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(71) Applicant (for all designated States except US): **MS RE-
SEARCH A/S** [DK/DK]; Mosedalvej 1s, DK-2500 Valby
(DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHRISTENSEN,
Tove** [DK/DK]; Tammerisvej 26, DK-8240 Risskov (DK).
MOLLER LARSEN, Anne [DK/DK]; Fuglebakken 21,
Strib, DK-5500 Middelfart (DK). **DISSING SORENSEN,
Pernille** [DK/DK]; Jellerod Have 123, DK-2980 Kokkedal
(DK). **ANDERSSON, Poul** [DK/DK]; Stockflethsvej 9,1,
DK-2000 Frederiksberg (DK).

(74) Agent: **BOULT WADE TENNANT**; Verulam Gardens,
70 Gray's Inn Road, London WC1X 8BT (GB).

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HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, 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, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA,
ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, 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, TR),
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MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

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

8 August 2002

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

(54) Title: AN INFECTIVE ENDOGENOUS RETROVIRUS IN ASSOCIATION WITH DEMYELINATING DISEASES E.G. MULTIPLE SCLEROSIS

(57) Abstract: Retroviral sequences were characterised by RT-PCR with gag and env primers on RNA from RT-positive retrovi-
ral particles produced by multiple sclerosis (MS) derived B-lymphoblastoid cell lines. Sequence variants with high homology to
the potentially functional subgroup RGH of the human endogenous retrovirus RTVL-H/HERV-H family were found. The same se-
quences were also specifically found in the particulate fraction of a series of MS patient plasma samples and were absent in controls.
South-Western blots demonstrated the presence of a nucleic acid binding protein, corresponding in size and function to the nucleo-
capsid protein, Gag NC, of other retroviruses. Indications for transmission of the retrovirus to mononuclear blood cells from healthy
human individuals and non-human animals were found. Cell cultures derived from peripheral blood from MS patients contained
5-15 % CD3+ T-cells and a specific splice variant of the env sequence comprising a region of the pol region was identified in such
cultures.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N7/00 C12Q1/70 C07K14/15 C12Q1/68

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 C12N 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)

BIOSIS, EP0-Internal, EMBL

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 53103 A (MOELLER LARSEN ANNE ;HAAHR SVEN (DK); MS RESEARCH A S (DK); CHRIST) 21 October 1999 (1999-10-21) examples 2,3	1-47
Y		5-7, 14-21, 28-47
X	--- CHRISTENSEN T ET AL: "Expression of sequence variants of endogenous retrovirus RGH in particle form in multiple sclerosis" THE LANCET, vol. 352, 26 September 1998 (1998-09-26), page 1033 XP002902107 the whole document	1-13, 22-27
Y	---	14-21, 28-47
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☒ 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

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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

Carl-Olof Gustafsson

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHRISTENSEN T ET AL: "Reverse transcriptase activity and particle production in B lymphoblastoid cell lines established from lymphocytes of patients with multiple sclerosis" AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 15, no. 3, 1999, pages 285-291, XP002902108 page 286, left-hand column	1-13, 22-27
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LINDESKOG M ET AL: "Spliced human endogenous retroviral HERV-H env transcripts in T-cell leukaemia cell lines and normal leukocytes: alternative splicing pattern of HERV-H transcripts" JOURNAL OF GENERAL VIROLOGY, vol. 78, 1997, pages 2575-2585, XP002902117	1-4,8-27
Y	page 2577 -page 2578; figure 3 -& DATABASE EMBL [Online] LINDESKOG M ET AL: "Human endogenous retrovirus" retrieved from EMBL, accession no. HE53031 XP002902111 about 80-98% identity in 100-200 nt overlap to SEQ.ID. 44 - SEQ.ID. 50 -& DATABASE EMBL [Online] LINDESKOG M ET AL : "Human endogenous retrovirus" retrieved from EMBL, accession no. HE35032 XP002902112 about 80-98% identity in 100-200 nt overlap to SEQ. ID. 44 - SEQ. ID. 50 -& DATABASE EMBL [Online] LINDESKOG M ET AL : "Human endogenous retrovirus" retrieved from EMBL, accession no. HE35033 XP002902113 about 80-98% identity in 100-200 nt overlap to SEQ.ID. 44- SEQ. ID. 50 -& DATABASE EMBL [Online] LINDESKOG M ET AL : "Human endogenous retrovirus" retrieved from EMBL, accession no. HSU88896 XP002902114 about 80-98% identity in 100-200 nt overlap to SEQ. ID. 44 - SEQ. ID. 50 -& DATABASE EMBL [Online] LINDESKOG M ET AL : "Human endogenous retrovirus" retrieved from EMBL, accession no. HSU88897 XP002902115 about 80-98% identity in 100-200 nt overlap to SEQ. ID. 44- SEQ. ID. 50. -& DATABASE EMBL [Online] LINDESKOG M ET AL: "Human endogenous retrovirus" retrieved from EMBL, accession no. HSU88898 XP002902116 about 80-98% identity in 100-200 nt overlap to SEQ. ID. 44- SEQ. ID. 50. -/--	5-7, 28-47

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/03272

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>---</p> <p>LINDESKOG M ET AL: "Coamplification and dispersion of adjacent human endogenous retroviral HERV-H and HERV-E elements; presence of spliced hybrid transcripts in normal leukocytes." VIROLOGY, vol. 244, 1998, pages 219-229, XP002902119 page 220 -page 222; figure 5 -& DATABASE EMBL [Online] LINDESKOG M ET AL : "Human endogenous retrovirus clone" XP002902118 about 70% identity in about 140 nt overlap to SEQ. ID.44- SEQ. ID. 50.</p>	1-4,8-27
X	<p>---</p> <p>LINDESKOG M ET AL: "Isolation of a human endogenous retroviral HERV-H element with an open env reading frame." VIROLOGY , vol. 258, 1999, pages 441-450, XP002902120 page 446,discussion. figure 1</p>	1-4,8-27
A	<p>---</p> <p>GOODCHILD N L ET AL: "Spliced HERV-H endogenous retroviral sequences in human genomic DNA: evidence for amplification via retrotransposition." VIROLOGY, vol. 206, 1995, pages 164-173, XP002902121 see discussion page 170 -page 173</p>	1-13
Y	<p>---</p> <p>US 5 650 318 A (PERRON HERVE ET AL) 22 July 1997 (1997-07-22) example 7</p>	14-21
Y	<p>---</p> <p>US 6 001 987 A (PERRON HERVE ET AL) 14 December 1999 (1999-12-14) column 42 -column 47; example 7</p>	28-47
X	<p>---</p> <p>GARSON J A ET AL: "Detection of virion-associated MSRV-RNA in serum of patients with multiple sclerosis." LANCET, vol. 351, 1 March 1998 (1998-03-01), page 33 XP002902122 the whole document</p>	28-43
Y	<p>---</p> <p>-/--</p>	46,47

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/03272

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KOMURIAN-PRADEL F ET AL: "Molecular cloning and characterization of MSRV-related sequences associated with retrovirus-like particles" VIROLOGY, vol. 260, 1999, pages 1-9, XP002902123 page 8	1-13, 22-24
A	--- BLOND J-L ET AL : "Molecular characterization and placental expression of HERV-W, a new human endogenous retrovirus family." JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1175 1175-1185, XP002902124 page 1183, left-hand column -----	1

INTERNATIONAL SEARCH REPORT

International application No.
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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:
2. ☒ Claims Nos.: 28-31, 36-38
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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 28-31, 36-38

Claims 28-31,36-38 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule 39.1.(iv).

Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

The applicant's attention is drawn to the fact that claims, or parts of 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/03272

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