



(51) International Patent Classification:

A61K 38/04 (2006.01) A61P 35/00 (2006.01)
A61K 39/395 (2006.01)

(21) International Application Number:

PCT/IL2016/050764

(22) International Filing Date:

14 July 2016 (14.07.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/193,201	16 July 2015 (16.07.2015)	US
62/259,182	24 November 2015 (24.11.2015)	US
62/291,006	4 February 2016 (04.02.2016)	US
62/291,039	4 February 2016 (04.02.2016)	US

(71) Applicants: **BIOKINE THERAPEUTICS LTD.** [IL/IL];
Building 13a, Einstein Street, Science Park, Kiryat Weiz-
mann, 7403617 Nes Ziona (IL). **BIOLINERX LTD.**
[IL/IL]; 2 HaMaayan Street, 7177871 ModiIn (IL).

(72) Inventors: **PELED, Amnon**; 55 Nahmani Street, 6777634
Tel-Aviv (IL). **PEREG, Yaron**; 4 Adolam Street, P.O.
Box 379, 6085000 Shoham (IL).

(74) Agents: **EHRlich, Gal** et al.; G. E. EHRlich (1995)
LTD., 11 Menachem Begin Road, 5268104 Ramat Gan
(IL).

(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).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— 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:

23 February 2017

(54) Title: COMPOSITIONS AND METHODS FOR TREATING CANCER

(57) Abstract: Use of a CXCR4 antagonistic peptide and an immune-check point regulator in the treatment of cancer is provided. Accordingly there is provided a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide having an amino acid sequence as set forth in SEQ ID NO: 1 or an analog or derivative thereof; and a therapeutically effective amount of a PD1 antagonist, a PDL-1 antagonist, a CTLA-4 antagonist, a LAG-3 antagonist, a TIM-3 antagonist, a KIR antagonist, an IDO antagonist, an OX40 agonist, a CD137 agonist, a CD27 agonist, a CD40 agonist, a GITR agonist, a CD28 agonist or an ICOS agonist, thereby treating the cancer in the subject. Also provided are pharmaceutical compositions and articles of manufacture.



INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2016/050764

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/04 A61K39/395 A61P35/00
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)

A61K A61P

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/160895 A1 (BIOKINE THERAPEUTICS LTD [IL]) 31 October 2013 (2013-10-31) claims 1-18	1,15,16, 19, 33-35, 39-44
Y	WO 2004/087068 A2 (UNIV EMORY [US]; SHIM HYUNSUK [US]; LIANG ZHONGXING [US]; UMBREIT JAY) 14 October 2004 (2004-10-14) claims 1-46 ----- -/--	1,15,16, 19, 33-35, 39-44

☒ 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

10 October 2016

Date of mailing of the international search report

11/01/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Rodrigo-Simón, Ana

INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2016/050764

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EDWARD B. GARON ET AL: "Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer", NEW ENGLAND JOURNAL OF MEDICINE, THE - NEJM -, vol. 372, no. 21, 21 May 2015 (2015-05-21) , pages 2018-2028, XP055306209, ISSN: 0028-4793, DOI: 10.1056/NEJMoa1501824 the whole document	1,15,16, 19, 33-35, 39-44
A	----- WO 2015/019284 A2 (CAMBRIDGE ENTPR LTD [GB]) 12 February 2015 (2015-02-12) cited in the application claims 1-33 page 2, line 14; claim 16 -----	1,15,16, 19, 33-35, 39-44
A	WO 2015/069770 A1 (COGNATE BIOSERVICES INC [US]; NORTHWEST BIOTHERAPEUTICS [US]; UNIV CAL) 14 May 2015 (2015-05-14) claims 1-5 claims 10,18 -----	1,15,16, 19, 33-35, 39-44
A	DUHA FAHHAM ET AL: "In vitro and in vivo therapeutic efficacy of CXCR4 antagonist BKT140 against human non-small cell lung cancer", THE JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, vol. 144, no. 5, 1 November 2012 (2012-11-01), pages 1167-1175.e1, XP055076134, ISSN: 0022-5223, DOI: 10.1016/j.jtcvs.2012.07.031 the whole document -----	1,15,16, 19, 33-35, 39-44
A	WO 2014/155376 A1 (BIOKINE THERAPEUTICS LTD [IL]; BIOLINERX LTD [IL]) 2 October 2014 (2014-10-02) claims 1-29 -----	1,15,16, 19, 33-35, 39-44
A	WO 2015/016718 A1 (BIONOVION HOLDING B V [NL]) 5 February 2015 (2015-02-05) claims 1-18 ----- -/--	1,15,16, 19, 33-35, 39-44

INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2016/050764

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S.-R. WOO ET AL: "Immune Inhibitory Molecules LAG-3 and PD-1 Synergistically Regulate T-cell Function to Promote Tumoral Immune Escape", CANCER RESEARCH, vol. 72, no. 4, 20 December 2011 (2011-12-20), pages 917-927, XP055151722, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-11-1620 the whole document -----	1,15,16, 19, 33-35, 39-44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2016/050764

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, 19(completely); 15, 16, 33-35, 39-44(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, 19(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a PD1 antagonist as well as their use in the treatment of cancer

2. claims: 2, 20(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a PD1-L1 antagonist as well as their use in the treatment of cancer

3. claims: 3, 21(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a CTLA-4 antagonist as well as their use in the treatment of cancer

4. claims: 4, 22(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a LAG-3 antagonist as well as their use in the treatment of cancer

5. claims: 5, 23(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a TIM-3 antagonist as well as their use in the treatment of cancer

6. claims: 6, 24(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a KIR antagonist as well as their use in the treatment of cancer

7. claims: 7, 25(completely); 15, 16, 33-35, 39-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a IDO antagonist as well as their use in the treatment of cancer

8. claims: 8, 26(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SEQ.1 or an analog or derivate thereof and a OX40 agonist as well as their use in the treatment of cancer

9. claims: 9, 27(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a CD137 agonist as well as their use in the treatment of cancer

10. claims: 10, 28(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a CD27 agonist as well as their use in the treatment of cancer

11. claims: 11, 29(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a CD40 agonist as well as their use in the treatment of cancer

12. claims: 12, 30(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a GITR agonist as well as their use in the treatment of cancer

13. claims: 13, 31(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a CD28 agonist as well as their use in the treatment of cancer

14. claims: 14, 32(completely); 17, 18, 36-44(partially)

Compositions comprising a CXCR4 antagonistic peptide of SEQ.1 or an analog or derivate thereof and a ICOS agonist as well as their use in the treatment of cancer

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IL2016/050764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013160895 A1	31-10-2013	EP 2841084 A1	04-03-2015
		US 2015125549 A1	07-05-2015
		WO 2013160895 A1	31-10-2013
WO 2004087068 A2	14-10-2004	CA 2520406 A1	14-10-2004
		EP 1608318 A2	28-12-2005
		JP 2006524242 A	26-10-2006
		US 2007258893 A1	08-11-2007
		WO 2004087068 A2	14-10-2004
WO 2015019284 A2	12-02-2015	CA 2920377 A1	12-02-2015
		EP 3030322 A2	15-06-2016
		JP 2016527303 A	08-09-2016
		US 2015216843 A1	06-08-2015
		US 2015352208 A1	10-12-2015
		WO 2015019284 A2	12-02-2015
WO 2015069770 A1	14-05-2015	AU 2014346852 A1	16-06-2016
		CA 2929407 A1	14-05-2015
		CN 105828834 A	03-08-2016
		EA 201690912 A1	31-10-2016
		EP 3065772 A1	14-09-2016
		JP 2016540042 A	22-12-2016
		KR 20160093012 A	05-08-2016
		US 2015202291 A1	23-07-2015
		US 2015273033 A1	01-10-2015
		WO 2015069770 A1	14-05-2015
WO 2014155376 A1	02-10-2014	AU 2014240733 A1	22-10-2015
		CA 2906314 A1	02-10-2014
		CN 105163749 A	16-12-2015
		EP 2978439 A1	03-02-2016
		HK 1215790 A1	15-09-2016
		JP 2016516080 A	02-06-2016
		KR 20150135432 A	02-12-2015
		US 2016082071 A1	24-03-2016
		WO 2014155376 A1	02-10-2014
WO 2015016718 A1	05-02-2015	AU 2014296887 A1	28-01-2016
		CA 2917858 A1	05-02-2015
		CN 105682683 A	15-06-2016
		EP 3027210 A1	08-06-2016
		JP 2016531907 A	13-10-2016
		KR 20160037989 A	06-04-2016
		US 2016185870 A1	30-06-2016
		WO 2015016718 A1	05-02-2015