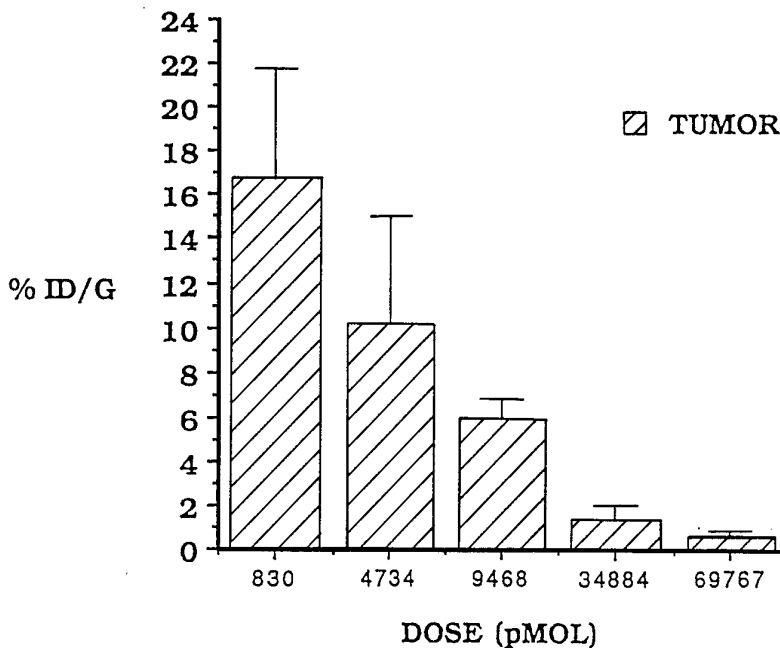




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> A61K 47/48, 43/00		<b>A3</b>	<b>(11) International Publication Number:</b> WO 93/25240
			<b>(43) International Publication Date:</b> 23 December 1993 (23.12.93)
<b>(21) International Application Number:</b> PCT/US93/05406		<b>(72) Inventors; and</b>	
<b>(22) International Filing Date:</b> 7 June 1993 (07.06.93)		<b>(75) Inventors/Applicants (for US only) :</b> AXWORTHY, Donald, B. [US/US]; 3615 227th Street S.W., Brier, WA 98036 (US). THEODORE, Louis, J. [US/US]; 622 152nd Place S.W., Lynnwood, WA 98037 (US). GUSTAVSON, Linda, M. [US/US]; 19809 31st Street N.E., Seattle, WA 98155 (US). RENO, John, M. [US/US]; 2452 Elm Drive, Brier, WA 98036 (US).	
<b>(30) Priority data:</b> 07/895,588 9 June 1992 (09.06.92) US 07/995,381 23 December 1992 (23.12.92) US 07/995,383 23 December 1992 (23.12.92) US		<b>(74) Agent:</b> SHELTON, Dennis, K.; Christensen, O'Connor, Johnson & Kindness, 2800 Pacific First Centre, 1420 Fifth Avenue, Seattle, WA 98101 (US).	
<b>(60) Parent Applications or Grants</b> <b>(63) Related by Continuation</b> US 07/995,381 (CIP) Filed on 23 December 1992 (23.12.92) US 07/995,383 (CIP) Filed on 23 December 1992 (23.12.92)		<b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
<b>(71) Applicant (for all designated States except US):</b> NEORX CORPORATION [US/US]; 410 West Harrison, Seattle, WA 98119-4007 (US).		<b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
		<b>(88) Date of publication of the international search report:</b> 17 February 1994 (17.02.94)	

**(54) Title:** PRETARGETING METHODS AND COMPOUNDS**(57) Abstract**

Methods, compounds, compositions and kits that relate to pretargeted delivery of diagnostic and therapeutic agents are disclosed. In particular, methods for radiometal labeling of biotin and for improved radiohalogenation of biotin, as well as related compounds, are described. Also, clearing agents, anti-ligand-targeting moiety conjugates, target cell retention enhancing moieties and additional methods are discussed.

**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.

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

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 93/05406

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61K47/48 A61K43/00

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 5 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.
Y	CHEMICAL ABSTRACTS, vol. 106, no. 8, 23 February 1987, Columbus, Ohio, US; abstract no. 55742f, see abstract & HEPATOLOGY vol. 6, no. 4, 1986, BALTIMORE pages 723 - 728 P. VAN DER SLUIJS ET AL. 'DRUG TARGETING TO THE LIVER WITH LACTOSYLATED ALBUMINS: DOES THE GLYCOPROTEIN TARGET THE DRUG OR IS IT THE DRUG TARGETING THE GLYCOPROTEIN?' --- -/--	1-20

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

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"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)

"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

"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

"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

3 Date of the actual completion of the international search  
26 November 1993

Date of mailing of the international search report  
22 12 93

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  
Berte, M

## INTERNATIONAL SEARCH REPORT

In tional Application No  
PCT/US 93/05406

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	<p>WO,A,88 08422 (SCHERING AG.) 3 November 1988  see page 5, paragraph 5 - page 6, paragraph 4; example 25  see page 14, paragraph 4  see page 15, paragraph 4  see page 17, paragraph 2  ---</p>	1-20
Y	<p>NUCL. MED. BIOL.  vol. 18, no. 7 , 1991  pages 719 - 726  F. VIRZI ET AL. 'NEW INDIUM-111 LABELED BIOTIN DERIVATES FOR IMPROVED IMMUNOTARGETING.'  cited in the application  see figure 1  ---</p>	1-20
Y	<p>EP,A,0 251 494 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 7 January 1988  cited in the application  see page 3, line 53 - page 4, line 28  see page 5, line 25 - line 35; claims; examples 1,2  &amp; US,A,4 863 713  -----</p>	1-20

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/05406

**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 14-20 are directed to a method of treatment of (diagnostic method practised on) the human/animal body (Rule 39.1(IV)) the search has been carried out and based on the alleged effects of the compound/<sup>COMPOSITION.</sup>
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 search for the subject matter of claims 9-20 has been restricted for economic reasons to clearing agents and methods in relation to the biotin-DOTA conjugate specified in claims 1-8 (Guidelines B-II,7, last sentence, and B-III, 3.7). Claims searched completely: 1-9, incompletely: 9-20.
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 <b>PCT/US 93/05406</b>
--

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8808422	03-11-88	DE-A- 3713842	17-11-88
		EP-A- 0355097	28-02-90
		JP-T- 2503910	15-11-90
-----			
EP-A-0251494	07-01-88	US-A- 4863713	05-09-89
		DE-A- 3781946	05-11-92
		JP-A- 63005033	11-01-88
-----			
US-A-4863713	05-09-89	DE-A- 3781946	05-11-92
		EP-A, B 0251494	07-01-88
		JP-A- 63005033	11-01-88
-----			