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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
10 December 2015

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(54) Title: MATERIALS AND METHODS FOR THE TREATMENT OF LATENT VIRAL INFECTION

(57) Abstract: The subject invention pertains to materials and methods for the treatment of latent viral infections.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/24094

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/62, 15/66, 15/31 (2015.01)
CPC - C07K 2319/00
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(8): C12Q 1/68; C40B 40/06; C12N 15/62, 15/66, 15/31, 5/00; C07K 14/24 (2015.01)
CPC- C12Q 1/6806; C07K 2319/24, 2319/41, 2319/43, 2319/00; C12P 19/34; C40B 50/06, 40/08; C12N 9/22

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google/Google Scholar; NCBI/PubMed/BLAST; ProQuest; The Lens.org; 'TAL,' binding, domain, effector, virus, viral, protein, peptide, 'target gene,' 'HSV,' herpes, 'ISP0,' latent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/012674 A1 (THE GENERAL HOSPITAL CORPORATION); January 24, 2013; page 5 lines 15-20, page 9 lines 18-20, page 10 lines 23-28, page 19 lines 1-10, page 23 lines 20-25, page 30 line 30 – page 31 line 1, page 31 lines 10-20, page 40 lines 19-20; table 5	1-10, 19-26, 29-32, 35-42
Y	WO 1999/053043 A2 (COFFIN, RS et al.); October 21, 1999; page 1 lines 10-15	1-10, 19-26, 29-32, 35-42
Y	US 2013/0122581 A1 (REGENTS OF THE UNIVERSITY OF MINNESOTA, et al.); May 16, 2013; paragraph [0140]	10
Y	WO 2013/173129 A2 (AVALANCHE AUSTRALIA PTY LTD.); November 21, 2013; paragraphs [00100], [00108]; SEQ ID NO:27	22, 23

☐ 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 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
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/24094

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 Supplemental Page-***-

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.:

Groups I+: Claims 1-6, 7 (in-part), 8-10, 19 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 23 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 39 (in-part), 40 (in-part), 41 (in-part), 42 (in-part), SEQ ID NOs: 18 (vector promoter Gallus gallus DNA sequence), 19 (TAL binding domain synthetic amino acid sequence)

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
Information on patent family members

International application No.
PCT/US15/24094

-***-Continued from Box No. 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.

Groups I+: Claims 1-6, 7 (in-part), 8-10, 19 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 23 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 39 (in-part), 40 (in-part), 41 (in-part) and 42 (in-part) are directed toward a non-naturally occurring fusion protein comprising a TAL binding domain that binds to a target gene of a latent virus and an effector domain, wherein said fusion protein modulates the target gene of the latent virus.

The non-naturally occurring fusion protein will be searched to the extent that the TAL binding domain encompasses SEQ ID NOs: 18 (vector promoter Gallus gallus DNA sequence) and 19 (TAL binding domain synthetic amino acid sequence). It is believed that Claims 1-6, 7 (in-part), 8-10, 19 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 23 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 39 (in-part), 40 (in-part), 41 (in-part) and 42 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 18 (vector promoter Gallus gallus DNA sequence) and 19 (TAL binding domain synthetic amino acid sequence). Additional TAL binding domain sequence(s) will be searched upon the payment of additional fees. 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 TAL binding domain sequence encompassing SEQ ID NO: 20 (TAL binding domain amino acid sequence).

Groups II+: Claims 11-17, 18 (in-part), 19 (in-part), 20 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 39 (in-part), 40 (in-part), 41 (in-part), 42 (in-part) and 43 (in-part) are directed toward a targeted nuclease comprising a guide RNA sequence bound to an endonuclease.

The targeted nuclease can be searched to the extent that the guide RNA sequence encompasses SEQ ID NOs: 8 (gRNA sequence) and 18 (vector promoter Gallus gallus DNA sequence). It is believed that Claims 11-17, 18 (in-part), 19 (in-part), 20 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 40 (in-part), 41 (in-part), 42 (in-part) and 43 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 8 (gRNA sequence) and 18 (vector promoter Gallus gallus DNA sequence). Additional guide RNA sequence(s) can be searched upon the payment of additional fees. 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: SEQ ID NO: 9 (gRNA sequence).

The inventions listed as Groups I+-II+ 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: the special technical features of Groups I + include a TAL binding domain that binds to a target gene of a latent virus, which is not present in Groups II+, the special technical features of Groups II+ including a targeted nuclease comprising a guide RNA sequence.

No technical features are shared between the TAL binding domain sequences of Groups I+ and, accordingly, these groups lack unity a priori.

No technical features are shared between the guide RNA sequences of Groups II+ and, accordingly, these groups lack unity a priori.

Groups I+-II+ share the technical features including binding to a target gene and an effector domain; a vector encoding a fusion protein or a targeted nuclease; and a method of treating a latent viral infection comprising the administration of a vector, fusion protein or targeted nuclease to a subject having a latent viral infection. Groups I+ share the technical features including a non-naturally occurring fusion protein comprising a TAL binding domain that binds to a target gene of a latent virus and an effector domain, wherein said fusion protein modulates the target gene of the latent virus; and a polynucleotide encoding the fusion protein. Groups II+ share the technical features including a targeted nuclease comprising a guide RNA sequence bound to an endonuclease.

-***-Continued on Next Supplemental Page-***-

-***-Continued from Previous Supplemental Page:

However, these shared technical features are previously disclosed by WO 2014/039585 A2 (THE SCRIPSS RESEARCH INSTITUTE) (hereinafter 'Scripps') in view of WO 1995/032283 A1 (INDIANA UNIVERSITY FOUNDATION) (hereinafter 'IU').

Scripps discloses binding to a target gene (binding to a desired nucleotide (target gene); paragraph [0012]) and an effector domain (a recombinase, nuclease or transcription factor (an effector domain); paragraph [0011]); a vector encoding a fusion protein (a TALER or ZFR expression vector (a vector encoding a fusion protein); paragraphs [0034], [0087]); and a method of treating a latent viral infection (a method of performing gene therapy for a viral infection, including removal or inactivation of Lentiviral or HIV promoter sequences; paragraphs [0024], [0027], [0095]; Claim 22) comprising the administration of a vector to a subject (paragraphs [0024], [0027]) having a latent viral infection (wherein the vector encodes a construct that targets Lentiviral or HIV promoter sequences; paragraphs [0024], [0095]); a non-naturally occurring fusion protein (a chimeric polypeptide; paragraph [0011]) comprising a TAL binding domain (comprising a TALE protein binding domain; paragraph [0012]) that binds to a target gene (that binds to a desired nucleotide (target gene); paragraph [0012]) of a latent virus (of a Lentivirus or HIV (of a latent virus); paragraph [0095]) and an effector domain (and a recombinase, nuclease or transcription factor (and an effector domain); paragraph [0011]), wherein said fusion protein modulates the target gene of the latent virus (wherein said expression of said fusion protein results in the removal or silencing of a viral gene product (wherein said fusion protein modulates the target gene of the latent virus); paragraphs [0024], [0027], [0095], Claim 22); and a polynucleotide encoding the fusion protein (an isolated nucleic acid molecule (a polynucleotide) encoding the chimeric polypeptide (fusion protein); paragraph [0019]). Scripps does not disclose a targeted nuclease comprising a guide RNA sequence bound to an endonuclease. IU discloses an RNase P-RNA conjugate (an RNase P -RNA conjugate; abstract), wherein the conjugate comprises an attached internal RNA guide sequence (wherein the conjugate comprises an attached internal RNA guide sequence; abstract, page 4, lines 3-16) and an endonuclease domain (page 4, lines 3-16), for antiviral therapy (abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Scripps, for providing a base-pairing targeting mechanism, such as the internal RNA guide sequence, as previously disclosed by IU, for providing specific targeting of a sequence within a latent virus genome, for enabling the removal of the sequence from infected cells, or suppressing expression of the viral gene, for providing effective long-term treatment of latent virus infections, such HIV infections, as previously disclosed by Scripps.

Since none of the special technical features of the Groups I+-II+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Scripps and IU references, unity of invention is lacking.