(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2019 (19.12.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/241802 A3

(51) International Patent Classification:
A61K 31/4015 (2006.01) *A61K 48/00* (2006.01)
A61P 35/00 (2006.01) *C12N 15/113* (2010.01)
A61K 31/7105 (2006.01) *G01N 33/50* (2006.01)

(21) International Application Number:
PCT/US2019/037559

(22) International Filing Date:
17 June 2019 (17.06.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/685,866 15 June 2018 (15.06.2018) US

(71) Applicant: **IDEAYA BIOSCIENCES, INC.** [US/US]; 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US).

(72) Inventors: **BELMONT, Lisa**; 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **HAGER, Jeff**; 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **HATA, Yujiro**; 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **KATEGAYA, Lorn**; 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US).

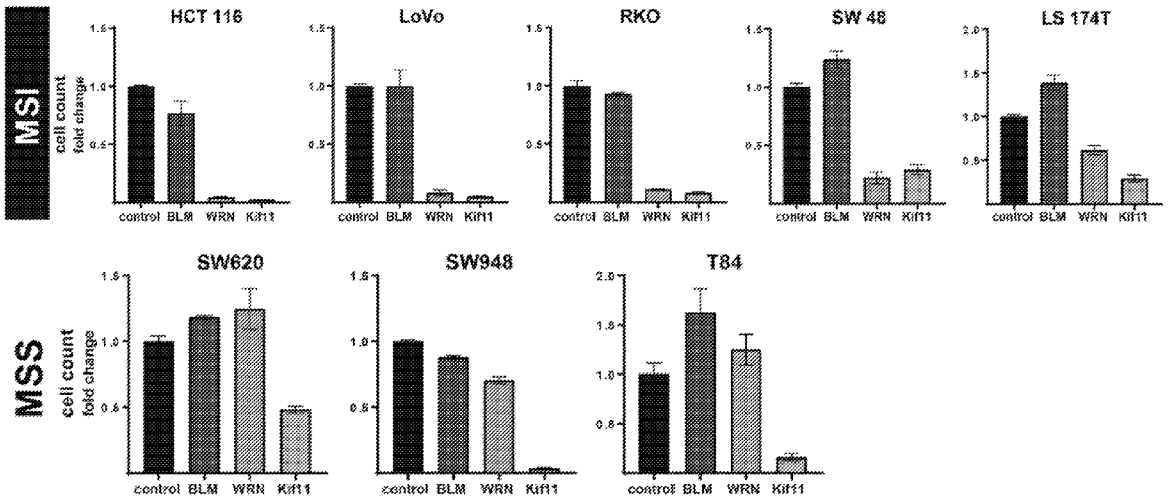
(74) Agent: **VANEVSKI, Filip** et al.; Mintz Levin Cohn Ferris Glovsky & Popeo, P.C., One Financial Center, Boston, Massachusetts 02111 (US).

(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: METHODS OF INHIBITING PROLIFERATIVE CELLS

FIG. 2



(57) Abstract: The present invention provides methods of negatively modulating the Werner protein (WRN) to inhibit proliferative cells characterized by high microsatellite instability (MSI-H), for example to treat proliferative diseases (such as cancer) characterized by high MSI (MSI-H). Further provided are compositions used in such methods.

[Continued on next page]

WO 2019/241802 A3

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:
23 January 2020 (23.01.2020)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/037559

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4015 A61P35/00 A61K31/7105 A61K48/00 C12N15/113
G01N33/50
ADD.
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)
A61K A61P C12N G01N

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, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAZUNOBU FUTAMI ET AL: "RECQL1 and WRN DNA repair helicases: potential therapeutic targets and proliferative markers against cancers", FRONTIERS IN GENETICS, vol. 5, no. 441, 1 January 2015 (2015-01-01), pages 1-11, XP055362411, DOI: 10.3389/fgene.2014.00441 the whole document figure 2 -----	1
X	WO 02/068690 A1 (ISIS PHARMACEUTICALS INC [US]; WARD DONNA T [US]; WATT ANDREW T [US]) 6 September 2002 (2002-09-06) the whole document claims 1,2,14-18 ----- -/--	1

[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

"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
18 September 2019	19/12/2019

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	Jakobs, Andreas

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. AGGARWAL ET AL: "Inhibition of helicase activity by a small molecule impairs Werner syndrome helicase (WRN) function in the cellular response to DNA damage or replication stress", NATIONAL ACADEMY OF SCIENCES, vol. 108, no. 4, 10 January 2011 (2011-01-10), pages 1525-1530, XP055618576, US ISSN: 0027-8424, DOI: 10.1073/pnas.1006423108 the whole document page 1526, column 2, paragraph 2-3; figures 1,2	1-4, 33-67, 76-78, 99-102, 131-145
X	WO 00/06088 A2 (KIRKPATRICK D LYNN [CA]; POWIS GARTH [US]) 10 February 2000 (2000-02-10) the whole document page 7, lines 1-2 page 11, lines 12-18 page 26, line 3; table 1 page 28, paragraph 1 page 29, line 5; table 2 page 38, line 14; table 3	1-4, 33-67, 76-78, 99-102, 131-145
X	R. MOLES ET AL: "WRN-targeted therapy using inhibitors NSC 19630 and NSC 617145 induce apoptosis in HTLV-1-transformed adult T-cell leukemia cells", JOURNAL OF HEMATOLOGY & ONCOLOGY, vol. 9, no. 1, 9 November 2016 (2016-11-09), XP055618606, DOI: 10.1186/s13045-016-0352-4 the whole document tables 1,2 page 9, column 2, paragraph 3 - page 10, column 1, paragraph 1	1-4, 33-50, 52-67, 76-78, 99-102, 131-143, 145
X	VLADIMIR J. N. BYKOV ET AL: "Reactivation of Mutant p53 and Induction of Apoptosis in Human Tumor Cells by Maleimide Analogs", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 280, no. 34, 1 July 2005 (2005-07-01) , pages 30384-30391, XP055618503, US ISSN: 0021-9258, DOI: 10.1074/jbc.M501664200 the whole document figures 1a,2; table II	1-4, 33-50, 52-67, 76-78, 99-102, 131-143, 145

-/--

2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/24692 A1 (KAROLINSKA INNOVATIONS AB [SE]; BYKOV VLADIMIR [SE] ET AL.) 28 March 2002 (2002-03-28) the whole document claims 3-7	1-4, 33-50, 52-67, 76-78, 99-102, 131-143, 145
X	WO 03/070250 A1 (KAROLINSKA INNOVATIONS AB [SE]; BYKOV VLADIMIR [SE] ET AL.) 28 August 2003 (2003-08-28) the whole document page 19, line 25 - page 22, line 2; figures 1a, 2d	1-4, 33-67, 76-78, 99-102, 131-145
X	M N SAHA ET AL: "Small molecule MIRA-1 induces in vitro and in vivo anti-myeloma activity and synergizes with current anti-myeloma agents", BRITISH JOURNAL OF CANCER, vol. 110, no. 9, 1 April 2014 (2014-04-01), pages 2224-2231, XP055618599, GB ISSN: 0007-0920, DOI: 10.1038/bjc.2014.164 the whole document page 2226, column 2, paragraph 2 - page 2227, column 2, paragraph 3	1-4, 33-50, 52-67, 76-78, 99-102, 131-143, 145
X	WO 2011/014825 A2 (US HEALTH [US]; ZUDAIRE ENRIQUE [US] ET AL.) 3 February 2011 (2011-02-03) claims 18-24	1-4, 33-50, 52-67, 76-78, 99-102, 131-143, 145

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/037559

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.:

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.:

3, 4, 101, 102(completely); 1, 2, 33-67, 76-78, 99, 100, 131-145(partially)

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, 4, 101, 102(completely); 1, 2, 33-67, 76-78, 99, 100, 131-145(partially)

   a pharmaceutical agent for use in a method for treating a proliferative disease in an individual in need thereof, the proliferative disease being characterized by proliferating cells having a high microsatellite instability (MSI-H), said method comprising administering to the individual said pharmaceutical agent, wherein said pharmaceutical agent is effective for decreasing the helicase activity of WRN in the proliferative cells, wherein the pharmaceutical agent is an inhibitor of WRN, wherein the inhibitor of WRN is a small molecule inhibitor, in particular a molecule of the formula of claim 4

   ---

2. claims: 5-9, 31, 32, 103-105(completely); 1, 2, 33-67, 76-78, 99, 100, 106, 107, 125-145(partially)

   a pharmaceutical agent for use in a method for treating a proliferative disease in an individual in need thereof, the proliferative disease being characterized by proliferating cells having a high microsatellite instability (MSI-H), said method comprising administering to the individual said pharmaceutical agent, wherein said pharmaceutical agent is effective for decreasing the helicase activity of WRN in the proliferative cells, wherein the pharmaceutical agent is an inhibitor of WRN, wherein the inhibitor of WRN is a ADC comprising an antibody conjugated to a WRN inhibitor, an inhibitory nucleic acid targeting WRN mRNA, a nuclease capable of modifying the helicase activity of WRN, a nucleic acid construct according to claim 27, a proteolysis targeting chimera according to claim 31; and compositions comprising a gRNA and a RNA-guided endonuclease according to claim 79; and a composition according to claim 95 comprising same.

   ---

3. claims: 68-75(completely); 76-78(partially)

   An in vitro method for detecting a high microsatellite instability (MSI-H) or a marker associated with high microsatelite instability and the helicase activity of WRN in an individual diagnosed with or thought to have a proliferative disease, the method comprising: (a) contacting a biological sample from the individual with one or more reagents for detecting the presence of an MSI and the helicase activity of WRN; and (b) detecting (i) the presence of an MSI-H; and (ii) the helicase activity of WRN.

   ---

4. claims: 10-30, 79-94, 108-124(completely); 1, 2, 33-67, 76-78,

99, 106, 107, 125-145(partially)

compositions comprising a gRNA and a RNA-guided endonuclease according to claim 79; and a composition according to claim 95 comprising.

---

5. claims: 95-98(completely); 1, 2, 33-67, 76-78, 106, 107, 131-145(partially)

A composition comprising a nucleic acid construct comprising a donor nucleic acid, wherein the nucleic acid construct is configured such that insertion of the donor nucleic acid into the genome of a proliferative cell by homologous recombination decreases the helicase activity of WRN in the proliferative cell.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/037559

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02068690 A1	06-09-2002	US 6448080 B1	10-09-2002
		US 2005075299 A1	07-04-2005
		WO 02068690 A1	06-09-2002
WO 0006088 A2	10-02-2000	AU 5463099 A	21-02-2000
		CA 2339233 A1	10-02-2000
		MX PA01001255 A	29-11-2002
		US 6372772 B1	16-04-2002
		WO 0006088 A2	10-02-2000
WO 0224692 A1	28-03-2002	AT 413176 T	15-11-2008
		AU 9042201 A	02-04-2002
		AU 2001290422 B2	15-06-2006
		CA 2423192 A1	28-03-2002
		DK 1319000 T3	16-02-2009
		EP 1319000 A1	18-06-2003
		ES 2316473 T3	16-04-2009
		JP 4865982 B2	01-02-2012
		JP 2004509890 A	02-04-2004
		US 2003166674 A1	04-09-2003
		US 2005090540 A1	28-04-2005
		WO 0224692 A1	28-03-2002
WO 03070250 A1	28-08-2003	AT 333280 T	15-08-2006
		AU 2003206329 A1	09-09-2003
		CA 2476825 A1	28-08-2003
		DE 60306896 T2	15-02-2007
		EP 1476166 A1	17-11-2004
		ES 2269975 T3	01-04-2007
		US 2005090510 A1	28-04-2005
		WO 03070250 A1	28-08-2003
WO 2011014825 A2	03-02-2011	AU 2010278738 A1	16-02-2012
		CA 2769038 A1	03-02-2011
		EP 2461806 A2	13-06-2012
		JP 5886743 B2	16-03-2016
		JP 6023143 B2	09-11-2016
		JP 2013501004 A	10-01-2013
		JP 2015038122 A	26-02-2015
		JP 2017014276 A	19-01-2017
		US 2012129775 A1	24-05-2012
		US 2016030508 A1	04-02-2016
		WO 2011014825 A2	03-02-2011