.1	14.7	7
MDSC	**Healthy**	1.9	2.0	0.04	1.05	6.94	14
	AD	1.7	1.8	0.2	0.9	5.8	16
	ALS	11.0	10.5	1.4	9.2	32.6	7

[0082] Gamma-delta (γδ)-T cells were found to be significantly elevated in the AD patients in comparison to the healthy controls, but less than in the ALS patients. This group of cells has a complex behavior; they were shown to act as "first line of defense", "regulatory cells", and as "bridge between innate and adaptive responses". Their exact role in the pathological cascade of AD should be further investigated. Yet, the preliminary results suggest that they may be used for AD diagnosis with relatively high accuracy.

[0083] Elevated levels of the pro-inflammatory sub-set of monocytes ($CD14^+/CD16^+$) were found in the AD patients but not in the ALS patients. More particularly, while in the healthy donors these cells accounted for about 10% of all monocytes, in the AD patients they accounted for about 16% of all monocytes. The $CD14^+/CD16^+$ cells have been shown to efficiently produce the pro-inflammatory cytokine TNFα, while they produce no or little of the anti-inflammatory cytokine IL-10 (Belge *et al.*, 2002). This may dictate the phenotype of the adaptive immune response towards a Th1 type of response instead of the beneficial Th2 response. It is thus important to examine the correlation between the level of the cells and the severity of the disease.

[0084] Within the monocyte population, while a dramatic elevation was found in the percentage of cells with the markers $CD14^-/CD11b^+/CD15^+$, a phenotype associated with myeloid-derived suppressor cells (MDSCs), in the blood of patients with ALS, no difference in the percentage of these cells was found between the AD patients and the healthy controls. These cells constitute a population of immature myeloid cells with potent immunosuppressive functions.

[0085] The significant differences described above in white blood cells profile of AD patients in comparison to age-matched controls and to ALS patients can be used for accurate diagnosis of AD.

[0086] An analysis was performed so as to evaluate the potential of the findings described herein to be used as biomarkers for accurate diagnosis of AD. The analysis included the evaluation of the above-described independent immune system antigens, coupled with a sophisticated analytical algorithm for data processing in an effort to clearly define the molecular relationship of these antigens and the test's performance in regard with AD diagnosis. At this stage, and to evaluate the potential of the individual markers, per each of the above described markers, we determined meaningful results based on accuracy levels. In particular, we examined the maximal sum of sensitivity and specificity and area under the receiver operator characteristic curve (AUC of ROC). AUC is an overall measure

of the accuracy of a test. As a general rule, with exceptions, AUC should be at about 0.8 or higher before a marker is considered feasible.

[0087] The ROC curve for γδ-T-cells is shown in **Fig. 3**. This marker appears to be highly sensitive and accurate for AD diagnosis, as shown in **Table 5**. It may be expected that the combination of this marker with the additional markers, will contribute to the sensitivity, selectivity and specificity of this test. Furthermore, it is suggested that the level of these cells may also correlate with disease severity.

Table 5: The sensitivity and specificity of the biomarkers found for diagnosis of AD

	Sensitivity	**Specificity**	**AUC**	***P***
γδ-T-cells	87%	85%	0.87	<0.001
$CD14^+/CD16^+$	60%	85%	0.70	0.064

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CLAIMS

1. A method for diagnosing the likelihood of Alzheimer's disease (AD) in a tested individual, comprising:

    (i) measuring the levels of gamma-delta (γδ) T-cells and at least one cell type of myeloid derived suppressor cells (MDSCs) in a peripheral blood sample obtained from said individual; and

    (ii) comparing the levels measured in (i) with reference levels representing range levels of γδ T-cells and said at least one cell type of MDSCs, respectively, in blood samples of age-matched controls, thus obtaining a profile expressing the levels measured in (i) relative to said reference levels, respectively,

    wherein an increase in the level of γδ T-cells; and no change in the level of each one of said at least one cell type of MDSCs indicate that said individual has a higher likelihood of having AD than said age-matched controls.

2. The method of claim 1, wherein said at least one cell type of MDSCs is $CD11b^+/CD14^-$, $CD11b^+/CD14^-/CD15^+$, $CD11b^+/CD14^+/CD15^+$, Lin^-/DR^-, $Lin^-/DR^-/CD33^+$, $CD34^+/CD33^+/CD13^+$, $ARG^+/CD14^+$, $CD34^+/Lin^-/DR^-/CD11b^+/CD15^+$, $CD14^+/HLA\text{-}DR^-/low$, or $Lin^-/HLA\text{-}DR^-/low/CD11b^+/CD33^+$ cells.

3. The method of claim 2, wherein said at least one cell type of MDSCs are $CD11b^+/CD14^-/CD15^+$ cells.

4. The method of any one of claims 1 to 3, further comprising measuring in step (i) the level of at least one cell type of pro-inflammatory monocytes in said blood sample; and comparing in step (ii) the level of said at least one cell type of pro-inflammatory monocytes with a reference level representing a range level of said at least one cell type of pro-inflammatory monocytes in blood samples of age-matched controls,

    wherein an increase in the level of γδ T-cells; no change in the level of each one of said at least one cell type of MDSCs; and an increase in the level of at least one of said at least one cell type of pro-inflammatory monocytes indicate that said individual has a higher likelihood of having AD than said age-matched controls.

5. The method of claim 4, wherein said at least one cell type of pro-inflammatory monocytes are $CD14^+/CD16^+$ cells.

6. The method of claim 4 or 5, wherein the levels of γδ T-cells, $CD11b^+/CD14^-/CD15^+$ cells and $CD14^+/CD16^+$ cells are measured in step (i).

7. The method of claim 6, wherein the level of γδ T-cells in the blood sample obtained from said individual is by at least 50%, 60%, 70%, 80%, 90%, or 100% higher than the level of γδ T-cells in blood samples of age-matched controls; and the level of $CD14^+/CD16^+$ cells in the blood sample obtained from said individual is by at least 30%, 35%, 40%, 45%, or 50% higher than the level of $CD14^+/CD16^+$ cells in blood samples of age-matched controls.

8. A method for diagnosing the likelihood of Alzheimer's disease in a tested individual, comprising:

(i) measuring the levels of gamma-delta (γδ) T-cells, $CD11b^+/CD14^-/CD15^+$ cells and $CD14^+/CD16^+$ cells in a peripheral blood sample obtained from said individual; and

(ii) comparing the levels measured in (i) with reference levels representing range levels of γδ T-cells, $CD11b^+/CD14^-/CD15^+$ cells and $CD14^+/CD16^+$ cells, respectively, in blood samples of age-matched controls, thus obtaining a profile expressing the levels measured in (i) relative to said reference levels, respectively,

wherein an increase in the level of γδ T-cells; no change in the level of $CD11b^+/CD14^-/CD15^+$ cells; and an increase in the level of $CD14^+/CD16^+$ cells indicate that said individual has a higher likelihood of having AD than said age-matched controls.

9. A method for determining the efficacy of a treatment for Alzheimer's disease (AD) in a patient diagnosed as suffering from AD, comprising:

(i) measuring the levels of gamma-delta (γδ) T-cells in a peripheral blood sample obtained from said patient at two consecutive instants, the earlier of said instants is prior to or during said treatment and the later of said instants is during said treatment; and

(ii) comparing the levels measured for γδ T-cells at said two instants,

wherein a decrease in the level measured for γδ T-cells at said later instant compared with the level measured for γδ T-cells at said earlier instant towards a reference level representing a range level of γδ T-cells in blood samples of age-matched controls is correlated with the efficacy of said treatment.

10. The method of claim 9, further comprising measuring in step (i) the level of at least one cell type of pro-inflammatory monocytes in said blood sample at said two instants; and comparing in step (ii) the level measured for said at least one cell type of pro-inflammatory monocytes at said two instants,

wherein a decrease in the level measured for γδ T-cells and/or at least one of said at least one cell type of pro-inflammatory monocytes at said later instant compared with the level measured for γδ T-cells and/or at least one of said at least one cell type of pro-inflammatory monocytes, respectively, at said earlier instant towards a reference level representing range levels of γδ T-cells and said at least one of said at least one cell type of pro-inflammatory monocytes, respectively, in blood samples of age-matched controls is correlated with the efficacy of said treatment.

11. The method of claim 10, wherein said at least one cell type of pro-inflammatory monocytes are $CD14^{+}/CD16^{+}$ cells.

12. The method of any one of claims 9 to 11, wherein the earlier of said instants is prior to or during said treatment and the later of said instants is about 1, 2, 3, 4, 5, 6 months or more later than the earlier instant.

13. A kit for diagnosing the likelihood of Alzheimer's disease (AD) in a tested individual; or for determining the efficacy of a treatment for AD in a patient diagnosed as suffering from AD, said kit comprising:

(i) a list of cell types including gamma-delta (γδ) T-cells and at least one cell type of myeloid derived suppressor cells (MDSCs);
(ii) antibodies against each one of said cell types;
(iii) reagents for detecting said antibodies;
(iv) a list of reference levels representing range levels of said cell types in blood samples of age-matched controls; and
(v) instructions for use.

14. The kit of claim 13, wherein said list of cell types further includes at least one cell type of pro-inflammatory monocytes.

15. The kit of claim 14, wherein said at least one cell type of pro-inflammatory monocytes are $CD14^{+}/CD16^{+}$ cells.

Fig. 1A

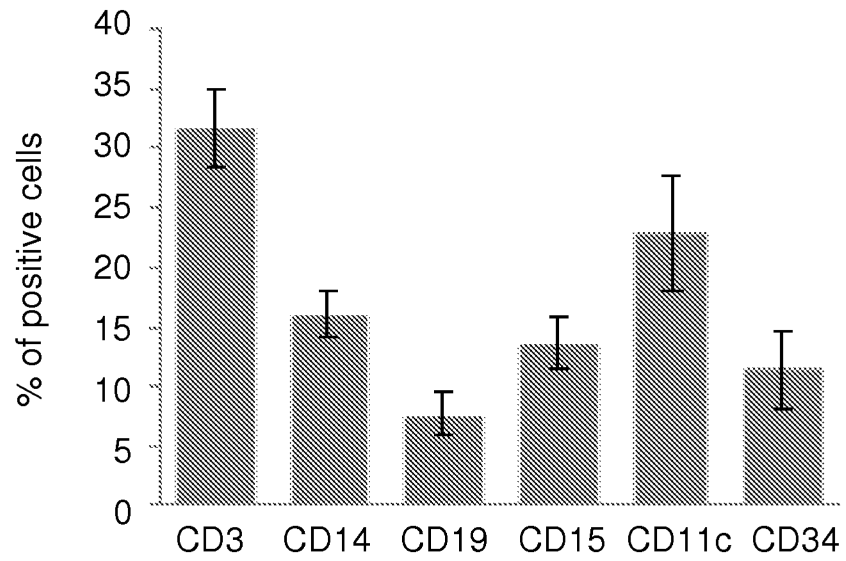


Fig. 1B

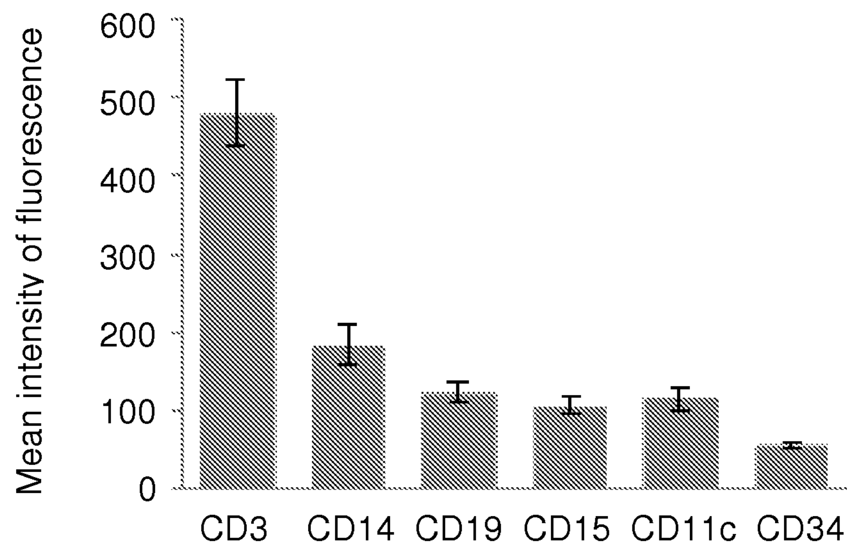


Fig. 2A

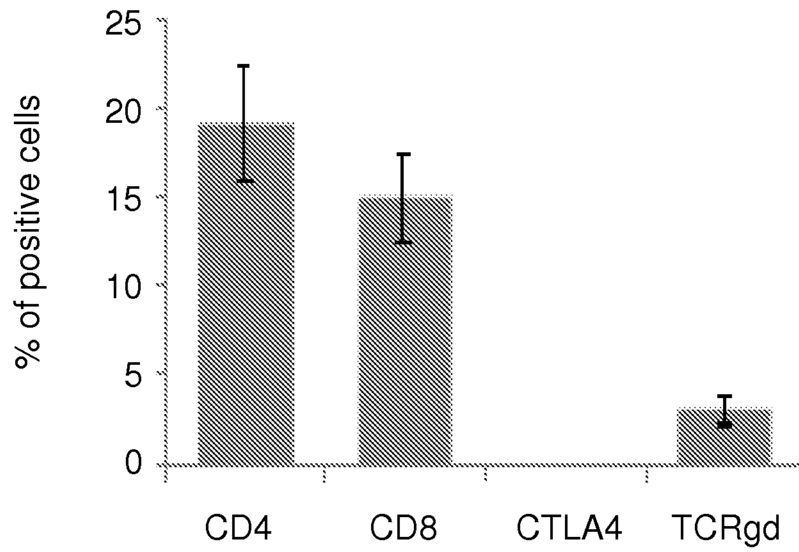


Fig. 2B

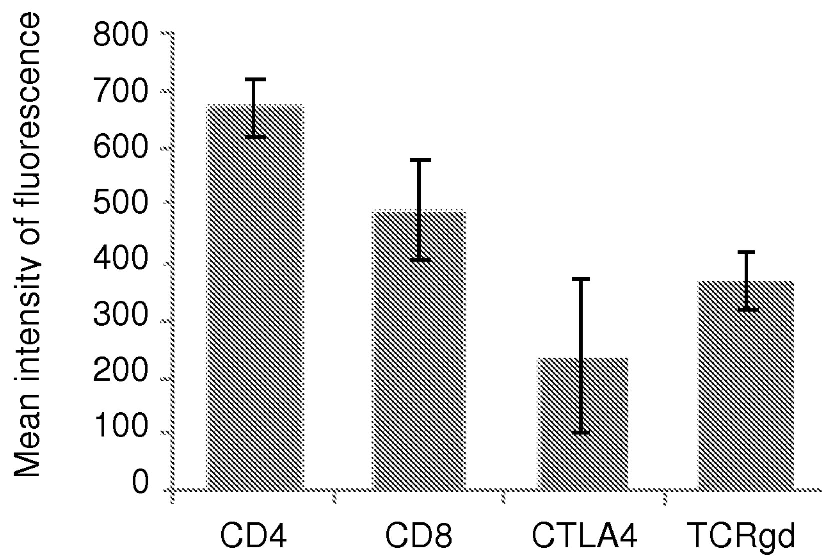
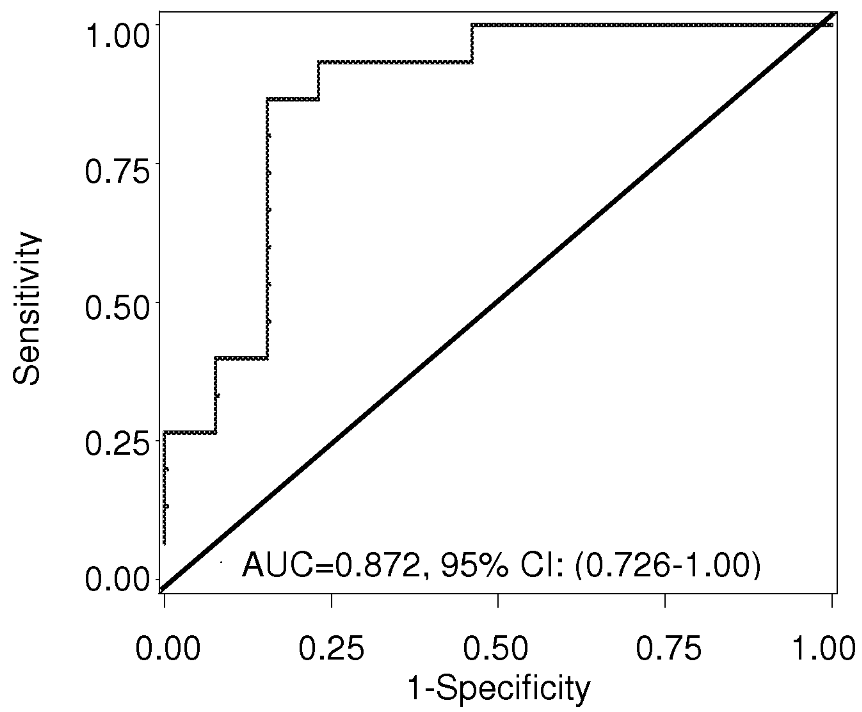


Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2013/050277

A. CLASSIFICATION OF SUBJECT MATTER
IPC (2013.01) G01N 33/53

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)
IPC (2013.01) G01N 33/53

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)
Databases consulted: NCBI, THOMSON INNOVATION, CAPLUS, BIOSIS, WPI Data, EPODOC, Google Scholar
Search terms used: gamma-delta T cells, alzheimer, AD, neurodegenerative, dementia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/111043 A1 YEDA RES & DEV [IL] 15 Sep 2011 (2011/09/15) examples, figures	1-15
A	Fiszer U (1995) Role of gamma-delta T-cells and heat shock proteins in immunological response and in pathogenesis of neurological diseases. Neurol Neurochir Pol 29 (5): 737. Abstract (Article in Polish) Retrieved from the Internet: <URL: http://europepmc.org/abstract/MED/8584100> 31 Oct 1995 (1995/10/31) abstract	1-15

☐ 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
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"P" document published prior to the international filing date but later than the priority date claimed
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"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 Jun 2013	01 Jul 2013

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	KEDAR Laura Telephone No. 972-5651743

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2013/050277

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
WO 2011/111043 A1	15 Sep 2011	NONE	