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- (88) Date of publication of the international search report: 1 September 2005
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/020405 A3

(54) Title: MODIFIED TRANSFERRIN FUSION PROTEINS

(57) Abstract: Modified fusion proteins of transferrin and therapeutic proteins or peptides including soluble toxin receptors, with increased serum half-life or serum stability are disclosed. Preferred fusion proteins include those modified so that the transferrin moiety exhibits no or reduced glycosylation, binding to iron and/or binding to the transferrin receptor.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/26818

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 38/40, 38/41, 38/16; C07K 14/79 US CL : 530/394, 387.3, 350; 514/2, 8; 435/440, 69.7 According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 530/394, 387.3, 350; 514/2, 8; 435/440, 69.7</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>WARD, P. P. et al. system for production of commercial quantities of human lactoferrin: a broad spectrum natural antibiotic. Biotechnology (N Y). May 1995, Vol. 13, pages 498-503. The entire document.</td> <td>1, 8-10, 12-13, 18, 22, 26, 28, 46-47, 50 and 87</td> </tr> <tr> <td>X</td> <td>SALMON, V. et al. Production of human lactoferrin in transgenic tobacco plants. Protein Expr Purif. June 1998, Vol. 13, pages 127-135. The entire document.</td> <td>1, 8-10, 15-16, 18, 22, 26, 28, 46-47, 50 and 87</td> </tr> <tr> <td>X</td> <td>US 5,817,789 A (HEARTLEIN et al.) 06 October 1998, abstract, Examples 5 and 7-14, claims 1 and 10, and especially, Table 2 and columns 33-34.</td> <td>1, 15-16, 18, 28, 46-47, 50 and 87</td> </tr> <tr> <td>X</td> <td>US 6,262,026 B1 (HEARTLEIN et al.) 17 July 2001, abstract, Examples 5 and 7-14, and Table 2 and columns 33-34.</td> <td>1, 15-16, 18, 28, 46-47, 50 and 87</td> </tr> <tr> <td>X</td> <td>US 6,027,921 A (HEARTLEIN, M. W. et al.) 22 February 2000, claims 1-25, Examples 5 and 7-14, and Table 2 and columns 33-34.</td> <td>1, 15-16, 18, 28, 46-47, 50 and 87</td> </tr> <tr> <td>Y</td> <td>US 5,986,067A (FUNK et al.) 16 November 1999, abstract, columns 1-6 and 13-18, and claims 1-23.</td> <td>1-3, 5-10, 12-14, 18-23, 26-29, 46-50 and 75-77</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WARD, P. P. et al. system for production of commercial quantities of human lactoferrin: a broad spectrum natural antibiotic. Biotechnology (N Y). May 1995, Vol. 13, pages 498-503. The entire document.	1, 8-10, 12-13, 18, 22, 26, 28, 46-47, 50 and 87	X	SALMON, V. et al. Production of human lactoferrin in transgenic tobacco plants. Protein Expr Purif. June 1998, Vol. 13, pages 127-135. The entire document.	1, 8-10, 15-16, 18, 22, 26, 28, 46-47, 50 and 87	X	US 5,817,789 A (HEARTLEIN et al.) 06 October 1998, abstract, Examples 5 and 7-14, claims 1 and 10, and especially, Table 2 and columns 33-34.	1, 15-16, 18, 28, 46-47, 50 and 87	X	US 6,262,026 B1 (HEARTLEIN et al.) 17 July 2001, abstract, Examples 5 and 7-14, and Table 2 and columns 33-34.	1, 15-16, 18, 28, 46-47, 50 and 87	X	US 6,027,921 A (HEARTLEIN, M. W. et al.) 22 February 2000, claims 1-25, Examples 5 and 7-14, and Table 2 and columns 33-34.	1, 15-16, 18, 28, 46-47, 50 and 87	Y	US 5,986,067A (FUNK et al.) 16 November 1999, abstract, columns 1-6 and 13-18, and claims 1-23.	1-3, 5-10, 12-14, 18-23, 26-29, 46-50 and 75-77
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<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>																							
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"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</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"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	"E" 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												
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"P" document published prior to the international filing date but later than the priority date claimed																							
<p>Date of the actual completion of the international search 13 May 2005 (13.05.2005)</p>		<p>Date of mailing of the international search report 14 JUL 2005</p>																					
<p>Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner of Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230</p>		<p>Authorized officer Samuel W. Liu Telephone No. 571-272-1600</p>																					

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/26818

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.: 1-29,46-50,69-73 and 75-87
- Remark on Protest The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ADRIAN, G. S. et al. Human transferrin: Expression and iron modulation of chimeric genes in transgenic mice. J. Biol. Chem. 05 August 1990, Vol. 265, pages 13344-13350. The entire document.	1, 7-8, 10, 14-17, 26-28, 46-47 and 87

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claims 1-29, 46-50, 69-73 and 75-87, drawn to a fusion protein comprising a modified transferrin (Tf) protein and pharmaceutical composition comprising the fusion protein.

Group 2, claims 30-39, drawn to a polynucleotide encoding the fusion protein, a vector comprising the polynucleotide, and a host comprising the vector, and a method of expressing a Tf protein in the host cell.

Group 3, claims 40-44, drawn to a transgenic animal comprising the polynucleotide and a method of producing THE Tf protein in the transgenic animal thereof.

Group 4, claims 45, 51-68 and 88-89, drawn to a method of treating a disease state comprising administering to a subject the fusion protein.

Group 5, claim 74, drawn to a method of regulating glucose level in a subject comprising administering to said subject a fusion protein comprising the modified Tf protein which is fused to a GLP-1 or analog thereof.

This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups 1-5 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. (1) Ward, P. P. et al. (*Bio/Technology* (1995) 13, 498-503) teach a biologically active fusion protein comprising a Tf protein, i.e., lactoferrin and N-terminal portion of a glucoamylase in *Aspergillus awamori* transformant cell; the said fusion protein has reduced glycosylation (see especially Figure 1). The Ward's teachings anticipate the instant claim 1. Thus, the special technical feature(s) recited in the instant claims do not define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. (2) The compositions represented in Groups 1, 2 and 3 are structurally and functionally distinct from one another, i.e., Group 1 is directed to a protein, Group 2 or polynucleotide whereas Group 3 to a transgenic animal.

Therefore, Groups 1-5 are not so linked by the same or corresponding special technical features within meaning of PCT Rule 13.2, i.e., the current application lacks a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

Databases: Medline, US Pre-Grant publication Full-Text database, US Patent Full-Text database, EPO Abstracts database, IPO Abstracts database, Derwent World Patent Index, and, issued patents AA, pending patents AA and Genebank (for sequence search).
Search terms: transferrin/lactoferrin, chimeric/fusion protein, glycosylation.