



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C12N 15/51, C07K 14/18, G01N 33/53, A61K 39/29, C12Q 1/68, 1/70, C07K 16/10</p>	<p>A3</p>	<p>(11) International Publication Number: WO 96/05315 (43) International Publication Date: 22 February 1996 (22.02.96)</p>
<p>(21) International Application Number: PCT/US95/10398 (22) International Filing Date: 15 August 1995 (15.08.95) (30) Priority Data: 08/290,665 15 August 1994 (15.08.94) US (71) Applicant: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES, Office of Technology Transfer National Institutes of Health [US/US]; Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US). (72) Inventors: BUKH, Jens; 5805 Sonoma Road, Bethesda, MD 20817 (US). MILLER, Roger, H.; 15504 White Willow Lane, Rockville, MD 20853 (US). PURCELL, Robert, H.; 17517 White Grounds Road, Boyds, MD 20841 (US). (74) Agent: FEILER, William, S.; Morgan & Finnegan, L.L.P., 345 Park Avenue, New York, NY 10154 (US).</p>	<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, 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), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p>Published <i>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.</i></p> <p>(88) Date of publication of the international search report: 4 April 1996 (04.04.1996)</p>	
<p>(54) Title: NUCLEOTIDE AND AMINO ACID SEQUENCES OF THE ENVELOPE 1 AND CORE GENES OF HEPATITIS C VIRUS</p>		
<p>(57) Abstract</p> <p>The nucleotide and deduced amino acid sequences of cDNAs encoding the envelope (1) genes and core genes of isolates of hepatitis C virus (HCV) are disclosed. The invention relates to the oligonucleotides, peptides and recombinant envelope (1) and core proteins derived from these sequences and their use in diagnostic methods and vaccines.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No
PC1/US 95/10398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/51 C07K14/18 G01N33/53 A61K39/29 C12Q1/68
C12Q1/70 C07K16/10

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 C07K G01N A61K C12Q

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	PROC. NATL. ACAD. SCI. USA., vol. 89, no. 11, June 1992 pages 4942-4946, JENS BUKH ET AL. 'Sequence analysis of the 5' noncoding region of hepatitis C virus.'	1,2,21, 31,32,38
Y	see the whole document	5-20, 22-30, 33-37, 39-51, 53,54, 56-59
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
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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

20 February 1996

Date of mailing of the international search report

01.03.96

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/10398

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PROC NATL ACAD SCI U S A 90 (17). 1993. 8234-8238. CODEN: PNASA6 ISSN: 0027-8424, September 1993 BUKH J ET AL 'AT LEAST 12 GENOTYPES OF HEPATITIS C VIRUS PREDICTED BY SEQUENCE ANALYSIS OF THE PUTATIVE E1 GENE OF ISOLATES COLLECTED WORLDWIDE.'	1,2,5, 21-23, 26-32,38
Y	see the whole document	5-20,24, 25, 33-37, 39-51, 53,54, 56-59

X	JOURNAL OF GENERAL VIROLOGY 75 (5). 1994. 1053-1061. ISSN: 0022-1317, May 1994 SIMMONDS P ET AL 'Identification of genotypes of hepatitis C virus by sequence comparisons in the core, E1 and NS-5 regions.'	21,28
Y	see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59

X	JOURNAL OF BIOMEDICAL SCIENCE 1 (3). 1994. 158-162. ISSN: 1021-7770, June 1994 KAO J-H ET AL 'Detection of divergent hepatitis C virus envelope sequences.'	21,28
Y	see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59

X	BIOCHEM BIOPHYS RES COMMUN 192 (2). 1993. 635-641. CODEN: BBRC9 ISSN: 0006-291X, 30 April 1993 STUYVER L ET AL 'ANALYSIS OF THE PUTATIVE E1 ENVELOPE AND NS4A EPITOPE REGIONS OF HCV TYPE 3.'	21,28
Y	see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59

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INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 95/10398

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARCHIVES OF VIROLOGY SUPPLEMENTUM 0 (7). 1993. 27-39. ISSN: 0939-1983, ROGGENDORF M ET AL 'Variability of the envelope regions of HCV in European isolates and its significance for diagnostic tools.'	21,28
Y	see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59
X	--- PROC. NATL. ACAD. SCI. U. S. A. (1992), 89(15), 7144-8 CODEN: PNASA6;ISSN: 0027-8424, 1 August 1992	21,28
Y	CHA, T. A. ET AL 'At least five related, but distinct, hepatitis C viral genotypes exist' see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59
X	--- BIOCHEM. BIOPHYS. RES. COMMUN. (1994), 199(3), 1474-81 CODEN: BBRC99;ISSN: 0006-291X, 30 March 1994	21,28
Y	LI, JI-SU ET AL 'Identification of the third major genotype of hepatitis C virus in France' see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59
X	--- WO,A,94 01778 (CHIRON CORP) 20 January 1994	53,54, 56-58
Y	see the whole document	1,2, 5-51,59
X	--- WO,A,92 19743 (CHIRON CORP) 12 November 1992	21,28
Y	see the whole document	1,2, 5-20, 22-27, 29-51, 53,54, 56-59
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INTERNATIONAL SEARCH REPORT

 International Application No
 PC1/US 95/10398

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,A,92 21759 (PASTEUR INSTITUT) 10 December 1992 see the whole document ---	1,2, 5-51,53, 54,56-59
X	EP,A,0 586 065 (TONEN CORP) 9 March 1994 see the whole document ---	53,54, 56-58
X	PROC. NATL. ACAD. SCI. USA, vol. 89, January 1992 pages 187-191, J. BUKH ET AL 'Importance of primer selection for the detection of hepatitis C virus RNA with the polymerase chain reaction assay' see the whole document ---	21,28
P,X	WO,A,95 01442 (US HEALTH) 12 January 1995 see the whole document ---	1,2, 5-51,53, 54,56-59
P,X	WO,A,94 25601 (INNOGENETICS NV ;MAERTENS GEERT (BE); STUYVER LIEVEN (BE)) 10 November 1994	21,28
Y	see the whole document ---	1,2, 5-20, 22-27, 29-51, 53,54, 56-59
P,X	WO,A,94 27153 (CHIRON CORP) 24 November 1994	21,28, 53-58
Y	see the whole document ---	1,2, 5-20, 22-27, 29-51,59
P,X	PROC. NATL. ACAD. SCI. U. S. A. (1994), 91(21), 10134-8 CODEN: PNASA6;ISSN: 0027-8424, 11 October 1994 STUYVER, LIEVEN ET AL 'Classification of hepatitis C viruses based on phylogenetic analysis of the envelope 1 and nonstructural 5B regions and identification of five additional subtypes' see the whole document ---	1,2, 5-51,53, 54,56-59
7	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/10398

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>JOURNAL OF CLINICAL MICROBIOLOGY 32 (9). 1994. 2280-2284. ISSN: 0095-1137, September 1994 RAVAGGI A ET AL 'Distribution of viral genotypes in Italy determined by hepatitis C virus typing by DNA immunoassay.' see the whole document ---</p>	<p>1,2, 5-51,53, 54,56-59</p>
P,X	<p>SEMINARS IN LIVER DISEASE, vol. 15, no. 1, February 1995 pages 41-63, J. BUKH ET AL. 'Genetic Heterogeneity of hepatitis C virus: Quasispecies and genotypes' see the whole document ---</p>	<p>1,2, 5-51,53, 54,56-59</p>
P,X	<p>BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 202, no. 3, 15 August 1994 pages 1308-1314, L. STUYVER 'Cloning and phylogenetic analysis of the core, E2 and NS3/NS4 regions of the hepatitis C virus type 5a+' see the whole document -----</p>	<p>1,2, 5-51,53, 54,56-59</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 10398

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.: 18,45,49
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although these claims 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:

- 26 subjects

See continuation-sheets PCT/ISA/210

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.:

1,2,5-51,53,54,56-59 (partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

claims:

1. 1,2,5-51,53,54,56 to 59 (partially):

Genotypes specific peptides from E1 Seq. ID 1-8 and 52-59 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype I/1a.

2. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 103-108 and 155-160 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype I/1a.

3. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 9-25 and 60-76 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype II/1b.

4. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 109-124 and 161-176 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype II/1b.

5. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 26-29 and 77-80 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype III/2a.

6. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 125-128 and 177-180 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype III/2a.

7. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 30-33 and 81-84 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype IV/2b.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

8. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 129-133 and 181-185 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype IV/2b.

9. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 34 and 85 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype IV/2c.

10. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 134 and 186 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype IV/2c.

11. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 35-39 and 86-90 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype V/3a.

12. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 135-138 and 187-190 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype V/3a.

13. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 40 and 91 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4a.

14. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 139 and 191 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4a.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

15. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 41 and 92 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4b.

16. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 141 and 193 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4b.

17. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 42-43 and 93-94 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4c.

18. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 143-144 and 195-196 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4c.

19. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 44 and 95 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4d.

20. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 145 and 197 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4d.

21. 3-52,55 and 59 (partially):

Genotype specific peptides Core Seq. ID 142 and 194 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4e.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

22. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 140 and 192 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 4f.

23. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 45-50 and 96-101 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 5a.

24. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. 146-153 and 198-205 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 5a.

25. 1,2,5-51,53,54,56 to 59 (partially):

Genotype specific peptides from E1 Seq. ID 51 and 102 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 6a.

26. 3-52,55 and 59 (partially):

Genotype specific peptides from Core Seq. ID 154 and 206 used in the recombinant protein expression, detection of antibodies against HCV, vaccines and methods of detection using PCR primers and Identification of Genotype 6a.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 95/10398

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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