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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))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

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

(88) Date of publication of the international search report:
30 October 2014

(54) Title: MODULATION OF MITOPHAGY AND USE THEREOF

(57) Abstract: The present invention relates to an agent or composition comprising at least one of: (i) a micro-RNA targeting a mitophagy-associated gene or a variant thereof, (ii) a vector comprising a nucleic acid encoding said micro-RNA or variant thereof, (iii) an inducer of said micro-RNA, and (iv) an inhibitor of said micro-RNA, for use as a medicament. In particular, the invention relates to substances and compositions useful in the treatment of mitochondria-related diseases, in a subject, or to enhance protocols of in vitro production of red blood cells.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/713 A61K31/7088 A61P7/06 A61P43/00
C12Q1/68 C12N5/078
ADD. C07K14/47
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 A61K

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)
EPO-Internal, BIOSIS, MEDLINE, WPI Data

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X	WO 2009/029681 A2 (UNIV CALIFORNIA [US]; DAVID MICHAEL [US]) 5 March 2009 (2009-03-05) claims 1, 4, 12-15; figure 5	1-3, 9-11,22, 24
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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 2014	15/07/2014

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, Fax: (+31-70) 340-3016	Spindler, Mark-Peter

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2008/142567 A2 (KAROLINSKA INST INNOVATIONS AB [SE]; PIVARCSI ANDOR [SE]; SONKOLY ENIK) 27 November 2008 (2008-11-27) claims 1, 5, 14, 36; figure 1	1-3, 9-11,22, 24
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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.
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International application No
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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.
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T	G ASHRAFI ET AL: "The pathways of mitophagy for quality control and clearance of mitochondria", CELL DEATH AND DIFFERENTIATION, vol. 20, no. 1, 29 June 2012 (2012-06-29), pages 31-42, XP055112607, ISSN: 1350-9047, DOI: 10.1038/cdd.2012.81 page 39 -----	14-16

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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:

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 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.:

3-5, 7, 8, 13, 15, 16, 21(completely); 1, 2, 6, 9-12, 14, 22-24(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 3-5, 7, 8, 13, 15, 16(completely); 1, 2, 6, 9-12, 14, 22-24(partially)

an agent or composition comprising (i) a microRNA selected from hsa-miR125a-5p, hsa-miR125b-5p, mmu-miR-351 or mmu-miR125a-5p, (ii) a vector encoding said microRNA, (iii) an inducer of said microRNA or (iv) an inhibitor of said microRNA for use as a medicament; pharmaceutical composition comprising one of (i) to (iv); methods of reducing or increasing mitophagy in a subject using one of (i) to (iv); method of treating, preventing or attenuating a mitochondria-related disease using one of (i) to (iv)

2-8. claims: 1, 2, 6, 9-12, 14, 22-24(all partially)

as specified for invention 1) but wherein said microRNA is either mmu-miR-135a*, mmu-miR-149, mmu-miR-338-3p, mmu-miR-683, mmu-miR-574-3p, mmu-miR-467d* or mmu-miR-467a*, or mmu-miR-669f, respectively

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9. claims: 18(completely); 17, 20(partially)

a method of prognosis and/or diagnosis of a mitochondria-related disease comprising determining the level of and/or the presence of a mutation within a microRNA targeting a mitophagy-associated gene

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10. claims: 19(completely); 17, 20(partially)

a method of prognosis and/or diagnosis of a mitochondria-related disease comprising determining the level of and/or the presence of a mutation within a KRAB-ZFP selected from human ZNF205, human ZNF689, mouse ZFP13 and mouse ZFP689, or the presence of a mutation within a DNA target sequence of said KRAB-ZFP

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11. claims: 17, 20(all partially)

a method of prognosis and/or diagnosis of a mitochondria-related disease comprising determining the level of and/or the presence of a mutation within a mitophagy-associated gene

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12. claim: 21

a method for producing in vitro red blood cells using an inhibitor of a microRNA targeting a mitophagy-associated

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

gene

INTERNATIONAL SEARCH REPORT

Information on patent family members

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