PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year)  see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2011/034998

International filing date (day/month/year) 03.05.2011

Priority date (day/month/year) 03.05.2010

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/78 C07K14/435 A61K38/59 C12N15/62 A61K47/48

Applicant
BRISTOL-MYERS SQUIBB COMPANY

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 43bis.1(a)(i) with regard to novelty, inventive step and 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 usually 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/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

Name and mailing address of the ISA:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of this opinion
see form PCT/ISA210

Authorized Officer
Chavanne, Franz
Telephone No. +49 89 2399-8399

Form PCT/ISA237 (Cover Sheet) (July 2009)
Box No. I  Basis of the 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 43bis.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:
Box No. III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application
☒ claims Nos. 1-65(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (specify):

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (specify):

☒ no international search report has been established for the whole application or for said claims Nos. 1-65(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
  ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
  ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
  ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ See Supplemental Box for further details
Box No. IV  Lack of unity of invention

1. ☑ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
   □ paid additional fees
   ☑ paid additional fees under protest and, where applicable, the protest fee
   □ paid additional fees under protest but the applicable protest fee was not paid
   □ not paid additional fees

2. □ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   □ complied with
   ☑ not complied with for the following reasons:
     
     see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:
   □ all parts.
   ☑ the parts relating to claims Nos. 1-65(partially)

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

<table>
<thead>
<tr>
<th>Novelty (N)</th>
<th>Yes: Claims</th>
<th>No: Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2, 6, 7, 17-26, 28-30, 48, 49, 54(all partially)</td>
<td>1, 3-5, 8-16, 27, 31-47, 50-53, 55-65(all partially)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inventive step (IS)</th>
<th>Yes: Claims</th>
<th>No: Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-65(partially)</td>
<td>1-65(partially)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Industrial applicability (IA)</th>
<th>Yes: Claims</th>
<th>No: Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-65(partially)</td>
<td>1-65(partially)</td>
</tr>
</tbody>
</table>

2. Citations and explanations
   
   see separate sheet
<table>
<thead>
<tr>
<th>Box No. VI</th>
<th>Certain documents cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Certain published documents (Rules 43bis.1 and 70.10)</td>
</tr>
<tr>
<td></td>
<td>and/or</td>
</tr>
<tr>
<td>2.</td>
<td>Non-written disclosures (Rules 43bis.1 and 70.9)</td>
</tr>
<tr>
<td></td>
<td>see form 210</td>
</tr>
</tbody>
</table>
III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 An objection of lack of unity has been raised by the Searching Authority. The Applicant paid two additional search fees under protest, relating to SEQ ID No.4 and 132. The International Search Report has been restricted to the searched inventions, covered by claims 1-65, all partially. Consequently, an opinion with regard to novelty, inventive step and industrial applicability can only be partially formulated, limited to the searched claims (claims 1-65, partially).

IV. Lack of unity of invention

1 Claims 1-65 lack unity under Rule 13.1 PCT, for the following reasons:

The problem underlying claims 1-65 can be seen in the provision of a polypeptide comprising a fibronectin type III tenth (10Fn3) domain, which has been modified to bind to a target molecule not bound by the wild-type 10Fn3 domain. The present application solves this problem by modifying said 10Fn3 domain in one or more of the AB, BC, CD, DE, EF and FG loops. However, the prior art discloses such modified 10Fn3 domains (see e.g. WO 2009/133208; WO 2009/102421; WO 2008/066752), including 10Fn3 domains which have been modified to bind to human serum albumin (see e.g. WO 2009/133208). Such knowledge destroys the linking unit between the different claimed polypeptides comprising a modified 10Fn3. Since no other technical feature can be distinguished which, in light of the prior art, could be regarded as a special common technical feature, the ISA is of the opinion, that there is no single inventive concept underlying the plurality of inventions in the sense of Rule 13.2 PCT.

Correspondingly, claims 1-65 do not relate to one single invention but to at least 25 different inventions, which are not linked by a single inventive concept, namely:

**Invention 1 (claims 1-65, partially)**

Polypeptide comprising a fibronectin type III tenth (10Fn3) domain of SEQ ID No.8, fusion polypeptide comprising this polypeptide and a heterologous protein, pharmaceutical composition comprising said polypeptide or said
fusion polypeptide, therapeutical methods using said fusion polypeptide, nucleic acid encoding said polypeptide or fusion polypeptide, vector comprising said nucleic acid, host cell comprising said vector.

Inventions 2-25 (claims 1-65, partially)
Polypeptide comprising a fibronectin type III tenth (10Fn3) domain of SEQ ID No.12, 16, 20 and 24-44, respectively, fusion polypeptide comprising this polypeptide and a heterologous protein, pharmaceutical composition comprising said polypeptide or said fusion polypeptide, therapeutical methods using said fusion polypeptide, nucleic acid encoding said polypeptide or fusion polypeptide, vector comprising said nucleic acid, host cell comprising said vector.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:


2 First searched invention (SEQ ID No.8)

3 D1 describes modification of the tenth Fn3 domain of human fibronectin at one or more of the AB, CD, EF and/or BC, DE and FG loops to alter binding to a target molecule while retaining structural and conformational stability for e.g. therapeutical applications. D1 explicitly refers to modifications of the Fn3 domain which result in binding capacities to e.g human serum albumin to increase its half-life (abstract; pages 2-5, 8, 12-14, 23, 24, 26-32, 34;
examples 1-7). D1 does not explicitly disclose e.g. the Kd at which the modified \(^{10}\text{Fn3}\) binds to human serum albumin. However, as a general rule, the elucidation of a novel feature (e.g. Kd) of a known product (e.g. modified \(^{10}\text{Fn3}\)) is not enable to reinstate the novelty of said product. Thus, in view of D1, the subject-matter of claims 1, 3-5, 8-16, 27, 31-47, 50, 51, 53, 55-65 is not novel (Article 33(2) PCT).

4 D2 and D3 describes the modification of the BC, DE and/or FG loop of the tenth Fn3 domain of fibronectin to bind to the human epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor (IGFR), respectively. The polypeptide comprising said modified \(^{10}\text{Fn3}\) may further comprise human serum albumin to increase its half-life. Both D2 and D3 describe the method for obtaining modified \(^{10}\text{Fn3}\) binding to a specific target molecule. Several of the sequences disclosed in both D2 or D3 have a high identity (more than 70\%) with SEQ ID No.8 of the present application (D2: abstract; pages 3, 4, 6, 18-20, 28, 29; D3: abstract; pages 8, 9, 12, 13, 27, 28, 37-39).

Thus, in view of either D2 or D3, the subject-matter of claims 46, 47, 50, 51, 55-65 is not novel (Article 33(2) PCT).

5 The subject-matter of claims 1-45 differs from the teachings of either D2 or D3 in the target molecule binding to the modified \(^{10}\text{Fn3}\) domain. However, both D2 and D3 describe the methods for obtaining any target molecule binding to a modified \(^{10}\text{Fn3}\) and not to the wild-type \(^{10}\text{Fn3}\). Hence, in view of either D2 or D3, the man skilled in the art, faced with the problem of providing a polypeptide comprising a \(^{10}\text{Fn3}\) domain binding to serum albumin, by applying the teachings of either D2 or D3 would automatically and in a straightforward manner come to the \(^{10}\text{Fn3}\) domains of SEQ ID No.8 without the need of applying any inventive skills. The subject-matter of claims 1-45 is, thus, not inventive (Article 33(3) PCT).

Moreover, the man skilled in the art, aware of any of D2 or D3, by applying common knowledge and routinely used technics would automatically come to the subject-matter of claims 48, 49 and 52-54. Hence, this subject-matter is not inventive (Article 33(3) PCT).
Second searched invention (SEQ ID No.4)

D1 describes modification of the tenth Fn3 domain of human fibronectin at one or more of the AB, CD, EF and/or BC, DE and FG loops to alter binding to a target molecule while retaining structural and conformational stability for e.g. therapeutical applications. D1 explicitly refers to modifications of the Fn3 domain which result in binding capacities to e.g. human serum albumin to increase its half-life (abstract; pages 2-5, 8, 12-14, 23, 24, 26-32, 34; examples 1-7). D1 does not explicitly disclose e.g. the Kd at which the modified $^{10}$Fn3 binds to human serum albumin. However, as a general rule, the elucidation of a novel feature (e.g. Kd) of a known product (e.g. modified $^{10}$Fn3) is not enable to reinstate the novelty of said product. Thus, in view of D1, the subject-matter of claims 1, 3-5, 8-16, 27, 31-47, 50, 51, 53, 55-65 is not novel (Article 33(2) PCT).

The subject-matter of claims 1-45 differs from the teachings of either D2 or D3 in the target molecule binding to the modified $^{10}$Fn3 domain. However, both D2 and D3 describe the methods for obtaining any target molecule binding to a modified $^{10}$Fn3 and not to the wild-type $^{10}$Fn3. Hence, in view of either D2 or D3, the man skilled in the art, faced with the problem of providing a polypeptide comprising a $^{10}$Fn3 domain binding to serum albumin, by applying the teachings of either D2 or D3 would automatically and in a straightforward manner come to the $^{10}$Fn3 domains of SEQ ID No.4 without the need of applying any inventive skills. The subject-matter of claims 1-45 is, thus, not inventive (Article 33(3) PCT).

Moreover, the man skilled in the art, aware of any of D2 or D3, by applying common knowledge and routinely used technics would automatically come to the subject-matter of claims 48, 49 and 52-54. Hence, this subject-matter is not inventive (Article 33(3) PCT).

VI. Certain documents cited

1. WO 2011/130354
2. WO 2011/103105