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(71) Applicant: **DOUBLE HELIX CORPORATION** [CA/CA]; 1201 Nicholson Rd, Suite 200, Newmarket, Ontario L3Y 9C4 (CA).

(72) Inventors; and
(71) Applicants *(for US only)*: **COYLE, Douglas** [CA/CA]; 203 Willow Farm Lane, Aurora, Ontario L4G 6L9 (CA). **FOSSEL, Michael** [US/US]; 9464 Conservation Avenue NE, Ada, MI 49301 (US).

(74) Agent: **STORELLA, John, R.**; Storella, P.C., 2625 Alcatraz Ave. #197, Berkeley, CA 94705 (US).

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

(88) Date of publication of the international search report:
12 November 2015

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(54) Title: COMPOSITIONS AND METHODS FOR PROVIDING ACTIVE TELOMERASE TO CELLS IN VIVO

(57) Abstract: This invention provides liposomes for delivering to target cells in a subject, nucleic acids for expressing telomerase reverse transcriptase and/or telomerase RNA component. Expression of active telomerase can extend the length of telomeres in the cell. Such lengthening can be useful in subjects suffering from diseases associated with shortened telomeres.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/71991

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12P 21/06, C12N 9/00, C12N 1/20, C12N 15/00 (2015.01)
CPC - A61K 38/00, C12N 9/93, C12N 15/86

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) - C12P 21/06, C12N 9/00, C12N 1/20, C12N 15/00 (2015.01)
CPC - A61K 38/00, C12N 9/93, C12N 15/86

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/69.1, 435/183, 435/252.3, 425/320.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, Search Terms: telomerase reverse transcriptase, pegylated liposome, targeting agent, vector, telomerase component, shortened telomeres

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/0202684 A1 (GEALL et al.) 08 August 2013 (08.08.2013) entire document, especially paras [0005]; [0006]; [0032]; [0037]; [0039]; [0124]	1-17
Y	US 2003/0143228 A1 (CHEN et al.) 31 July 2003 (31.07.2003) entire document, especially paras [0009]; [0056]; [0178]; [0180]	1-17
Y	US 2011/0243910 A1 (Hahn et al.) 06 October 2011 (06.10.2011) entire document, especially paras [0055]; [0158]; [0180]	2
Y	US 2002/0025313 A1 (Micklus et al.) 28 February 2002 (28.02.2002) abstract	5-8
Y	US 2011/0177043 A1 (Liu et al.) 21 July 2011 (21.07.2011) para [0007], [0014], [0096], [0097], [0104], [0324]	10-17
Y	US 2007/0065415 A1 (KLEINSEK et al.) 22 March 2007 (22.03.2007) entire document, especially paras [0220]; [0391]; [0574]; [0577]	11-17

☐ 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	Date of mailing of the international search report
29 April 2015 (29.04.2015)	28 MAY 2015
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. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/71991

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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/71991

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:
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, drawn to a method of expressing telomerase in a target cell in a subject and a method of treating a subject suffering from a disease associated with shortened telomeres.

Group II: claims 18-44, drawn to a liposome for delivering at least one nucleic acid vector encoding telomerase reverse transcriptase to a target cell.

The inventions listed as Groups I and 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:

---continued on extra 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 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.:
1-17

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.

Continuation of:

Box NO III. Observations where unity of invention is lacking

Special Technical Features

Group I includes the special technical feature of a method of expressing telomerase in a target cell in a subject, not required by Group II.

Group II includes the special technical feature of a process of a liposomal composition, not required by Group I.

Common Technical Features

Groups I and II are related to each other as a composition (Group II) and a method of using the composition (Group I) and share the technical feature of a lipomal delivery vehicle of claim 18. However, this shared technical feature does not represent a contribution over prior arts in view of US 2013/0202684 A1 to Geall et al. (hereafter 'Geall') and US 2003/0143228 A1 to Chen et al. (hereafter 'Chen').

Geall teaches a liposome for delivering at least one nucleic acid vector encoding telomerase reverse transcriptase to a target cell (para [0006], the invention provides a liposome within which RNA encoding an immunogen of interest is encapsulated; para [0037], Liposomes of the invention include a RNA molecule which (unlike siRNA, as in reference 2) encodes an immunogen; para [0039], Preferred +-stranded RNAs are self-replicating; para [0124], the immunogen is terlomerase catalytic protein), wherein the liposome comprises a PEG-ylated lipid membrane (para [0005], The liposome includes a PEGylated lipid i.e. the lipid is modified by covalent attachment of a polyethylene glycol. PEG provides the liposomes with a coat which can confer favourable pharmacokinetic characteristics) having an external surface and defining an internal compartment (para [0032], unilamellar vesicles), wherein:
b) the internal compartment contains a nucleic acid vector comprising a nucleotide sequence encoding telomerase reverse transcriptase (TERT) (para [0124], the immunogen is terlomerase catalytic protein), but does not specifically teach a vector comprising an expression control sequence operative in the target cell and operatively linked to a nucleotide sequence and a).

Chen teaches a vector comprising an expression control sequence operative in the target cell and operatively linked to a nucleotide sequence of TERT epitope (para [0009], polynucleotide and amino acid sequences of human telomerase reverse transcriptase MHC-I and MHC-II restricted epitopes ... inserted into an expression vector that is administered to a subject; para [0056], Expression vectors can contain a variety of control sequences, which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operatively linked coding sequence in a particular host organism); and
a) the external surface has attached thereto a targeting agent directed against a receptor on a target cell involved in receptor-mediated endocytosis or macropinocytosis (para [0180], A polynucleotide delivery vehicle component of a cell-specific polynucleotide targeting vehicle comprises a specific binding ligand in combination with a liposome. The polynucleotide(s) to be delivered are housed within the liposome and the specific binding ligand is functionally incorporated into the liposome membrane. ?.. for example, epidermal growth factor (EGF) is used in the receptor-mediated delivery of a polynucleotide to cells that exhibit upregulation of the EGF receptor). One of ordinary skill in the art would have applied the targeted liposomal vehicle of Chen to the liposome of Geall, because Chen teaches that targeted delivery of cargo polynucleotide by liposome comprising receptor-specific ligand offers increased specificity (para [0178]). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

Groups I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.