

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

(19) World Intellectual Property  
Organization  
International Bureau



(10) International Publication Number  
**WO 2017/192662 A3**

(43) International Publication Date  
09 November 2017 (09.11.2017)

WIPO | PCT

(51) International Patent Classification: *G06F 19/22* (2011.01) *G06F 19/24* (2011.01) (88) Date of publication of the international search report:  
11 January 2018 (11.01.2018)

(21) International Application Number:  
PCT/US2017/030750

(22) International Filing Date:  
03 May 2017 (03.05.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
62/331,276 03 May 2016 (03.05.2016) US

(71) Applicant: INSTITUTE FOR SYSTEMS BIOLOGY  
[US/US]; 401 Terry Avenue North, Seattle, WA 98109  
(US).

(72) Inventors: BALIGA, Nitin, S.; 401 Terry Avenue North,  
Seattle, WA 98109 (US). PLAISIER, Christopher, L.;  
401 Terry Avenue North, Seattle, WA 98109 (US).

(74) Agent: PROTAS, Jeremy, D.; Marshall, Gerstein & Borun  
LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL  
60606-6357 (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, 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).

**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))

(54) Title: METHODS FOR IDENTIFYING TREATMENT TARGETS BASED ON MULTIOMICS DATA

(57) Abstract: The invention includes methods and systems for identifying targets for therapeutic intervention for various diseases and conditions; and provides specific materials and methods for treatment of specific diseases and conditions.



WO 2017/192662 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/30750

<p>A. CLASSIFICATION OF SUBJECT MATTER                  IPC(8) - G06F 19/22, 19/24 (2017.01)                  CPC - G06F 19/22, 19/24, 19/16, 19/18; C12N 2310/141, 2320/11, 15/111</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>																	
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols)                  See Search History Document</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                  See Search History Document</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)                  See Search History Document</p>																	
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X ---- Y</td> <td>Sun et al. Uncovering MicroRNA and Transcription Factor Mediated Regulatory Networks in Glioblastoma. PLoS Comput Biol 19 July 2012 Vol 8 No 7 Pages e1002488 1-14. Especially pg 2 col 2 para 3, pg 3 fig 1, pg 6 col 2 para 3, pg 11 col 2 para 3, Table S1</td> <td>1 ----- 2-5, 23-27</td> </tr> <tr> <td>Y</td> <td>Reiss et al. cMonkey2: Automated, systematic, integrated detection of co-regulated gene modules for any organism. Nucleic Acids Res 27 July 2015 Vol 43 No 13 Pages e87 1-13. Especially abstract, pg 7 col 2 para 5, pg 10 col 1 para 3.</td> <td>2-5, 24-27</td> </tr> <tr> <td>Y</td> <td>US 2006/0185027 A1 (Bartel et al.) 17 August 2006 (17.08.2006). Especially para [0017], [1290], [1291], [1503]</td> <td>23-27</td> </tr> <tr> <td>Y</td> <td>Yue et al. Survey of Computational Algorithms for MicroRNA Target Prediction. Curr Genomics November 2009 Vol 10 No 7 Pages 478-492. Especially pg 483 col 1 para 3, pg 483 col 2 para 5 continued to pg 484 col 1 para 1.</td> <td>4, 5/4, 26, 27/26</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X ---- Y	Sun et al. Uncovering MicroRNA and Transcription Factor Mediated Regulatory Networks in Glioblastoma. PLoS Comput Biol 19 July 2012 Vol 8 No 7 Pages e1002488 1-14. Especially pg 2 col 2 para 3, pg 3 fig 1, pg 6 col 2 para 3, pg 11 col 2 para 3, Table S1	1 ----- 2-5, 23-27	Y	Reiss et al. cMonkey2: Automated, systematic, integrated detection of co-regulated gene modules for any organism. Nucleic Acids Res 27 July 2015 Vol 43 No 13 Pages e87 1-13. Especially abstract, pg 7 col 2 para 5, pg 10 col 1 para 3.	2-5, 24-27	Y	US 2006/0185027 A1 (Bartel et al.) 17 August 2006 (17.08.2006). Especially para [0017], [1290], [1291], [1503]	23-27	Y	Yue et al. Survey of Computational Algorithms for MicroRNA Target Prediction. Curr Genomics November 2009 Vol 10 No 7 Pages 478-492. Especially pg 483 col 1 para 3, pg 483 col 2 para 5 continued to pg 484 col 1 para 1.	4, 5/4, 26, 27/26
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.															
X ---- Y	Sun et al. Uncovering MicroRNA and Transcription Factor Mediated Regulatory Networks in Glioblastoma. PLoS Comput Biol 19 July 2012 Vol 8 No 7 Pages e1002488 1-14. Especially pg 2 col 2 para 3, pg 3 fig 1, pg 6 col 2 para 3, pg 11 col 2 para 3, Table S1	1 ----- 2-5, 23-27															
Y	Reiss et al. cMonkey2: Automated, systematic, integrated detection of co-regulated gene modules for any organism. Nucleic Acids Res 27 July 2015 Vol 43 No 13 Pages e87 1-13. Especially abstract, pg 7 col 2 para 5, pg 10 col 1 para 3.	2-5, 24-27															
Y	US 2006/0185027 A1 (Bartel et al.) 17 August 2006 (17.08.2006). Especially para [0017], [1290], [1291], [1503]	23-27															
Y	Yue et al. Survey of Computational Algorithms for MicroRNA Target Prediction. Curr Genomics November 2009 Vol 10 No 7 Pages 478-492. Especially pg 483 col 1 para 3, pg 483 col 2 para 5 continued to pg 484 col 1 para 1.	4, 5/4, 26, 27/26															
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C.      <input type="checkbox"/> See patent family annex.</p>																	
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"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</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"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						
"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																	
<p>Date of the actual completion of the international search</p> <p>17 August 2017</p>		<p>Date of mailing of the international search report</p> <p><b>28 NOV 2017</b></p>															
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents                  P.O. Box 1450, Alexandria, Virginia 22313-1450                  Facsimile No. 571-273-8300</p>		<p>Authorized officer:</p> <p>Lee W. Young</p> <p>PCT Helpdesk: 571-272-4300                  PCT OSP: 571-272-7774</p>															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/30750

**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.: 6-22, 28-39, 43, 44, 49-93, 97-102  
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:  
----Go to Extra Sheet for continuation-----

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.:  
Claims 1-5, 23-27

- 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 III (Lack of Unity)-----

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 1-5, 23-27, drawn to a method or system for identifying treatment targets for a condition that includes receiving and analyzing multiomics data.

Group II: Claims 40-42, 45-48, drawn to a method, composition or kit for treating glioblastoma multiforme (GBM) comprising a first and second agents that target, comprise or mimic, independently, transcription factors and/or miRNAs.

Group III: Claims 94-96, drawn to a method of treating glioblastoma multiforme (GBM) comprising a first agent directed at an oncogene and a miRNA second agent that targets the mRNA of the same oncogene.

The inventions listed as Groups I-III 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 has the special technical feature of identifying a set of disease-relevant biclusters of genes [i.e. co-regulated gene clusters] from multiomics data including transcriptomics, not required by Groups II or III.

Group II has the special technical feature of administering two agents that target, comprise, or mimics two separate gene regulators selected from transcription factors or miRNAs, not required by Groups I or III.

Group III has the special technical feature of administering a first agent that inhibits an oncogene [note: the oncogene is not a transcription factor, see claims 94 or 95], and a second agent that is a miRNA that targets the mRNA of the oncogene, not required by Groups I or II.

Common Technical Features:

1. Groups I-II share the common technical feature of co-regulated genes and gene transcription.
2. Groups II and III share the common technical feature of administering two agents for treatment of GBM.
3. Group II and III share the common technical feature of miRNAs related to GBM.

However, said common technical features do not represent a contribution over the prior art, and are obvious over the publication titled "Uncovering MicroRNA and Transcription Factor Mediated Regulatory Networks in Glioblastoma" by Sun et al. (hereinafter "Sun") [published 19 July 2012 in PLoS Comput Biol Vol 8 No 7 Pages e1002488 1-14] in view of US 2009/0227533 A1 to Bader et al. (hereinafter "Bader")

As to common technical feature #1, Sun teaches (abstract; "In this study, we have developed a computational framework to construct a miRNA-TF regulatory network and generated the first miRNA-TF regulatory network for GBM, providing a valuable resource for further understanding the complex regulatory mechanisms in GBM. The observation of critical miRNAs in the Notch signaling pathway, with partial verification from previous studies, demonstrates that our network-based approach is promising for the identification of new and important miRNAs in GBM and, potentially, other cancers").

As to common technical features #2 and #3, Bader teaches (para [0042]; "In still further aspects, miR-34 or miR-34 inhibitor and miR-16 are administered to patients with...glioblastoma"; para [0035]; "A second therapy can include administration of a second miRNA or therapeutic nucleic acid such as a siRNA or antisense oligonucleotide, or may include various standard therapies, such as pharmaceuticals, chemotherapy, radiation therapy, drug therapy, immunotherapy, and the like").

As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I-III lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note Re: Item 4: Claims 6-22, 28-39, 43, 44, 49-93, 97-102 are held unsearchable because they are not drafted according to the second and third sentences of PCT Rule 6.4(a).