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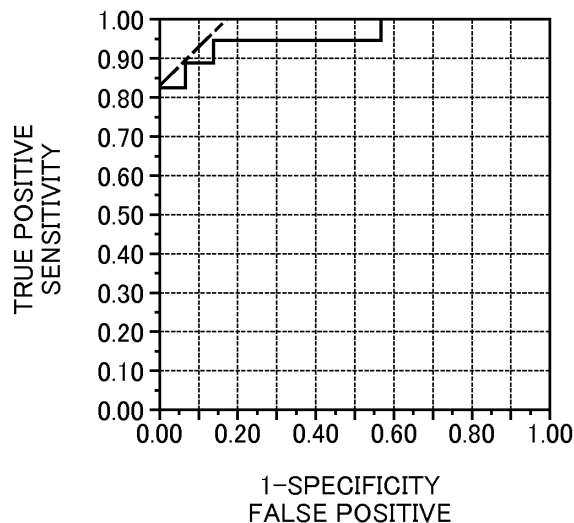
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(54) **NOVEL TEST METHOD FOR RHEUMATOID ARTHRITIS AND KIT FOR RHEUMATOID ARTHRITIS TEST**

(57) Provided are: a novel test method for rheumatoid arthritis; and a kit for rheumatoid arthritis test, which is used in the novel test method for rheumatoid arthritis. A test method for rheumatoid arthritis according to the present invention is characterized by comprising a step for measuring the amount of talin in the plasma or serum

of an animal subject. This measurement is carried out, for example, by an immunological method using an antibody which binds to talin. A kit for rheumatoid arthritis test according to the present invention is used for such a test method and contains, for example, a solid-phase carrier to which an antibody that binds to talin is affixed.

FIG. 1



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Description

TECHNICAL FIELD

5 **[0001]** The present invention relates to a test method for rheumatoid arthritis, and a kit for rheumatoid arthritis test, which is used in such a test method.

BACKGROUND ART

10 **[0002]** Rheumatoid arthritis (RA) is a chronic inflammatory disease, in which the lesion occurs mainly in the synovial membrane tissue of the joint, and the prevalence rate of the disease is about 1% of the population. In rheumatoid arthritis, synovitis is found in the first stage, then cartilage or bone is gradually invaded, and the joint is destroyed and deformed in the advanced stage. Furthermore, the consequence of the symptom includes various examples such as an example in which arthritis undergoes remission and reoccurrence, repeatedly, then is completely cured, and an example in which arthritis rapidly progresses.

15 **[0003]** Diagnosis of rheumatoid arthritis is carried out mainly based on symptoms. Recently, however, attention has been paid to a diagnostic method using, as a marker, an autoantibody contained in the serum of a patient. As such an autoantibody, a rheumatoid factor (an autoantibody with respect to the deformed IgG), an anti-cyclic citrullinated peptide antibody (an anti-CCP antibody), and the like, are known (see Non-Patent Literature 1).

20 **[0004]** However, in previous reports, the sensitivity of the rheumatoid factor is 75 to 80%, the specificity thereof is 50 to 70%, and the sensitivity of the anti-CCP antibody is 50 to 75%, and the specificity is 85 to 95%, which are not necessarily satisfactory (see Non-Patent Literatures 2 and 3).

Non-Patent Literature 1: Martinus A. M. et al., Arthritis Res. Ther., 4: 87-93, 2002

25 Non-Patent Literature 2: Avouac J. et al., Ann. Rheum. Dis. 65: 845-851, 2006

Non-Patent Literature 3: van Venrooij WJ. et al. Ann. N.Y. Acad. Sci. 1143: 268-285, 2008

DISCLOSURE OF THE INVENTION

30 Problems to be Solved by the Invention

[0005] The present invention aims to provide a test method for rheumatoid arthritis and a kit for rheumatoid arthritis test by searching novel markers that have not been previously known and being based on the found novel markers in the searching.

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Means for Solving the Problems

40 **[0006]** In patients with rheumatoid arthritis, it is known that the peripheral blood lymphocyte is activated, so that cell adhesion with respect to the blood vessel endothelial cell is increased and at the same time, the lymphocyte migration is also increased, resulting in the infiltration of the lymphocyte to the outside of the blood vessel to cause various inflammations. In searching novel markers, the present inventor has focused on talin that is a high-molecular-weight cytoskeletal protein expressed in a concentrated manner mainly in regions in which the cell and the substrate are brought into contact with each other, in particular, in a cell adhesion region in the lymphocyte.

45 **[0007]** Talin is a protein formed of an N-terminal region having a molecular weight of 47 kDa and including an FERM region, and a C-terminal region having a molecular weight of 190 kDa and including one bundle of α -helix. The FERM region is classified into three sub-regions, that is, an F1 domain, an F2 domain, and an F3 domain, sequentially from the N-terminal side. In a living body, it is known that polypeptide in the N-terminal region, which is cleaved by Calpain, the F3 domain among them binds to an integrin β sub-unit increases signaling of the integrin from the inside of the cell to the outside of the cell, and thus the cell adhesion and cell migration are increased.

50 **[0008]** The present inventor has investigated the presence of talin in the plasma or the serum of a patient with rheumatoid arthritis. As a result, surprisingly, it is found that in a patient with rheumatoid arthritis, talin is dominantly present in the plasma or the serum. Furthermore, it is found that the amount of talin is significantly reduced when rheumatoid arthritis reaches a low disease activity or remission with the therapeutic agent for rheumatoid arthritis.

55 **[0009]** The present invention has been made based on such findings, and the present invention specifically includes the followings.

(1) A test method for rheumatoid arthritis, the method including a step of measuring an amount of talin in plasma or serum of an animal subject.

(2) The test method for rheumatoid arthritis described in the above (1), further including a step of obtaining plasma or serum from blood collected from the animal subject.

(3) The test method for rheumatoid arthritis described in the above (1) or (2), wherein the amount of talin in the plasma or the serum is measured by using an antibody which binds to talin.

5 (4) The test method for rheumatoid arthritis described in any of the above (1) to (3), wherein the animal subject is a human subject.

(5) The test method for rheumatoid arthritis described in any of the above (1) to (4), wherein the method is carried out for determining a diagnosis of rheumatoid arthritis or a treatment effect of a therapeutic agent for rheumatoid arthritis.

10 (6) A kit for rheumatoid arthritis test used for the test method for rheumatoid arthritis described in any of the above (1) to (5).

(7) The kit for rheumatoid arthritis test described in the above (6), including a solid-phase carrier to which an antibody that binds to talin is affixed.

15 Effects of the Invention

[0010] The present invention can provide a novel test method for rheumatoid arthritis and a kit for rheumatoid arthritis test to be used for such a test method.

20 BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

25 Fig. 1 is a graph showing an ROC curve of a diagnosis of rheumatoid arthritis (Example 1) by the Sandwich ELISA method using an H-18 antibody and an H-300 antibody.

Fig. 2 is a graph showing an ROC curve of a diagnosis of rheumatoid arthritis (Example 2) by the Sandwich ELISA method using an H-18 antibody and an M54246M antibody.

Fig. 3 is a graph showing an ROC curve of a diagnosis of rheumatoid arthritis (Comparative Example 1) using an anti-CCP antibody.

30 PREFERRED MODE FOR CARRYING OUT THE INVENTION

Test Method for Rheumatoid Arthritis

35 **[0012]** A test method for rheumatoid arthritis according to the present invention includes a step of measuring an amount of talin in the plasma or the serum of an animal subject. This test method may further include a step of obtaining the plasma or the serum from the blood collected from an animal subject.

[0013] The animal subject is not particularly limited as long as it can contract rheumatoid arthritis, and it can be selected depending upon purposes. Examples thereof include a human, a rat, a mouse, a dog, a cow, a cat, a rabbit, and a guinea pig, and preferable example is a human.

40 **[0014]** Furthermore, a method for obtaining the plasma or the serum is not particularly limited, it is possible to employ conventional methods, for example, a method for separating the plasma or the serum, which are obtained as specimen for clinical laboratory examination, from the blood. For example, the plasma can be obtained by taking the blood into an EDTA tube, a heparin tube, or the like, and the centrifuging thereof. Furthermore, the serum can be obtained by taking

45 the blood into a test tube, and the centrifuging thereof.
[0015] With the test method for rheumatoid arthritis according to the present invention, an amount of talin in the thus obtained plasma or serum is measured. Herein, the "amount of talin" denotes an amount of protein of the talin. When talin has plurality of isoforms, any one of them may be measured. For example, in the case of human, two isoforms, that is, talin 1 and talin 2 are present. The mRNA sequence and the amino acid sequence of the talin 1 are shown in SEQ ID NOs: 1 and 2. Furthermore, the mRNA sequence and the amino acid sequence of the talin 2 are shown in SEQ ID NOs: 3 and 4.

[0016] The amount of talin in the plasma or the serum of an animal subject can be measured by an immunochemical method by using an antibody which binds to talin.

50 **[0017]** The antibody which binds to talin may be a polyclonal antibody or may be a monoclonal antibody, and, in some case, fragments of the antibody, for example, Fab', Fab, F(ab')₂ can be used. These antibodies can be prepared by conventionally known methods.

[0018] Examples of commercial products include an H-18 antibody (Santa Cruz Biotechnology Inc.), an H-300 antibody (Santa Cruz Biotechnology Inc.), a TA205 antibody (Abcam Inc.), and an M54246M antibody (Bio-design Co., Ltd.).

[0019] The amount of talin can be measured by employing well-known methods such as an enzyme immunoassay (EIA), a chemiluminescent immunoassay, a radioimmunoassay (RIA), a fluoro immunoassay, and a latex agglutination assay. Specific examples include a competitive assay using an antibody and label antigen, a Sandwich EIA method using combination of two types of antibodies, i.e., a monoclonal antibody or a polyclonal antibody (or a monoclonal antibody and a polyclonal antibody) whose recognition sites with respect to an antigen are different, and a latex agglutination assay using latex particles to which an antibody is affixed.

[0020] In these measurement methods, if necessary, an antigen or an antibody can be affixed to a solid-phase carrier. Examples of the solid-phase carrier include synthetic resin such as polystyrene, polyethylene, polypropylene, polyvinyl chloride, polyester, polyacrylic acid ester, nylon, polyacetal and fluorocarbon resin, polysaccharides such as cellulose and agarose, glass, metal, and the like. This solid-phase carrier can be formed in various shapes including a micro-plate shape, a spherical shape, a fibrous shape, a rod shape, a board shape, a container shape, a cell, a test tube, and the like.

[0021] In the above-mentioned immunochemical method, antibodies or antigens which are labeled may be used if necessary. Examples of such labels include radioisotope (^{124}I , ^{14}C , and ^3H), fluorescence materials (fluorescein isothiocyanate, and the like), and the like, in addition to enzymes (peroxidase, alkaline phosphatase, and the like), luminescent material (acridinium ester, isoluminol, luciferin, and the like). Besides, methods using combination of a biotin label and streptavidin can be employed.

[0022] As mentioned above, by measuring and quantifying the amount of talin in the plasma or the serum of an animal subject, it is possible to diagnose easily whether or not the subject has contracted rheumatoid arthritis. That is to say, when the amount of talin in the plasma or the serum is larger than a predetermined threshold, it can be determined that the subject has contracted rheumatoid arthritis. The predetermined threshold can be set, for example, based on a mean value and the like in the plasma or the serum in a control animal that has not contracted rheumatoid arthritis.

[0023] Furthermore, by measuring and quantifying the amount of talin before and after a therapeutic agent for rheumatoid arthritis is administered, a therapeutic effect by the therapeutic agent can be determined in a simple and easy manner. That is to say, when the amount of talin after the therapeutic agent for rheumatoid arthritis is administered is significantly lowered from the amount of talin before the administration, it can be determined that the therapeutic agent is effective.

[0024] Herein, the therapeutic agent for rheumatoid arthritis can include all the conventionally known therapeutic agents and all of therapeutic agents that will be developed in the future. Examples of the conventionally known therapeutic agent for rheumatoid arthritis include biological preparations, nonsteroidal anti-inflammatory agents (anti-inflammatory analgesic agents), steroid drugs, immunosuppressive agents, and the like.

[0025] Examples of the biological preparations include chimeric anti-TNF- α antibody preparations, soluble TNF receptors, complete human anti-TNF- α antibody preparations, anti-IL-6-receptor antibody preparations, and the like. The nonsteroidal anti-inflammatory agents include prostaglandin production suppressing agents. They can reduce pain or swelling in the joint, but it is said that it is difficult to suppress the progress of the disease itself and suppress the destruction of the bone and the joint. The steroid drug has excellent anti-inflammation effect, so that it is used as specific medicine for rheumatoid arthritis. However, adverse effects thereof pose problems. The immunosuppressive agent reduces immunopathy of a rheumatoid arthritis patient, thereby suppressing the inflammation of rheumatoid arthritis, and is used for the purpose of introducing remission induction. Since this may be able to inhibit the progress of rheumatoid arthritis, this agent is also called disease modification anti-rheumatism drug. This is also called a slow acting anti-rheumatism drug because it takes a long time to exhibit an effect.

[0026] As mentioned above, there are various types of the therapeutic agents for rheumatoid arthritis, but the test method according to the present invention is also useful for determining the level of the effect of the therapeutic agent, and selecting the most effective therapeutic agent.

45 Kit for Rheumatoid Arthritis Test

[0027] A kit for rheumatoid arthritis test according to the present invention is provided for the use in a test method for rheumatoid arthritis according to the present invention. This diagnosis kit includes, for example, a solid-phase carrier to which an antibody that binds to talin is affixed. Furthermore, it may include a labeled secondary antibody, a coloring substrate, or the like.

EXAMPLES

[0028] Hereinafter, the present invention is described in detail with reference to Examples, but the present invention is not construed as being limited to the following description. Note here that in the following Examples 1 and 2, and Comparative Example 1, subjects include 17 patients with rheumatoid arthritis (RA patients), 14 controls (8 patients with osteoarthritis, 1 patient with systemic lupus erythematoses, 1 patient with diabetes, and 4 healthy subjects). Furthermore, in the following Example 3, subjects are 5 RA patients.

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Example 1

[0029] Blood of each subject is collected into an EDTA tube, and is centrifuged at 2500 rpm at room temperature for 10 min so as to obtain the plasma.

[0030] An amount of talin in the plasma was measured by a Sandwich ELISA method.

[0031] Firstly, an H- 18 antibody (Santa Cruz Biotechnology Inc.) recognizing the N- terminal of talin was diluted with a phosphate buffer solution (PBS) so that the concentration became 1 $\mu\text{g/mL}$, and added to a 96- well micro- plate at 100 μL / well, which was incubated at 4°C overnight, followed by washing with 200 μL / well of washing solution three times. Next, the plasma from each subject was added to the 96- well micro- plate at 100 μL / well, which was incubated at 25°C for one hour, followed by washing with 200 μL / well of washing solution three times. Next, an H- 300 antibody (Santa Cruz Biotechnology Inc.) as a primary antibody recognizing the N- terminal of talin was diluted with PBS so that the concentration became 2 $\mu\text{g/mL}$, and added to the 96- well micro- plate at 100 μL / well, which was incubated at 25°C for one hour, followed by washing with 200 μL / well of washing solution three times. Next, an HRP- labeled anti- goat IgG antibody (KPL) as a secondary antibody was diluted with PBS so that the concentration became 2 $\mu\text{g/mL}$, and added to the 96- well micro- plate at 100 μL / well, which was incubated at 25°C for one hour, followed by washing with 200 μL / well of washing solution three times.

[0032] Next, a substrate was added to a 96- well micro- plate at 100 μL / well, which was incubated at 25°C for 15 min, and then, an OD value at wavelength of 630 nm was measured by using a microplate reader.

[0033] An ROC curve in Example 1 is shown in Fig. 1. As a result of the ROC analysis, an area below the ROC curve (AUC) in Fig. 1 was 0.954. Furthermore, whether being positive or negative based on the cut-off value of OD = 0.20 is shown in Table 1.

[Table 1]

H-300 antibody		RA patient	Control	Total
	Positive	14	0	14
	Negative	3	14	17
	Total	17	14	31

[0034] From the results, diagnosis of rheumatoid arthritis by the Sandwich ELISA method using the H-18 antibody and the H-300 antibody showed that the sensitivity was $14/17 \times 100 = 82.4\%$ and the specificity was $14/14 \times 100 = 100\%$.

Example 2

[0035] The amount of talin in the plasma was measured by the Sandwich ELISA method by the same method as in Example 1 except that an M54246M antibody (Bio-design Co., Ltd.) recognizing the C-terminal of talin was used as a primary antibody.

[0036] An ROC curve in Example 2 is shown in Fig. 2. As a result of the ROC analysis, an area below the ROC curve (AUC) in Fig. 2 was 0.819. Furthermore, whether being positive or negative based on the cut-off value of OD = 0.05 is shown in Table 2.

[Table 2]

M54246M antibody		RA patient	Control	Total
	Positive	15	3	18
	Negative	2	11	13
	Total	17	14	31

[0037] From the results, diagnosis of rheumatoid arthritis by the Sandwich ELISA method using the H-18 antibody and the M54246M antibody showed that the sensitivity was $15/17 \times 100 = 88.2\%$ and the specificity was $11/14 \times 100 = 78.6\%$.

Comparative Example 1

[0038] Blood from each subject was collected into a blood collecting tube for serum, and it was centrifuged at 2,500

rpm at room temperature for 10 min, and thus the serum was obtained. An anti-CCP antibody titer in the serum was measured by using a commercially available kit (MESACUP CCP manufactured by Medical & Biological laboratories Co., Ltd (MBL)) .

[0039] An ROC curve in Comparative Example 1 is shown in Fig. 3. As a result of the ROC analysis, an area below the ROC curve (AUC) in Fig. 3 was 0.838. Furthermore, whether being positive or negative based on the cut-off value of antibody titer = 6.60 is shown in Table 3.

[Table 3]

Anti-CCP antibody		RA patient	Control	Total
	Positive	11	1	12
	Negative	6	13	19
	Total	17	14	31

[0040] From the results, diagnosis of rheumatoid arthritis by using the anti-CCP antibody showed that the sensitivity was $11/17 \times 100 = 64.7\%$ and the specificity was $13/14 \times 100 = 92.9\%$.

[0041] As is shown from the above-mentioned results, talin was dominantly present in the blood from a RA patient. Therefore, by measuring the amount of talin in the blood, it is possible to examine whether or not a subject contracted rheumatoid arthritis in a simple and easy manner. Moreover, the test method was more excellent in the sensitivity as compared with the existing method using anti-CCP antibody.

Example 3

[0042] A therapeutic effect of the therapeutic agent for rheumatoid arthritis for 5 RA patients was confirmed by measuring the amount of talin. The amount of talin was measured by measuring the OD value by the Sandwich ELISA method by using an H-18 antibody and an H-300 antibody as in Example 1. Furthermore, an amount of CRP and an amount of MMP-3 were measured by the same method as in usual clinical examination. Furthermore, the score of DAS (Disease Activity Score) 28 recommended by European League Against Rheumatism (EULAR) was calculated. The score of DAS28 of not less than 5.1 is determined to be high disease activity, the score of not less than 3.2 and less than 5.1 is determined to be middle disease activity, and the score of less than 3.2 is determined to be low disease activity. The results are shown in Table 4.

[Table 4]

Case 1: Male (ADA remarkable effective example)		Before (MTX treatment)	After (MTX + ADA treatment)
	Talin (OD value)	0.068	0.139
CRP (mg/dL)	1.74	0.08	
MMP-3 (mg/mL)	60.6	57.4	
DAS28	5.43	2.62	
Case 2: Female (SASP no effective example)		Before (non-treatment)	After (SASP treatment)
	Talin (OD value)	0.258	0.294
	CRP (mg/dL)	0.36	0.19
	MMP-3 (mg/mL)	70.6	106.6
DAS28	5.12	4.21	
Case 3: Female (IFX no effective example)		Before (MTX treatment)	After (MTX + IFX treatment)
	Talin (OD value)	0.205	0.223
	CRP (mg/dL)	2.82	2.68
	MMP-3 (mg/mL)	962.1	523.8
DAS28	4.87	3.95	

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(continued)

		Before (BUC treatment)	After (BUC + ADA treatment)
5	Case 4: Female (ADA remarkable effective example)	Talin (OD value)	0. 258
		CRP (mg/dL)	5. 01
		MMP-3 (mg/mL)	323. 2
		DAS28	4. 55
10	Case 5: Female (TCZ no effective example)		Before (non-treatment)
		Talin (OD value)	2. 093
		CRP (mg/dL)	3. 83
15		MMP-3 (mg/mL)	117. 8
		After (TCZ treatment)	
		DAS28	5. 09
			4. 50

20 **[0043]** A case 1 is an example in which when ADA (adalimumab) was used together in treatment with MTX (methotrexate), good responder (DAS28: 5.43 → 2.62) was shown based on the reactivity basis of EULAR. The amount of talin showed a high value (OD value: 0.568) when only MTX was used, but it showed a normal value (OD value: 0.139) when ADA was used together. On the other hand, the amount of MMP- 3 did not show significant reduction even when ADA was used together, which did not reflect the activity of rheumatoid arthritis.

25 **[0044]** A case 2 is an example in which also when treatment with SASP (salazosuffapyridine) was carried out, none responder (DAS28: 5.12 → 4.21) was shown based on the reactivity basis of EULAR. The amount of talin remained high (OD value: 0.258 → 0.294) even with SASP treatment. On the other hand, the CRP amount showed a normal value (0.19 mg/dL) after the SASP treatment was carried out, which did not reflect the pathology of rheumatoid arthritis.

30 **[0045]** A case 3 is an example in which none responder (DAS28: 4.87 → 3.95) was shown although IFX (infliximab) was used together with treatment with MTX (methotrexate). The amount of talin remained high (OD value: 0.205 → 0.223) even when treatment together with IFX was carried out.

[0046] A case 4 is an example in which good responder (DAS28: 4.55 → 2.45) was shown when ADA (adalimumab) was used together with treatment with BUC (bucillamine). The amount of talin showed a high value (OD value: 0.258) when only BUC was used, but it showed a normal value (OD value: 0.164) when ADA was used together.

[0047] A case 5 is an example in which none responder (DAS28: 5.09 → 4.50) was shown also when treatment using TCZ (tocilizumab) was carried out. The amount of talin remained high (OD value: 2.093 → 1.787) even with TCZ treatment.

35 **[0048]** As is shown from the above-mentioned results, the amount of talin in the blood correlates with the activity of rheumatoid arthritis, and it reflects the activity of rheumatoid arthritis more precisely as compared with the other factors such as CRP and MMP-3. Therefore, by measuring the amount of talin in the blood, it is possible to precisely determine the therapeutic effect of a therapeutic agent for rheumatoid arthritis.

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SEQUENCE LISTING

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15 35 40 45
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45 225 230 235 240
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Ile Lys Gln Arg Gly Ala Glu Lys Arg Ile Phe Gln Glu His Lys Asn
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40	Leu	Leu	Val	Ser	Gly	Ala	Ala	Ser	Thr	Pro	Asp	Lys	Leu	Ala	Gln	Ala
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2515

2520

2525

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 2530 2535 2540

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Claims

- 1. A test method for rheumatoid arthritis, the method comprising a step of measuring an amount of talin in plasma or serum of an animal subject.
- 2. The test method for rheumatoid arthritis according to claim 1, further comprising a step of obtaining plasma or serum from blood collected from the animal subject.
- 3. The test method for rheumatoid arthritis according to claim 1 or 2, wherein the amount of talin in the plasma or the serum is measured by using an antibody which binds to talin.
- 4. The test method for rheumatoid arthritis according to any one of claims 1 to 3, wherein the animal subject is a human subject.
- 5. The test method for rheumatoid arthritis according to any one of claims 1 to 4, wherein the method is carried out for diagnosing rheumatoid arthritis or determining a treatment effect of a therapeutic agent for rheumatoid arthritis.
- 6. A kit for rheumatoid arthritis test used for the test method for rheumatoid arthritis according to any one of claims 1 to 5.
- 7. The kit for rheumatoid arthritis test according to claim 6, comprising a solid-phase carrier to which an antibody that binds to talin is affixed.

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FIG. 1

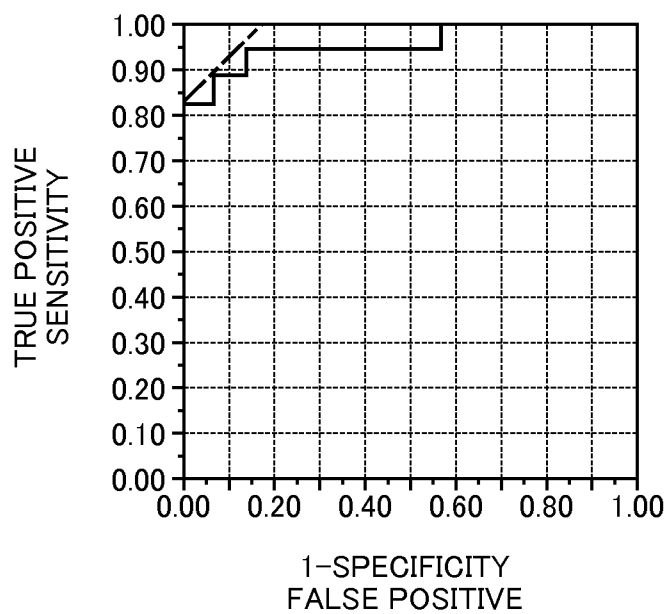


FIG. 2

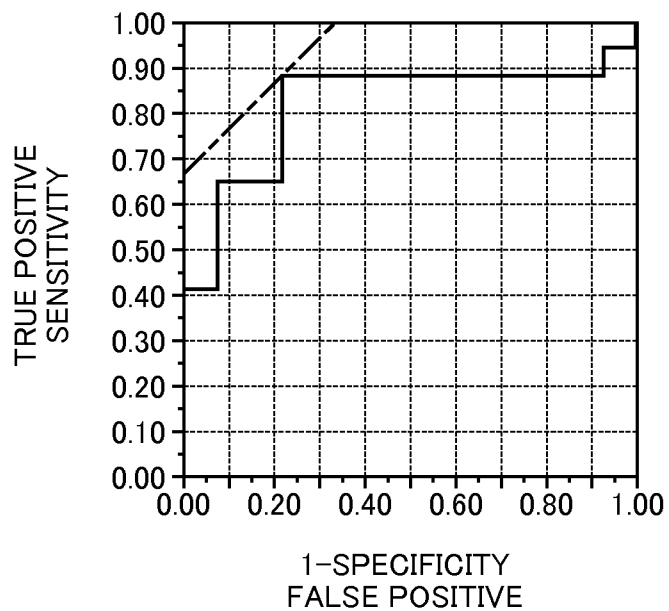
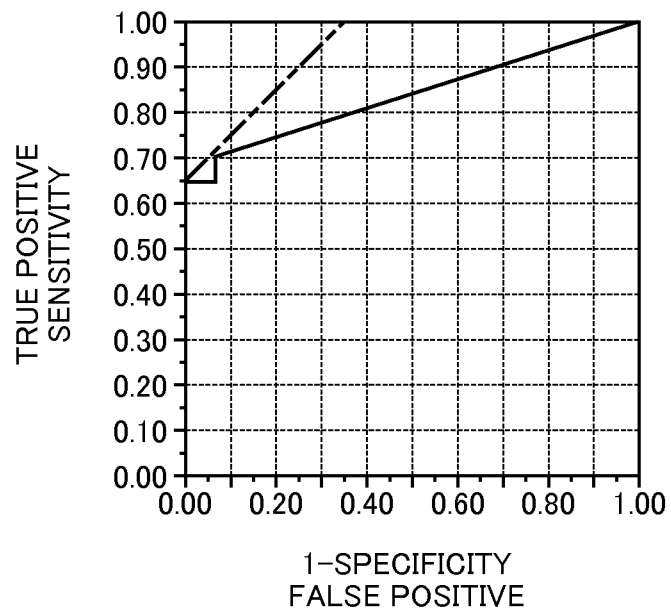


FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2011/063563

A. CLASSIFICATION OF SUBJECT MATTER G01N33/68(2006.01)i, G01N33/53(2006.01)i, G01N33/564(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) G01N33/68, G01N33/53, G01N33/564		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2011 Kokai Jitsuyo Shinan Koho 1971-2011 Toroku Jitsuyo Shinan Koho 1994-2011		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) JSTPlus/JMEDPlus/JST7580 (JDreamII), CPlus (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2009-510464 A (F. Hoffmann-LA Roche AG.), 12 March 2009 (12.03.2009), claim 1 & US 2007/0148704 A1 & EP 1934612 A & WO 2007/039280 A1 & CA 2623167 A & CN 101283278 A	1-5,7
A	JP 2003-024099 A (Applied Cell Biotechnologies, Inc.), 28 January 2003 (28.01.2003), claim 1 & WO 2003/006985 A1	1-5,7
A	JP 2004-012447 A (Takashi MURAMATSU), 15 January 2004 (15.01.2004), claim 1 (Family: none)	1-5,7
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> 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	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 08 September, 2011 (08.09.11)	Date of mailing of the international search report 27 September, 2011 (27.09.11)	
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer	
Facsimile No.	Telephone No.	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2011/063563

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2005-127754 A (Japan Science and Technology Agency), 19 May 2005 (19.05.2005), claim 4 (Family: none)	1-5,7
A	JP 2010-071833 A (Kyoto University), 02 April 2010 (02.04.2010), claim 1 (Family: none)	1-5,7
A	Hajime YOSHIFUJI, "Calpain · Calpastatin to Rheumatoid Arthritis", Rinsho Rheumatism, 30 September 2005 (30.09.2005), vol.17, no.3, pages 160 to 165	1-5,7
A	Martinus A.M. et al., Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value, Arthritis Res., 2002, Vol.4, P.87-93	1-5,7
A	Avouac J. et al., Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review, Ann. Rheum. Dis., 2006, Vol.65, P.845-851	1-5,7
A	Van Venrooij W.J. et al., Anti-CCP antibody, a marker for the early detection of rheumatoid arthritis, Ann. N. Y. Acad. Sci., 2008, Vol.1143, P.268-285	1-5,7

Form PCT/ISA/210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No. PCT/JP2011/063563
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Since it is unclear what components a kit for inspection of articular rheumatism set forth in claim 6 includes, the invention in claim 6 lacks definiteness.

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **MARTINUS A. M. et al.** *Arthritis Res. Ther.*, 2002, vol. 4, 87-93 [0004]
- **AVOUAC J. et al.** *Ann. Rheum. Dis.*, 2006, vol. 65, 845-851 [0004]
- **VAN VENROOIJ WJ. et al.** *Ann. N.Y. Acad. Sci.*, 2008, vol. 1143, 268-285 [0004]

专利名称(译)	用于类风湿性关节炎的新型试验方法和用于类风湿性关节炎试验的试剂盒		
公开(公告)号	EP2653871A4	公开(公告)日	2014-09-24
申请号	EP2011849351	申请日	2011-06-14
[标]申请(专利权)人(译)	KAYTEE生物		
申请(专利权)人(译)	KAYTEEBIO CO.LTD及.		
当前申请(专利权)人(译)	KAYTEEBIO CO.LTD及.		
[标]发明人	TSUZAKA KENSEI		
发明人	TSUZAKA, KENSEI		
IPC分类号	G01N33/68 G01N33/53 G01N33/564		
CPC分类号	G01N33/564 G01N2333/4703 G01N2800/102		
优先权	2010279005 2010-12-15 JP		
其他公开文献	EP2653871B1 EP2653871A1		
外部链接	Espacenet		

摘要(译)

提供了一种新的类风湿性关节炎试验方法;用于类风湿性关节炎试验的试剂盒,用于类风湿性关节炎的新型试验方法。根据本发明的类风湿性关节炎的测试方法的特征在于包括测量动物受试者的血浆或血清中的踝蛋白量的步骤。该测量例如通过使用与踝蛋白结合的抗体的免疫学方法进行。根据本发明的用于类风湿性关节炎测试的试剂盒用于这种测试方法,并且包含例如固定有与踝蛋白结合的抗体的固相载体。