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(54) BIOMARKER COMPOSITION FOR DIAGNOSING STILL'S DISEASE, DIAGNOSTIC KIT, AND DIAGNOSTIC METHOD

(57) The present invention relates to a biomarker composition for diagnosing Still's disease, a diagnostic kit, and a diagnostic method, and more particularly, the present invention can accurately diagnose Still's disease in children and adults using the expression level of CD11b or CD32 and the frequency of granulocytes to lymphocytes as indexes.

FIG. 1

	P1% / Whole cells			CD11b / Whole cells			CD32/ Whole cells		
	healthy	stills	RA	healthy	stills	RA	healthy	stills	RA
	72.5	70.95	52.55	50.0	77.7	45.6	33.4	75.6	37.6
	78.5	78.35	71.5	47.4	81.8	68.5	28.8	50.7	70.4
	55.3	77.05	83.4	58.7	80.7	84.3	58.5	79.6	83.5
	51	65.8	56.8	40.1	92.9	68.8	37.9	93.7	68.1
	76.4	61	83.6	53.7	71.2	91.5	58	70.6	94.1
	61.4	97.4	66.95	35.5	97	66.4	37.5	95.6	67.8
	55.3	63.1	67.55	37	66.6	77.7	36.3	75.8	74.9
	68.6	79	40.6	30.2	72.3	56.6	34.9	73.2	57.1
	62.0	72.75	61.15	33	90.6	48.6	32.9	87.8	51.2
	59.8	70.35	80.1	61.2	75.4	63.4	66.1	79.1	68.9
	73.7	74.1	67.65	60	78.7	55.6	67.2	77.5	62.6
	70.0	92.65	67.95	66.3	44.4	38.9	66.8	51.8	40.7
	79.6	67.5	61.4	58.5	86.3	40.3	59.7	90.9	45.6
	71.7	90	56.6	67.8	63.5	31	63.8	65.9	33.3
	53.2	91.2	69.45	55.5	87.2	47.6	43.1	88.5	50.5
	75.5	43.7	61.9	67.5	93.8	32.8	63.2	93.9	34.9
	64.4	78.1	70.7	56.4	87.5	43	59.5	81.4	46.2
	84.6	71.45	68.35	60.3	89.5	38.8	69	85.7	45.7
	70.9		68.6	52.2		57	55.2		57
Avg	**67.6**	**74.6**	**66.1**	**52.1**	**79.8**	**55.6**	**51.1**	**78.7**	**57.3**
SD	9.7	12.9	10.4	11.8	13.0	17.3	14.2	13.0	16.8

EP 3 285 071 A1

Description

TECHNICAL FIELD

[0001] The present invention relates to a biomarker composition for diagnosing Still's disease, a diagnostic kit, and a method of providing information for diagnosis.

BACKGROUND ART

[0002] Still's disease which is the systemic form of juvenile rheumatoid arthritis is a disease that has not yet elucidated its cause since the disease was first described by Dr. Still, and the disease occurs in both children and adults. Adult-onset Still's disease occurring in adults was first reported by Bywaters in 1971, and since then, it has been reported in all around the world and is known as a rare disease or a causative disease of fever of unknown origin.

[0003] Adult-onset Still's disease has been usually reported as a benign disease having a favorable prognosis. However, fatal cases where some patients die from adult-onset Still's disease have also been reported. Patients may be in a condition where the patients may die in the case of hemophagocytotic syndrome, worsening liver function, and liver infection. Domestic studies have also reported a prognosis of death in about 10% of the affected patients.

[0004] A diagnosis of Still's disease is mainly based on clinical findings. The disease is diagnosed through clinical findings, such as high fever, arthralgia or arthritis, characteristic skin lesion, lymph node enlargement, hepatomegaly, splenomegaly, sclerosis and sore throat, and laboratory findings, such as leukocytosis, accelerated erythrocyte sedimentation, a negative antinuclear antibody, and a negative rheumatoid factor.

[0005] Most of the studies on adult-onset Still's disease are associated with inflammatory cytokines using serum of a patient, a simple enzyme-linked immunospecific assay (ELISA) study with respect to an acute reactant material, or a genetic research, but there has been no report of systematic biomarkers. Furthermore, due to lack of understanding of the pathogenesis, the treatment of the disease depends on experience, and there is no consensus thereon.

[0006] According to a genetic research of adult-onset Still's disease, it has been reported that the disease is associated with a human leucocyte antigen (HLA), specifically with HLA-DR4 and HLA-DR7, HLA-Bw35, HLA-Cw4, and the like. However, there has been a case of adult Still's disease occurring in only one of an enzygotic twin reported by foreign researchers, and thus, environmental factors are being more focused than genetic factors.

[0007] In addition, it has been also suggested that the disease is associated with a virus, and in this regard, human parvo virus B19, cytomegalovirus, rubella virus, echovirus 7, or the like has been reported. It has been also suggested that the disease is associated with *Toxoplasma gondii* and *Yersinia enterocolitica*.

[0008] The association with the bacteria above or viral infections is also a reflection of the importance of innate immunity in the pathogenesis of adult-onset Still's disease. The studies of the pathogenesis of adult-onset Still's disease are very limited to cytokine changes in inflammatory state of acute phase and to inflammatory cells, and Interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), IL-6, and IL-18 are known as related cytokines.

[0009] Viral and bacterial infections are considered as causative factors of the pathogenesis of adult-onset Still's disease. However, there is still little research on how these infections cause adult-onset Still's disease.

[0010] A pattern recognition receptor that plays an important role in recognizing a damage-associated molecular pattern (DAMP) and a microbe-associated molecular pattern (MAMP) in the early stages of the innate immunity currently attracts attention as an important key. However, there has been no report of changes in such a pattern recognition receptor in a patient with adult-onset Still's disease.

DETAILED DESCRIPTION OF THE INVENTION

TECHNICAL PROBLEM

[0011] The present invention has thus an object in providing a biomarker composition that can diagnose Still's disease.

[0012] The present invention also has an object in providing a kit that can diagnose Still's disease.

[0013] The present invention also has an object in providing a method of providing information for diagnosis of Still's disease.

TECHNICAL SOLUTION

[0014] To achieve the objects above, the present invention provides a biomarker composition for diagnosing Still's disease, the biomarker composition including at least one protein selected from CD11b and CD32.

[0015] To achieve the objects above, the present invention also provides a kit for diagnosing Still's disease, the kit including an antibody specifically binding to a CD11b or CD32 cell-surface antigen.

[0016] To achieve the objects above, the present invention provides a method of providing information for diagnosis of Still's disease, the method including: measuring an expression level of at least one protein selected from CD11b and CD32 in a sample; comparing the measured expression level with a protein expression level of a normal control sample; and diagnosing Still's disease, when the expression level of the at least one protein selected from CD11b and CD32 in the sample is higher than that of the protein expression of the normal control sample.

[0017] In addition, the present invention provides a

method of providing information for diagnosis of Still's disease, the method including: measuring a frequency ratio of granulocytes to lymphocytes in a sample; comparing the measured frequency ratio with a frequency ratio of a normal control sample; and diagnosing Still's disease, when the frequency ratio of the granulocytes to the lymphocytes in the sample is higher than that of the granulocytes to the lymphocytes in the normal control sample.

ADVANTAGEOUS EFFECTS OF THE INVENTION

[0018] According to the present invention, when peripheral blood mononuclear cells (PBMCs) of a patient with Still's disease are compared with those of a normal person, the PBMCs of the patient show high frequency of cells expressing CD11b and cells expressing CD32, and high frequency ratio of granulocytes to lymphocytes. Such information can be used for providing a biomarker composition for diagnosing Still's disease, the biomarker composition including at least one protein selected from CD11b and CD32, a kit for diagnosing Still's disease, the kit including an antibody specifically binding to a CD11 b or CD32 cell-surface antigen, and a method of providing information for diagnosis of Still's disease. Accordingly, the diagnosis of Still's disease can be accurately made in children and adults, thereby further improving the therapeutic effects.

DESCRIPTION OF THE DRAWINGS

[0019]

FIG. 1 is a table showing frequencies of living cells (P1%) in peripheral blood mononuclear cells (PBMCs), frequencies of cells expressing CD11 b, and frequencies of cells expressing CD32.

FIG. 2 is an image showing frequencies of living cells (P1%) in PBMCs, frequencies of cells expressing CD11b, and frequencies of cells expressing CD32.

FIG. 3 is a table showing ratios of granulocytes, ratios of lymphocytes, and ratios of granulocytes to lymphocytes, in PBMCs.

FIG. 4 is an image showing ratios of granulocytes and ratios of lymphocytes, in PBMCs.

BEST MODE

[0020] While the inventors of the present invention were studying a biomarker capable of diagnosing Still's disease, differences in the frequency of cells expressing CD11b, the frequency of cells expressing CD32 and the frequency ratio of granulocytes to lymphocytes between a normal person and a patient with Still's disease were found, thereby completing the present invention.

[0021] The frequency refers to the number of cells expressing CD11b, the number of cells expressing CD32, and the number of frequency occupied by with granulocytes or lymphocytes, with respect to the total number of cells

[0022] Therefore, the present invention provides a biomarker composition for diagnosing Still's disease, the biomarker composition including at least one protein selected from CD11b and CD32.

[0023] In an embodiment of the present invention, the frequency of cells expressing CD11b and the frequency of cells expressing CD32 in peripheral blood mononuclear cells (PBMCs) of the patient with Still's disease are each found to be higher than that of cells expressing CD11b or cells expressing CD32 in PBMCs of a normal person or a patient with rheumatoid arthritis.

[0024] In addition, in one or more embodiments of the present invention, the ratio of granulocytes in PBMCs of the patient with Still's disease was found to be higher than that of granulocytes in PBMCs of a normal person or a patient with rheumatoid arthritis, and the ratio of lymphocytes was found to be lower.

[0025] The present invention also provides a kit for diagnosing Still's disease, the kit including an antibody specifically binding to a CD11b or CD32 cell-surface antigen.

[0026] The antibody may be a polyclonal antibody or a monoclonal antibody.

[0027] The polyclonal antibody may be prepared by injecting an immunogen, such as CD11 b or CD32 protein or a fragment thereof, into a foreign host according to methods known in the art. The foreign host may include a mammal, such as a mouse, a rat, a sheep, or a rabbit. The immunogen may be injected via an intramuscular, intraperitoneal, or subcutaneous injection method, and is generally administered with an adjuvant to increase antigenicity. Serum is collected periodically from a foreign host to collect serum having improved titer and showing specificity to antigens, or to separate and purify antibodies therefrom.

[0028] The monoclonal antibody may be prepared by an immortalized cell line generation technique using a fusion method known in the art. For example, a protein expressed in a gene may be immunized in a mouse, or a peptide may be synthesized and bound to a bovine serum albumin to be immunized in a mouse. Antigen-secreting B lymphocytes separated from the mouse may be then fused with myeloma of a human or a mouse to produce immortalized hybridomas, and the hybridomas may be subjected to an indirect enzyme-linked immunoabsorbent assay (ELISA) to confirm whether the monoclonal antibody is produced. Then, positive clones may be selected and cultured, and antibodies may be separated and purified. Alternatively, antibodies may be injected into the abdominal cavity of a rat, and ascites may be collected, thereby preparing the monoclonal antibody.

[0029] The monoclonal antibody may be quantitatively analyzed by performing a color reaction using a secondary antibody to which an enzyme such as alkaline phosphatase (AP) or horseradish peroxidase (HRP) is bound, and a substrate of the secondary antibody. Alternatively, the monoclonal antibody may be directly quantitatively

by using an antibody to which an enzyme such as AP or HRP is bound for the monoclonal antibody against the protein above. In addition, an antibody labeled with various fluorescent markers such as fluorescein isothiocyanat (FITC) and phycoerythrin (PE) may be used.

[0030] The reaction between the protein above and the antibody may be confirmed by protein identification experiments such as western blot, Immunoprecipitation (IP), ELISA, immunohistochemistry (IHC), and flow cytometry analysis (FACS), but embodiments of the present invention are not limited thereto.

[0031] The kit including the antibody may typically include an antibody and a buffer that are in the lyophilized form, a stabilizer, an inactive protein, or the like, wherein the antibody may be labeled with a radionuclide, a fluorescer, an enzyme, or the like.

[0032] The present invention also provides a method of providing information for diagnosis of Still's disease, the method including: measuring an expression level of at least one protein selected from CD11b and CD32 in a sample; comparing the measured expression level with a protein expression level of a normal control sample; and diagnosing Still's disease, when the expression level of the at least one protein selected from CD11b and CD32 in the sample is higher than that of the protein expression of the normal control sample.

[0033] The present invention also provides a method of providing information for diagnosis of Still's disease, the method including: measuring a frequency ratio of granulocytes to lymphocytes in a sample; comparing the measured frequency ratio with a frequency ratio of a normal control sample; and diagnosing Still's disease, when the frequency ratio of the granulocytes to the lymphocytes in the sample is higher than that of the granulocytes to the lymphocytes in the normal control sample.

[0034] When the frequency ratio of the granulocytes to the lymphocytes is in a range of about 3.0 to about 50.0, it is diagnosed as Still's disease.

[0035] An example of the sample may be blood, and more preferably, may be PBMCs separate from blood, but embodiments of the present invention are not limited thereto.

MODE OF THE INVENTION

[0036] Hereinafter, to promote understanding of one or more exemplary embodiments, reference has been made to the exemplary embodiments. However, the present invention should not be construed as being limited to the exemplary embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the concept of the inventive concept to those skilled in the art.

<Example 1> Preparation of peripheral blood mononuclear cells (PBMC)

[0037] Human PBMCs were separated from human blood of a healthy donor by using an ammonium-chloride-potassium (ACK) lysis buffer. Then, 2 mL of blood was added to a tube treated with ethylenediaminetetraacetic acid (EDTA), and the tube was inverted 15 times. Afterwards, the resultant blood was added to 40 mL of the ACK lysis buffer, and was left at room temperature for 5 minutes. The centrifugation was performed thereon at a speed of 300 xg for 5 minutes. After white blood cells (WBC) were collected, the supernatant was discarded and the precipitated cells were mixed in 5 ml of PBS. The centrifugation was repeatedly performed thereon twice at a speed of 300 xg at a temperature of 4°C, thereby preparing PBMCs.

<Example 2> Measurement of cells expressing CD11b or cells expressing CD32 in PBMCs

[0038] The frequencies of cells expressing CD11b and cells expressing CD32 were each measured in the PBMCs prepared according to Example 1, with respect to normal people (19 people), patients with rheumatoid arthritis (RA) (19 people), and patients with Still's disease (18 people).

[0039] Here, red blood cells were removed from each blood, and leukocytes were collected. Then, by a reaction with anti-CD11b and anti-CD32 antibodies each labeled with different fluorescence, the leukocytes were reacted with the antibodies, and the number of cells to which the antibodies bound was counted according to FACS. In this regard, the frequency of these cells occupied over the entire cells was analyzed.

[0040] Consequently, as shown in FIGS. 1 and 2, it was confirmed that the frequencies of the cells expressing CD11b and the cells expressing CD32 were significantly high when compared with the normal control group and the test group of patients with RA.

[0041] Here, there was no bid difference overall regarding the frequency of living cells over the entire cells (P1 %).

<Example 3> Measurement of frequencies of granulocytes and lymphocytes in PBMCs

[0042] In the same manner as in Example 2, the frequencies of granulocyte and lymphocyte and the ratio of granulocytes to lymphocytes were measured with respect to normal people (19 people), patients with RA (19 people), and patients with Still's disease (18 people).

[0043] Consequently, as shown in FIGS. 3 and 4, it was confirmed that the frequency of granulocytes of the group of patients with Still's disease was higher than that of granulocytes of the normal control group and the test group of patients with RA, and that the frequency of lymphocyte of the group of patients with Still's disease was

significantly lower than that of lymphocyte of the normal control group and the test group of patients with RA.

[0044] In particular, referring to FIG. 3, as a result of confirming the ratio of granulocytes to lymphocytes, the ratio of the group of patients with Still's disease was about 7 times higher than that of the normal control group, and accordingly, it was confirmed that the ratio of granulocytes was significantly high in PBMCs of the patients with Still's disease.

[0045] Overall, when the PBMCs of the patients with Still's disease are compared with those of the normal control group, the frequencies of the cells expressing CD11b and the cells expressing CD32 were high, as well as the ratio of granulocytes to lymphocytes. Thus, through analysis, the present invention can be utilized for the diagnosis of Still's disease.

[0046] While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by one of ordinary skill in the art that the detailed embodiments disclosed herein are only preferred embodiments and that the scope of the present invention is not limited thereby. Therefore, it is intended that the scope of the present invention be defined by the claims and equivalents thereof.

Claims

1. A biomarker composition for diagnosing Still's disease, the biomarker composition comprising at least one protein selected from CD11b and CD32.

2. A kit for diagnosing Still's disease, the kit comprising an antibody specifically binding to a CD11b or CD32 cell-surface antigen.

3. The kit of claim 2, wherein the antibody is a monoclonal antibody or a polyclonal antibody.

4. A method of providing information for diagnosis of Still's disease, the method comprising:

   measuring an expression level of at least one protein selected from CD11b and CD32 in a sample;
   comparing the measured expression level with a protein expression level of a normal control sample; and
   diagnosing Still's disease, when the expression level of the at least one protein selected from CD11b and CD32 in the sample is higher than that of the protein expression of the normal control sample.

5. A method of providing information for diagnosis of Still's disease, the method comprising:

   measuring a frequency ratio of granulocytes to lymphocytes in a sample;
   comparing the measured frequency ratio with a frequency ratio of a normal control sample; and
   diagnosing Still's disease, when the frequency ratio of the granulocytes to the lymphocytes in the sample is higher than that of the granulocytes to the lymphocytes in the normal control sample.

6. The method of claim 5, wherein the frequency ratio of the granulocytes to the lymphocytes is in a range of about 3.0 to about 50.0.

7. The method of claim 4 or 5, wherein the sample is blood.

8. The method of claim 4 or 5, wherein the sample is a peripheral blood mononuclear cell (PBMC).

FIG. 1

	P1% / Whole cells			CD11b / Whole cells			CD32/ Whole cells		
	healthy	stills	RA	healthy	stills	RA	healthy	stills	RA
	72.5	70.95	52.55	50.0	77.7	45.6	33.4	75.6	37.6
	78.5	78.35	71.5	47.4	81.8	68.5	28.8	50.7	70.4
	55.3	77.05	83.4	58.7	80.7	84.3	58.5	79.6	83.5
	51	65.8	56.8	40.1	92.9	68.8	37.9	93.7	68.1
	76.4	61	83.6	53.7	71.2	91.5	58	70.6	94.1
	61.4	97.4	66.95	35.5	97	66.4	37.5	95.6	67.8
	55.3	63.1	67.55	37	66.6	77.7	36.3	75.8	74.9
	68.6	79	40.6	30.2	72.3	56.6	34.9	73.2	57.1
	62.0	72.75	61.15	33	90.6	48.6	32.9	87.8	51.2
	59.8	70.35	80.1	61.2	75.4	63.4	66.1	79.1	68.9
	73.7	74.1	67.65	60	78.7	55.6	67.2	77.5	62.6
	70.0	92.65	67.95	66.3	44.4	38.9	66.8	51.8	40.7
	79.6	67.5	61.4	58.5	86.3	40.3	59.7	90.9	45.6
	71.7	90	56.6	67.8	63.5	31	63.8	65.9	33.3
	53.2	91.2	69.45	55.5	87.2	47.6	43.1	88.5	50.5
	75.5	43.7	61.9	67.5	93.8	32.8	63.2	93.9	34.9
	64.4	78.1	70.7	56.4	87.5	43	59.5	81.4	46.2
	84.6	71.45	68.35	60.3	89.5	38.8	69	85.7	45.7
	70.9		68.6	52.2		57	55.2		57
Avg	**67.6**	**74.6**	**66.1**	**52.1**	**79.8**	**55.6**	**51.1**	**78.7**	**57.3**
SD	9.7	12.9	10.4	11.8	13.0	17.3	14.2	13.0	16.8

FIG. 2

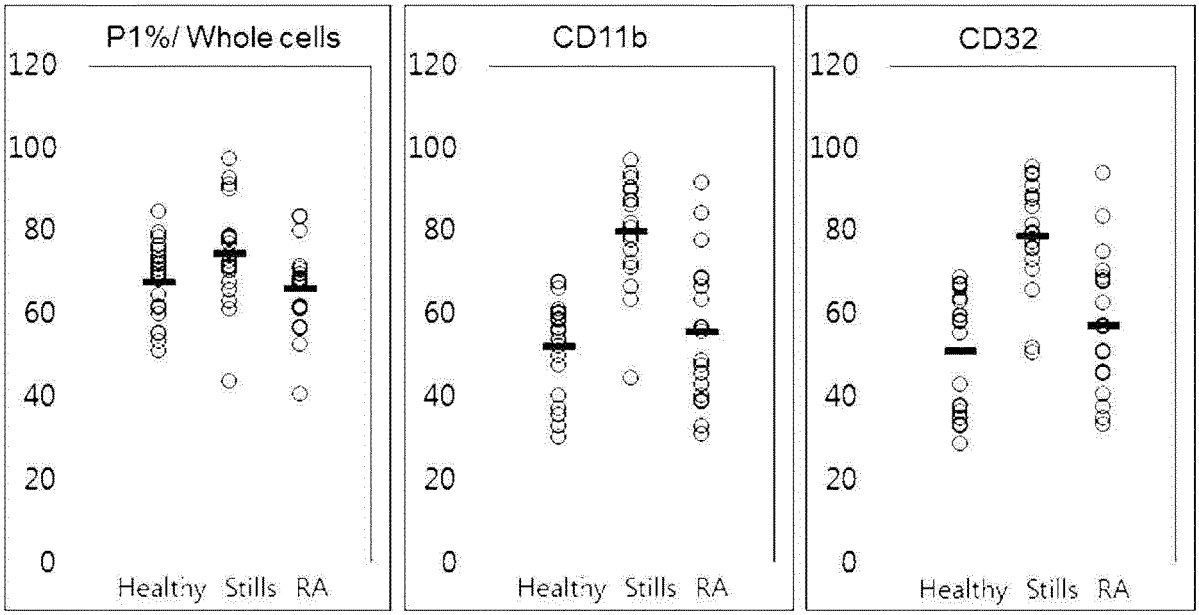
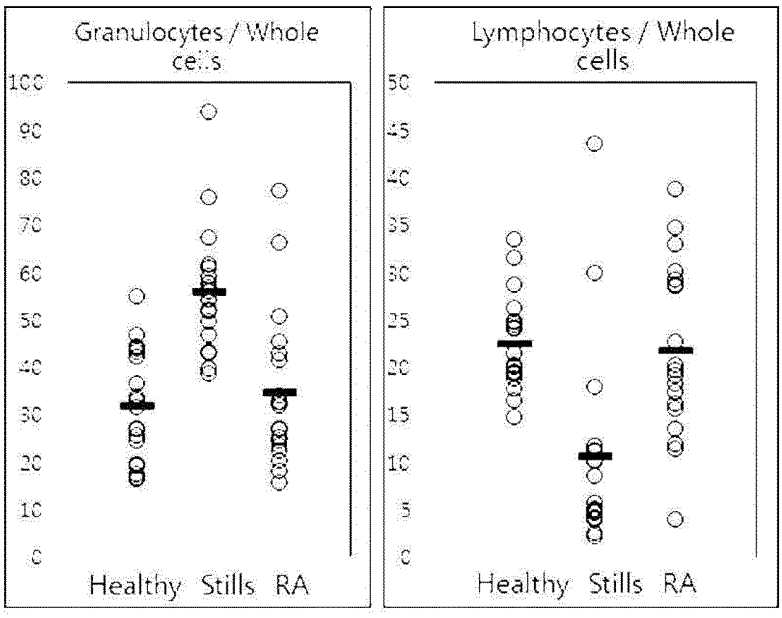


FIG. 3

	Granulocytes			Lymphocytes			Granulocytes/ Lymphocytes		
	healthy	stills	RA	healthy	stills	RA	healthy	stills	RA
	25.5	46.6	23.45	19.2	5	22.6	2.80	9.32	1.03
	26.75	59	45.35	24.35	5.7	18.25	1.09	10.35	2.48
	27	60.6	66.15	21.4	11.6	11.85	1.26	5.22	5.58
	17.4	57.5	32.45	28.6	4.65	16.15	0.60	12.36	2.00
	33.6	38.4	76.95	31.4	17.8	3.95	1.07	2.15	19.48
	19.25	93.65	41.3	24.65	2.2	17.35	0.78	42.56	2.38
	19.6	42.9	50.6	16.5	10.1	11.4	1.18	4.24	4.43
	16.6	51.5	22.35	33.4	11.1	15.6	0.49	4.63	1.43
	16.25	56	32.5	26.1	3.85	28.55	0.62	14.54	1.13
	33.05	53.95	42.85	17.6	11.1	19.55	1.87	4.86	2.19
	44.1	56.45	33.95	23.95	8.45	13.4	1.84	6.68	2.53
	43	43.15	24.95	19.5	43.45	19.15	2.20	0.99	1.30
	42	49.6	24.55	24	4.15	30.05	1.75	11.95	0.81
	43.9	51.85	15.65	18.65	29.8	32.85	2.35	1.73	0.47
	24.5	75.5	26.7	20	10.05	29.15	1.225	7.51	0.91
	46.55	39.5	18.2	19.2	2.55	38.7	2.42	15.49	0.47
	31.45	67.15	26.85	14.65	5	28.45	2.14	13.43	0.94
	54.75	61.55	20.15	20.2	4.8	34.6	2.71	12.82	0.58
	36.45		31.7	24.65		20.1	1.47		1.57
Avg	**31.66**	**55.82**	**34.56**	**22.52**	**10.63**	**21.66**	**1.57**	**10.04**	**2.72**
SD	11.60	13.44	16.19	4.97	10.52	9.12	0.72	9.33	4.26

FIG. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2016/003898

A. CLASSIFICATION OF SUBJECT MATTER

G01N 33/53(2006.01)i, G01N 33/68(2006.01)i, G01N 33/577(2006.01)i, C07K 16/28(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N 33/53; C12N 5/00; C12N 15/12; G01N 33/68; G01N 33/577; C07K 16/28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Utility models and applications for Utility models: IPC as above
Japanese Utility models and applications for Utility models: IPC as above

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

eKOMPASS (KIPO internal) & Keywords: still's disease, diagnosis marker, CD11b, CD32, granulocyte

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JUNG, Yoon Suk et al., "A Case of Adult-onset Still's Disease Combined with Sjogren's Syndrome", The Korean Journal of Internal Medicine, 2009, vol. 77, no. 1, pages S240-S244 See page S243, left column.	5-8
A		1-4
X	YAMAGUCHI, M. et al., "Preliminary Criteria for Classification of Adult Still's Disease", The Journal of Rheumatology, March 1992, vol. 19, no. 3, pages 424-430 See abstract.	5-8
A		1-4
X	SEUNG, O. P. et al., "Adult-onset Still's Disease: a Case Report", Oman Medical Journal, 2011, vol. 26, no. 5, inner pages 1-3 See page 2, paragraph [5].	5-8
A		1-4
A	KR 10-2014-0093901 A (SNU. R&DB FOUNDATION) 29 July 2014 See claim 1; paragraph [0107].	1-8
A	EP 1111049 A1 (ASAHI KASEI KABUSHIKI KAISHA) 27 June 2001 See claims 14-16.	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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专利名称(译)	用于诊断静脉疾病的生物标志物组合物，诊断试剂盒和诊断方法		
公开(公告)号	EP3285071A4	公开(公告)日	2018-12-19
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其他公开文献	EP3285071A1		
外部链接	Espacenet		

摘要(译)

本发明涉及用于诊断Still病的生物标志物组合物，诊断试剂盒和诊断方法，更具体地，本发明可以使用CD11b或CD32的表达水平和频率来准确诊断儿童和成人的Still病。粒细胞以淋巴细胞为指标。