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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.

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(54) Title: CELLS TRANSFECTED WITH A NUCLEOTIDE SEQUENCE ENCODING GLP-1 AND SECRETING INSULIN IN A GLUCOSE-DEPENDENT MANNER

(57) Abstract: Disclosed herein are cells that secrete insulin in a glucose-dependent manner. The cell line comprises insulin-secreting cells that have been transfected with a minigene construct comprising a nucleotide sequence encoding for glucagon-like peptide-1 (GLP-1). In preferred embodiments, the minigene construct is operatively associated with a promoter. The cell line may be used to treat diabetes or other conditions in which delivering insulin in a glucose-dependent manner would be advantageous, to investigate the function and development of pancreatic cells, and to test the efficacy of drugs that stimulate insulin secretion. The cells may be implanted in a mammal, or may be included in a device that resides exterior to the mammal, yet which delivers insulin to the mammal in response to the glucose level of a body fluid in contact therewith. The minigene construct may also be implemented in conjunction with an *in vivo* gene transfer approach.

INTERNATIONAL SEARCH REPORT

Intern[illegible] [illegible]pplication No
PCT/[illegible] 03/07210

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/605 A61K38/26

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 7 C07K

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 practical, search terms used)
BIOSIS, EPO-Internal, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HUI HONGXIANG ET AL: "Transfection of pancreatic-derived beta-cells with a minigene encoding for human glucagon-like peptide-1 regulates glucose-dependent insulin synthesis and secretion." ENDOCRINOLOGY, vol. 143, no. 9, September 2002 (2002-09), pages 3529-3539, XP002255079 September, 2002 ISSN: 0013-7227 abstract page 3532, right-hand column, paragraph 3 -page 3538, left-hand column, paragraph 4 --- -/--	1-46

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document 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

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"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 September 2003	22.12.03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Weiland, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PERFETTI R ET AL: "Gene therapy of pancreatic-derived beta-cells with GLP-1 restores glucose-dependent insulin production." DIABETOLOGIA, vol. 44, no. Supplement 1, August 2001 (2001-08), page A 121 XP009017662 37th Annual Meeting of the European Association for the Study of Diabetes;Glasgow, Scotland, UK; September 09-13, 2001 ISSN: 0012-186X the whole document	1-46
X	PERFETTI RICCARDO ET AL: "Transfection with GLP-1 to produce glucose-dependent insulin-secreting cells." CELL TRANSPLANTATION, vol. 10, no. 6, 2001, pages 515-516, XP009017701 10th Anniversary Congress of the Cell Transplant Society;Keystone, Colorado, USA; October 14-17, 2001 ISSN: 0963-6897 the whole document	1-46
X	WO 01 39784 A (ZULEWSKI HENDRIK ;VALLEJO MARIO (ES); ABRAHAM ELIZABETH J (US); GE) 7 June 2001 (2001-06-07) page 6, line 6 - line 13; claim 47; figure 10; example 7	1-46
A	HUI H ET AL: "Glucagon-like peptide 1 induces differentiation of islet duodenal homeobox-1-positive pancreatic ductal cells into insulin-secreting cells" DIABETES, NEW YORK, NY, US, vol. 50, no. 4, April 2001 (2001-04), pages 785-796, XP002226311 ISSN: 0012-1797 cited in the application abstract	1-46

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEPURNY OLEG G ET AL: "Over-expression of the glucagon-like peptide-1 receptor on INS-1 cells confers autocrine stimulation of insulin gene promoter activity: A strategy for production of pancreatic beta-cell lines for use in transplantation." CELL & TISSUE RESEARCH, vol. 307, no. 2, February 2002 (2002-02), pages 191-201, XP002255080 ISSN: 0302-766X abstract page 191, right-hand column, paragraph 2 -page 192, left-hand column, paragraph 3 page 200, left-hand column, paragraph 2 ---	1-46
A	ORSKOV C ET AL: "COMPLETE SEQUENCES OF GLUCAGON-LIKE PEPTIDE-1 FROM HUMAN AND PIG SMALL INTESTINE" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 264, no. 22, 5 August 1989 (1989-08-05), pages 12826-12829, XP000036795 ISSN: 0021-9258 abstract; figure 1; table 2 page 12828, right-hand column, paragraph 3 -page 12829, left-hand column, paragraph 4	1-46
A	-& DATABASE SWISSPROT 'Online! EBI; 1 November 1990 (1990-11-01) Database accession no. P01274 XP002255213 the whole document -----	1-46

INTERNATIONAL SEARCH REPORT

Int ional application No.
'CT/US 03/07210

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 34-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 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:

see additional 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. [X] 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, 6-11, 15-22, 27-34, 39-46 (in part) and 2-5, 12-14, 23-26, 35-38 (complete)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1-3: 1, 6-11, 15-22, 27-34,
39-46 (in part) and 2-5, 12-14, 23-26,
35-38 (complete)

Insulin-secreting cells transfected with a nucleotide sequence, e.g. according to SEQ ID NO:6, encoding glucagon-like peptide-1 (GLP-1) according to SEQ ID NO:2 or cells transfected with a nucleotide sequence encoding the precursor protein of GLP-1 (SEQ ID NO:1) or the inactive form thereof (SEQ ID NO:3) ; method for producing said cells; method for testing a drug by means of said cells and a method for supplying insulin to a subject by means of said cells.

Invention 4: 1, 6-11, 15-22, 27-34,
39-46 (all in part)

Insulin-secreting cells transfected with a nucleotide sequence encoding exendin-4 according to SEQ ID NO:4 (an agonist of the GLP-1 receptor); method for producing said cells; method for testing a drug by means of said cells and a method for supplying insulin to a subject by means of said cells.

Invention 5: 1, 6-11, 15-22, 27-34,
39-46 (all in part)

Insulin-secreting cells transfected with a nucleotide sequence encoding exendin-9 according to SEQ ID NO:5 (an antagonist of the GLP-1 receptor); method for producing said cells; method for testing a drug by means of said cells and a method for supplying insulin to a subject by means of said cells.

INTERNATIONAL SEARCH REPORT

ıation on patent family members

Interna Application No
PCT/[redacted] 03/07210

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WO 0139784 A	07-06-2001	AU 1817301 A	12-06-2001
		CA 2392615 A1	07-06-2001
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