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WO 2004/040262 A3

(54) Title: COMPOSITIONS AND METHODS FOR MODIFYING TOXIC EFFECTS OF PROTEINACEOUS COMPOUNDS

(57) Abstract: The present invention provides methods to produce immunotoxins (ITs) and cytokines with a reduced ability to promote vascular leak syndrome (VLS). The invention also provides ITs and cytokines which have been mutated to lack amino acid sequences which induce VLS.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/34425

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(7) : A61K 38/00;
 US CL : 530/350, 300, 391.7, 370, 396, 403; 514/2, 12; 435/69.1, 252.3, 320.1, 183.1; 536/23.1
 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)
 U.S. : 530/350, 300, 391.7, 370, 396, 403; 514/2, 12; 435/69.1, 252.3, 320.1, 183.1; 536/23.1

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)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- X	SMALLSHAW, J.E. et al., A Novel Recombinant Vaccine Which Protects Mice Against Ricin Intoxication, Vaccine. September 2002, pages 3422-3427, see pages 3422-3424.	1-3, 5-9, 15-18, 20-25, 27, 28, 34-38, 41, 48-50, 52 and 53
X --- X	HUR, Y. et al., Isolation and Characterization of Pokeweed Antiviral Protein Mutations in Saccharomyces cerevisiae: Identification of Residues Important for Toxicity, Proc. Natl. Acad. Sci. USA August 1995, Vol. 92, pages 8448-8452, see pages 8448 and 8450-8451, Table 1.	16, 18, 19 and 21-23
X --- X	SHEN, W.H. et al., Participation of Lysine 516 and Phenylalanine 530 of Diphtheria Toxin in Receptor Recognition. J. Biol. Chem. November 1994, Vol. 269, No. 46, pages 29077-29084, see pages 29080-29083.	16 and 19-23
X	WO00/58456 A2 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 05 October 2000 (05.10.00), whole document.	1-67

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	"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
"B" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"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 27 April 2004 (27.04.2004)	Date of mailing of the international search report 22 JUN 2004
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. (703)305-3230	Authorized Officer Chih-Min Kam Telephone No. (703) 308-0196 <i>Janice Ford</i> <i>JF</i>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/34425

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim 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. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation 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 fee, this Authority did not invite payment of any additional fee.
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.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

The inventions listed as Groups I-II 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 feature of Group I is the specific modified proteinaceous composition comprising a toxin having a (x)D(y) sequence and at least one amino acid mutation that alters the ability of a (x)D(y) sequence to induce Vascular Leak syndrome and the specific method of reducing the ability of a proteinaceous composition to reduce induction of VLS, or the specific method of preparing an immunotoxin with a reduced ability to induce VLS claimed therein. In contrast, the special technical feature of Group II are the particular modified proteinaceous composition comprising a cytokine having a (x)D(y) sequence and at least one amino acid mutation that alters the ability of a (x)D(y) sequence to induce Vascular Leak syndrome and the particular method of reducing the ability of a proteinaceous composition to reduce induction of VLS claimed therein; and the special technical feature of Group III are the particular modified proteinaceous composition comprising a viral protein having a (x)D(y) sequence and at least one amino acid mutation that alters the ability of a (x)D(y) sequence to induce Vascular Leak syndrome and the particular method of reducing the ability of a proteinaceous composition to reduce induction of VLS claimed therein. Since the special technical feature of Group I is not present in the claims of Groups II and III, and the special technical features of Groups II-III are not present in the claims of Group I. Thus, unity of invention is lacking.

Group I, Claims 1-67, drawn to a modified proteinaceous composition comprising a protein having a (x)D(y) sequence and at least one amino acid mutation that alters the ability of a (x)D(y) sequence to induce Vascular Leak syndrome; a method of reducing the ability of a proteinaceous composition to reduce induction of VLS, or a method of preparing an immunotoxin with a reduced ability to induce VLS, by identifying a protein or a toxin comprising at least one amino acid sequence of (x)D(y) sequence, altering at least one amino acid residue flanking the (x)D(y) sequence, optionally conjugating the toxin to an antibody to produce an immunotoxin, wherein the protein is a toxin.

Group II, Claims 1-6, 15-21, 34 and 49-52, drawn to a modified proteinaceous composition comprising a protein having a (x)D(y) sequence and at least one amino acid mutation that alters the ability of a (x)D(y) sequence to induce Vascular Leak syndrome; a method of reducing the ability of a proteinaceous composition to reduce induction of VLS, wherein the protein is a cytokine.

Group III, Claims 1-6, 15-21, 34 and 49-52, drawn to a modified proteinaceous composition comprising a protein having a (x)D(y) sequence and at least one amino acid mutation that alters the ability of a (x)D(y) sequence to induce Vascular Leak syndrome; a method of reducing the ability of a proteinaceous composition to reduce induction of VLS, wherein the protein is a viral protein.

Continuation of B. FIELDS SEARCHED Item 3:

EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN Search on MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA; Search term used: toxin, cytokine, viralprotein, ricin A chain, abrin A chain, diptheria toxin a chain, pseudomonas exotoxin, shiga toxin a chain, gelonin or momordin or pokeweed antiviral protein, saporin, trichosanthin, barley toxin modif? muta? vascular leak, aphasia, myalgia, fatigue, hypotension, rhabdomyolysis,(x)D(y), r48, arg48, n97, asn97, alter? immunotoxin, reduc?toxicity, point mutation