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(71) Applicants: THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, 6011 Executive Blvd., Suite 325, Rockville, MD 20852 (US). IHSAN DOGRAMACI BILKENT UNIVERSITY [TR/TR]; BILKENT UNIVERSITY, 06800 Ankara (TR).

(72) Inventors: PAVLAKIS, George, N.; 9 Purdue Court, Rockville, MD 20850 (US). WATSON, Dionysios, Christos; 1001 Carroll Parkway, Apt 220, Frederick, MD 21701 (US). FELBER, Barbara, K.; 9 Purdue Court, Rockville, MD 20850 (US). BAYIK, Defne; 1001 Carroll Parkway, Apt 220, Frederick, MD 21701 (US). GURSEL, Ihsan; Bilkent University, Merkez Lojmanlari, 06800 Ankara (TR). BERGAMASCHI, Cristina; 6 E. Patrick Street, Frederick, MD 21702 (US).

(74) Agent: LOCKYER, Jean, M. et al.; Kilpatrick Townsend & Stockton LLP, Mailstop: IP Docketing - 22, 1100 Peachtree Street, Suite 2800 Atlanta, GA 30309 (US).

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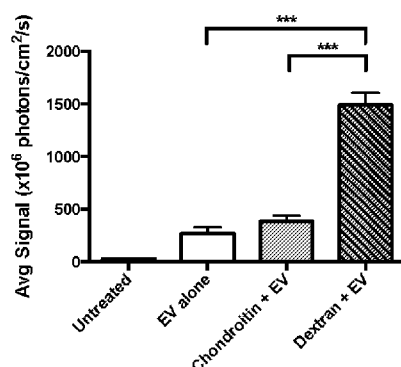
- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

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14 December 2017 (14.12.2017)

(54) Title: EXTRACELLULAR VESICLES, METHODS OF MAKING THEM, AND METHODS OF REDUCING LIVER UPTAKE OF EXTRACELLULAR VESICLES

2C.



(57) Abstract: An isolated or purified extracellular vesicle comprising a membrane comprising a phospholipid bilayer and a heterodimeric complex of interleukin-15 and interleukin-15 receptor alpha is disclosed. Also provided are methods of preparing isolated or purified extracellular vesicles comprising a therapeutic protein, methods of reducing liver uptake of extracellular vesicles administered to a mammal, and methods of treating or preventing cancer in a mammal.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/025550

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/54 A61K9/127 C07K14/715 C07K14/47
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 A61K

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, BIOSIS, EMBASE, 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	VADER PIETER ET AL: "Extracellular vesicles for drug delivery", ADVANCED DRUG DELIVERY REVIEWS, vol. 106, 27 February 2016 (2016-02-27), pages 148-156, XP029786400, ELSEVIER, AMSTERDAM, NL ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2016.02.006	28
Y	*Abstract, items 2, 4 and 5*; figure 1 ----- -/-	1-27, 29-46



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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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

Bulcao de Melo B., T

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/025550

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN DER MEEL ROY ET AL: "Extracellular vesicles as drug delivery systems: Lessons from the liposome field", JOURNAL OF CONTROLLED RELEASE, vol. 195, December 2014 (2014-12), pages 72-85, XP002772267, ISSN: 0168-3659, DOI: 10.1016/J.JCONREL.2014.07.049	28
Y	*Abstract, item 2.3*; figure 6	1-27, 29-46
X	----- SAMIR EL ANDALOUSSI ET AL: "Extracellular vesicles: biology and emerging therapeutic opportunities", NATURE REVIEWS DRUG DISCOVERY, vol. 12, 15 April 2013 (2013-04-15), pages 347-357, XP055096689, DOI: 10.1038/nrd3978	28
Y	*Abstract*; page 353 - page 355; figure 3	1-27, 29-46
Y	----- OCHOA MARIA C ET AL: "Interleukin-15 in Gene Therapy of Cancer", CURRENT GENE THERAPY, vol. 13, no. 1, February 2013 (2013-02), pages 15-30, XP002772268, ISSN: 1875-5631	1-27, 29-46
	Whole document, in particular: Abstract and item 10; figure 1	
Y	----- BERGAMASCHI C ET AL: "Intramuscular delivery of heterodimeric IL-15 DNA in macaques produces systemic levels of bioactive cytokine inducing proliferation of NK and T cells", GENE THERAPY, vol. 22, no. 1, January 2015 (2015-01), pages 76-86, XP002772269, ISSN: 0969-7128, DOI: 10.1038/GT.2014.84	1-27, 29-46
	Whole document, in particular: Abstract and Discussion	
Y	----- E. CHERTOVA ET AL: "Characterization and Favorable in Vivo Properties of Heterodimeric Soluble IL-15{middle dot}IL-15R Cytokine Compared to IL-15 Monomer", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 288, no. 25, 6 May 2013 (2013-05-06), pages 18093-18103, XP055134195, ISSN: 0021-9258, DOI: 10.1074/jbc.M113.461756	1-27, 29-46
	Abstract and Discussion	
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/025550

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WATSON DIONYSIOS C ET AL: "Efficient production and enhanced tumor delivery of engineered extracellular vesicles", BIOMATERIALS, vol. 105, October 2016 (2016-10), pages 195-205, XP002771478, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.2016.07.003 *Whole document, in particular: Abstract and items 3.4-3.6 and 4*; figures 3-6 -----	1-46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/025550

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.:

1-46

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: 1-46

Invention 1 concerns extracellular vesicles comprising a phospholipid bilayer membrane and a heterodimeric complex of interleukin-15 and interleukin-15 receptor alpha, compositions comprising them, methods of preparing them, as well as a method of reducing liver uptake of extracellular vesicles and a method of treating or preventing cancer using said extracellular vesicles.

2. claims: 47-51

Invention 2 concerns a mammalian host cell comprising a DNA construct encoding interleukin-15 and an interleukin-15 receptor alpha-lactadherin carrier polypeptide.
