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29.11.2002 EP 02026643

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
08002793.1 / 1 953 556
03792291.1 / 1 535 076

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(54) **Polypeptide biomarkers for diagnosing Alzheimer's disease**

(57) A method for assessing the state of Alzheimer's disease in patients is disclosed. A method for monitoring the progression of Alzheimer's disease in patients is also disclosed. The method applies detection of specific markers in body fluids (e.g. CSF), using mass spectrometric

analysis (SELDI-TOF MS). The specific markers are: human cystatin C, human beta-2-microglobulin, human myoglobin neurosecretory protein VGF or fragments of these proteins.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number

under Rule 62a and/or 63 of the European Patent Convention.
This report shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 10 16 4475

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 00/25138 A (NITSCH ROGER ;GROWDON JOHN (US)) 4 May 2000 (2000-05-04)	4	INV. G01N33/68
Y	* the whole document * * example 1 *	3-8	
X	----- WEI, LIHONG ET AL: "Cystatin C: Icelandic-like mutation in an animal model of cerebrovascular.beta.-amyloidosis" STROKE, vol. 27, no. 11, 1996, pages 2080-2085, XP000998699	3,4	
Y	DALLAS * the whole document * * figure 2 *	3-8	
	----- -/--		
			TECHNICAL FIELDS SEARCHED (IPC)
			G01N
INCOMPLETE SEARCH			
The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC so that only a partial search (R.62a, 63) has been carried out.			
Claims searched completely :			
Claims searched incompletely :			
Claims not searched :			
Reason for the limitation of the search: see sheet C			
1	Place of search The Hague	Date of completion of the search 1 October 2010	Examiner Tuyman, Antonin
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

EPO FORM 1503 03 82 (P04E07)



PARTIAL EUROPEAN SEARCH REPORT

 Application Number
 EP 10 16 4475

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	UTAL A ET AL: "Preliminary expression analysis in Alzheimer's disease using SELDI protein chips." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, pages Abstract No.-83.7, XP000989844 30th Annual Meeting of the Society of Neuroscience;New Orleans, LA, USA; November 04-09, 2000 ISSN: 0190-5295 * abstract *	3,4,6	
A	----- WO 01/63294 A (OXFORD GLYCOSCIENCES UK LTD ;HERATH HERATH MUDIYANSELAGE AT (GB)); 30 August 2001 (2001-08-30) * the whole document *	3,4	TECHNICAL FIELDS SEARCHED (IPC)
X,P	----- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2003 (2003-03), CARRETTE ODILE ET AL: "A new sensitive and highly specific test for the diagnosis of Alzheimer disease using the ProteinChip(R) technology." XP002265308 Database accession no. PREV200300358956 * abstract *	3-8,10	
X,P	& FASEB JOURNAL, vol. 17, no. 4-5, March 2003 (2003-03), page Abstract No. 80.3, FASEB Meeting on Experimental Biology: Translating the Genome;San Diego, CA, USA; April 11-15, 2003 ISSN: 0892-6638 (ISSN print) ----- -/--	3-8,10	



PARTIAL EUROPEAN SEARCH REPORT

 Application Number
 EP 10 16 4475

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 01/75454 A (OXFORD GLYCOSCIENCES UK LTD [GB]; PFIZER [US]; DURHAM KATHRYN L [US];) 11 October 2001 (2001-10-11)	3,4,7,8	
Y	* the whole document * * in particular: * * table IV * * claims 1,9 *	3-8	
A	WO 01/62787 A (OXFORD GLYCOSCIENCES UK LTD [GB]; HERATH HERATH MUDIYANSELAGE AT [GB];) 30 August 2001 (2001-08-30) * the whole document * * in particular: * * table IV * * page 46, paragraph 3 *	3-8,10	TECHNICAL FIELDS SEARCHED (IPC)
A	WO 01/71357 A (OXFORD GLYCOSCIENCES UK LTD [GB]; HERATH HERATH MUDIYANSELAGE AT [GB];) 27 September 2001 (2001-09-27) * tables VI,X *	3-8,10	
X	DAVIDSSON PIA ET AL: "Proteome analysis of cerebrospinal fluid proteins in Alzheimer patients" NEUROREPORT, vol. 13, no. 5, 16 April 2002 (2002-04-16) , pages 611-615, XP009012635 ISSN: 0959-4965 * abstract *	4-8	
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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 10 16 4475

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	RUOTOLO BRANDON T ET AL: "Observation of conserved solution-phase secondary structure in gas-phase tryptic peptides" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 124, no. 16, 24 April 2002 (2002-04-24), pages 4214-4215, XP002499269 ISSN: 0002-7863 * the whole document *	3-8	
A	----- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1999, AZAMI YASUSHI: "A case of diabetic hyperosmolar nonketotic coma with rhabdomyolysis accompanied by Alzheimer's disease" XP002499331 Database accession no. PREV200000005485 * abstract * & JOURNAL OF THE JAPAN DIABETES SOCIETY, vol. 42, no. 6, 1999, pages 461-465, ISSN: 0021-437X -----	3-8,10	TECHNICAL FIELDS SEARCHED (IPC)
E	EP 1 373 905 A (BIOVISION AG [DE]) 2 January 2004 (2004-01-02) * the whole document * * claims 1,5,17-20 *	4,7,8	
X,P	& WO 02/082075 A (BIOVISION AG [DE]; LAMPING NORBERT [DE]; ZUCHT HANS-DIETER [DE]; HEINE) 17 October 2002 (2002-10-17) * the whole document * * claims 1,5,17-20 *	4,7,8	
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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 10 16 4475

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X,P	WO 03/028543 A (PFIZER PROD INC [US]; OXFORD GLYCOSCIENCES UK LTD [GB]; DURHAM L KATHR) 10 April 2003 (2003-04-10) * claim 1 * * table IV * * sequences 20,273 *	3,4,7,8	
E	& EP 1 408 333 A (PFIZER PROD INC [US]; OXFORD GLYCOSCIENCES UK LTD [GB]) 14 April 2004 (2004-04-14) * claim 1 * * table IV * * sequences 20,273 * -----	3,4,7,8	
			TECHNICAL FIELDS SEARCHED (IPC)

EPO FORM 1503 03.02 (P04C10) 1

**INCOMPLETE SEARCH
SHEET C**Application Number
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Claim(s) completely searchable:
3-8, 10

Claim(s) not searched:
1, 2, 9

Reason for the limitation of the search:

Present claims 1,2 and 9 relate to an extremely large number of possible compounds (polypeptides) in methods and kits for the detection of the state of Alzheimer disease, for which a lack of clarity (and conciseness) and support within the meaning of Article 84 EPC arises to such an extent as to render a meaningful search of the claims impossible.

Polypeptide markers that are only characterized by their molecular weight, comprise an enormous amount of polypeptides that have no relation to Alzheimer's disease at all, which can therefore not be distinguishable for Alzheimer's disease. Therefore the claims are not supported (Article 84 EPC) and do not enable (Article 83 EPC) the person skilled in the art over the whole breadth of the claim.

Consequently, the search has been not carried out for these claims. The applicant was requested to file a statement indicating the subject-matter to be searched, within a period of two months (pursuant to Rule 63(1) EPC). In response thereto the applicant has indicated to limit to group 4 of inventions (see item 2). From this reply with the letter of 21.9.2010 it can be concluded that the applicant has mistaken the Rule 63 EPC communication for a Rule 64 EPC communication. Pursuant to Rule 63(2) EPC, the claims have therefore been searched to the extent of the subject-matter of dependent claims 3-8 and 10, which inter alia includes group 4 of inventions.



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

- Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
- The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number

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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 7.

2. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 8.

3. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 9.

4. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 10.

5. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 11.

6. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 12.

7. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 13.



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number

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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

8. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 14.

9. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 15.

10. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 16.

11. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C fragment of

12. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human beta-2-microglobulin or fragments thereof.

13. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human myoglobin or a fragment thereof.

14. claims: 3-8, 10(all partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is neurosecretory



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number
EP 10 16 4475

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

protein VGF or a fragment thereof.

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 10 16 4475

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

01-10-2010

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0025138 A	04-05-2000	AT 286253 T	15-01-2005
		AU 1153300 A	15-05-2000
		DE 69922987 D1	03-02-2005
		DE 69922987 T2	04-05-2006
		EP 1123509 A2	16-08-2001
		ES 2235550 T3	01-07-2005
		JP 2002531063 T	24-09-2002
		US 2009023145 A1	22-01-2009
WO 0163294 A	30-08-2001	AU 3395501 A	03-09-2001
		AU 3395701 A	03-09-2001
		EP 1259539 A1	27-11-2002
		EP 1259819 A2	27-11-2002
		WO 0162787 A1	30-08-2001
WO 0175454 A	11-10-2001	AU 4983501 A	15-10-2001
		EP 1325338 A2	09-07-2003
		JP 2004505609 T	26-02-2004
WO 0162787 A	30-08-2001	AU 3395501 A	03-09-2001
		AU 3395701 A	03-09-2001
		EP 1259539 A1	27-11-2002
		EP 1259819 A2	27-11-2002
		WO 0163294 A2	30-08-2001
WO 0171357 A	27-09-2001	AU 4090901 A	03-10-2001
		EP 1266225 A2	18-12-2002
		US 2003064419 A1	03-04-2003
EP 1373905 A	02-01-2004	AU 2002338348 A1	21-10-2002
		CA 2446886 A1	17-10-2002
		WO 02082075 A2	17-10-2002
		DE 10291524 D2	01-07-2004
		JP 2004531250 T	14-10-2004
		US 2004142388 A1	22-07-2004
WO 03028543 A	10-04-2003	AU 2002330215 A1	14-04-2003
		EP 1408333 A2	14-04-2004
		JP 2003284574 A	07-10-2003
		SG 121733 A1	26-05-2006

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

专利名称(译)	用于诊断阿尔茨海默病的多肽生物标志物		
公开(公告)号	EP2221620A3	公开(公告)日	2010-11-24
申请号	EP2010164475	申请日	2003-08-11
[标]申请(专利权)人(译)	拜耳先灵制药公司		
申请(专利权)人(译)	拜耳先灵制药公司		
当前申请(专利权)人(译)	拜耳药品AKTIENGESELLSCHAFT		
[标]发明人	YALKINOGLU OEZKAN DR HOCHSTRASSER DENIS FRANCOIS PROF DR SANCHEZ JEAN CHARLES DR CARETTE ODILE DR		
发明人	YALKINOGLU, OEZKAN, DR. KÖNIG, GERHARD, DR. HOCHSTRASSER, DENIS FRANCOIS, PROF.DR. SANCHEZ, JEAN-CHARLES, DR. CARETTE, ODILE, DR.		
IPC分类号	G01N33/68 G01N27/62 C07K14/47 C07K14/74 C07K14/805 C07K14/81 C12Q1/37 G01N33/53		
CPC分类号	G01N33/6896 C07K14/70539 C07K14/805 C07K14/8139 G01N2800/2821		
优先权	2002026643 2002-11-29 EP 2002018283 2002-08-23 EP		
其他公开文献	EP2221620B1 EP2221620A2		
外部链接	Espacenet		

摘要(译)

公开了一种用于评估患者中阿尔茨海默病状态的方法。还公开了一种用于监测患者中阿尔茨海默病进展的方法。该方法使用质谱分析 (SELDI-TOF MS) 应用体液 (例如CSF) 中特定标志物的检测。具体标记是：人朊抑素C，人β-2-微球蛋白，人肌红蛋白神经分泌蛋白VGF或这些蛋白的片段。

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to subject	CLASSIFICATION OF THE DOCUMENT (IPC)
X	NO 06/25138 A (NITSCH ROGER ;GRONDON JOHN (US)) 4 May 2000 (2000-05-04) * the whole document *	4 3-8	INV. G01N33/68
X	WEI LIHONG ET AL: "Cystatin C: Icelandic-like mutation in an animal model of cerebrovascular beta.-amyloidosis" STROKE, vol. 27, no. 11, 1996, pages 2080-2085, 2000098659 DALLAS * the whole document * * figure 2 *	3,4 3-8	
INCOMPLETE SEARCH The search did not cover all the prior art known to the examiner. Reasons for this are: Claims searched completely: Claims searched incompletely: Claims not searched: Reason for the limitation of the search: see sheet C			
Place of search		Date of completion of the search	Examiner
The Hague		1 October 2010	Tuyman, Antonin
CATEGORY OF CITED DOCUMENTS 1: Bibliographic reference of the prior art 2: Bibliographic reference of the prior art, document of the same category 3: Bibliographic reference of the prior art, document of a different category 4: Intermediate document 5: Document cited for other reasons 6: Document cited in the application 7: Document cited in the application 8: Document cited for other reasons 9: Document of the same patent family, corresponding document			