



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

<p>(51) International Patent Classification <sup>7</sup> : <b>A61K 31/7105, A61P 35/00, 43/00</b></p>	<p><b>A3</b></p>	<p>(11) International Publication Number: <b>WO 00/27340</b></p> <p>(43) International Publication Date: 18 May 2000 (18.05.00)</p>																		
<p>(21) International Application Number: PCT/US99/26696</p> <p>(22) International Filing Date: 12 November 1999 (12.11.99)</p> <p>(30) Priority Data: 60/108,036 12 November 1998 (12.11.98) US</p> <p>(71) Applicant (for all designated States except US): THE CHILDREN'S MEDICAL CENTER CORPORATION [US/US]; 300 Longwood Avenue, Boston, MA 02225 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SHING, Yuen [US/US]; 16 Tiffany Drive, Randolph, MA 02368 (US). ZHAO, Hui [CN/US]; 1201 Melville Square, Apt. 204, Richmond, CA 94804 (US). BOJANOWSKI, Krzysztof [PL/US]; 1201 Melville Square, Apt. 204, Richmond, CA 94804 (US). FOLKMAN, M., Judah [US/US]; 18 Chatham Circle, Brookline, MA 02115 (US).</p> <p>(74) Agents: WARREN, William, L. et al.; Jones &amp; Askew, LLP, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (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, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, 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><b>Published</b> <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 17 August 2000 (17.08.00)</p>																			
<p>(54) Title: USE OF t-RNA AND FRAGMENTS FOR INHIBITING ANGIOGENESIS AND COMPOSITIONS THEREOF</p>																				
<p>(57) Abstract</p>																				
<p>A therapeutic composition comprising an angiogenesis-inhibiting amount of a transfer ribonucleic acid (tRNA) or a fragment of tRNA and a pharmaceutically acceptable excipient are provided. Methods of administering the composition to inhibit an angiogenesis-dependent disease, such as cancer, are also provided.</p>	<p><b>3H-Thymidine Incorporation</b></p> <table border="1"> <thead> <tr> <th>Concentration (µg/ml medium)</th> <th>3H-Thymidine Incorporation (cpm x 10<sup>4</sup>)</th> </tr> </thead> <tbody> <tr> <td>0.0</td> <td>10.5</td> </tr> <tr> <td>0.25</td> <td>3.0</td> </tr> <tr> <td>0.5</td> <td>1.5</td> </tr> <tr> <td>1.0</td> <td>1.0</td> </tr> </tbody> </table> <p><b>Cell Proliferation Inhibition, %</b></p> <table border="1"> <thead> <tr> <th>Concentration (µg/ml medium)</th> <th>Cell Proliferation Inhibition (%)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0</td> </tr> <tr> <td>0.5</td> <td>25</td> </tr> <tr> <td>1</td> <td>70</td> </tr> </tbody> </table>		Concentration (µg/ml medium)	3H-Thymidine Incorporation (cpm x 10 <sup>4</sup> )	0.0	10.5	0.25	3.0	0.5	1.5	1.0	1.0	Concentration (µg/ml medium)	Cell Proliferation Inhibition (%)	0	0	0.5	25	1	70
Concentration (µg/ml medium)	3H-Thymidine Incorporation (cpm x 10 <sup>4</sup> )																			
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Concentration (µg/ml medium)	Cell Proliferation Inhibition (%)																			
0	0																			
0.5	25																			
1	70																			

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/26696

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/7105 A61P35/00 A61P43/00

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 7 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	BE 876 739 A (BOEHRINGER SOHN INGELHEIM) 3 December 1979 (1979-12-03)  Whole document, in particular page 1 and page 4, paragraph 3.	1-4, 7-9, 12-19, 22-24, 27
X	SUK, D. ET AL: "Toxicological and antiproliferative effects of N6-(.DELTA.2-isopentenyl)adenosine, a natural component of mammalian transfer RNA" CANCER RES. (1970), 30(5), 1429-36 , XP000901623 page 1429, column 1, paragraph 2 page 1430, column 2, paragraph 4  --- -/--	12, 17-19, 22-24, 27

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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- \*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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- \*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

14 April 2000

Date of mailing of the international search report

10/05/2000

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

Bonzano, C

## INTERNATIONAL SEARCH REPORT

Int. J. Application No

PCT/US 99/26696

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>HWANG J.-M. ET AL: "Optic neuropathy associated with mitochondrial tRNA (Leu(UUR)) A3243G mutation." OPTHALMIC GENETICS, (1997) 18/2 (101-105). , XP000901440 page 105, paragraph 3</p> <p>---</p>	1-27
A	<p>SMITH P R (REPRINT) ET AL: "Pigmentary retinal dystrophy and the syndrome of maternally inherited diabetes and deafness caused by the mitochondrial DNA 3243 tRNA (Leu) A to G mutation" OPTHALMOLOGY, (JUN 1999) VOL. 106, NO. 6, PP. 1101-1108. PUBLISHER: LIPPINCOTT WILLIAMS &amp; WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0161-6420. , XP000901445 QUEEN ELIZABETH HOSP, DEPT MED, BIRMINGHAM B15 2TH, W MIDLANDS, ENGLAND (Reprint);UNIV BIRMINGHAM, DEPT MED, BIRMINGHAM, W MIDLANDS, ENGLAND; BIRMINGHAM &amp; MIDLAND EYE HOSP, CITY HOSP NHS TRUST, BIRMINGHAM B3 2NS, W MIDLANDS, ENGLAND; BIRMINGHAM HEARTLANDS HOSP, DEPT OPTHALMOL, BIRMINGHA B9 5ST, W M page 1106, column 2, paragraph 3</p> <p>---</p>	1-27
P,X	<p>ZHAO, HUI ET AL: "New role for tRNA and its fragment purified from human urinary bladder carcinoma conditioned medium: Inhibition of endothelial cell growth." JOURNAL OF CELLULAR BIOCHEMISTRY, (NOV., 1999) VOL. 76, NO. 1, PP. 109-117. , XP002135747 page 109, column 1, paragraph 1 page 114</p> <p>-----</p>	1-4, 7-12, 17-19, 22-27

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/26696

## 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.: 1-26  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 1-26 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:
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 99/26696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE 876739 A	03-12-1979	DE 2824411 A	13-12-1979
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