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Declarations under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

Published:

— 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))

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

22 June 2017

(54) Title: CHIMERIC POST-TRANSCRIPTIONAL REGULATORY ELEMENT

(57) Abstract: The present disclosure relates to chimeric post-transcriptional regulatory elements (PRE) and vectors useful for expressing a protein in a cell. The PRE contains alpha, beta and optionally gamma subelements selected from different native PRE sequences and are discovered to be more potent than their native counterparts.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/59151

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 15/36, 15/86, 15/85; C07K 14/02; C12Q 1/68 (2017.01)

CPC - C12N 2830/00, 2830/48, 2730/10043, 15/85, 15/86, C12Q 1/6897

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---------------|---|--|
| Y --- A | US 6,287,814 B1 (Hope et al.) 11 September 2001 (11.09.2001). Especially col 4 ln 8-9, sheet 1 fig 1B, sheet 2 fig 1C, sheet 11 fig 8A, SEQ ID NO: 1 | 12, 13, 15/(12,13), 20, 22/20 ----- 1-5, (7,8)/(3-5), 9, 10, 19, 22/19 |
| Y --- A | US 2015/0291975 A1 (DNA2.0 Inc.) 15 October 2015 (15.10.2015). Especially SEQ ID NO: 104 | 12, 13, 15/(12,13), 20, 22/20 ----- 1-5, (7,8)/(3-5), 9, 10, 19, 22/19 |
| A | GenBank Accession K02715.1 Ground squirrel hepatitis virus (GSHV), complete genome [online] 10 February 1994 [retrieved 24 January 2017]. Available on the internet: <https://www.ncbi.nlm.nih.gov/nucore/K02715>. Especially pg 2. | 1-5, (7,8)/(3-5), 9, 10, 19, 22/19 |

☐ Further documents are listed in the continuation of Box C.

* 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 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

28 March 2017

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/59151

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. ☐ forming part of the international application as filed:

☐ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.4.1 SEQ ID NOs: 3, 7, 14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/59151

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.: 18, 23-26
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:
-----Go to Extra Sheet for continuation-----

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 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.: 1-5, (7-8) (in part), 9, 10, 12, 13, 15 (in part), 19, 20, 22 (in part) limited to SEQ ID NOs: 14, 3, 7

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/US 16/59151

-----continued from Box III (Lack of Unity of Invention)-----

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 I+: Claims 1-17, 19-22, drawn to a polynucleotide having first, second and third fragments. The polynucleotide will be searched to the extent that the first, second and third fragment encompass SEQ ID NOs: 14, 3, and 7, respectively. It is believed that claims 1-5, (7-8) (in part), 9, 10, 12, 13, 15 (in part), 19, 20, 22 (in part) read on this first named invention and thus these claims will be searched without fee to the extent that they encompass a nucleic acid consisting of SEQ ID NOs: 14, 3, 7. Additional polynucleotide(s) will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected polynucleotide(s). Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be: a polynucleotide having first, second and third fragment comprising SEQ ID NOs: 5, 3, and 7, respectively (claims 12, 13, 15 (in part), 16, 17, 20, 21, 22 (in part)).

The inventions listed as Group I+ 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:

Special Technical Features:

Among the inventions listed as Groups I+ are the specific polynucleotide fragments, recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among polynucleotide fragment sequences.

Common Technical Features:

1. Group I+ claims share the common technical feature of a polynucleotide comprising:
(a) a first fragment consisting of the nucleic acid sequence and (b) a second fragment consisting of the nucleic acid sequence.
2. Groups I+ claims further comprise a post-transcriptional regulatory element (PRE). Some claims include an alpha PRE and other claims include a gamma PRE.
3. In Group I+, some claims share the common technical feature of a protein coding sequence.

However, said common technical feature does not represent a contribution over the prior art, and is anticipated by the publication titled "Woodchuck hepatitis virus contains a tripartite posttranscriptional regulatory element" by Donello et al. (hereinafter "Donello") [published June 1998 in J Virol Vol 72 No 6 Pages 5085-5092].

As to common technical features #1, #2, and #3, Donello teaches (abstract; We find that the closely related woodchuck hepatitis virus (WHV), which has been shown to lack a functional enhancer I, also contains a posttranscriptional regulatory element (WPRE). Deletion analysis suggests that the WPRE consists of three independent subelements. Comparison of the bipartite HBVPRE and tripartite WPRE activities reveals that the tripartite WPRE is two to three times more active than the bipartite HBVPRE"; pg 5086 fig 1B; Comparison of the PRE and enhancer I regions of HBV and WHV. The darkened regions correspond to the open reading frames of the polymerase (Pol) and X proteins. The regions containing the HPRE.alpha and HBVPRE.beta subelements are indicated. Homologous nucleotides (nt) are aligned, and the fragments are drawn to scale"; pg 5091, fig 6A; FIG. 6. Tripartite PRE are stronger than bipartite elements. (A) Schematic representation of transfected constructs. Fragments, chimeric elements, and WPRE.alpha (Wa), WPRE.beta (Wb), and WPRE.gamma (Wg) subelements are marked").

As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical feature that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature