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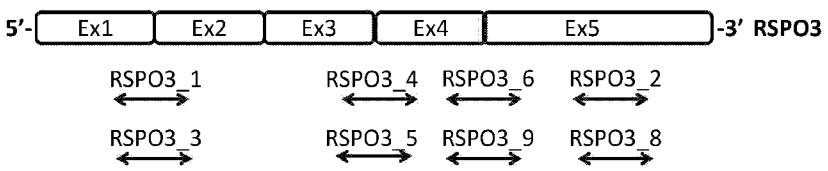
13 July 2017

(54) Title: METHODS FOR TREATING CANCER USING RSPO3 ANTAGONISTS

Figure 1A



(57) Abstract: The present invention provides compositions for identifying tumors likely to respond to treatment with an RSPO3 antagonist (e.g., anti-RSPO3 antibody). Also provided are methods for identifying tumors and/or patients that are likely to be responsive or non-responsive to treatment with an RSPO3 antagonist (e.g., anti-RSPO3 antibody). Methods for treating a patient with cancer are provided, wherein the cancer is predicted to respond to an RSPO3 antagonist (e.g., anti-RSPO3 antibody).

WO 2017/095918 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/64207

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C12Q 1/68; G01N 33/50, 33/574 (2017.01)
CPC - C12Q 1/6883, 1/6886; G01N 33/5008, 33/574

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	WO 2013/120056 A1 (GENENTECH, INC.) August 15, 2013; paragraphs [0006]-[0007], [0009]-[0014], [0016], [0019], [0033], [0069], [0074], [0088], [0104], [0106], [0121], [0125], [0128]-[0129], [0132], [0147], [0151]; figure 3A; SEQ ID NOs: 93-99	26-39, 40/26-39, 56-59, 141-146, 147/141-146, 148/141-146
A	WO 2014/165232 A1 (CUREGENIX, INC.) October 9, 2014; paragraphs [0026], [0028], [0101], [0125]-[0126], [0142], [0145]; figure 3, 6; SEQ ID NOs: 17, 19	1-4, 7, 14, 16, 22, 41/40/26-39, 62-69, 138, 140
A	WO 2012/178058 A1 (INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION) December 27, 2012; paragraphs [005], [0039], [0041], [0087]; page 63, bases 311-465; page 64, lines 4-6	1-4, 7, 14, 16, 22, 41/40/26-39, 138, 140
A	WO 2007/100357 A2 (NUVELO, INC.) September 7, 2007; page 3, lines 1-2; page 4, line 17; page 27, lines 21-22; SEQ ID NO: 11	1-4, 14, 16,41/40/26-39
A	US 2007/0244061 A1 (NIEHRS et al.) October 18, 2007; page 71, lines 8-9; claims 1, 4; SEQ ID NO: 30	7, 138
A	(SESHAGIRI, S et al.) Recurrent R-spondin fusions in colon cancer. 30 August 2012. Nature Letter. Vol. 488, pp. 660-664, DOI: 10.1038/nature11282; abstract; page 662, first column, second paragraph; page 664, first column, first paragraph; methods, first page, first column, first paragraph	62-69

☒ 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	Date of mailing of the international search report
11 May 2017 (11.05.2017)	02 JUN 2017

Name and mailing address of the ISA/	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/64207

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, 9-13, 20, 21, 23-25, 42-55, 60, 61, 99-137, 139, 149-158
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:
-***-Please see supplemental page-***-

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 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 7 (in-part), 14 (in-part), 16 (in-part), 22 (in-part), 26-40, 41 (in-part), 56-59, 62-69, 138 (in-part), 140 (in-part) and 141-148; SEQ ID NOs: 30-32

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/US16/64207

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/058132 A2 (GENENTECH, INC.) April 23, 2015; paragraphs [0029]-[0030], [0108], [0116], [0310], [0314], [0319]	62-69

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US16/64207

-***-Continued from Box No. III: Observations Where Unity of Invention Is Lacking-***-

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.

Groups I+, Claims 1-5, 14-19, 22, 26-41, 56-59, 138, 140-148 and SEQ ID NOs: 30, 31 and 32 are directed toward isolated polynucleotide probes and primers; methods of using said probes and primers for determining RPSO3 expression, and associated methods of identifying, classifying and determining the responsiveness of a cancer to treatment with a RSPO3 antagonist using said primers and probe.

The isolated polynucleotides, primers, probe, and methods will be searched to the extent they encompass a probe encompassing SEQ ID NO: 30 (first exemplary probe sequence) and a pair of primers encompassing SEQ ID NO: 31 (first exemplary forward primer) and SEQ ID NO: 32 (first exemplary reverse primer). Applicant is invited to elect additional set(s) of primer(s) with corresponding probe(s), with specified SEQ ID NO: for each, to be searched. Additional set(s) of sequences of primer(s) and corresponding probe(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 7 (in-part), 14 (in-part), 16 (in-part), 18, 19, 22 (in-part), 26-40, 41 (in-part), 56-69, 138 (in-part), 140 (in-part) and 141-148 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 30 (probe sequence), SEQ ID NO: 31 (forward primer) and SEQ ID NO: 32 (reverse primer). Applicants must specify the claims that encompass any additionally elected set(s) of primer sequence(s) and corresponding probe sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a probe encompassing SEQ ID NO: 33 (first exemplary elected probe sequence) and a pair of primers encompassing SEQ ID NOs: 34 (first exemplary elected forward primer) and SEQ ID NO: 35 (first exemplary elected reverse primer).

Group II, Claims 62-98 are directed toward a tumor that comprises an RSPO3 translocation that produces a transcript comprising a junction between PTPRK exon 13 and RSPO3 exon 2.

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: the special technical features of Groups I+ include SEQ ID NO: 30, not present in Group II; the special technical features of Group II include a junction between PTPRK exon 13 and RSPO3 exon 2, not present in any of Groups I+.

No technical features are shared between the primer and/or probe sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ and II share the technical features including: a method of identifying and classifying a human tumor and identifying and selecting patient with cancer that is likely to be responsive or non-responsive to treatment with an RSPO3 antagonist, the method comprising: (a) obtaining a sample of the human tumor; (b) detecting a RSPO3 transcript in the sample; and (c) identifying and classifying the tumor as likely to be responsive or non-responsive to the treatment; a method of determining the responsiveness of a human tumor to treatment with an RSPO3 antagonist, the method comprising: (a) obtaining a sample of the human tumor; (b) determining the presence of a transcript of RSPO3 in the sample; and (c) determining the responsiveness of the tumor to the treatment; a method of treating cancer in a patient, including increasing the likelihood of effective treatment, comprising: (a) identifying if the patient has a tumor that is likely to respond to treatment with an RSPO3 antagonist, wherein the identification comprises: (i) obtaining a sample from the patient; (ii) determining the presence of a transcript of RSPO3 in the sample; and (iii) identifying the patient who is likely to respond to the treatment; and (b) administering an effective amount of an RSPO3 antagonist to the patient who is likely to respond to the treatment; a method of inhibiting tumor growth, comprising contacting the tumor with an effective amount of an RSPO3 antagonist, wherein the tumor is predicted to respond to treatment with the RSPO3 antagonist based upon the presence of a transcript of RSPO3 in a tumor sample.

Groups I+ share the further technical features including: an isolated polynucleotide consisting of a nucleotide sequence; a composition comprising (i) a polynucleotide consisting of a nucleotide sequence and (ii) a detectable label, wherein the label is covalently attached to the polynucleotide; a combination of a probe, forward primer, and reverse primer; a method of determining RSPO3 mRNA in a sample comprising (a) contacting the sample with a combination of a probe, forward primer, and reverse primer; and (b) performing a quantitative amplification reaction; determining the expression level of RSPO3 in the sample using a pair of a forward primer and reverse primer that spans the junction between RSPO3 exon 1 and exon 2, exon 2 and exon 3, exon 3 and exon 4, or exon 4 and exon 5; and identifying and classifying a tumor as likely to be responsive or non-responsive to the treatment based upon the expression level of RSPO3, wherein likely to be responsive tumors have elevated expression levels of RSPO3 in the tumor sample; identifying a patient who is likely to respond to the treatment based upon an elevated expression level of RSPO3; a kit for detecting RSPO3 in a sample, comprising a combination of a probe, forward primer, and reverse primer; and a method of detecting an RSPO3 translocation in a human tumor in a patient with cancer, comprising (a) obtaining a human tumor sample from the patient; (b) analyzing the sample with an assay capable of determining the level of mRNA corresponding to the RSPO3 mRNA region at the exon 2 to exon 3 junction or 3' from the exon 2 to exon 3 junction; and (c) analyzing the sample with an assay capable of determining the level of mRNA corresponding to the RSPO3 mRNA region at the exon 1 to exon 2 junction or 5' from the exon 1 to exon 2 junction; wherein higher mRNA level detected in step (b) than in step (c) indicates that the tumor comprises an RSPO3 translocation.

However, these shared technical features are previously disclosed by WO 2013/120056 A1 to Genentech, Inc. et al. (hereinafter 'Genentech').

-***-Continued on Next Supplemental Page-***-

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Genentech discloses a method of identifying (a method of identifying; paragraph [0011]) and classifying (classifying; paragraph [0078]) a human tumor (a human cancer (tumor); paragraphs [0005], [0011]) and identifying (identifying; paragraph [0011]) and selecting patient with cancer (and selecting a patient with cancer; paragraph [0010]) that is likely to be responsive or non-responsive to treatment (that is likely to be responsive or non-responsive to treatment; paragraph [0011]) with an RSPO3 antagonist (with an R-spondin translocation antagonist (with an RSPO3 antagonist) paragraphs [0007], [0014]), the method comprising: (a) obtaining a sample of the human tumor (the method comprising: (a) obtaining a sample of the human tumor; paragraphs [0009], [0080]); (b) detecting a RSPO3 transcript in the sample (detecting a RSPO3 transcript in the sample; paragraphs [0014], [0069]); and (c) identifying and classifying the tumor as likely to be responsive or non-responsive to the treatment ((c) identifying and classifying the tumor as likely to be responsive or non-responsive to the treatment; paragraphs [0011], [0078]); a method of determining the responsiveness of (a method of determining the responsiveness of; paragraph [0011]) a human tumor (a human cancer (tumor); paragraphs [0005], [0011]) to treatment with an RSPO3 antagonist (to treatment with an R-spondin translocation antagonist (a RSPO3 antagonist); paragraphs [0007], [0011], [0014]), the method comprising: (a) obtaining a sample of the human tumor (the method comprising: (a) obtaining a sample of the human tumor; paragraphs [0009], [0080]); (b) detecting a RSPO3 transcript in the sample (detecting a RSPO3 transcript in the sample; paragraphs [0014], [0069]); and (c) determining the responsiveness of the tumor to the treatment (and (c) determining the responsiveness of the tumor to the treatment; paragraphs [0007], [0011], [0014]); a method of treating cancer in a patient (a method of treating cancer in a patient; paragraph [0010]), including increasing the likelihood of effective treatment (including selecting a patient with an increased likelihood of benefitting from treatment(including increasing the likelihood of effective treatment); paragraphs [0010], [0011]), comprising: (a) identifying if the patient has a tumor that is likely to respond to treatment (comprising: (a) identifying if the patient has a tumor that is likely to respond to treatment; paragraph [0011]) with an RSPO3 antagonist (with an R-spondin translocation antagonist (with an RSPO3 antagonist) paragraphs [0007], [0014]), wherein the identification comprises: (i) obtaining a sample from the patient (wherein the identification comprises: (i) obtaining a sample from the patient; paragraphs [0009], [0011], [0080]); (ii) determining the presence of a transcript of RSPO3 in the sample (detecting a RSPO3 transcript in the sample; paragraphs [0014], [0069]); and (iii) identifying the patient who is likely to respond to the treatment ((iii) identifying the patient who is likely to respond to the treatment; paragraph [0011]); and (b) administering an effective amount (administering an effective amount; paragraph [0010]) of an RSPO3 antagonist (of an R-spondin translocation antagonist (of an RSPO3 antagonist) paragraphs [0007], [0010], [0014]) to the patient who is likely to respond to the treatment (to the patient who is likely to respond to the treatment; paragraphs [0010], [0011]); a method of inhibiting tumor growth (a method of treating cancer in a subject, including the use of a tumor growth inhibitory agent (a method of inhibiting tumor growth); paragraphs [0010], [0100], [0253]), comprising contacting the tumor with an effective amount (comprising administering to the subject (comprising contacting the tumor with) an effective amount; paragraph [0010]) of an RSPO3 antagonist (of an R-spondin translocation antagonist (of an RSPO3 antagonist) paragraphs [0007], [0010], [0014]), wherein the tumor is predicted to respond to treatment (wherein the tumor is predicted to respond to treatment; paragraph [0011]) with the RSPO3 antagonist (with an R-spondin translocation antagonist (with an RSPO3 antagonist) paragraphs [0007], [0014]) based upon the presence of a transcript of RSPO3 (based upon the presence of a transcript of RSPO3; paragraph [0014]) in a tumor sample (in a tumor sample; paragraphs [0009], [0080]); an isolated polynucleotide consisting of a nucleotide sequence (a primer comprising a nucleotide sequence (an isolated polynucleotide consisting of a nucleotide sequence); paragraph [0125]); a composition comprising (i) a polynucleotide consisting of a nucleotide sequence and (ii) a detectable label, wherein the label is covalently attached to the polynucleotide (a composition comprising (i) a polynucleotide consisting of a nucleotide sequence and (ii) a detectable label, wherein the label is covalently attached to the polynucleotide; paragraphs [0033], [0088]); a combination of a probe, forward primer, and reverse primer (forward and reverse primers for amplification of RSPO3 translocation transcripts and probes for hybridization thereto (a combination of a probe, forward primer, and reverse primer); paragraphs [0125], [0133], [0135]); a method of determining RSPO3 mRNA in a sample (a method of determining RSPO3 mRNA in a sample; paragraphs [0125], [0133]) comprising (a) contacting the sample with a combination of a probe, forward primer, and reverse primer (contacting the sample with a combination of a probe, forward primer, and reverse primer; paragraphs [0125], [0133], [0135]); and (b) performing a quantitative amplification reaction (performing a quantitative amplification reaction; paragraph [0131]); determining the expression level of a RSPO3 translocation in a sample using a pair of a forward primer and reverse primer (determining the expression level of a RSPO3 translocation in a sample using a pair of a forward primer and reverse primer; paragraphs [0125], [0131], [0133]) that spans the junction between a fusion partner and RSPO3 exon 2 (that spans the junction between a fusion partner and RSPO3 exon 2; paragraphs [0125]); and identifying and classifying a tumor as likely to be responsive or non-responsive to the treatment based upon the expression level of RSPO3 (identifying and classifying a tumor as likely to be responsive or non-responsive to the treatment based upon the expression level of a RSPO3 fusion in comparison to normal RSPO3 (based upon the expression level of RSPO3); paragraphs [0011], [0014], [0070], [0315]), wherein likely to be responsive tumors have elevated expression levels of RSPO3 in the tumor sample (wherein tumors having translocations have increased expression levels (wherein likely to be responsive tumors have elevated expression levels of RSPO3 in the tumor sample); paragraphs [0011], [0080], [0315]); identifying a patient who is likely to respond to the treatment (identifying a patient who is likely to respond to the treatment; paragraphs [0010], [0011]) based upon an elevated expression level of RSPO3 (based on elevated expression of a RSPO3 gene comprising a transposition (based upon an elevated expression level of RSPO3); paragraphs [0011], [0070], [0315]); a kit for detecting (a kit for detecting; paragraph [0106]) RSPO3 (RSPO3; paragraphs [0014], [0125]) in a sample (in a sample; paragraphs [0009], [0080]), comprising a combination of a probe, forward primer, and reverse primer (comprising a combination of a probe, forward primer, and reverse primer; paragraphs [0106], [0131], [0133]). Genentech further discloses determining the sequence of the junction in order to determine the source gene exon (determining the sequence of the junction in order to determine the source gene exon; paragraphs [0125], [0315]); and wherein the translocation produces in-frame fusions including downstream RSPO3 sequences (wherein the translocation produces in-frame fusions including downstream RSPO3 sequences; para [0315]).

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Genentech does not disclose determining the expression level of RSPO3 in the sample using a pair of a forward primer and reverse primer that spans the junction between RSPO3 exon 1 and exon 2, exon 2 and exon 3, exon 3 and exon 4, or exon 4 and exon 5; and a method of detecting an RSPO3 translocation in a human tumor in a patient with cancer, comprising (a) obtaining a human tumor sample from the patient; (b) analyzing the sample with an assay capable of determining the level of mRNA corresponding to the RSPO3 mRNA region at the exon 2 to exon 3 junction or 3' from the exon 2 to exon 3 junction; and (c) analyzing the sample with an assay capable of determining the level of mRNA corresponding to the RSPO3 mRNA region at the exon 1 to exon 2 junction or 5' from the exon 1 to exon 2 junction; wherein higher mRNA level detected in step (b) than in step (c) indicates that the tumor comprises an RSPO3 translocation. However, it would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Genentech to have specified wherein a control for determination of the expression levels of an intact RSPO3 gene from a normal sample from a patient would have targeted a region not included in a detected transposition, such as upstream of exon 2, including the exon 1 junction with exon 2, using primers spanning the junction, in order to amplify and determine the expression of solely normal RSPO3 in the sample as a control. It further would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Genentech to have determined the degree of overexpression of a RSPO3 translocation-comprising transcript in a sample from a tumor using primers directed to a region downstream (3') of one or more known translocation junctions, such as at the exon 2 - exon 3 junction, in order to enable the subtractive comparison of amplified products from the RSPO3 translocation-comprising transcript and a normal control, as above, on the basis of the RSPO3 sequence, alone, in order to simplify a determination of potential responsiveness to a RSPO3 antagonist, as disclosed by Genentech, without the additional complexity of determining the source gene exon and sequence of the junction, as disclosed by Genentech.

Since none of the special technical features of the Groups I+ and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Gnenetech reference, unity of invention is lacking.