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61/184,475 5 June 2009 (05.06.2009) US(71) Applicant (for all designated States except US): **THE GENERAL HOSPITAL CORPORATION** [US/US]; 55 Fruit Street, Boston, Massachusetts 02114 (US).

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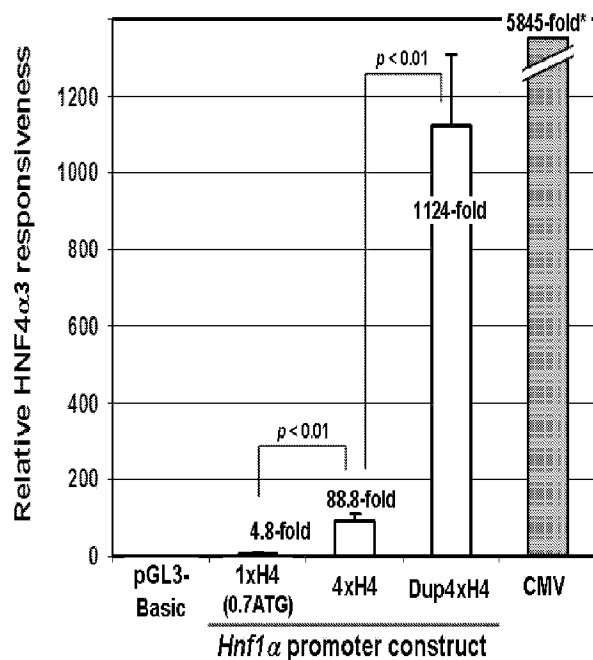
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[Continued on next page]

(54) Title: ENHANCED ENGINEERED NATIVE PROMOTERS AND USES THEREOF



(57) Abstract: We describe methods and DNA constructs / engineered mammalian promoters to enhance native promoter activity while retaining inherent regulation by inserting multi-copy response elements (REs) into non-adjacent locations. Multiple copies of REs are clustered in a group forming a transcription factor response element segment. The segment is at least duplicated in tandem upstream of the ATG start codon. Spacers of 0.2-0.7 kilo base pairs are introduced between the two segments and smaller spacers of about between 9-15 bp are introduced between the copies of REs within a segment.

**Published:****(88) Date of publication of the international search report:**

21 April 2011

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

A. CLASSIFICATION OF SUBJECT MATTER*C12N 15/67(2006.01)i, C12N 15/85(2006.01)i*

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)

C12N 15/67; C07K 14/39; C12N 15/74; C12N 15/00

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)

eKOMPASS(KIPO internal) & Keywords: transcription factor response element (TFRE), response element (RE), transcription factor, enhanced promoter.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006-0089492 A1 (SUCKOW, M.) 27 April 2006 See abstract and claim 1.	1-3,28-30
A	US 7267978 B1 (CAREY, M. F. et al.) 11 September 2007 See abstract.	1-3,28-30
A	SANDER, M. et al. A novel glucose-responsive element in the human insulin gene functions uniquely in primary cultured islets. PNAS, 1998, vol. 95, pages 11572-11577. See abstract.	1-3,28-30
A	GERMAN, M. S. et al. The insulin and islet amyloid polypeptide genes contain similar cell-specific promoter elements that bind identical β -cell nuclear complexes. Molecular and Cellular Biology, 1992, vol. 12, no. 4, pages 1777-1788. See abstract.	1-3,28-30



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 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 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

11 FEBRUARY 2011 (11.02.2011)

Date of mailing of the international search report

11 FEBRUARY 2011 (11.02.2011)

Name and mailing address of the ISA/KR

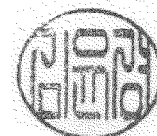
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2010/037551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006-0089492 A1	27.04.2006	AU 2003-240610 A1	11.11.2003
		CA 2485119-A1	20.11.2003
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US 7267978 B1	11.09.2007	AU 2001-12038 A1	23.04.2001
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		WO 01-27256 A3	13.09.2001
		WO 01-27256 A3	19.04.2001
		WO 01-27256 A9	04.10.2001

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/037551

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.: 9,11,12,14-19,22,24,25,34-36
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:
Claims 9,11,12,14-19,22,24,25,34-36 are referring to the multiple dependent claims.

3. ☒ Claims Nos.: 4-8,10,13,20,21,23,26,27,31-33
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:

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 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.