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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 (Rule 48.2(h))
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[Continued on next page]

(54) Title: DETERMINATION OF PLATELET-MIRNAS IN ALZHEIMER'S DISEASE

Figure 2 :

SEQ ID NO.	miRNA	Healthy Control median	Alzheimer median	Fold Change (g1/g2)	ttest adjpval	limma adjpval	AUC	wwn adjpval
1	hsa-miR-30c-5p	2226	5055	2.27	7.72E-04	7.30E-04	0.22	1.32E-03
2	hsa-miR-425-5p	3756	7571	2.02	9.91E-05	2.84E-06	0.17	1.75E-04
3	hsa-miR-151a-3p	2693	5302	1.97	1.65E-07	1.33E-07	0.09	4.60E-06
4	hsa-miR-30d-5p	9762	18120	1.86	1.92E-10	3.82E-08	0.07	2.73E-06
5	hsa-miR-186-5p	3474	6160	1.77	3.00E-04	6.87E-06	0.17	1.75E-04
6	hsa-miR-125a-5p	508	890	1.75	5.06E-02	2.80E-02	0.30	3.04E-02
7	hsa-miR-191-5p	103136	179039	1.74	2.06E-01	1.65E-01	0.39	1.67E-01
8	hsa-let-7f-5p	18120	11686	0.64	2.78E-07	5.47E-07	0.92	2.73E-06
9	hsa-miR-185-5p	549	347	0.63	2.73E-02	7.66E-02	0.66	7.56E-02
10	hsa-miR-103a-3p	7015	4396	0.63	6.53E-05	1.66E-03	0.76	2.79E-03
11	hsa-let-7a-5p	19907	12395	0.62	3.15E-06	1.38E-06	0.90	5.47E-06
12	hsa-miR-107	6607	3756	0.57	3.92E-05	1.10E-03	0.78	1.77E-03
13	hsa-miR-148b-3p	418	218	0.52	4.64E-03	2.37E-03	0.75	3.90E-03
14	hsa-miR-98	298	153	0.51	8.12E-05	3.37E-05	0.83	1.75E-04
15	hsa-let-7g-5p	4396	2226	0.51	1.36E-05	6.87E-06	0.86	4.62E-05
16	hsa-miR-15a-5p	1959	860	0.44	9.21E-06	8.19E-06	0.86	4.62E-05
17	hsa-miR-451a	179039	75965	0.42	1.71E-01	2.22E-01	0.65	1.05E-01
18	hsa-miR-221-3p	193	80	0.41	1.02E-02	2.06E-02	0.72	1.53E-02
19	hsa-miR-21-5p	469	193	0.41	2.38E-02	2.06E-02	0.69	3.36E-02
20	hsa-miR-126-5p	525	183	0.35	1.88E-02	1.51E-02	0.71	2.20E-02

(57) Abstract: The present invention relates to methods, kits and uses for determining platelet-miRNAs in a from a platelet-comprising fraction derived from a whole blood sample from a subject affected or suspected to be affected by Alzheimer's Disease.



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

13 August 2015

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/078638

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

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)
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 practicable, search terms used)

EPO-Internal, 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	LEIDINGER P ET AL: "A blood based 12-miRNA signature of Alzheimer disease patients", GENOME BIOLOGY, BIOMED CENTRAL LTD., LONDON, GB, vol. 14, no. 7, 29 July 2013 (2013-07-29), page R78, XP021162883, ISSN: 1465-6906, DOI: 10.1186/GB-2013-14-7-R78	1-16,18
Y	abstract page 2, column 2, paragraph 2 page 9, column 2, paragraph 2 page 13, column 1, paragraph 5 ----- -/--	17



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 application or patent 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

18 June 2015

Date of mailing of the international search report

24/06/2015

Name and mailing address of the ISA/

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Werner, Andreas

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/078638

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/036236 A1 (UNIV OHIO STATE RES FOUND [US]; MARSH CLAY B [US]; HUNTER MELISSA G [U] 19 March 2009 (2009-03-19)	1-16,18
Y	claims 1, 29 paragraph [0122]; figure 4	17
Y	----- SHEINERMAN K S ET AL: "Plasma microRNA biomarkers for detection of mild cognitive impairment", Aging, vol. 4, no. 9 19 September 2012 (2012-09-19), pages 590-605, XP055159533, United States Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pubmed/23001356 [retrieved on 2014-12-18]	17
A	abstract table 1 page 601, column 1, paragraph 2 - column 2, paragraph 1	1-16,18
A	----- GEEKIYANAGE H ET AL: "Blood serum miRNA: Non-invasive biomarkers for Alzheimer's disease", EXPERIMENTAL NEUROLOGY, vol. 235, no. 2, 1 June 2012 (2012-06-01), pages 491-496, XP055058220, ISSN: 0014-4886, DOI: 10.1016/j.expneurol.2011.11.026 abstract Material and methods	1-18
A	----- CHENG L ET AL: "The detection of microRNA associated with Alzheimer's disease in biological fluids using next-generation sequencing technologies", FRONTIERS IN GENETICS, vol. 4, 1 January 2013 (2013-01-01), XP055173013, DOI: 10.3389/fgene.2013.00150 the whole document	1-18
A	----- Jonathan Shaffer ET AL: "miRNA profiling from blood - challenges and recommendations", 1 January 2012 (2012-01-01), pages 1-10, XP055173087, Retrieved from the Internet: URL:http://www.sabiosciences.com/manuals/Whitepaper_Serumplasma.pdf [retrieved on 2015-03-02] the whole document	1-18
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/078638

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/150105 A1 (FEBIT HOLDING GMBH [DE]) 10 October 2013 (2013-10-10) page 19, paragraph 1 - paragraph 3 page 40, line 23 - page 41, line 14 -----	12-15
A	CN 101 622 349 A (ASURAGEN INC) 6 January 2010 (2010-01-06) the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/078638

Box No. 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.:
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 No. 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 fees, this Authority did not invite payment of additional fees.
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.:

1-18(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ 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: 1-18(partially)

Methods for diagnosing a platelet-related component of AD, or AD, or for monitoring the progression of AD, or for determining the platelet activity, or for monitoring the efficacy of an anti-platelet therapy in a subject affected by AD; comprising using an expression profile of a set comprising at least one platelet-miRNA (miRNA expressed in thrombocytes, preferably those of Fig.1) from a platelet-comprising fraction of a whole blood sample of a subject affected or suspected to be affected by Alzheimer's Disease; comprising at least SEQ ID NO:19;
Kits therefor with means for determining an expression profile of a set of platelet-miRNAs comprising at least SEQ ID NO:19.

2-20. claims: 1-18(partially)

Same as above, but comprising at least SEQ ID NO:1-18 or 20 (in the order of appearance, each marking a separate invention);

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/078638

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 2190992 A1	02-06-2010
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