



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/11, A61K 31/70, C07H 21/00</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 98/49287</b> <b>(43) International Publication Date:</b> 5 November 1998 (05.11.98)
<b>(21) International Application Number:</b> PCT/US98/08722 <b>(22) International Filing Date:</b> 30 April 1998 (30.04.98) <b>(30) Priority Data:</b> 60/045,230                      30 April 1997 (30.04.97)                      US <b>(71) Applicant:</b> HYBRIDON, INC. [US/US]; 620 Memorial Drive, Cambridge, MA 02139 (US). <b>(72) Inventors:</b> SCHMITZ, John, C.; Apartment 2, 81 Edwards Street, New Haven, CT 06511 (US). AGRAWAL, Sudhir; 61 Lamplighter Drive, Shrewsbury, MA 01545 (US). CHU, Edward; 346 Saybrook Road, Orange, CT 06477 (US). <b>(74) Agents:</b> KERNER, Ann-Louise et al.; Hale and Dorr LLP, 60 State Street, Boston, MA 02109 (US).	<b>(81) Designated States:</b> 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, 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, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 4 February 1999 (04.02.99)	
<b>(54) Title:</b> ANTISENSE OLIGONUCLEOTIDES SPECIFIC FOR THYMIDYLATE SYNTHASE		
<b>(57) Abstract</b>		
<p>The present invention discloses synthetic oligonucleotides complementary to thymidylate synthase and methods of downregulating at least a portion of thymidylate synthase mRNA translation or protein expression in a malignant cell and of preventing or overcoming resistance to thymidylate synthase inhibitor compounds in a malignant cell using such oligonucleotides. Also disclosed is a therapeutic composition and a method of treating malignant tumor growth in a mammal utilizing such a composition.</p>		

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/08722

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C12N15/11 A61K31/70 C07H21/00

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 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.
X	JU, JINGFANG : "INCREASED DRUG SENSITIVITY OF TUMOR CELLS BY MANIPULATION OF CELL CYCLE CONTROL GENES" PH.D. THESIS PRESENTED IN DECEMBER 1996 AT THE FACULTY OF THE GRADUATE SCHOOL UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, XP002081365	1-5, 11, 22-26
Y	see page 100 - page 130	7-21, 27-29
Y	WO 94 02498 A (WORCESTER FOUND EX BIOLOGY ;METELEV VALERI (US); AGRAWAL SUDHIR (U) 3 February 1994 see the whole document	7-21, 27-29
	-/--	

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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"&" document member of the same patent family

Date of the actual completion of the international search

20 October 1998

Date of mailing of the international search report

02/11/1998

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Andres, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/08722

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHU E ET AL: "New concepts for the development and use of antifolates." STEM CELLS, (1996 JAN) 14 (1) 41-6. , XP002081366 see page 44, left-hand column, last paragraph - right-hand column, line 18; figure 3</p> <p style="text-align: center;">---</p>	1,2,12, 24,27
X	<p>KOBAYASHI H ET AL: "Reversal of drug-resistance or inhibition of tumor cell growth by hammerhead ribozymes;" GENE THER.:(1995) 2, PAGE 689; ABSTRACT 065, XP002081367 see paragraph 3</p> <p style="text-align: center;">---</p>	1,2,4, 12, 22-24,27
X	<p>WO 93 13740 A (WORCESTER FOUND EX BIOLOGY) 22 July 1993 see page 10 - page 11 see page 14, line 4 - line 11 see page 15, line 19 - page 16, line 20 see page 23; table 1</p> <p style="text-align: center;">---</p>	1,4-19, 22,23
X	<p>KOROPATNICK J ET AL: "Discrimination of run-on transcription from constitutive genes and antisense expression vectors in the same cells." BIOTECHNIQUES;(JAN 1997) 22, 1, 64-66, XP002081368 see the whole document</p> <p style="text-align: center;">---</p>	1-5,12, 27
A	<p>LIU Y ET AL: "Levamisole potentiation of 5-fluorouracil and other anti-tumour drugs in cultured cells: Protein tyrosine phosphatase as an alternative to thymidylate synthase as a target." CELLULAR PHARMACOLOGY 2 (6). 1995. 271-277., XP002081369 see the whole document</p> <p style="text-align: center;">---</p>	1-29
A	<p>CHU E ET AL: "Identification of an RNA binding site for human thymidylate synthase." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 JAN 15) 90 (2) 517-21., XP002081370 cited in the application</p> <p style="text-align: center;">---</p>	
A	<p>CHU E ET AL: "Autoregulation of human thymidylate synthase messenger RNA translation by thymidylate synthase." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1991 OCT 15) 88 (20) 8977-81., XP002081371 cited in the application</p> <p style="text-align: center;">---</p>	

**INTERNATIONAL SEARCH REPORT**

International Application No

PCT/US 98/08722

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BLACK A R ET AL: "Expression of rTS correlates with altered growth regulation of thymidylate synthase."                      CANCER RESEARCH, (1996 FEB 15) 56 (4) 700-5., XP002081372</p> <p align="center">----</p>	
P,X	<p>SCHMITZ J C ET AL: "Specific repression of human TS mRNA translation by antisense oligoribonucleotides."                      PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 39 (0). MARCH 1998. PAGE 645; ABSTRACT 4391, XP002081373                      see abstract                      &amp; 89TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW ORLEANS, LOUISIANA, USA, MARCH 28-APRIL 1, 1998. ,</p> <p align="center">-----</p>	1-29

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/08722

## 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 23 and 24 (as far as in vivo methods are concerned) and claim 26 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:  
The application contains twice claim 19. All dependent claims have been searched as being dependent on both claims 19.
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 98/08722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9402498    A	03-02-1994	US 5652355 A	29-07-1997
		AU 674158 B	12-12-1996
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		CZ 9500143 A	17-07-1996
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