



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/11, A61K 31/70, C07H 21/04	A3	(11) International Publication Number: WO 96/23065 (43) International Publication Date: 1 August 1996 (01.08.96)
(21) International Application Number: PCT/US96/01189 (22) International Filing Date: 26 January 1996 (26.01.96) (30) Priority Data: 08/378,860 26 January 1995 (26.01.95) US (71) Applicants: HYBRIDON, INC. [US/US]; One Innovation Drive, Worcester, MA 01605 (US). CHILDREN'S MEDICAL CENTER CORPORATION [US/US]; 300 Longwood Avenue, Boston, MA 02115 (US). (72) Inventors: ROBINSON, Gregory, S.; 194 School Street, Acton, MA 01720 (US). SMITH, Lois, Elaine, Hodgson; 167 Valentine Street, West Newton, MA 02165 (US). (74) Agents: KERNER, Ann-Louise; Lappin & Kusmer, Two Hundred State Street, Boston, MA 02109 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 26 September 1996 (26.09.96)
(54) Title: INHIBITION OF NEOVASCULARIZATION USING VEGF-SPECIFIC OLIGONUCLEOTIDES		
(57) Abstract Disclosed are methods of reducing neovascularization and of treating various disorders associated with neovascularization. These methods include administering to a tissue or subject a synthetic oligonucleotide specific for vascular endothelial growth factor nucleic acid effective in inhibiting the expression of vascular endothelial growth factor.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/01189

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N13/11 A61K31/70 C07H21/04

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)
IPC 6 C12N A61K C07H

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
O,X	ANTISENSE RES.DEV. 5 (SPRING 95); PAGE 91; ABSTRACT OP-18 , XP002008710 NOMURA, M. ET AL.: "Expression and function of VEGF gene in hypoxia-induced proliferation of vascular cells"	1-5,9
Y	see abstract & 1ST INT.ANTISENSE CONF.JAPAN, 4 - 7 December 1994, ---	1-13
Y	THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 331, 1 December 1994, pages 1480-1487, XP000574787 AIELLO, L. ET AL.: "Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders" cited in the application see the whole document ---	1,9,12, 13
-/--		

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p>
--	--

Date of the actual completion of the international search <p style="text-align: center;">18 July 1996</p>	Date of mailing of the international search report <p style="text-align: center;">25. 07. 96</p>
--	---

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Authorized officer <p style="text-align: center;">Andres, S</p>
---	--

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 96/01189

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL REVIEWS, vol. 90, no. 4, 1 June 1990, pages 543-584, XP000141412 UHLMANN, E. ET AL.: "ANTISENSE OLIGONUCLEOTIDES: A NEW THERAPEUTIC PRINCIPLE" cited in the application see the whole document ---	2-8
P,Y	INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 36 (4). S871. ABSTRACT 3990, 15 March 1995, XP002008711 PIERCE, E. ET AL.: "Regulation of retinal vascular endothelial growth factor (VEGF/VPF) levels by hyperoxia and hypoxia: a possible etiology for ROP" see abstract & ANNUAL MEETING OF THE INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, FORT LAUDERDALE, FLORIDA, USA, MAY 14-19, 1995, ---	10,11
A	ANTISENSE RES.DEV. 5 (SPRING 95); PAGES 87-8; ABSTRACT OP-10 , XP002006442 UCHIDA, K. ET AL.: "Selection of antisense oligodeoxyribonucleotides that inhibit VEGF/VPF expression in a cell-free system" cited in the application see abstract & 1ST INT.ANTISENSE CONF.JAPAN , 4 - 7 December 1994, ---	1-15
A	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 193, 15 June 1993, ORLANDO, FL US, pages 631-638, XP002008712 ADAMIS, A. ET AL.: "Synthesis and secretion of vascular permeability factor/vascular endothelial growth factor by human retinal pigment epithelial cells" cited in the application ---	
P,X	WO,A,95 04142 (HYBRIDON INC ;ROBINSON GREGORY S (US)) 9 February 1995 see the whole document --- ---	1-9,12, 13

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/01189

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 36 (4). S871, ABSTRACT 3992, 15 March 1995, XP002008713 SMITH, L. ET AL.: "Inhibition of proliferative retinopathy using antisense phosphorothioate oligonucleotides against vascular endothelial growth factor (VEGF - VPF)." see abstract & ANNUAL MEETING OF THE INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, FORT LAUDERDALE, FLORIDA, USA, MAY 14-19, 1995,</p>	1-4,9
T	<p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 93/10 (4851-4856), May 1996, XP002008714 ROBINSON, G. ET AL.: "Oligodeoxynucleotides inhibit retinal neovascularization in a murine model of proliferative retinopathy." see the whole document -----</p>	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/01189

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:
Remark: Although claims 1-8, 10-15 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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:

1. claims 1-9 Method for reducing neovascularization in a tissue
 2. claims 10-11 Method for treating retinopathy of prematurity
 3. claims 12-13 Method of treating diabetic retinopathy
 4. claims 14-15 Method of treating age-related macular degeneration
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.:
 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

Information on patent family members

International Application No

PCT/US 96/01189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9504142	09-02-95	AU-B- 7516894	28-02-95
		CA-A- 2167680	09-02-95
		EP-A- 0711343	15-05-96
		FI-A- 960374	25-03-96
		NO-A- 960303	13-03-96
