

REVISED VERSION

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2016/014799 A9

(43) International Publication Date
28 January 2016 (28.01.2016)

- (51) International Patent Classification:
A61K 39/395 (2006.01) *A61P 35/00* (2006.01)
C07K 16/28 (2006.01)
- (21) International Application Number:
PCT/US2015/041738
- (22) International Filing Date:
23 July 2015 (23.07.2015)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
62/028,109 23 July 2014 (23.07.2014) US
- (71) Applicant: UNIVERSITY OF IOWA RESEARCH
FOUNDATION [US/US]; Iowa Centers for Enterprise,
2660 University Capitol Centre, Iowa City, IA 52242-5500
(US).
- (72) Inventors: WEINER, George; 235 Kennedy Parkway,
Iowa City, IA 52246 (US). MILHEM, Mohammed; 2425
Biltmore Lane, Coralville, IA 52241 (US). MAKKOUK,
Amani; 714 Westgate St., Apt. 83, Iowa City, IA 52246
(US). BALLAS, Zuhair, K.; 42 Denbigh Dr., Iowa City,
IA 52246 (US). NORIAN, Lyse; 8 Lime Kiln Lane NE,
Iowa City, IA 52240 (US).
- (74) Agents: MCBRIDE, Scott, M. et al.; Andrus Intellectual
Property Law, LLP, 100 East Wisconsin Avenue, Suite
1100, Milwaukee, WI 53202 (US).
- (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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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.

- (84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

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

25 February 2016

- (15) Information about Correction:
see Notice of 25 February 2016

(54) Title: EPIDERMAL GROWTH FACTOR AND BLOCKADE OF IMMUNE CHECKPOINTS IN CANCER IMMUNOTHER-
APY

(57) Abstract: Disclosed are methods, compositions, kits, and systems for diagnosing and/or treating a patient via immunotherapy. The diagnostic methods including detecting epidermal growth factor (EGF) and administering to the patient a therapeutic antibody that binds to a cell surface receptor of a regulatory T cell (T_{reg}) based on the detected EGF. The treatment methods include adminis-
tering EGF or an agonist of the EGF receptor and administering the therapeutic antibody that binds to a cell surface receptor of a
T_{reg}.



WO 2016/014799 A9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2015/041738

A. CLASSIFICATION OF SUBJECT MATTER

A61K 39/395 (2006.01)**C07K 16/28** (2006.01)**A61P 35/00** (2006.01)

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)

A61K 39/395, C07K 16/28, A61P 35/00

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)

CIPO, NCBI, PatSearch(RUPTO internal), ESPACENET, USPTO, WIPO, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YURKOVETSKY Z.R. et al. Multiplex analysis of serum cytokines in melanoma patients treated with interferon- α 2b. Clin Cancer Res, .2007 April 15, 13(8), pp.2422-2428	1-7, 10
Y	PARDOLL D.M. et al. The blockade of immune checkpoints in cancer immunotherapy, Nature Reviews Cancer, 2012 April , vol.12, pp.252-264	1-7, 17-22, 25, 26
Y	PIVEN N.V. et al. Jmmunochemical epidermal growth factor detection in oncopathology, Jmmunopathology, allergology, infectology, 2013, no.4, pp.10-16	1-7, 17-22
X Y	GENOVA C. et al. Ipilimumab (MDX-010) in the treatment of non-small cell lung cancer, Expert Opin. Biol. Ther., 2012, Vol.12, no.7, pp.939-948	9, 11, 13, 24 10, 25, 26



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier document but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

21 October 2015 (21.10.2015)

Date of mailing of the international search report

05 November 2015 (05.11.2015)

Name and mailing address of the ISA/RU:
Federal Institute of Industrial Property,
Berezhkovskaya nab., 30-1, Moscow, G-59,
GSP-3, Russia, 125993

Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37

Authorized officer

N.Tarasova

Telephone No. 495 531 65 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2015/041738

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.: 8, 12-16, 27-28
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:

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 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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2015/041738

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OTT P.A. et al. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients, Clin Cancer Res, 2013, October 1, 19(9), pp.5300-5309	1-7, 9-11, 17-26
A	POLIMENO M. et al. Regulatory T cells, interleukin (IL)-6, IL-8, Vascular endothelial growth factor (VEGF), CXCL10, CXCL11, epidermal growth factor (EGF) and hepatocyte growth factor (HGF) as surrogate markers of host immunity in patients with renal cell carcinoma, BJU International, 2013, no.112, pp.686-696	1-7, 9-11, 17-26