



(51) International Patent Classification:

A61K 48/00 (2006.01) C12N 15/867 (2006.01)
C12N 15/90 (2006.01)

(21) International Application Number:

PCT/US2018/024407

(22) International Filing Date:

26 March 2018 (26.03.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/477,271 27 March 2017 (27.03.2017) US

(71) Applicant: THE SCHEPENS EYE RESEARCH INSTITUTE, INC. [US/US]; 20 Staniford Street, Boston, MA 02114 (US).

(72) Inventor: ARBOLEDA-VELASQUEZ, Joseph, F.; 321 Waltham Street, Newton, MA 02465 (US).

(74) Agent: BEATTIE, Ingrid, A. et al.; Mintz Levin Cohn Ferris Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available):

ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: NUCLEIC ACID-BASED COMPOSITIONS AND METHODS FOR TREATING SMALL VESSEL DISEASES

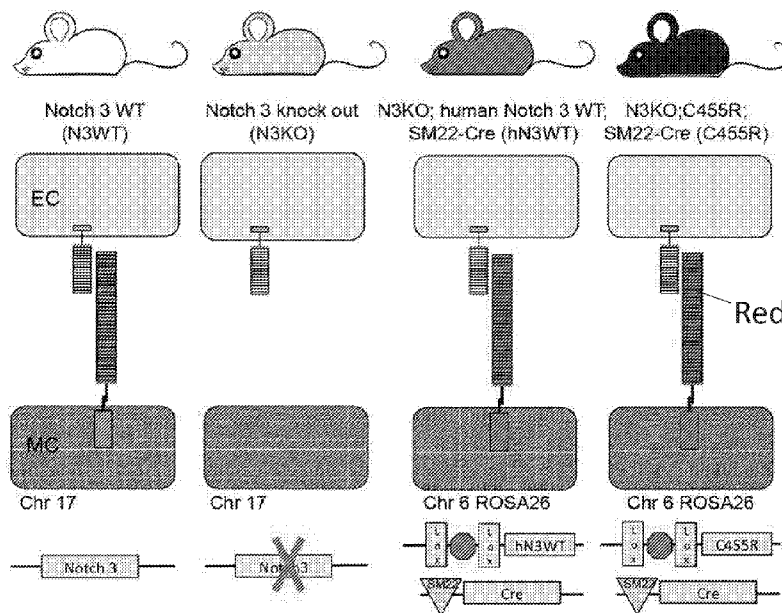


FIG. 1A

(57) Abstract: The present subject matter provides, *inter alia*, compositions, formulations, and methods for inhibiting, treating, and preventing small vessel diseases.



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:

01 November 2018 (01.11.2018)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/24407

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 48/00 , C12N 15/90, C12N 15/867 (2018.01)
CPC - C12Q 2600/156, C12Q 1/6883, C12N 15/907 , A61K 48/005, C12N 5/0691

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.
X --- Y	US 2003/0186290 A1 (TOURNIER-LASSERVE) 2 October 2003 (02.10.2003)abstract, para [0002], [0010], [0012], [0015]-[0024], [0026], [0029], [0072]-[0074], [0076], [0077], [0089], [0095], [0101], [0121], [0125], [0126], [0170], Fig. 3	1, 6-16, 22-23, 27-29, 32-33, 37-39, 45-47, 53-55, 58-61 ----- 2-5, 17-21, 24-26, 30-31, 34-36, 40-44, 48-52, 56-57
Y	US 2011/0223183 A1 (KITAJEWSKI et al.) 15 September 2011 (15.09.2011) para [0020], [0021], [0026], [0029], [0107], [0108], [0164], SEQ ID NO: 16	2, 5, 31, 34-35
Y	ARBOLEDA-VELASQUEZ et al. Hypomorphic Notch 3 alleles link Notch signaling to ischemic cerebral small-vessel disease. PNAS, 24 May 2011, Vol 108, No 21, pp E128-E135; abstract, pg E128, col 2, para 3, pg E129, col 1, para 1-3, pg E131, col 1, para 3, Fig. 6C	3-5, 17-19, 40, 42, 44, 48-49
Y	US 2002/0182733 A1 (NALDINI et al.) 5 December 2002 (05.12.2002) abstract, para [0027], [0028]	17, 20-21

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 13 August 2018	Date of mailing of the international search report 18 SEP 2018
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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
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/24407

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0115453 A1 (ACADEMISCH ZIEKENHUIS LEIDEN) 28 April 2016 (28.04.2016) para [0002], [0032], [0110]	24-26
Y	TIKKA et al. CADASIL and CARASIL. Brain Pathology, September 2014, Vol 24, No 5 Pages 525-544, abstract, pg 528, col 2, para 1, 4; pg 531, col 1, para 5, pg 540, col 1, para 5	30, 36, 50, 56-58
Y	MONET-LEPRETRE et al. Abnormal recruitment of extracellular matrix proteins by excess Notch3 ^{sup.ECD} : a new pathomechanism in CADASIL. Brain, 1 June 2013, Vol 136, No 6, pp 1830-1845, Abstract, pg 1842, col 2, para 2	41, 51-52
Y	US 2015/0119278 A1 (NANOSOMIX, INC.) 30 April 2015 (30.04.2015) para [0005]	43

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/24407

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 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.:
1-61

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 18/24407

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 1-61, drawn to a method for treating or preventing a small vessel disease (SVD) in a subject.

Group II: Claims 62-70, drawn to a composition comprising a vector further comprising a coding sequence that encodes NOTCH3 operably linked to a promoter, and use of said composition.

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:

Special Technical Features

Group I requires method steps for treatment for SVD, not required by Group II.

Group II requires an isolated composition comprising a vector not required by Group I.

The feature shared by Groups I and II is a vector comprising a coding sequence that encodes NOTCH3 operably linked to a promoter. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is disclosed by the article entitled "Biochemical Characterization and Cellular Effects of CADASIL Mutants of NOTCH3" by Meng et al. (hereinafter 'Meng') (PLoS ONE 18 September 2012 vol 7 no 9, article no e44964, pp1-13). Meng discloses a vector comprising a coding sequence that encodes NOTCH3 operably linked to a promoter (p 2, col 1, para 3 "We constructed a clone for NOTCH3 in the expression vector pCMV-Sport6 ... by using publicly available cDNA clones and RT-PCR from human brain"; note: in said (commercially available) vector, the CMV promoter is operably linked to the NOTCH3 sequence.).

As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

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