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- (71) Applicant: **VEDANTRA PHARMACEUTICALS, INC.**  
[US/US]; One Kendall Square, Building 1400 West, Suite 14303, Cambridge, MA 02139 (US).
- (72) Inventors: **LI, Adrienne**; 170 Gore Street, Unit 217, Cambridge, MA 02141 (US). **EBY, Jackson**; 101 Varnum Street, Arlington, MA 02474 (US). **DEMUTH, Peter, C.**; 74A Brookings Street, Medford, MA 02155 (US).
- (74) Agents: **BIEKER-BRADY, Kristina** et al.; Clark & Elbing LLP, 101 Federal Street, 15th Floor, Boston, MA 02110 (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.
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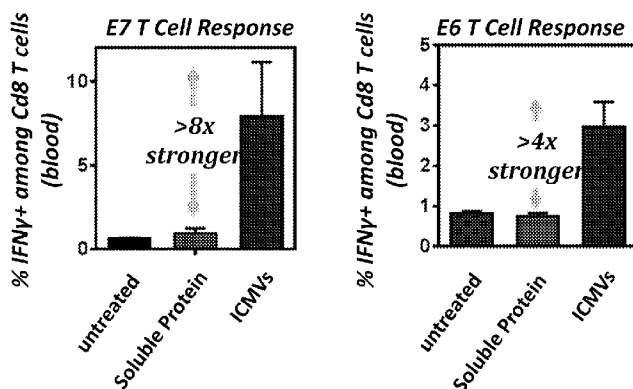
[Continued on next page]

(54) Title: MULTILAMELLAR LIPID VESICLE COMPOSITIONS AND METHODS OF USE

FIG. 1

ICMVs induce strong + effective T cells against HPV tumors

Therapeutic treatment of TC-1 tumors with ICMVs:  
ICMVs greatly enhance induction of functional, cytokine-producing anti-tumor T-cell responses:



(57) Abstract: The present invention provides novel and inventive drug delivery systems with higher loading capability, a capacity to sequester high levels of both hydrophobic and hydrophilic agents simultaneously, and longer release profiles. Some aspects of these delivery systems include compositions including stabilized multilamellar lipid vesicles having crosslinked lipid bilayers (referred to herein as inter-bilayer-crosslinked multilamellar vesicles or ICMV) covalently conjugated to an agent (e.g., an antigen).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- 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))

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

2 June 2016

**Published:**

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

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/49819

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/56, 9/127 (2016.01)

CPC - A61K 31/7088; C07K 14/705

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)

IPC(8) Classification(s): A61K 31/56, 9/127, 9/14; CPC Classification(s): A61K 31/7088, 39/0011; C07K 14/705; USPC Classification(s): 514/44R; 424/450

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)

USPTO Web Page; PatSeer (US, EP, WO); Google; Google Scholar; EBSCO; Entrez Pubmed; Science Direct; Search terms -- multilamellar, vesicle, lipid, lipophilic, mutant HPV, peptide, substitutions, HPV16, E6, E7, fusion protein, genotype

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2012/0177724 A1 (IRVINE, DJ et al.) July 12, 2012; abstract; paragraphs [0004], [0006], [0007], [0009]-[0013], [0082], [0106]-[0108], [0130], [0161], [0221]	36-40, 41/36-40, 113-116 ----- 1-2, 3/1-2, 21-22, 90, 117/114-116, 118/117/114-116, 119/117/114-116, 118/117/114-116, 119/117/114-116, 120/119/117/114-116, 121/119/117/114-116
Y	US 2012/0171290 A1 (COURSAGET, PL et al.) July 05, 2012; paragraphs [0012], [0022], [0024], [0035], [0047], [0055], [0069], [0073], [0087], [0116], [0245]; figure 13	1-2, 3/1-2, 21-22, 90, 117/114-116, 118/117/114-116, 119/117/114-116, 118/117/114-116, 119/117/114-116, 120/119/117/114-116, 121/119/117/114-116
A	(LA PORTA, RF et al.) Human Papilloma Viral DNA Replicates as a Stable Episome in Cultured Epidermal Keratinocytes. Proceedings of the National Academy of Sciences, USA, June 1982, Vol. 79, pages 3393-3397; page 3396, figure 4	1-3, 21-22, 36-40, 90, 113-121
A	US 2010/0120700 A1 (LU, PS et al.) May 13, 2010; entire document	1-3, 21-22, 36-40, 90, 113-121

☐ 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

25 March 2016 (25.03.2016)

Date of mailing of the international search report

08 APR 2016

Name and mailing address of the ISA/

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P.O. Box 1450, Alexandria, Virginia 22313-1450

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Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300  
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/49819

## 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.: 4-20, 23-35, 42-89, 91-112, 122-136  
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:

\*\*\*-Continued Within the Next Supplemental Box-\*\*\*

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

Information on patent family members

International application No.

PCT/US15/49819

\*\*\*\*-Continued from Box III: Lack of Unity of Invention-\*\*\*\*

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3, 21, 22 and 39-41 are directed toward a composition comprising: (a) a multilamellar lipid vesicle having crosslinks between lipid bilayers; and (b) one or more mutant human papilloma virus (HPV) peptides; wherein at least one of said one or more mutant HPV peptides is conjugated to a lipid of said multilamellar lipid vesicle.

Group II: Claims 36, 37, 90 and 113-127 are directed toward a composition comprising: (a) a multilamellar lipid vesicle having crosslinks between lipid bilayers; and (b) one or more agents; wherein said one or more agents are not terminal-cysteine-bearing antigens; and wherein at least one molecule of said one or more agents is conjugated to a lipid of said multilamellar lipid vesicle; a method comprising administering said composition to a subject; a method of forming said composition; and kits comprising said composition.

Group III: Claim 38 is directed toward a composition comprising: (a) a multilamellar lipid vesicle having crosslinks between lipid bilayers; and (b) one or more agents; wherein at least one molecule of said one or more agents is conjugated to a lipid of said multilamellar lipid vesicle, and wherein said conjugation does not comprise a cysteine.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a mutant HPV peptide, which is not present in either of Groups II or III, the special technical features of Group II include an immunomodulatory which is not a CT-011 antibody, which is not present in either of Groups I or III, the special technical features of Group III including wherein conjugation does not comprise a cysteine, which is not present in either of Groups I or II.

Groups I-III share the technical features including a composition comprising a multilamellar lipid vesicle having crosslinks between lipid bilayers, and one or more agents conjugated to a lipid of said multilamellar lipid vesicle. Groups I and II share the technical feature, which includes antigens.

However, these shared technical features are previously disclosed by US 2012/0177724 A1 to Irvine, et al. (hereinafter 'Irvine').

Irvine discloses a composition (paragraph [0015]) comprising multilamellar lipid vesicles (abstract, paragraph [0004]) having crosslinks between lipid bilayers (paragraph [0004]), and one or more antigenic agents (abstract; paragraph [0009]) conjugated to a lipid of said multilamellar vesicle (surface conjugated to the vesicle, including conjugation to a lipid (conjugated to a lipid of said multilamellar vesicle); paragraphs [0041], [0131]).

Since none of the special technical features of the Groups I-III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Irvine reference, unity of invention is lacking.