Highly Potent Antibodies Binding to Death Receptor 4 and Death Receptor 5

A61K 39/395 (2006.01)  C12P 21/08 (2006.01)  C07K 16/28 (2006.01)  A61P 35/00 (2006.01)

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Abstract: The present invention is directed toward monoclonal antibodies that bind to death receptor 4 and/or death receptor 5, a pharmaceutical composition comprising same, and methods of treatment comprising administering such a pharmaceutical composition to a patient.
Published: 22 June 2017

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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 2a 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 2a).
      - on paper or in the form of an image file (Rule 1d and Administrative Instructions, Section 7.13).

2. ☑ 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.

3. Additional comments:
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/59517

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.: 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:

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:

-**-Please See Supplemental Page***.

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.:

Groups 1, Claims 1-10; and SEQ ID NO: 20 (CDR-L1), SEQ ID NO: 21 (CDR-L2), SEQ ID NO: 22 (CDR-L3), SEQ ID NO: 23 (CDR-H1), SEQ ID NO: 24 (CDR-H2) and SEQ ID NO: 25 (CDR-H3)

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.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/59517

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 39/395; C07K 16/28; C12P 21/08; A61P 35/00 (2017.01)
CPC - A61K 39/395; C07K 16/28; 16/2878; 14/70578

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 2004/0120947 A1 (ASHKENAZI, A et al.) June 24, 2004; paragraphs [0022], [0023], [0047]</td>
<td>1-10</td>
</tr>
<tr>
<td>A</td>
<td>US 2005/0265998 A1 (ELSON, G) December 1, 2005; Figure 25F</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* 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

"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search
28 March 2017 (28.03.2017)

Date of mailing of the international search report
25 APR 2017

Name and mailing address of the ISA/
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Form PCT/ISA/210 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

**Information on patent family members**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I, Claims 1-10; and SEQ ID NO: 20 (CDR-L1), SEQ ID NO: 21 (CDR-L2), SEQ ID NO: 22 (CDR-L3), SEQ ID NO: 23 (CDR-H1), SEQ ID NO: 24 (CDR-H2) and SEQ ID NO: 25 (CDR-H3) of D114 are directed toward a monoclonal antibody (mAb) that binds to a death receptor; and method of treating a patient therewith.

The monoclonal antibody will be searched to the extent that it encompasses SEQ ID NO: 20 (first exemplary CDR-L1), SEQ ID NO: 21 (first exemplary CDR-L2), SEQ ID NO: 22 (first exemplary CDR-L3), SEQ ID NO: 23 (first exemplary CDR-H1), SEQ ID NO: 24 (first exemplary CDR-H2) and SEQ ID NO: 25 (first exemplary CDR-H3). Applicant is invited to elect additional set(s) of CDR sequence(s), with specified SEQ ID NO: for each, to be searched. Additional set(s) of CDR sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 6 (in-part), 7 (in-part), 8 (in-part), 9 (in-part), and 10 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 20 (CDR-L1), SEQ ID NO: 21 (CDR-L2), SEQ ID NO: 22 (CDR-L3), SEQ ID NO: 23 (CDR-H1), SEQ ID NO: 24 (CDR-H2) and SEQ ID NO: 25 (CDR-H3). Applicants must specify the claims that encompass any additionally elected set(s) of sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the *-"* group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a monoclonal antibody encompassing SEQ ID NO: 26 (first exemplary elected CDR-L1), SEQ ID NO: 27 (first exemplary elected CDR-L2), SEQ ID NO: 28 (first exemplary elected CDR-L3), SEQ ID NO: 29 (first exemplary elected CDR-H1), SEQ ID NO: 30 (first exemplary elected CDR-H2) and SEQ ID NO: 31 (first exemplary elected CDR-H3).

Group II, Claims 11-17 are directed toward a bispecific antibody that binds to a DR4 and DR5 domain.

Group III, Claims 18-21 are directed toward a monoclonal antibody that binds to a death receptor comprising a human constant region having two or more mutations, each of which increases binding to a human Fc gamma receptor.

The inventions listed as Groups I, II, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I include a monoclonal antibody (mAb) comprising CDRs from D114, which is not present in Groups II and III; the special technical features of Group II include a bispecific antibody, which is not present in any of Groups I and III; the special technical features of Group III include a monoclonal antibody comprising a mutated human constant region, which is not present in any of Groups I and III.

No technical features are shared between the CDR sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I, II and III share the technical features including an antibody that binds to a death receptor. Groups I share the technical features including: a monoclonal antibody (mAb) that binds to a death receptor and which comprises a light chain variable (V) region having three CDRs and a heavy chain V region having three CDRs; a pharmaceutical composition comprising said antibody in a pharmaceutically acceptable carrier; a method of treating a patient suffering from cancer, comprising administering said pharmaceutical composition.

However, these shared technical features are previously disclosed by the publication entitled US 2004/0129047 A1 to Ashkenazi et al. (hereinafter 'Ashkenazi').

Ashkenazi discloses a monoclonal antibody (mAb) that binds to a death receptor (a monoclonal antibody (mAb) that binds to a death receptor; abstract; paragraph [0022]) and which comprises a light chain variable (V) region having three CDRs (comprising a light chain variable (V) region having three CDRs; paragraphs [0023]; [0047]) and a heavy chain V region having three CDRs (a heavy chain V region having three CDRs; paragraphs [0023], [0047]); a pharmaceutical composition comprising the antibody in a pharmaceutically acceptable carrier (a pharmaceutical composition comprising the antibody in a pharmaceutically acceptable carrier; paragraph [0233]); a method of treating a patient suffering from cancer (a method of treating a patient suffering from cancer; paragraphs [0022], [0211]-[0212]), comprising administering the pharmaceutical composition (administering the pharmaceutical composition; paragraph [0211]).

Since none of the special technical features of the Groups I+, II and III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Ashkenazi reference, unity of invention is lacking.