PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference N-ST009-10P	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2010/068909	International filing date *(day/month/year)* 26 October 2010 (26.10.2010)	Priority date *(day/month/year)* 24 November 2009 (24.11.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant KayteeBio Co. & Ltd.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 12 June 2012 (12.06.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yukari Nakamura e-mail: pt07.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28.12.2010
Applicant's or agent's file reference N-ST009-10P	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2010/068909	26.10.2010	24.11.2009

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

C12Q1/68(2006.01)i, C12M1/00(2006.01)i, C12M1/34(2006.01)i, G01N33/50(2006.01)i, C12N15/09(2006.01)n

Applicant

Kaytee Bio Co. & Ltd.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2010/068909

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2010/068909

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 5-8	YES
	Claims	1, 3, 4	NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations:

Document 1: Japan College of Rheumatology Sokai Gakujutsu Shukai Kokusai Rheumatology Symposium Program Shorokushu, March 2009, vol. 53rd-18th, page 274 (W40-2)

Document 2: WO 02/31163 A1

Claims 1, 3, and 4

Document 1 indicates that the prediction of the efficacy of infliximab (INF) for rheumatoid arthritis (RA) was investigated by using the level of ADAMTS5 expression in the blood prior to treatment. More specifically, peripheral blood was collected from thirty randomly selected RA patients prior to INF treatment, and the level of ADAMTS5 mRNA in the blood was measured by real-time PCR. The results showed that the level of ADAMTS5 mRNA expression in the GR (good response) group was significantly lower than in the NGR (no response + moderate response) group, that when the ADAMTS5 mRNA value was low, the positive predictive value for predicting GR was a high 75.0%, that likewise the level of ADAMTS5 mRNA expression in the remission group was

significantly lower than in the non-remission group, and that when the ADAMTS5 mRNA value was low, the positive predictive value for predicting remission was a high 68.8%. Consequently, document 1 indicates that a method for predicting INF efficacy for RA that uses the level of ADAMTS5 expression prior to treatment as an indicator is an extremely useful method.

As a result, the invention as set forth in claims 1, 3, and 4 is either the invention disclosed in document 1, or a person skilled in the art could easily arrive at this invention from the disclosures of document 1, and therefore the invention is not novel and does not involve an inventive step.

Claims 2-4

The decision concerning novelty and inventive step of the invention as set forth in claims 1, 3, and 4 has been rendered above. Hence, a person skilled in the art can suitably select the antibody to be used when carrying out the abovementioned method as needed, and said selection cannot be considered to involve any particular technical difficulty.

Claims 5-8

It is found that the invention as set forth in claims 5-8 is a device for implementing the invention as set forth in claims 1-4.

In this case, when a certain measurement method is developed, it is common practice for a person skilled in the art to create a device for implementing that measurement method. Therefore, a person skilled in the art could easily create a device for implementing the

abovementioned method for predicting INF efficacy for RA that uses the level of ADAMTS5 expression prior to treatment as an indicator. As a result, the invention as set forth in claims 5-8 does not involve an inventive step.

Claims 1-8

Document 1 indicates that the prediction of the efficacy of infliximab (INF) for rheumatoid arthritis (RA) was investigated by using the level of expression in the blood of ADAMTS5 prior to treatment. More specifically, peripheral blood was collected from thirty randomly selected RA patients prior to INF treatment, and the level of ADAMTS5 mRNA in the blood was measured by real-time PCR. The results showed that the level of ADAMTS5 mRNA expression in the GR (good response) group was significantly lower than in the NGR (no response + moderate response) group, that when the ADAMTS5 mRNA value was low, the positive predictive value for predicting GR was a high 75.0%, that likewise the level of ADAMTS5 mRNA expression in the remission group was significantly lower than in the non-remission group, and that when the ADAMTS5 mRNA value was low, the positive predictive value for predicting remission was a high 68.8%. Consequently, document 1 indicates that the method for predicting INF efficacy for RA that uses the level of ADAMTS5 expression prior to treatment as an indicator is an extremely useful method. Document 2 indicates that ADAMTS4 and ADAMTS5 both cleave aggrecan as a substrate between glutamic acid residue 373 and alanine residue 374. Document 2 also indicates that cleavage at this site is one early sign of articular

diseases such as chronic rheumatoid arthritis and osteoarthritis that are accompanied by articular cartilage destruction, and that inhibitors of ADAMTS4 and ADAMTS5 have been noted as therapeutic agents for these diseases.

This being the case, from the disclosures of document 2 a person skilled in the art could easily understand that ADAMTS4 and ADAMTS5 both have common activity, and that ADAMTS4 and ADAMTS5 are both linked to chronic rheumatoid arthritis, and could easily modify the method disclosed in document 1 for predicting INF efficacy for RA that uses the level of ADAMTS5 expression prior to treatment as an indicator in order to analyze the level of expression of ADAMTS4, and attempt to predict the INF efficacy.

Moreover, a person skilled in the art can suitably select the antibody to be used when carrying out the abovementioned method as needed, and said selection cannot be considered to involve any particular technical difficulty.

In addition, it is found that the invention as set forth in claims 5-8 is a device for implementing the invention as set forth in claims 1-4. In this case, when a certain measurement method is developed, it is common practice for a person skilled in the art to create a device for implementing that measurement method. Therefore, a person skilled in the art could easily create a device for implementing the abovementioned method for predicting INF efficacy for RA that uses the level of ADAMTS4 expression prior to treatment as an indicator. As a result, the invention as set forth in the abovementioned claims does not involve an inventive

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

step.