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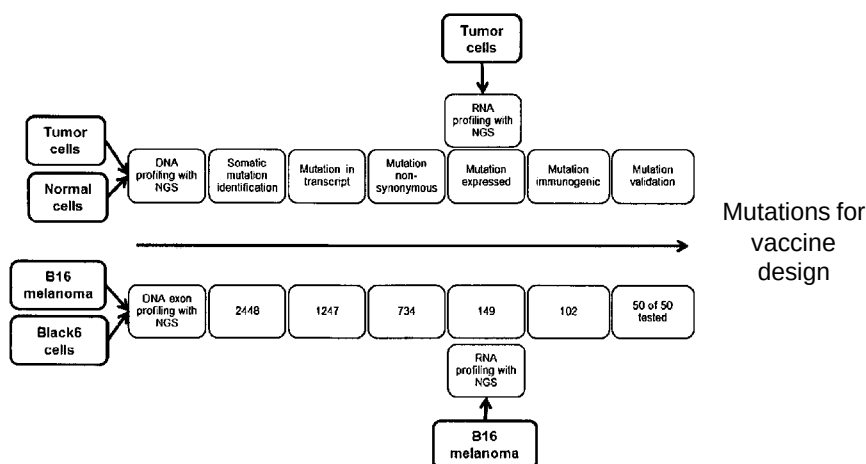
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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[Continued on nextpage]

(54) Title: INDIVIDUALIZED VACCINES FOR CANCER

Fig. 1



(57) Abstract: The present invention relates to the provision of vaccines which are specific for a patient's tumor and are potentially useful for immunotherapy of the primary tumor as well as tumor metastases. In one aspect, the present invention relates to a method for providing an individualized cancer vaccine comprising the steps: (a) identifying cancer specific somatic mutations in a tumor specimen of a cancer patient to provide a cancer mutation signature of the patient; and (b) providing a vaccine featuring the cancer mutation signature obtained in step (a). In a further aspect, the present invention relates to vaccines which are obtainable by said method.

- with international search report (Art. 21(3))
- 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))

— with sequence listing part of description (Rule 5.2(a))

(88) **Date of publication of the international search report:**
27 June 2013

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/002209

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/00 C12Q1/68 A61P35/00 G01N33/50 G06F19/18
G06F19/24

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)

C07K C12Q A61K G01N G06F

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 , EMBASE, BIOSIS, Sequence Search , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	wo 99/34015 A2 (IMP CANCER RES TECH [GB] ; GANESAN TRIVADI SUNDARAM [GB]) 8 July 1999 (1999-07-08)	18,22
Y	example 1 claims 38,39 ----- -/- .	1-17 , 19-21



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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/002209

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAHMA OSAMA E ET AL: "A pilot clinical trial testing mutant von Hippel-Lindau peptide as a novel immune therapy in metastatic Renal Cell Carcinoma", JOURNAL OF TRANSLATIONAL MEDICINE, BIOMED CENTRAL, LONDON, GB, vol. 8, no. 1, 28 January 2010 (2010-01-28), page 8, XP021068353, ISSN: 1479-5876	18,22
Y	abstract page 2, right-hand column, paragraph 1 - page 3, left-hand column, paragraph 2 tables 1,2	1-17 , 19-21
X	----- Wo 97/40156 AI (US GOV NAT INST HEALTH [US]; SCHLOM JEFFREY [US]; ABRAMS SCOTT [US]) 30 October 1997 (1997-10-30)	18,22
Y	page 11, line 30 - line 32 examples 1,2 claims 1,36	1-17 , 19-21
X	----- GJERTSEN ET AL: "Mutated ras peptides as vaccines in immunotherapy of cancer", VOX SANGUINIS, S. KARGER AG, BASEL, CH, vol. 74, no. 2, 1 January 1998 (1998-01-01), pages 489-495, XP002127145, ISSN: 0042-9007	18,22
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Y	----- GIORGIO PARMIANI ET AL: "Unique human tumor antigens: immunobiology and use in clinical trials.", THE JOURNAL OF IMMUNOLOGY, vol. 178, no. 4, 1 February 2007 (2007-02-01), pages 1975-1979, XP055044894, ISSN: 0022-1767 page 1977, left-hand column, paragraph 2	1-17 , 19-21
X,P	----- J. C. CASTLE ET AL: "Exploiting the melanoma for tumor vaccination", CANCER RESEARCH, 1 January 2012 (2012-01-01), XP055018897, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-11-3722 the whole document ----- -/--	1-22

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/002209

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TOBIAS SJÖBLOM ET AL: "The Consensus Coding Sequences of Human Breast and Colorectal Cancers" , SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, WASHINGTON, DC; US, vol . 314, 13 October 2006 (2006-10-13) , pages 268-274, XP007901261 , ISSN: 0036-8075 , DOI : 10.1126/SCIENCE.1133427 abstract page 268, right-hand column, paragraph 3 - page 269, right-hand column, paragraph 1 page 274, left-hand column, paragraph 1 -----	1-22
A	N. H. SEGAL ET AL: "Epitope Landscape in Breast and Colorectal Cancer" , CANCER RESEARCH , vol . 68, no. 3, 1 February 2008 (2008-02-01) , pages 889-892 , XP055044926, ISSN: 0008-5472 , DOI : 10.1158/0008-5472 .CAN-07-3095 abstract page 889 , right-hand column, paragraph 3 -----	1-22
A	KESSLER J H ET AL: "Identification of T-cell epitopes for cancer immunotherapy" , LEUKEMIA, MACMILLAN PRESS LTD, US, vol . 21, no. 9, 1 September 2007 (2007-09-01) , pages 1859-1874, XP002516100, ISSN: 0887-6924, DOI : 10.1038/SJ .LEU .2404787 [retrieved on 2007-07-05] page 1860, left-hand column, paragraph 4 - page 1861, right-hand column, paragraph 2 -----	1-22
A	MATEO L ET AL: "An HLA-A2 polyepitope vaccine for melanoma immunotherapy" , THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol . 163, no. 7, 1 October 1999 (1999-10-01) , pages 4058-4063 , XP002244411 , ISSN: 0022-1767 the whole document -----	10, 11, 14, 15
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/002209

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PANTEL K ET AL: "Ci rcul ati ng tumour cel l s i n cancer pati ents : chal l enge s and perspecti ves", TRENDS I N MOLECULAR MEDICINE, ELSEVI ER CURRENT TRENDS, GB, vol . 16, no. 9, 1 September 2010 (2010-09-01) , pages 398-406, XP027433109 , ISSN: 1471-4914, DOI : 10.1016/J .MOLMED.2010.07 .001 [retri eved on 2010-07-29] cited i n the appl icati on the whol e document -----	3,4
A	SEBASTIAN KREITER ET AL: "Tumor vacci nati on usi ng messenger RNA: prospects of a future therapy" , CURRENT OPINION I N IMMUNOLOGY, vol . 23, no. 3, 13 April 2011 (2011-04-13) , pages 399-406, XP055018902 , ISSN: 0952-7915 , DOI : 10.1016/j .coi .2011 .03 .007 the whol e document -----	16
X	JOHN D. STOREY: "A direct approach to fal se di scovery rates" , PLOS COMPUTATIONAL BIOLOGY, vol . 64, no. 3, 1 August 2002 (2002-08-01) , pages 479-498, XP055061495 , ISSN: 1369-7412 , DOI : 10.1111/1467-9868.00346 the whol e document -----	23-44
X	FAWCETT ET AL: "An i ntroducti on to ROC analysi s", PATTERN RECOGNITION LETTERS, ELSEVI ER, AMSTERDAM, NL, vol . 27, no. 8, 1 June 2006 (2006-06-01) , pages 861-874, XP025053099 , ISSN: 0167-8655 , DOI : 10.1016/J .PATREC.2005 .10.010 [retri eved on 2006-06-01] cited i n the appl icati on the whol e document -----	45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP20 12/002209

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.:

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: 1-22

Method of providing an individualized cancer vaccine as defined in claim 1, the vaccine obtained thereby as defined in claim 18 and use thereof in the treatment of cancer as defined in claims 21 and 22; a vaccine comprising a recombinant polypeptide comprising mutation based neo-epitopes resulting from cancer specific somatic mutations in a tumour sample of a cancer patient, or a nucleic acid encoding said polypeptide and use thereof as defined in claim 22.

2. claims: 23-44

A method for determining a false discovery rate based on next generation sequencing data as defined in claim 23.

3. claim: 45

A method for determining an estimated receiver operating curve (ROC) as defined in claim 45.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/002209

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