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(71) Applicant (for all designated States except US): **TRIPEP AB** [SE/SE]; Halsovagen 7, S-141 57 Huddinge (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SALLBERG, Matti** [SE/SE]; Pukslagargatan 59, S-125 33 Alvsjo (SE). **FRE-LIN, Lars** [SE/SE]; Nedergardsvagen 2, S-147 40 Tumba (SE).

(74) Agent: **PLOUGMANN & VINGTOFT A/S**; Sundkrogs-
gade 9, Post Office Box 831, 2100 Copenhagen Ø (DK).

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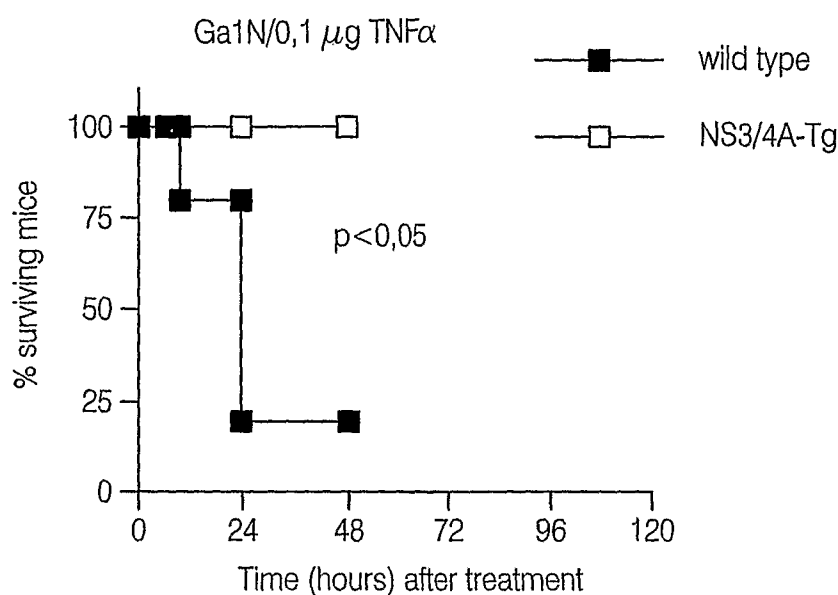
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Published:

— with international search report

[Continued on next page]

(54) Title: TRANSGENIC MOUSE MODELS OF HEPATITIS C VIRUS (HCV) AND IDENTIFICATION OF HCV THERAPEUTICS



(57) Abstract: Disclosed herein is the discovery of novel NS3/4A compositions with enhanced expression abilities. Embodiments of the invention include codon optimized NS3/4A compositions and compositions with the Semliki forest virus replicon. Additional embodiments include transgenic organisms containing these NS3/4A compositions, methods of using these transgenic mice to screen and refine drugs, and the drugs refined by these methods. Additional embodiments include protease activity dependent molecules that can indicate the presence or absence of a protease inhibitor.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/001668

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/18 A01K67/027 C12N15/85

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)

C12N

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)

EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/61039 A (MAX-PLANCK-GESELLSCHAFT ZUR FOERDERUNG DER WISSENSCHAFTEN E.V; HTUN, P) 2 December 1999 (1999-12-02) claims 1-22	17-19
X	US 2004/229936 A1 (HSIEH HSING-PANG ET AL) 18 November 2004 (2004-11-18) page 7, paragraphs 17,18 - page 8, paragraph 19-21	17,18
A	PATENT ABSTRACTS OF JAPAN vol. 2003, no. 12, 5 December 2003 (2003-12-05) & JP 2004 000179 A (TORAY IND INC; TOKYOTO IGAKU KENKYU KIKO), 8 January 2004 (2004-01-08) abstract	1-16, 27-29
	----- -/-	



Further documents are listed in the continuation of Box C.



See patent family 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

Date of the actual completion of the international search

30 October 2006

Date of mailing of the international search report

17. 01. 2007

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

Huber, Angelika

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/001668**Box II Observations where certain claims were found unsearchable (Continuation of item 2 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:
2. ☒ Claims Nos.: 17 (partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

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.:
1-19, 27-29

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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19, 27-29

Genetically modified mouse comprising an exogenous nucleic acid construct which comprises a promoter operably linked to a gene encoding a HCV nonstructural protein NS3; method of using said mouse to identify a compound that inhibits HCV replication; pharmaceutical or dietary supplement comprising the identified compound; totipotent mouse cell comprising a construct that comprises a mouse major urinary promoter operably linked to a gene encoding HCV NS3 protein.

2. claims: 20 (partially) 21-26 (completely)

Method of inhibiting HCV infection comprising identifying a subject infected with HCV and providing a composition comprising a p38 MAP kinase inhibitor. Use of a p38 MAP kinase inhibitor for the preparation of a medicament.

3. claims: 20 (partially), 30-38 (completely)

Method of inhibiting HCV infection comprising identifying a subject infected with HCV and providing a composition comprising an NF-kB inhibitor. Use of a NF-kB inhibitor for the preparation of a medicament.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 17 (partially)

The present claim 17 encompasses compounds defined only by their desired function, contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the compounds disclosed in the description, see page 11, l. 19-28, page 15, l. 20 to page 16, l. 27 and Claims 18 and 19. Undue experimentation would be required to screen compounds randomly. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search for claim 17.

The search of claim 17 was consequently restricted to compounds disclosed on page 11, l. 19 to page 12, l. 10, page 15, l. 20 to page 16, l. 27 and Claims 18 and 19.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/001668

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FRELIN L ET AL: "Codon optimization and mRNA amplification effectively enhances the immunogenicity of the hepatitis C virus nonstructural 3/4A gene" GENE THERAPY, MACMILLAN PRESS LTD., BASINGSTOKE, GB, vol. 11, no. 6, 2004, pages 522-533, XP002285893 ISSN: 0969-7128 the whole document	1,2,9,10
A	LERAT HERVE ET AL: "Steatosis and liver cancer in transgenic mice expressing the structural and nonstructural proteins of hepatitis C virus" GASTROENTEROLOGY, vol. 122, no. 2, February 2002 (2002-02), pages 352-365, XP002372198 ISSN: 0016-5085 Discussion, p. 362-363, figure 1	1-15
A	MAJUMDER M ET AL: "Expression of hepatitis C virus non-structural 5A protein in the liver of transgenic mice" FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 555, no. 3, 18 December 2003 (2003-12-18), pages 528-532, XP004481044 ISSN: 0014-5793 the whole document	1,4
A	WO 01/35959 A (ASTRAZENECA AB; INGELMAN-SUNDBERG, MAGNUS; SIMI, ANASTASIA; TINDBERG,) 25 May 2001 (2001-05-25) claims 14,15	1
A	WO 99/38888 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE; PESSI, ANTONELLO; STEINKU) 5 August 1999 (1999-08-05) claims 20-22	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/001668

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9961039	A	02-12-1999	NONE
US 2004229936	A1	18-11-2004	NONE
JP 2004000179	A	08-01-2004	NONE
WO 0135959	A	25-05-2001	AU 1653101 A 30-05-2001
WO 9938888	A	05-08-1999	AU 2545099 A 16-08-1999
		CA 2319306 A1 05-08-1999	
		EP 1053249 A2 22-11-2000	
		IT RM980061 A1 02-08-1999	
		JP 2002509075 T 26-03-2002	