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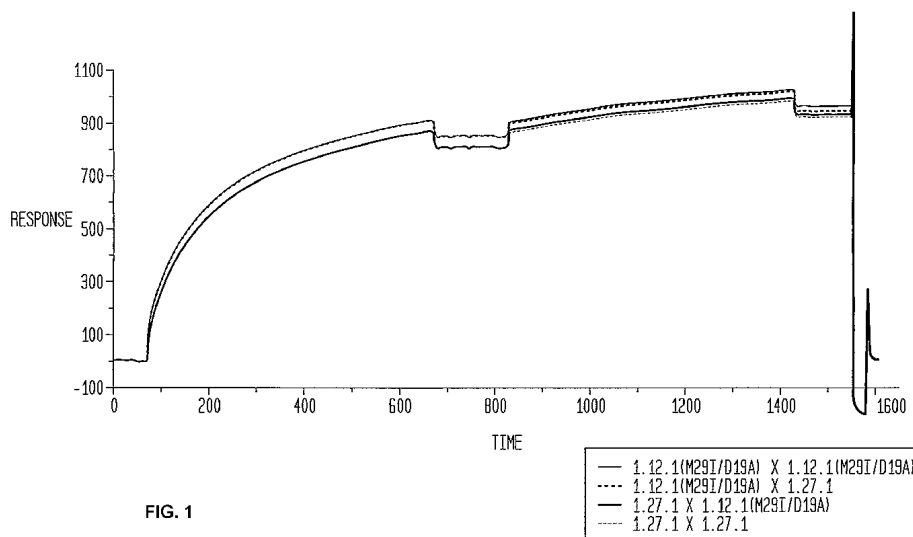
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[Continued on next page]

(54) Title: HUMAN MONOCLONAL ANTIBODIES TO ACTIVIN RECEPTOR-LIKE KINASE-1



(57) Abstract: The present invention relates to antibodies including human antibodies and antigen-binding portions thereof that bind to the extracellular domain (ECD) of activin receptor-like kinase-1 (ALK-1) and that function to abrogate the ALK-1/TGF-beta-1/Smad1 signaling pathway. The invention also relates to heavy and light chain immunoglobulins derived from human anti-ALK-1 antibodies and nucleic acid molecules encoding such immunoglobulins. The present invention also relates to methods of making human anti-ALK-1 antibodies, compositions comprising these antibodies and methods of using the antibodies and compositions. The invention also relates to transgenic animals or plants comprising nucleic acid molecules of the present invention.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/35096

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 5/06, 5/16; C07K 16/00 (2008.01)

USPC - 435/328

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)

USPC - 435/328

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/6, 7.1, 70.21, 330-331; 436/548; 530/388.1, 388.15; 424/133.1 (see search terms below)

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

PubWEST(USPT,PGPB,EPAB,JPAB); Google Patents; Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,968,752 A (ICHIJO et al.) 19 October 1999 (19.10.1999) col 3, ln 46-49; col 7, ln 30-34; col 9, ln 18-23; col 14, ln 28-38; col 15, ln 55-60; col 30, ln 20-30	6 ----- 7-14
X --- Y --- A	US 2003/0152514 A1 (GUDAS) 14 August 2003 (14.08.2003) para [0012] [0034], [0104]-[0106]	20 ----- 7 and 9-14 ----- 1 and 4-5
Y --- A	US 2005/0054019 A1 (MICHAUD et al.) 10 March 2005 (10.03.2005) para [0018], [0095], [0100], [0113], [0157], [0166]-[0167], [0220], [0263]-[0264], [0284]	8-9 and 12-14 ----- 1 and 4-5

☐ 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

11 January 2008 (11.01.2008)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/35096

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.: 15 and 22-23
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:
see extra sheet

Applicant's protest directed to SEQ ID NO: 8 is found persuasive because the antibody or antigen binding portion in claim 1 requires both sequences (SEQ ID NOs: 6 and 8).

Applicants' protest directed to claims 7-12, 20, 22, and 23 and SEQ ID NOs: 2, 4, 100, 102, 104 and 127 is not considered because Applicant did not pay the additional search fee for these additional inventions or species.

Furthermore, there is prior art, namely US 5,968,752 A (Ichijo et al.), of record that breaks the special technical feature of the claimed invention, i.e. antibody that binds to ALK-1. See PCT Rule 13.2.

However, in addition to claims 1-5 (as they relate to SEQ ID NOs: 6 and 8), claims 6-14, 20 and 21 (limited to SEQ ID NOs: 6 and 8) are being rejoined with the first claimed invention. Accordingly, the first claimed invention is deemed to be claims 1-14, 20 and 21 (limited to SEQ ID NOs: 6 and 8), i.e. claims 1, 4-14 and 20.

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.:
claims 1-14, 20 and 21 (limited to SEQ ID NOs: 6 and 8), i.e. claims 1, 4-14 and 20 (see above).
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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/35096

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

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. type of material

- ☒ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☒ on paper
☐ in electronic form

c. time of filing/furnishing

- ☒ contained in the international application as filed
☐ filed together with the international application in electronic form
☐ furnished subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto 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.

3. Additional comments:

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.

Group 1: Claims 1-5 directed to antibody or antigen binding portion that binds ALK-1.
 Group 2: Claims 6-12, and 14 directed to antibody or antigen binding portion that binds ALK-1.
 Group 3: Claim 13 directed to antibody or antigen binding portion that binds ALK-1.
 Group 4: Claim 16 directed to an isolated nucleic acid molecule.
 Group 5: Claim 17 directed to an isolated nucleic acid molecule.
 Group 6: Claims 18-19 directed to a hybridoma.
 Group 7: Claims 20-21 directed to antibody or antigen binding portion that binds ALK-1.
 Group 8: Claim 24 directed to antibody or antigen binding portion that binds ALK-1.

The inventions listed as Groups 1-8 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 common technical feature of the listed groups is an antibody or antigen binding portion that binds ALK-1. However, this is not an improvement over the prior art of Ichijo et al. (US 5,968,752 A to Ichijo et al.). Ichijo discloses an antibody that binds ALK-1.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid.

The species listed below do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the reasons as stated below.

The species are as follows:

Species Pertaining to Group 1

The different species related to antibody domains: SEQ ID NOS: 6, 8, 2, 4, 100, and 102.

The different antibody domains are different structures that are not common to one another but are different because they are composed of unique amino acid sequences.

Species Pertaining to Group 2

The different species related to antibodies: 1.11.1; 1.12.1; 1.12.1(M29/D19A); 1.12.1(M29I); 1.12.1(D19A); 1.12.1(rWT); 1.13.1; 1.14.1; 1.151.1; 1.162.1; 1.183.1; 1.27.1; 1.29.1; 1.31.1; 1.8.1; 1.9.1; 4.10.1; 4.24.1; 4.38.1; 4.58.1; 4.62.1; 4.68.1; 4.72.1; 5.13.1; 5.34.1; 5.53.1; 5.56.1; 5.57.1; and 5.59.1.

The different species related to antibody domains: SEQ ID NOS: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, and 104.

The different species related to antibody domains: SEQ ID NOS: 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 and 127.

The different species related to human genes: Vka27, Vka2, Vka1, Vka3, Vkb3, Vkb2, Vkl1 and Vkl2.

The different antibodies, antibody domains and human genes are different structures that are not common to one another but are different because they are composed of unique amino acid and nucleic acid sequences.

Species Pertaining to Group 3

The different species related to human genes: Vh4-31, Vh3-11, Vh3-15, Vh3-33, Vh4-61 and Vh4-59.

The different human genes are different structures that are not common to one another but are different because they are composed of unique nucleic acid sequences.

Species Pertaining to Group 4

The different species related to SEQ ID NOS: 1, 3, 5, 7, 95, 101, 103, 126, 128 and 129

The different nucleic acids are different structures that are not common to one another but are different because they are composed of unique nucleic acid sequences.

Species Pertaining to Group 5

The different species related to SEQ ID NOS: 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89 and 91.

The different nucleic acids are different structures that are not common to one another but are different because they are composed of unique nucleic acid sequences.

Species Pertaining to Group 7

The different species related to SEQ ID NOS: 2, 4, 6, 8, 100, 102, 104 and 127

The different species related to clones: PTA-6864 and PTA-6865.

The different polypeptides and clones are different structures that are not common to one another but are different because they are composed of unique amino acid and nucleic acid sequences.

Species Pertaining to Group 8

The different species related to the named variations of SEQ ID NO: 136.

The different polypeptides are different structures that are not common to one another but are different because they are composed of unique amino acid sequences.

Claims 15 and 22-23 do not comply with the third sentence of rule 6.4(a) and thus are unsearchable.

The first named invention is antibody or antigen binding portion that binds ALK-1 of claims 1-5 limited to SEQ ID NO:6.