



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 48/00, 31/70, 9/00	A3	(11) International Publication Number: WO 98/40058 (43) International Publication Date: 17 September 1998 (17.09.98)
(21) International Application Number: PCT/US98/04914 (22) International Filing Date: 12 March 1998 (12.03.98) (30) Priority Data: 60/040,738 12 March 1997 (12.03.97) US 08/846,417 30 April 1997 (30.04.97) US (71) Applicant: HYBRIDON, INC. [US/US]; 620 Memorial Drive, Cambridge, MA 02139 (US). (72) Inventors: ZHANG, Ruiwen; 1824 Russet Woods Lane, Birmingham, AL 35244 (US). AGRAWAL, Sudhir; 61 Lamplighter Drive, Shrewsbury, MA 01545 (US). (74) Agents: KERNER, Ann-Louise et al.; Hale and Dorr LLP, 60 State Street, Boston, MA 02109 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, 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, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, 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</i> <i>and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 19 November 1998 (19.11.98)	
(54) Title: DOWN-REGULATION OF GENE EXPRESSION BY COLORECTAL ADMINISTRATION OF SYNTHETIC OLIGONUCLEOTIDES		
(57) Abstract Disclosed is a method of down-regulating the expression of a gene in an animal, wherein an oligonucleotide complementary to the gene is colorectally administered to an animal. Also disclosed is a method for introducing an intact oligonucleotide into a mammal by colorectal administration, whereby the oligonucleotide is present in intact form in the systemic plasma of the mammal at least four hours following administration.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/04914

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K48/00 A61K31/70 A61K9/00

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 A61K

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.
X	WO 94 17093 A (HYBRIDON INC.) 4 August 1994 see claims 1-8 see page 5, line 26 - page 6, line 3 see page 12, line 1 - page 13, line 30 ---	1-31
X	WO 97 05267 A (MAXIM PHARMACEUTICALS) 13 February 1997 see page 8, line 33 - page 9, line 18 see page 10, line 10 - line 15 see claims 1-20 ---	1-31
Y	WO 96 18390 A (THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA) 20 June 1996 see claims 1-4, 8-11, 15-17 see page 22, line 18 - page 23, line 4 see page 24, line 28 - page 26, line 16 --- -/--	1-31

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search

29 July 1998

Date of mailing of the international search report

28/09/1998

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/04914

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 12497 A (HYBRIDON INC.) 2 May 1996 see claims 1-15 see page 22, line 18 - page 25, line 20 see page 28, line 8 - line 14 ---	1-31
A	AGRAWAL S: "Antisense oligonucleotides: towards clinical trials" TRENDS IN BIOTECHNOLOGY, vol. 14, no. 10, October 1996, page 376-387 XP004035728 ---	1-31
A	PATERSON B M ET AL: "STRUCTURAL GENE IDENTIFICATION AND MAPPING BY DNA.MRNA HYBRID-ARRESTED CELL-FREE TRANSLATION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 74, no. 10, 1 October 1977, pages 4370-4374, XP000575587 cited in the application ---	1-31
A	AGRAWAL S ET AL: "OLIGODEOXYNUCLEOSIDE PHOSPHORAMIDATES AND PHOSPHOROTHIOATES AS INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 85, 1 October 1988, pages 7079-7083, XP000574956 cited in the application ---	1-31
A	SUDHIR AGRAWAL: "ANTISENSE OLIGONUCLEOTIDES AS ANTIVIRAL AGENTS" TRENDS IN BIOTECHNOLOGY, vol. 10, no. 5, 1 May 1992, pages 152-158, XP000272382 cited in the application ---	1-31
A	AGRAWAL S ET AL: "INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS IN EARLY INFECTED AND CHRONICALLY INFECTED CELLS BY ANTISENSE OLIGODEOXYNUCLEOTIDES AND THEIR PHOSPHOROTHIOATE ANALOGUES" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 86, no. 20, 1 October 1989, pages 7790-7794, XP000070876 cited in the application ---	1-31
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/04914

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	STEPHENSON M L ET AL: "INHIBITION OF ROUS SARCOMA VIRAL RNA TRANSLATION BY A SPECIFIC OLIGODEOXYRIBONUCLEOTIDE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 75, no. 1, 1 January 1978, pages 285-288, XP000575586 cited in the application -----	1-31

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/04914

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 claim(s) 1-19
is(are) directed to a method of treatment of 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. 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 98/04914

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