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21 February 2013

(54) Title: LEUKOTOXIN E/D AS A NEW ANTI-INFLAMMATORY AGENT AND MICROBICIDE

(57) Abstract: The present invention relates to methods for preventing or treating Human Immunodeficiency Virus (HIV) infection, inflammatory conditions, and graft-versus-host- disease (GVHD) in a subject. Therapeutic compositions of the present invention comprise Leukocidin E (LukE) and/or D proteins or polypeptides. The invention further relates to methods of treating *Staphylococcus aureus* infection by administering a composition comprising a CCR5 antagonist or any molecule that blocks LukE/D interaction with CCR5⁺ cells in an amount effective to treat the *S. aureus* infection in the subject.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/43182

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61P 31/18; A61P 29/00; A61P 31/04; A61K 38/00 (2012.01)
 USPC - 514/3.8; 514/12.2; 514/18.7; 514/2.7
 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 31/18; A61P 29/00; A61P 31/04; A61K 38/00 (2012.01)
 USPC: 514/3.8; 514/12.2; 514/18.7; 514/2.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC: 514/4.1
 (Text Search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST (PGPB, USPT, USOC, EPAB, JPAB); PatBase, Google Scholar and Web of Knowledge.
 Search Terms: leukocidin, HIV, inflammatory, graft, host, graft-versus-host-disease, zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, adefovir, dipivoxil, lobucavir, emicitabine, DAPD, lodenosine, nevirapine, delaviridine, staphylococcal,

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 2008/0131457 A1 (TAYLOR et al.) 05 June 2008 (05.06.2008) para [0007], [0008], [0009], [0013], [0049], [0158], [0178]-[0179], [0257].	24 and 27-30 ----- 1-8 and 25-26 and 31-33
Y	US 2005/0287167 A1 (ZUR MEGEDE et al.) 29 December 2005 (29.12.2005), para [0011], [0014], [0015], [0084], [0098], [0135], [0254], [0255], [0261]	1-8
Y	VYAS, K. et al. Recurrent Community Acquired Methicillin-Resistant Staphylococcus aureus Infections in an HIV-Infected Person. J. Clin. Microbiol. 09 March 2011, Vol 49(5), pages 2047-2053: abstract; pg 2051, col 1, para 2 to col 2, para 1	1-8
Y	KURODA, M. et al. Uniprot Direct Submission Accession Q99T53 [online]. 30 November 2010 [retrieved on 29 November 2012], retrieved from the Internet: <URL: http://www.uniprot.org/uniprot/Q99T53.txt?version=44>, page 1	2-3, 25 and 32
Y	KURODA, M. et al. Uniprot Direct Submission Accession Q99T54 [online]. 39 November 2010 [retrieved on 29 November 2012], retrieved from the Internet: <URL: http://www.uniprot.org/uniprot/Q99T54.txt?version=41>, page 1	4-5, 26 and 33
Y	TUMANG, J.R. et al. T helper cell-dependent, microbial superantigen-induced murine B cell activation: polyclonal and antigen-specific antibody responses. The Journal of Immunology. 15 July 1991, Vol 147(2), pages 432-438: abstract	31-33
A	LIN, Y.-C. et al. New insights into the prevention of staphylococcal infections and toxic shock syndrome. Expert Rev. Clin. Pharmacol. 2010, Vol 3(6), pages 753-767: abstract; pg 755, col 2, para 2	24-33

Further documents are listed in the continuation of Box C.

* 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 application or patent 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 29 November 2012 (29.11.2012)	Date of mailing of the international search report 13 DEC 2012
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/43182

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ASHORN, P. et al. Elimination of infectious human immunodeficiency virus from human T-cell cultures by synergistic action of CD4-Pseudomonas exotoxin and reverse transcriptase inhibitors. Proc Nat. Acad. Sci. November 1990, Vol 87, pages 8889-8893: abstract	1-8
A	CHAVAKIS, T. et al. The anti-inflammatory activities of Staphylococcus aureus. Trends in Immunology. 02 August 2007, Volume 28(9), Pages 408-418, entire document.	24-33

INTERNATIONAL SEARCH REPORT

International application No.
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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:
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 1-8 and 24-33, drawn to a method of preventing or treating Human Immunodeficiency Virus (HIV) infection in a subject comprising: administering a composition comprising an isolated Leukocidin E (LukE) protein, or polypeptide thereof, and an isolated Leukocidin D (LukD) protein, or polypeptide thereof, in an amount effective to prevent or treat HIV infection in the subject; AND a method of treating an inflammatory condition in a subject comprising: administering a composition comprising an isolated LukE protein or polypeptide thereof, and an isolated LukD protein, or polypeptide thereof, in an amount effective to treat an inflammatory condition in the subject; AND a method of preventing graft-versus-host-disease (GVHD) in a subject comprising: administering a composition comprising an isolated Leukocidin E (LukE) protein, or polypeptide thereof, and an isolated Leukocidin D (LukD) protein, or polypeptide thereof, in an amount effective to prevent graft-versus-host-disease (GVHD).

----- Please see attached additional sheet for continuation -----

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.:
1-8 and 24-33

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.

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Continuation of Box (III): Lack of Unity

Group II: Claims 9-23, drawn to a composition comprising: a therapeutically effective amount of an isolated LukE protein or polypeptide thereof, an isolated LukD protein or polypeptide thereof, or a combination thereof; and one or more additional agents selected from the group consisting of a lubricant, an antimicrobial agent, a humectant, an emulsifier, and a mixture of two or more thereof.

Group III: Claims 34-38, drawn to a method of treating Staphylococcus aureus infection in a subject comprising: selecting a subject having an S. aureus infection and administering a composition comprising a CCR5 antagonist in an amount effective to treat the S. aureus infection in the subject.

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:

Groups I-II do not include the inventive concept of selecting a subject having an S. aureus infection and administering a composition comprising a CCR5 antagonist in an amount effective to treat the S. aureus infection in the subject, as required by Group III.

Groups I and III do not include the inventive concept of a composition comprising one or more additional agents selected from the group consisting of a lubricant, an antimicrobial agent, a humectant, an emulsifier, and a mixture of two or more thereof, as required by Group II.

Groups II-III do not include the inventive concept of a method comprising administering a composition comprising an isolated Leukocidin E (LukE) protein, or polypeptide thereof, and an isolated Leukocidin D (LukD) protein, or polypeptide thereof, in an amount effective to prevent or treat a disease.

Groups I-III share the technical feature of a composition comprising a therapeutically effective amount of a therapeutic agent.

Groups I-II share the technical feature of a composition comprising: a therapeutically effective amount of an isolated LukE protein or polypeptide thereof, an isolated LukD protein or polypeptide thereof, OR a combination thereof.

Groups I and III share the technical feature of a method of treating an infection in a subject comprising: administering a composition comprising a therapeutic agent in an amount effective to treat said infection in the subject.

However, these shared technical features does not represent a contribution over the prior art, specifically, US 2008/0131457 A1 to Taylor et al. (hereinafter 'Taylor') teaches a method of preventing or treating infection in a subject comprising: administering a composition comprising (a therapeutically effective amount of) an isolated Leukocidin E (LukE), and/or an isolated Leukocidin D (LukD) protein, in an amount effective to prevent or treat infection in the subject (para [0008]-'provided a pentavalent Staphylococcal antigen composition comprising (i) an S. aureus Type 5 antigen... and (v) a Staphylococcal leukocidin antigen', [0009]-'In one embodiment, the Staphylococcal leukocidin antigen is selected from the group consisting of (i) a LukF-PV subunit of S. aureus PVL... (vi) LukD from S. aureus, (vii) LukE from S. aureus', [0013]-'a method for treating or preventing S. aureus infection comprising administering to a subject in need thereof any of the aforementioned antigen compositions', [0257]-'The compositions will comprise a "therapeutically effective amount" of the gene of interest such that an amount of the antigen can be produced in vivo so that an immune response is generated in the individual to which it is administered', [0049]-'Other antigens useful in accordance with the present invention include leukocidins. The class of leukocidins (also referred to as e.g. bicomponent leukotoxins) includes but is not limited to...LukE from S. aureus... LukD from S. aureus, and LukF-I (from S. intermedius). The present invention encompasses the use of any species of the leukocidin genus, including one or more of the S and F components described herein').

As said shared technical features were known at the time of the invention, these cannot be considered special technical feature that would otherwise unify the groups.

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.