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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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7 December 2006

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.

(54) Title: MODIFIED TRANSFERRIN FUSION PROTEINS

(57) Abstract: Modified fusion proteins of a transferrin moiety, a GLP-1 moiety and a linker moiety, with increased productivity, bioactivity and serum half-life are disclosed. Preferred fusion proteins include those modified so that the transferrin moiety exhibits no or reduced glycosylation. The fusion proteins of the invention are useful for the treatment of Type 2 diabetes, Type 1 diabetes, obesity, congestive heart failure, and non-fatty liver disease.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/07617

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61K 38/26**(2006.01),**38/40**(2006.01);**C12N 15/16**(2006.01),**15/17**(2006.01),**15/18**(2006.01);**C07K 14/76**(2006.01)
C07K 5/00(2006.01)

USPC: 530/394,402,350;435/69.7,440;424/192.1

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. : 530/394,402,350;435/69.7,440;424/192.1

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.
A	XIAO, Q. Biological activities of glucagon-like peptide-1 analogues in vitro and in vivo. Biochemistry. March 2001, Vol. 40, No.9, pages 2860-286, entire document.	1-31, 44 and 59
A	ALI, S.A. Transferrin trojan horses as a rational approach for the biological delivery of therapeutic peptide domains. J. Biol. Chem. 20 August 1999, Vol. 274, No. 34, pages 24066-24073. Figure 1, abstract and pages 24070-14072.	1-31, 44 and 59
A	XIA C.Q.Hypoglycemic effect of insulin-transferrin conjugate in streptozotocin-induced diabetic rats. J Pharmacol Exp Ther. 2000, Vol. 295, No. 2, pages 594-600, entire document.	1-31, 44 and 59
A	US 6069193 A (VARGAS et al.) 30 May 2000 (30.05.2000), claims 1-5.	1-31, 44 and 59
A	US 6458924 B2 ((KUNDSEN et al.) 01 October 2002 (01.10.2002), entire disclosure, especially column 4.	1-31, 44 and 59

☒ 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 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	Date of mailing of the international search report
24 July 2006 (24.07.2006)	20 SEP 2006
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 Samuel W. Liu Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/07617

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:
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 additional fees, this Authority did not invite payment of any 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.: 1-31,44 and 59

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/US06/07617

BOX 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 1, claims 1-31, 44 and 59, drawn to a fusion protein comprising GLP-1 ppeptide and a modified transferrin (mTf) polypeptide.

Group 2, claims 32-41 and 43, drawn to a polypnucleotide encoduing the fusiom protein, a vector compriisng the polynucleotide, a host compriisng the vector thereof, and a method of producing the fusion protein compriisng culturing the host cell under the condicitn of expressing the fusion protein.

Group 3, claim 42, drawn to a non-human transgenic animal.

Group 4, claims 45-50 and 54, drawn to a method of treating a condition associated with diabetes characterize by elevated levels of glucose in a subject comprising administering to said subject the fusion protein.

Group 5, claim 51, drawn to a method of decreasing food intake in a animal comprising administering to said animal the fusion protein.

Group 6, claims 52 and 55-56, drawn to a method of inducing beta cell proliferation in a subject comprising administering to said subject the fusion protein.

Group 7, claim 53, drawn to a method of inducing insulin secretion in a patient comprising administering to said patient the fusion protein.

Group 8, claim 57, drawn to a method of treating congestive heart failure in a patient comprising administering to said patient the fusion protein.

Group 9, claim 58, drawn to a method of treating non-fatty liver disease in a patient comprising administering to said patient the fusion protein.

The inventions listed as Groups 1-9 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. Group 1 invention is directed to polyppeptide whereas the Group 2 invention is directed to polnucleotide wherein polypeptide and polynucleotide are structural distinct from each other and would be expected to exhibit different physical and chemical properties, and are capable of separate manufacture or use. Furthermore, the Group 3 non-human transgenic animal is multicellular organism which structure and function are distinct from those of the biopolymers, e.g., the polypeptide and the polynucleotide; the processes of Groups 4-9 do not require use of the transgenic animal thereof. In addition, the methods of Groups 4-9 differ in starting material, ingredients, methodologies, and/or outcome of the treatment. Therefore, Groups 1-9 are not so linked by the same or corresponding special technical features within neaning 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, JPO Abstracts database, Derwent World Patent Index, and, issued patents AA, and pending patents AA.
Search terms: glucagon like peptide - or GLP-1; fusion, chimeria, or; conjugate; transferrin, lactoferin, melanotransferrin.