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(71) Applicant: WASHINGTON UNIVERSITY [US/US];
One Brookings Drive, St. Louis, Missouri 63130 (US).

(72) Inventors: KRUPNICK, Alexander Sasha; c/o WASHINGTON UNIVERSITY, One Brookings Drive, St. Louis, Missouri 63130 (US). LAZEAR, Eric Reed; c/o WASHINGTON UNIVERSITY, One Brookings Drive, St. Louis, Missouri 63130 (US). FREMONT, Daved Henry; c/o WASHINGTON UNIVERSITY, One Brookings Drive, St. Louis, Missouri 63130 (US).

(74) Agents: RILEY-VARGAS, Rebecca et al.; Polsinelli PC, 100 South Fourth Street, Suite 1000, St. Louis, Missouri 63102 (US).

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

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18 August 2016

(54) Title: COMPOSITIONS AND METHODS FOR TARGETED CYTOKINE DELIVERY

(57) Abstract: The present disclosure encompasses compositions and methods for targeted cytokine delivery. The compositions disclosed herein comprise a cytokine linked to a ligand and may improve immunotherapy by limiting side effects associated with immunotherapy.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/65872

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 35/00, A61P 31/12, C07K 14/705 (2016.01)

CPC - C12N 15/62, A61K 39/275, C07K 14/54

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): A61P 35/00, A61P 31/12, C07K 14/705 (2016.01)

CPC: C12N 15/62, A61K 39/275, C07K 14/54

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/85.2, 435/375, 435/69.52Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google Web, search terms: cytokine linked to a ligand, binding partner, IL2, IL7, IL15, IL21, R38A, F42K, C125S, MHC class-1-related glycoprotein, orthopoxvirus major histocompatibility complex class I-like protein, OMCP, CD8+, natural killer, NK, CTLs, linker, FLAG tag, His tag, (AAS)n, (AAAL)n, (GnS)n, (G2

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 2009/0098609 A1 (GILLIES et al.) 16 April 2009 (16.04.2009) para [0003], [0025], [0026], Fig. 1	1-4, 9, 38-39, 41-42
Y	US 2003/0124678 A1 (EPSTEIN et al.) 03 July 2003 (03.07.2003) para [0023], [0047], Figs. 2,9, SEQ ID NO: 3	6, (10-18)/(1-4,6,9), 43, (47-52, 54, 56)/(38-39,41-43), 57-58, 60-62, 66, 68, 70, (71-73)/(57-58,60-62,66,68,70), 77-79, 82-84, 86, 89, (90-95)/(77-79,82-84,86,89) 6, (10-15)/6, (16-18)/(1-4,6,9), 43, (47-51)/43, (52, 54, 56)/(38-39,41-43), 62, 66, 68, 70, (71-73)/(62,66,68,70), 77-79, 82-84, 86, 89, (90-95)/(77-79,82-84,86,89)

☒ Further documents are listed in the continuation of Box C.

* 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

11 April 2016

Date of mailing of the international search report

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/65872

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Lazear et al. Crystal Structure of the Cowpox Virus-Encoded NKG2D Ligand OMCP. J. Virol. (January 2013) vol. 87 no 2, pp 840-850, abstract, pg 840, col 1 para 1, col 2 para 2, pg 841, col 1 para 3	(10-11, 14-15)/(1-4,6,9), (47-48,50-51)/(38-39,41-43), 57-58, 60-62, 66, 68, 70, (71-73)/(57-58,60-62,66,68,70), (90-91, 94-95)/(77-79, 82-84,86,89)
Y	Campbell et al. Zoonotic orthopoxviruses encode a high-affinity antagonist of NKG2D. JEM (4 June 2007)vol. 204 no. 6, pp 1311-1317, abstract, pg 1311, col 1, para 2, pg 1314, col 1, para 4 - col 2, para 1, pg 1315 col 2 para 2, Fig. 3B	(12-13)/(1-4,6,9), 49/(38-39,41-43), (92-93)/(77-79, 82-84,86,89)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/65872

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.: 74-76
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 extra 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 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.: 1-4, 6, (9-18)(in part), 38-39, 41-43, (47-52, 54, 56)(in part), 57-58, 60-62, 66, 68, 70, (71-73)(in part), 77-79, 82-84, 86, 89, (90-95)(in part) limited to SEQ ID NO: 5, 7 and (AAS)_n wherein n = 7

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 15/65872

Continuation of Box NO. III Observations where unity of invention is lacking

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 1-21, 38-73, and 77-95, directed to a composition comprising a cytokine linked to a ligand, wherein the ligand is not a corresponding binding partner to the cytokine. The composition will be searched to the extent that the cytokine-ligand conjugate encompasses the first named cytokine, IL-2 of SEQ ID NO: 5, the first named ligand, OMCP of SEQ ID NO: 7, and the first named linker having 20-30 amino acids, (AAS)_n wherein n is 7. It is believed that claims 1-4, 6, (9-18)(in part), 38-39, 41-43, (47-52, 54, 56)(in part), 57-58, 60-62, 66, 68, 70, (71-73)(in part), 77-79, 82-84, 86, 89, (90-95)(in part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 5, 7 and (AAS)_n wherein n = 7. Additional cytokine-ligand conjugate will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected cytokine-ligand conjugate. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be wherein the cytokine is IL-1, the ligand is OMCP of SEQ ID NO: 13 and the linker is SEQ ID NO: 8 (claims 1, 7, (10-18, 20)(in part), 38, 40, (47-54, 56)(in part), 57, 59, 66-68, 70 (71-73)(in part), 77-79, 81, 87, (90-95)(in part)).

Group II: claim 22, directed to a nucleic acid molecule comprising SEQ ID NO: 1.

Group III: Claims 23-37, directed to a method of treating a disorder with a cytokine-ligand conjugate.

The groups of inventions listed above 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:

Group I+ requires a special technical feature of a composition comprising a cytokine-ligand conjugate, not required by Groups II and III.

Group II requires a special technical feature of a nucleic acid molecule comprising SEQ ID NO: 1, not required by Groups I+ and III.

Group III requires a special technical feature of a methods of treating a disorder, not required by Groups I+ and II.

The technical feature of each of the inventions listed as Group I+ is the specific cytokine-ligand conjugate recited therein. Significant functional and/or structural similarities cannot readily be ascertained among the cytokine-ligand combinations. Each invention requires an unique cytokine-ligand conjugate, not required by any of the other inventions..

The inventions of Group I+, II, III shared the common technical feature of a cytokine-ligand conjugate, wherein the ligand is not a corresponding binding partner to the cytokine. The inventions of Group I+ share the technical features of a IL-2 cytokine linked to a ligand, wherein the ligand is not a corresponding binding partner to the cytokine, wherein the cytokine and ligand comprise a linker, wherein the ligand is a MHC class-I-related glycoprotein binds to a NKG2D receptor on a NK or CD8+ cell (see instant claims 1, 38, 57, and 77).

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is made obvious by US 2009/0098609 A1 to GILLIES et al. (hereinafter 'Gillies') in view of the article entitled "ULBPs, Novel MHC Class I-Related Molecules, Bind to CMV Glycoprotein UL16 and Stimulate NK Cytotoxicity through the NKG2D Receptor" by Cosman et al. (hereinafter 'Cosman'). Gillies teaches a IL-2 fusion protein (para [0026] "fusion proteins including an IL-2 moiety fused to a non-IL-2 moiety. According to the invention, a non-IL-2 moiety can be a synthetic or a natural protein ... non-IL-2 moieties include Fc and albumin moieties.", para [0112] "the components (immunoglobulin molecule and IL-2 molecule) are genetically fused to each other ... through a linker sequence.", para [0042] "the Fc receptor on a cell surface may bind to the Fc part of an Ig moiety and thus tether the IL-2 to the surface of cells possessing both an Fc receptor and an IL-2 receptor", para [0003] "Interleukin-2 (IL-2) is a potent cytokine ... IL-2 has also been shown to stimulate ... NK cells", para [0035] "IL-2 is known to activate T cells and, for example, is known to enhance the cytotoxicity of CD8(+) T cells"). Gillies does not teach IL-2 fusion proteins wherein the ligand is a MHC class-I-related glycoprotein that binds to a NKG2D receptor. Cosman teaches fusion proteins comprising MHC I proteins that bind to said NKG2D receptors (pg 123, col 2, para 2-3 "it was recently shown that the nonclassical MHC class I antigens, MICA and MICB, could engage ... a heterodimeric complex of NKG2D, a C-type lectin, and DAP10 ... ULBPs and the MICs share the property of binding to the NKG2D/DAP10 receptor and provide a positive signal for NK cell activation and cytotoxicity", abstract "ULBPs are GPI-linked glycoproteins belonging to the extended MHC class I family", pg 125, col 1, para 2 "a series of fusion proteins was constructed in which the extracellular domains of the ULBPs and MICs were joined to the Fc region of human IgG1.", pg 127, col 2 para 1 - pg 128, col 1 para 1 "All the ULBP and MIC-Fc fusion proteins bound specifically to cells transfected with both NKG2D and DAP10, compared to background binding seen with a control Fc fusion protein. This result suggests that at least a component of the ULBP and MIC receptors detected on NK cells is probably NKG2D/DAP10, as this receptor is known to be expressed by all NK cells"). Based on the teaching of Gillies and Cosman, it would have been obvious to an artisan of ordinary skill to experiment with Cosman's MHC I glycoproteins (e.g. ULBPs), as non-IL-2 moieties for Gillies' fusion proteins, because as taught by Cosman, ULBP-Fc fusion proteins bind NKG2D/DAP10 receptors, and said binding provides a positive signal for NK cell activation and cytotoxicity, which could have a synergistic effect with IL-2 fusion proteins, as taught by Gillies to be a potent activator of NK/CD8+ cells, which may be enhanced by tethering by the non-IL-2 moiety, such as a ULBP bound to NKG2D. As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions.

Groups I+, II, and III therefore lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

Item 4, continued:

claims 74-76 are not not drafted in accordance with the second and third sentences of Rule 6.4(a) regarding multiply dependent claims.