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(71) Applicant: **PROMEGA CORPORATION** [US/US];
2800 Woods Hollow Road, Madison, Wisconsin 53711
(US).

(72) Inventors: **VASTA, James**; c/o Promega Corporation,
2800 Woods Hollow Road, Madison, Wisconsin 53711
(US). **ROBERS, Matthew**; c/o Promega Corporation, 2800
Woods Hollow Road, Madison, Wisconsin 53711 (US).

(74) Agent: **STAPLE, David, W.**; Casimir Jones, S.C., 2275
Deming Way, Suite 310, Middleton, Wisconsin 53562
(US).

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10 February 2022 (10.02.2022)

(54) Title: ENHANCEMENT OF KINASE TARGET ENGAGEMENT

(57) Abstract: Provided herein are systems and methods for enhanced engagement of protein kinases by kinase binding agents. In particular, the engagement of kinases by functional kinase binding agents is enhanced by the co-expression of the kinases with an active variant of KRAS.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/48 C07D241/20 C07D403/12
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)
C12Q C07D

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	DOS SANTOS EDMILSON OZORIO ET AL: "Aurora kinase targeting in lung cancer reduces KRAS-induced transformation", MOLECULAR CANCER, vol. 15, no. 1, 1 December 2016 (2016-12-01), XP055853349, DOI: 10.1186/s12943-016-0494-6 Retrieved from the Internet: URL:https://molecular-cancer.biomedcentral.com/track/pdf/10.1186/s12943-016-0494-6.pdf [retrieved on 2016-12-01]	1-13, 17, 23-34, 38
Y	the whole document	16, 37

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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 27 October 2021	Date of mailing of the international search report 17/01/2022
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer R. von Eggelkraut-G.
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INTERNATIONAL SEARCH REPORT

International application No.

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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 13ter.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 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.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.
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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.:

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.:
12, 13, 16, 33, 34, 37 (completely); 1-11, 17, 23-32, 38 (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: 12, 13, 16, 33, 34, 37 (completely); 1-11, 17, 23-32, 38 (partially)

A method and system comprising (a) a kinase co-expressed with (b) an active variant of KRAS; and (c) a kinase binding agent comprising a detectable element as the functional element.

2. claims: 14, 15, 35, 36 (completely); 1-11, 17, 23-32, 38 (partially)

A method and system comprising (a) a kinase co-expressed with (b) an active variant of KRAS; and (c) a kinase binding agent comprising a solid support as the functional element

3. claims: 18-22, 39-43 (completely); 1-11, 17, 23-32, 38 (partially)

A method and system comprising (a) a kinase expressed as a fusion with bioluminescent reporter, (b) an active variant of KRAS; and (c) a kinase binding agent comprising a functional element

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2021/033703

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ASHFORD ANNE L ET AL: "Identification of DYRK1B as a substrate of ERK1/2 and characterisation of the kinase activity of DYRK1B mutants from cancer and metabolic syndrome", CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHAUSER VERLAG, HEIDELBERG, DE, vol. 73, no. 4, 7 September 2015 (2015-09-07), pages 883-900, XP035801789, ISSN: 1420-682X, DOI: 10.1007/S00018-015-2032-X [retrieved on 2015-09-07]	1-13, 17, 23-34, 38
A	Fig. 3, p. 889, col. 2, 2nd paragraph - p. 890, col. 2, 1st paragraph -----	16, 37
X	LITO PIRO ET AL: "Disruption of CRAF-Mediated MEK Activation Is Required for Effective MEK Inhibition in KRAS Mutant Tumors", CANCER CELL, CELL PRESS, US, vol. 25, no. 5, 17 April 2014 (2014-04-17), pages 697-710, XP028653290, ISSN: 1535-6108, DOI: 10.1016/J.CCR.2014.03.011 [retrieved on 2014-04-17]	1-13, 17, 23-34, 38
A	the whole document -----	16, 37
X	WO 2014/176700 A1 (UNIVERSITÉ DE MONTRÉAL [CA]) 6 November 2014 (2014-11-06)	1-13, 17, 23-34, 38
A	pp. 3-5, Summary of the invention, claims 1-24 -----	16, 37
Y	WO 2008/092049 A1 (SMITHKLINE BEECHAM CORP [US]; AXTEN JEFFREY MICHAEL [US] ET AL.) 31 July 2008 (2008-07-31) pp. 10-12, "Biological assays", Ex. 7, claims 1-12 -----	16, 37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014176700	A1	06-11-2014	NONE

WO 2008092049	A1	31-07-2008	AR
		065015	A1
		AU 2008207809	A1
		2676257	A1
		CA 2676257	A1
		2008000197	A1
		CL 2008000197	A1
		2121637	A1
		EP 2121637	A1
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		JP 2010516780	A
		20081636	A1
		PE 20081636	A1
		200902010	A
		TW 200902010	A
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		US 2008182852	A1
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			31-07-2008
