



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : C07K 16/18</p>	<p>A3</p>	<p>(11) International Publication Number: WO 00/09657</p> <p>(43) International Publication Date: 24 February 2000 (24.02.00)</p>
<p>(21) International Application Number: PCT/US99/18539</p> <p>(22) International Filing Date: 13 August 1999 (13.08.99)</p> <p>(30) Priority Data: 60/096,515 14 August 1998 (14.08.98) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/096,515 (CON) Filed on 14 August 1998 (14.08.98)</p> <p>(71) Applicant (for all designated States except US): PRESIDENT AND FELLOWS OF HARVARD COLLEGE [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): LEE, Mu-En [CN/US]; 102 Nardell Road, Newton, MA 02159 (US). MAEMURA, Koji [JP/US]; Apartment #638, 185 Freeman Street, Brookline, MA 02446 (US). HIESH, Chung-Ming [CN/US]; 1716 Cambridge Street, Cambridge, MA 02138 (US).</p> <p>(74) Agent: BEATTIE, Ingrid, A.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 31 August 2000 (31.08.00)</p>
<p>(54) Title: METHODS OF MODULATING OF ANGIOGENESIS</p>		
<p>(57) Abstract</p> <p>A method of inhibiting angiogenesis in a mammal by administering to the mammal a compound which inhibits binding of endothelial PAS domain protein-1 to cis-acting transcription regulatory sequence in the promoter region of a gene encoding an angiogenic factor.</p>		

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18539

A. CLASSIFICATION OF SUBJECT MATTER																				
IPC(7) :C07K 16/18 US CL :424/130.1, 139.1; 530/387.9, 388.21 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) U.S. : 424/130.1, 139.1; 530/387.9, 388.21																				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST, MEDLINE search terms: EPAS1, Hif-2 alpha, MOP2, HLF, ARNT4, Tie-2, VEGF, flk-1, flt-1, KDR.																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT																				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
Y	TIAN, H. et al. Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells, Genes & Development. 1997, Vol. 11, page 72 (Abstract only).	1,6,7,16-20																		
Y	LUO, G. et al. Molecular Characterization of the Murine Hif-1 α Locus. Gene Expression. 1997, Vol. 6, pages 287-299, see entire article, esp. abstract.	19, 20																		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"> <tr> <td>* Special categories of cited documents:</td> <td>*T*</td> <td>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</td> </tr> <tr> <td>*A* document defining the general state of the art which is not considered to be of particular relevance</td> <td>*X*</td> <td>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</td> </tr> <tr> <td>*E* earlier document published on or after the international filing date</td> <td>*Y*</td> <td>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</td> </tr> <tr> <td>*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)</td> <td>*G*</td> <td>document member of the same patent family</td> </tr> <tr> <td>*O* document referring to an oral disclosure, use, exhibition or other means</td> <td></td> <td></td> </tr> <tr> <td>*P* document published prior to the international filing date but later than the priority date claimed</td> <td></td> <td></td> </tr> </table>			* Special categories of cited documents:	*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	*A* document defining the general state of the art which is not considered to be of particular relevance	*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	*E* earlier document published on or after the international filing date	*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	*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)	*G*	document member of the same patent family	*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		
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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																				
Date of the actual completion of the international search 08 MAY 2000		Date of mailing of the international search report 05 JUN 2000																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>Lorraine M. Spector</i> LORRAINE M. SPECTOR, PH.D. Telephone No. (703)308-0196																		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18539

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y - A	EMA, M. et al. A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1 α regulates the VEGF expression and is potentially involved in lung and vascular development. Proc. Natl. Acad. Sci. USA. April 1997, Vol. 94, pages 4273-4278, entire document, esp. abstract, p. 4274 end of 2nd col., p. 4278 1st col.	1-5,16-20 ----- 6,45,46
Y - A	US 5,695,963 A (McKNIGHT et al.) 09 December 1997, entire document, esp. col. 3.	1-6,16-20 ----- 45, 46

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international 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.: 8, 21, 23, 47-50
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:

Claims 8, 21, and 47-50 are unsearchable as each claim recites a nucleic acid or protein sequence; as the application has no computer-readable sequence listing, the sequences could not be searched.

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

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 an additional fee, this Authority did not invite payment of any additional fee.
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.:
1-7, 16-20, 45, 46

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.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

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

Group I, claim(s) 1-8, 16-21, and 23, drawn to anti EPAS-1 antibodies and methods of inhibiting angiogenesis using such.

Group II, claim(s) 1-8, 9-12, 17 and 18, drawn to methods of inhibiting angiogenesis by administration of EPAS1Δ protein.

Group III, claim(s) 1-8, 13, 14, 17 and 18, drawn to methods of inhibiting angiogenesis using nucleic acids encoding EPAS1Δ protein.

Group IV, claim(s) 1-8, 15, 17 and 18, drawn to methods of inhibiting angiogenesis using antisense polynucleotides.

Group V, claim(s) 22, drawn to methods of promoting angiogenesis using a compound that increases expression of VEGF or VEGF-receptor.

Group VI, claim(s) 24-33, 42 and 43, drawn to DNA encoding ARNT4 and related sequences.

Group VII, claim(s) 34-41, drawn to ARNT4 protein.

Group VIII, claim(s) 44, drawn to a transgenic animal.

Group IX, claim(s) 45-50, drawn to inhibition of angiogenesis by inhibiting binding of EPAS1 to ARNT4.

Group X, claims 51-56, drawn to EPAS1 protein deletion mutants and nucleic acids encoding.

The inventions listed as Groups do not relate to a single 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:

Pursuant to 37 C.F.R. 1.475(d), this Authority considers that the main invention in the instant application comprises the first-recited product, anti EPAS-1 antibodies, and the first-recited method of using that product, namely in the process of inhibiting angiogenesis. Note that there is no method of making the antibodies. Further, pursuant to 37 C.F.R.

1.475(b)-(d), the ISA/US considers that the materially and functionally dissimilar product of groups II-VIII and X and the additional methods of groups II-V and IX do not correspond to the main invention. The various products are structurally and functionally distinct, and the various methods require structurally and functionally distinct products. This Authority therefore considers that the several inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1.