

# PATENT COOPERATION TREATY

TRANSLATION

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

|                                     |                   |
|-------------------------------------|-------------------|
| Date of mailing<br>(day/month/year) | <b>06.09.2016</b> |
|-------------------------------------|-------------------|

|                                                           |                                                    |
|-----------------------------------------------------------|----------------------------------------------------|
| Applicant's or agent's file reference<br><b>GP185-PCT</b> | <b>FOR FURTHER ACTION</b><br>See paragraph 2 below |
|-----------------------------------------------------------|----------------------------------------------------|

|                                                           |                                                                 |                                                     |
|-----------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------|
| International application No.<br><b>PCT/JP2016/068738</b> | International filing date (day/month/year)<br><b>24.06.2016</b> | Priority date (day/month/year)<br><b>24.06.2015</b> |
|-----------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------|

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

Applicant  
**JCR PHARMACEUTICALS CO., LTD.**

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

- |                                     |              |                                                                                                                                                                      |
|-------------------------------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the opinion                                                                                                                                                 |
| <input type="checkbox"/>            | Box No. II   | Priority                                                                                                                                                             |
| <input type="checkbox"/>            | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability                                                                     |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention                                                                                                                                           |
| <input checked="" type="checkbox"/> | 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 |
| <input checked="" type="checkbox"/> | Box No. VI   | Certain documents cited                                                                                                                                              |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application                                                                                                                     |
| <input type="checkbox"/>            | 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 66.1bis(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.

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

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**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:
  - a. ☒ forming part of the international application as filed:

☒ in the form of an Annex C/ST.25 text file.  
☐ on paper or in the form of an image file.
  - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
  - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).  
☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
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 forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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**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 | 1-69 | YES |
|                               | Claims |      | NO  |
| Inventive step (IS)           | Claims |      | YES |
|                               | Claims | 1-69 | NO  |
| Industrial applicability (IA) | Claims | 1-69 | YES |
|                               | Claims |      | NO  |

2. Citations and explanations:

Citations

Document 1: JP 05-500944 A (ALKERMES, INC.) 25 February 1993, claim 1, example 14 & US 5527527 A, claim 1, example 14 & WO 1991/003259 A1 & EP 0490998 A1 & DE 69024057 C

Document 2: JP 2014-514313 A (ROCHE GLYCART AG) 19 June 2014, claim 1, example 2, fig. 7, 10a, 10b, paragraphs [0129]-[0135], [0163] & US 2012/0282176 A1, claim 1, example 2, fig. 7, 10a, 10b, paragraphs [0132]-[0138], [0172], [0175] & WO 2012/143379 A1 & EP 2699600 A1 & KR 10-2014-0031217 A & RU 2013150331 A

Document 3: WO 2013/177062 A2 (F. HOFFMANN-LA ROCHE AG) 28 November 2013, claim 7, example 7 & JP 2015-523336 A, claim 7, example 7 & US 2015/0353639 A1 & EP 2852618 A2 & IL 235806 A & KR 10-2015-0014503 A & CN 104520325 A & MX 2014014166 A & HK 1206369 A & TW 201400132 A

Document 4: SADE H. et al., A Human Blood-Brain Barrier

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Transcytosis Assay Reveals Antibody  
Transcytosis Influenced by pH-Dependent  
Receptor Binding., PLoS One. [online],  
2014, vol. 9, no. 4, e96340 特に fig. 6 の  
E-H,  
<<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005765/pdf/pone.0096340.pdf>> [retrieved  
on 18 August 2016 ], non-official-  
translation (SADE, H. et al., A Human  
Blood-Brain Barrier Transcytosis Assay  
Reveals Antibody Transcytosis Influenced by  
pH-Dependent Receptor Binding., PLoS One.,  
[online], 2014, vol. 9, no. 4, e96340 in  
particular, fig. 6, E-H,  
<<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005765/pdf/pone.0096340.pdf>> [retrieved  
on on 18 August 2016 ])

Document 5: FRIDEN PM. et al., Characterization,  
receptor mapping and blood-brain barrier  
transcytosis of antibodies to the human  
transferrin receptor., J Pharmacol Exp  
Ther., 1996, vol. 278, no. 3, pages 1491-  
1498 特にアブストラクト部分), non-official-  
translation (FRIDEN, PM. et al.,  
Characterization, receptor mapping and  
blood-brain barrier transcytosis of  
antibodies to the human transferrin  
receptor. & Pharmacol Exp Ther., 1996, vol.  
278, no. 3, pages 1491-1498 in particular,  
abstract)

Document 6: PARDRIDGE WM., Blood-brain barrier drug

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delivery of IgG fusion proteins with a transferrin receptor monoclonal antibody., Expert Opin Drug Deliv., 2015.02, vol. 12, no. 2, pages 207-222 特にアブストラクト部分、page 208 右欄, non-official-translation (PARDRIDGE, WM., Blood-brain barrier drug delivery of IgG fusion proteins with a transferrin receptor monoclonal antibody., Expert Opin Drug Deliv., 2015.02, vol. 12, no. 2, pages 207-222 in particular, abstract, page 208, right column)

Document 7: WO 2015/009961 A1 (ARMAGEN TECHNOLOGIES) 22 January 2015, claims 30-47 & US 2016/0152719 A1

Claims 1-69

Documents 1 and 2 (claim 1) and document 3 (claim 7) cited in the ISR disclose techniques for delivering a compound across the blood brain barrier (BBB) by using an antibody that binds to the human transferrin receptor (hTfR). Document 1 (example 14) indicates that when cynomolgus monkeys (*Macaca fascicularis*) were administered the anti-hTfR antibody intravenously, said antibody was detected in brain samples, which demonstrates that the blood brain barrier was traversed. Document 2 (example 2; fig. 7, 10a, 10b; paragraph [0163]) and document 4 (E-H in fig. 6) cited in the ISR indicate that when transcytosis assays were performed on a plurality of anti-hTfR antibodies, some underwent transcytosis but others did not. Document 2 (paragraphs [0129]-[0135]) discloses the sequence of a peptide linker

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when linking an effector moiety to an antibody. Document 3 (example 7) indicates that a bispecific antibody was prepared that binds with the human BBB receptor human TfR and the brain antigen BACE1, but does not exhibit ADCC activity. Document 5 (abstract) cited in the ISR indicates that an antibody that binds to human and monkey TfR was obtained, and that such an antibody is useful for passing through the BBB and delivering a therapeutic protein to the central nervous system. Document 6 (abstract) cited in the ISR indicates that fusing a biopharmaceutical with an anti-TfR antibody enables said drug to pass through the BBB, and that antihuman TfR antibody 128.1 can pass through the BBB of old world monkeys such as the cynomolgus monkey (page 208, right column).

Moreover, obtaining a new antibody or antigen-binding fragment thereof that has the same activity as a known antibody was an obvious problem before the priority date of the present application, and the chimerization and humanization of antibodies for therapy in humans, etc., is well-known and commonly practiced technology.

Therefore, a person skilled in the art could easily accomplish the following: prepare a new antibody or antigen binding fragment thereof that binds with hTfR based on the disclosures of documents 1-6, prepare a drug, etc.; select an antibody that also binds with a transferrin receptor derived from a monkey in consideration of the disclosures of documents 1, 5, and 6; humanize or chimerize said antibody; and by linking an unspecified publicly known therapeutic compound, etc., to the resulting antibody, produce a medication, etc., that is delivered by traversing the BBB. Moreover, the

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sequence of the linker when linking the compound to the antibody is a matter that a person skilled in the art could, as appropriate, design.

Furthermore, it is not found that the invention set forth in the abovementioned claims exhibits a particularly prominent advantageous effect.

As a result, a person skilled in the art could easily accomplish the invention as in claims 1-69 of the present application based on the inventions disclosed in documents 1-6, and said invention does not involve an inventive step.

Claims 52-57, 59-61, and 67-69

Document 7 (claims 30-47) cited in the ISR indicates that a central nervous system disease such as Hunter's syndrome, etc., is treated by administering a medication obtained by fusing a drug such as iduronate-2-sulfatase with an antibody that binds with a BBB receptor such as the transferrin-receptor.

In this case, the inventions disclosed in documents 1-7 all belong to the same technical field and all address the problem of traversing the BBB by linking a drug to an antibody that binds with the transferrin receptor.

Therefore, a person skilled in the art could easily link the iduronate-2-sulfatase, etc., disclosed in document 7 to an anti-hTfR antibody that was obtained based on the disclosures of documents 1-6.

Furthermore, it is not found that the invention set forth in the abovementioned claims exhibits a particularly prominent advantageous effect.

As a result, a person skilled in the art could

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easily accomplish the invention as in claims 52-57, 59-61, and 67-69 of the present application based on the inventions disclosed in documents 1-7, and said invention does not involve an inventive step.

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Box No. VI      Certain documents cited

1.    Certain published documents (Rule 43*bis*.1 and 70.10)

| Application No.<br>Patent No. | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority date (valid claim)<br>(day/month/year) |
|-------------------------------|--------------------------------------|---------------------------------|-------------------------------------------------|
| <b>WO 2015/098989 A1</b>      | <b>02.07.2015</b>                    | <b>24.12.2014</b>               | <b>25.12.2013</b>                               |
| 「E, X」                        |                                      |                                 |                                                 |

2.    Non-written disclosures (Rule 43*bis*.1 and 70.9)

| Kind of non-written disclosure | Date of non-written disclosure<br>(day/month/year) | Date of written disclosure<br>referring to non-written disclosure<br>(day/month/year) |
|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------------|
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**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

C12N15/09 (2006.01) i, A61K39/395 (2006.01) i,  
A61K45/00 (2006.01) i, A61P9/10 (2006.01) i,  
A61P21/02 (2006.01) i, A61P21/04 (2006.01) i,  
A61P25/00 (2006.01) i, A61P25/14 (2006.01) i,  
A61P25/16 (2006.01) i, A61P25/18 (2006.01) i,  
A61P25/24 (2006.01) i, A61P25/28 (2006.01) i,  
A61P31/04 (2006.01) i, A61P31/12 (2006.01) i,  
A61P35/00 (2006.01) i, C07K14/475 (2006.01) i,  
C07K16/18 (2006.01) i, C07K16/28 (2006.01) i,  
C07K16/46 (2006.01) i, C07K19/00 (2006.01) i,  
C12N5/10 (2006.01) i, C12N9/10 (2006.01) i,  
C12N9/16 (2006.01) i, C12N9/24 (2006.01) i,  
C12N9/64 (2006.01) i, C12N15/113 (2010.01) i,  
C12P21/08 (2006.01) n