R-SPONDIN TRANSLOCATIONS AND METHODS USING THE SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119 to United States Patent Application No. 61/597,746 filed on February 11, 2012 and 61/674,763 filed on July 23, 2012, the entire contents of which are incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing submitted via EFS-Web and hereby incorporated by reference in its entirety. Said ASCII copy, created on January 31, 2013, is named P4853R1WO_PCTSequenceListing.txt and is 58,980 bytes in size.

FIELD

[0003] Provided are therapies related to the treatment of pathological conditions, such as cancer.

BACKGROUND

[0004] Colorectal cancer (CRC) with over 100,000 new cases reported annually is the fourth most prevalent cancer and accounts for over 50,000 deaths per year in the United States (Siegel, R. *et al.*, *CA: A Cancer Journal for Clinicians* 61:212-236 (2011)). Approximately 15% of CRCs exhibit microsatellite instability (MSI) arising from defects in DNA mismatch repair (MMR) system (Fearon, E. R., *Annu. Rev. Pathol.* 6:479-507 (2011)). The other ~85% of microsatellite stable (MSS) CRCs are the result of chromosomal instability (CIN) (Fearon, E. R., *Annu. Rev. Pathol.* 6:479-507 (2011)). Genomic studies have identified acquisition of mutations in genes like *APC*, *KRAS*, and *TP53* during CRC progression (Fearon, E. R., *Annu. Rev. Pathol.* 6:479-507 (2011)). Sequencing colon cancer protein-coding exons and whole genomes in a small number of samples have identified several additional mutations and chromosomal structural variants that likely contribute to oncogenesis (Wood, L. D. *et al.*, *Science* 318:1108-1113 (2007); Timmermann, B. *et al.*, *PloS One* 5:e15661 (2010)). However, recent insertional mutagenesis screens in mouse models of colon cancer suggested involvement of additional genes and pathways in CRC development (Starr, T. K. *et al.*, *Science* 323:1747-1750 (2009); March, H. N. *et al.*, *Nat. Genet.* 43:1202-1209 (2011)).

[0005] There remains a need to better understand the pathogenesis of cancers, in particular, human colon cancers and also to identify new therapeutic targets.

SUMMARY

[0006] The ~~invention~~ disclosure provides wnt pathway antagonists including R-spondin-translocation antagonists and methods of using the same.

[0006a] In one aspect, there is provided an *in vitro* method of inhibiting proliferation of a cancer cell comprising contacting the cancer cell with an effective amount of an R-spondin-translocation

antagonist.

[0006b] In one aspect, there is provided the use of an effective amount of an R-spondin-translocation antagonist in the manufacture of a medicament for inhibiting proliferation of a cancer cell wherein said cancer cell is to be contacted with said medicament.

[0007] Provided herein are methods of inhibiting cell proliferation of a cancer cell comprising contacting the cancer cell with an effective amount of an R-spondin-translocation antagonist..

Further provided herein are methods of treating cancer in an individual comprising administering to the individual an effective amount of an R-spondin-translocation antagonist. In some embodiments of any of the methods, the cancer or cancer cell comprises an R-spondin translocation.

[0007a] In one aspect, there is provided the use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating cancer in an individual, wherein treatment is based upon the individual having cancer comprising an R-spondin translocation.

[0007b] In one aspect, there is provided the use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating a cancer cell, wherein the cancer cell comprises an R-spondin translocation.

[0007c] In one aspect, there is provided the use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating cancer in an individual provided that the individual has been found to have cancer comprising an R-spondin translocation.

[0008] Provided herein are methods of treating cancer in an individual comprising administering to the individual an effective amount of a wnt pathway antagonist, wherein treatment is based upon the individual having cancer comprising an R-spondin translocation. Provided herein are methods of treating a cancer cell, wherein the cancer cell comprises an R-spondin translocation, and wherein the method comprises providing an effective amount of a wnt pathway antagonist. Also provided herein are methods of treating cancer in an individual provided that the individual has been found to have cancer comprising an R-spondin translocation, the treatment comprising administering to the individual an effective amount of a wnt pathway antagonist.

[0008a] In one aspect, there is provided the use of an effective amount of an anti-cancer therapy comprising a wnt pathway antagonist in the manufacture of a medicament for treating cancer in an individual, wherein a sample obtained from the individual has been determined to comprise an R-spondin translocation, whereby the cancer is treated.

[0009] Further, provided herein are methods for treating cancer in an individual, the method comprising: determining that a sample obtained from the individual comprises an R-spondin translocation, and administering an effective amount of an anti-cancer therapy comprising a wnt pathway antagonist to the individual, whereby the cancer is treated.

[0009a] In one aspect, there is provided the use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to an individual having cancer that has been selected, wherein the cancer comprises an R-spondin translocation, whereby the cancer is treated.

[0010] Provided herein are methods of treating cancer, comprising: (a) selecting an individual having cancer, wherein the cancer comprising an R-spondin translocation; and (b) administering to

the individual thus selected an effective amount of a wnt pathway antagonist, whereby the cancer is treated.

[0011] ~~Provided herein are also~~In one aspect, there is provided a methods of identifying an individual with cancer who is more likely or less likely to exhibit benefit from treatment with an anti-cancer therapy comprising a wnt pathway antagonist, the method comprising: determining presence or absence of an R-spondin translocation in a sample obtained from the individual, wherein presence of the R-spondin translocation in the sample indicates that the individual is more likely to exhibit benefit from treatment with the anti-cancer therapy comprising the wnt pathway antagonist or absence of the R-spondin translocation indicates that the individual is less likely to exhibit benefit from treatment with the anti-cancer therapy comprising the wnt pathway antagonist. In some embodiments, the method further comprises administering an effective amount of the anti-cancer therapy comprising a wnt pathway antagonist.

[0012] ~~Provided herein are~~In one aspect, there is provided a methods for predicting whether an individual with cancer is more or less likely to respond effectively to treatment with an anti-cancer therapy comprising a wnt pathway antagonist, the method comprising determining an R-spondin translocation, whereby presence of the R-spondin translocation indicates that the individual is more likely to respond effectively to treatment with the wnt pathway antagonist and absence of the R-spondin translocation indicates that the individual is less likely to respond effectively to treatment with the wnt pathway antagonist. In

some embodiments, the method further comprises administering an effective amount of the anti-cancer therapy comprising a wnt pathway antagonist.

[0013] ~~Further provided herein are~~In one aspect, there is provided a methods of predicting the response or lack of response of an individual with cancer to an anti-cancer therapy comprising a wnt pathway antagonist comprising detecting in a sample obtained from the individual presence or absence of an R-spondin translocation, wherein presence of the R-spondin translocation is predictive of response of the individual to the anti-cancer therapy comprising the wnt pathway antagonist and absence of the R-spondin translocation is predictive of lack of response of the individual to the anti-cancer therapy comprising the wnt pathway antagonist. In some embodiments, the method further comprises administering an effective amount of the anti-cancer therapy comprising a wnt pathway antagonist.

[0013a] In one aspect, there is provided the use of an effective amount of an R-spondin-translocation antagonist in the manufacture of a medicament for treating cancer in an individual.

[0014] In some embodiments of any of the methods, the R-spondin translocation is a RSPO1 translocation, RSPO2 translocation, RSPO3 translocation and/or RSPO4 translocation. In some embodiments, the R-spondin translocation is a RSPO2 translocation. In some embodiments, the RSPO2 translocation comprises *EIF3E* and *RSPO2*. In some embodiments, the RSPO2 translocation comprises *EIF3E* exon 1 and *RSPO2* exon 2. In some embodiments, the RSPO2 translocation comprises *EIF3E* exon 1 and *RSPO2* exon 3. In some embodiments, the RSPO2 translocation comprises SEQ ID NO:71 In some embodiments, the R-spondin translocation is a RSPO3 translocation. In some embodiments, the RSPO3 translocation comprises *PTPRK* and *RSPO3*. In some embodiments, the RSPO3 translocation comprises *PTPRK* exon 1 and *RSPO3* exon 2. In some embodiments, the RSPO3 translocation comprises *PTPRK* exon 7 and *RSPO3* exon 2. In some embodiments, the RSPO3 translocation comprises SEQ ID NO:72 and/or SEQ ID NO:73. In some embodiments of any of the methods, the R-spondin translocation is detected at the chromosomal level (e.g., FISH), DNA level, RNA level (*e.g.*, RSPO1-translocation fusion transcript), and/or protein level (*e.g.*, RSPO1-translocation fusion polypeptide).

[0015] In some embodiments of any of the methods, the cancer is colorectal cancer. In some embodiments, the cancer is a colon cancer or rectal cancer.

1) In some embodiments of any of the methods, the wnt pathway antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the wnt pathway antagonist is an R-spondin antagonist. In some embodiments, the R-spondin antagonist is a RSPO1 antagonist, RSPO2 antagonist, RSPO3 antagonist, and/or RSPO4 antagonist. In some embodiments, the wnt pathway antagonist is an isolated monoclonal antibody which binds R-spondin. In some embodiments, the R-spondin is RSPO2 and/or RSPO3. In some embodiments, the R-spondin antagonist is an R-spondin-translocation antagonist. In some embodiments, the R-spondin-translocation antagonist binds a RSPO1-translocation fusion polypeptide and/or polynucleotide, RSPO2-translocation fusion polypeptide and/or polynucleotide, RSPO3-translocation fusion polypeptide and/or polynucleotide

and/or RSPO4-translocation fusion polypeptide and/or polynucleotide. In some embodiments, the R-spondin-translocation antagonist binds a RSPO2-translocation fusion polypeptide and/or polynucleotide. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* and *RSPO2*. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 2. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 3. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:71. In some embodiments, the R-spondin-translocation fusion polypeptide and/or polynucleotide is a RSPO3-translocation fusion polypeptide and/or polynucleotide. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* and *RSPO3*. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 1 and *RSPO3* exon 2. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 7 and *RSPO3* exon 2. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:72 and/or SEQ ID NO:73. In some embodiments, the method further comprises an additional therapeutic agent.

[0016] ~~Provided herein are~~In one aspect, there is provided an isolated R-spondin-translocation antagonists~~,~~ wherein the R-spondin-translocation antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide. In some embodiments, the R-spondin-translocation antagonist binds a RSPO1-translocation fusion polypeptide and/or polynucleotide, RSPO2-translocation fusion polypeptide and/or polynucleotide, RSPO3-translocation fusion polypeptide and/or polynucleotide and/or RSPO4-translocation fusion polypeptide and/or polynucleotide. In some embodiments, the R-spondin-translocation antagonist binds a RSPO2-translocation fusion polypeptide and/or polynucleotide. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* and *RSPO2*. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 2. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 3. In some embodiments, the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:71. In some embodiments, the R-spondin-translocation fusion polypeptide and/or polynucleotide is a RSPO3-translocation fusion polypeptide and/or polynucleotide. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* and *RSPO3*. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 1 and *RSPO3* exon 2. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 7 and *RSPO3* exon

2. In some embodiments, the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:72 and/or SEQ ID NO:73.

BRIEF DESCRIPTION OF THE FIGURES

[0017] Figure 1 | (**A**) Activation of an alternate novel 5' exon of *MRPL33* in a tumor specific manner alters the N-terminal end of MRPL33 and makes the protein longer. (**B**) The boxplot shows the read counts for the upstream exon normalized by total number of reads aligning to *MRPL33* for each sample. (**C**) Also shown is evidence of an alternate upstream *MRPL33* promoter region showing H3K27Ac marking by USCS genome browser as well as an EST mapping to the upstream exon. MRLP33 Amino Acid Sequence ***MFLSAVFF AKSKSN***ETKSPLRGKEKNTLPLNGGLKMTLIYKEKTEGG DTDSEIL (SEQ ID NO:9); MRLP33 alternative promoter amino acid sequence ***MMAHLDFFLTYKWRAPKSKSLDQLSPNFLLRGRS*** ETKSPLRGKEKNTLPLNGGLKMTLIYKEKTEGGDTDSEIL (SEQ ID NO:10).

[0018] Figure 2 | Recurrent R-spondin translocations. (**A**) List of the type and frequency of R-spondin gene fusions in colon cancer. (**B**) Cartoon depicting the location, orientation and exon-intron architecture of *EIF3E-RSPO2* fusion on the genome. The read evidence for *EIF3E(e1)-RSPO2(e2)* fusion identified using RNA-seq data are shown. (**C**) Independent RT-PCR derived products confirming the *EIF3E-RSPO2* somatic fusion resolved on an agarose gel. RT-PCR products were Sanger sequenced to confirm the fusion junction and a relevant representative chromatogram is presented. (**D**) Schematic of the resulting EIF3E-RSPO2 fusion protein. (**E**) Tumors harboring R-spondin fusions show elevated expression of the corresponding *RSPO* gene shows on a heatmap. Figure 2 discloses SEQ ID NOS 85-92 and 71, respectively, in order of appearance.

[0019] Figure 3 | Recurrence of *PTPRK-RSPO3* gene fusion. (**A**) Cartoon depicting the location, orientation and exon-intron architecture of *PTPRK-RSPO3* gene fusion on the genome. The read evidence for *PTPRK(e1)-RSPO3(e2)* fusion identified using RNA-seq data are shown. (**B**) Independent RT-PCR derived products confirming the *PTPRK-RSPO3* somatic fusion resolved on an agarose gel. RT-PCR products were Sanger sequenced to confirm the fusion junction and a relevant representative chromatogram is presented. (**C**) Schematic of PTPRK, RSPO3 and the resulting PTPRK-RSPO3 fusion proteins. Figure 3 discloses SEQ ID NOS 93-99 and 72, respectively, in order of appearance.

[0020] Figure 4 | (**A**) *PTPRK(e7)-RSPO3*(e2) fusion. (**B**) Gel showing the validation of this fusion by RT-PCR. (**C**) Schematic diagram of the native and fusion proteins. Figure 4 discloses SEQ ID NOS 100-104 and 73, respectively, in order of appearance.

CLAIMS

WHAT IS CLAIMED IS:

1) ~~A method of treating cancer in an individual comprising administering to the individual~~ Use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating cancer in an individual, wherein treatment is based upon the individual having cancer comprising an R-spondin translocation.

2) ~~A method of treating a cancer cell, wherein the cancer cell comprises an R-spondin translocation, the method comprising providing~~ Use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating a cancer cell, wherein the cancer cell comprises an R-spondin translocation.

3) ~~A method of treating cancer in an individual provided that the individual has been found to have cancer comprising an R-spondin translocation, the method comprising administering to the individual~~ Use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating cancer in an individual provided that the individual has been found to have cancer comprising an R-spondin translocation.

4) ~~A method for treating cancer in an individual, the method comprising: determining that a sample obtained from the individual comprises an R-spondin translocation, and administering~~ Use of an effective amount of an anti-cancer therapy comprising a wnt pathway antagonist in the manufacture of a medicament for treating cancer in an individual, wherein a sample obtained from the individual has been determined to comprise an R-spondin translocation~~to the individual~~, whereby the cancer is treated.

5) ~~A method of treating cancer, comprising: (a) selecting an individual having cancer, wherein the cancer comprising an R-spondin translocation; and (b) administering to the individual thus selected~~Use of an effective amount of a wnt pathway antagonist in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to an individual having cancer that has been selected, wherein the cancer comprises an R-spondin translocation, whereby the cancer is treated.

6) A method of identifying an individual with cancer who is more or less likely to exhibit benefit from treatment with an anti-cancer therapy comprising a wnt pathway antagonist, the method comprising: determining presence or absence of an R-spondin translocation in a sample obtained from the individual, wherein presence of the R-spondin translocation in the sample indicates that the individual is more likely to exhibit benefit from treatment with the anti-cancer therapy comprising the wnt pathway antagonist or absence of the R-spondin translocation indicates that the individual is less likely to exhibit benefit from treatment with the anti-cancer therapy comprising the wnt pathway antagonist.

7) A method for predicting whether an individual with cancer is more or less likely to respond effectively to treatment with an anti-cancer therapy comprising a wnt pathway antagonist, the method comprising determining an R-spondin translocation, whereby presence of the R-spondin translocation indicates that the individual is more likely to respond effectively to treatment with the wnt pathway antagonist and absence of the R-spondin translocation indicates that the individual is less likely to respond effectively to treatment with the wnt pathway antagonist.

8) A method of predicting the response or lack of response of an individual with cancer to an anti-cancer therapy comprising a wnt pathway antagonist comprising detecting in a sample obtained from the individual presence or absence of an R-spondin translocation, wherein presence of the R-spondin translocation is predictive of response of the individual to the anti-cancer therapy comprising the wnt pathway antagonist and absence of the R-spondin translocation is predictive of lack of response of the individual to the anti-cancer therapy comprising the wnt pathway antagonist.

9) The method of any one of claims 6-8, wherein the method further comprises administering to the individual an effective amount of a wnt pathway antagonist.

10) An *in vitro* method of inhibiting proliferation of a cancer cell comprising contacting the cancer cell with an effective amount of an R-spondin-translocation antagonist.

~~10)~~11) Use of an effective amount of an R-spondin-translocation antagonist in the manufacture of a medicament for inhibiting proliferation of a cancer cell wherein said cancer cell is to be contacted with said medicament.

~~11)~~12) ~~A method of treating cancer in an individual comprising administering to the individual~~ Use of an effective amount of an R-spondin-translocation antagonist in the manufacture of a medicament for treating cancer in an individual.

~~12)~~13) The method of ~~any one of~~ claims 10-~~11~~ or use of claims 11 or 12, wherein the cancer or cancer cell comprises an R-spondin translocation.

~~13)~~14) The use of any one of claims 1-5 or method of any one of claims ~~6~~1-9 ~~and~~ or the method or use of claim 13~~2~~, wherein the R-spondin translocation is a RSPO1 translocation, RSPO2 translocation, RSPO3 translocation and/or RSPO4 translocation.

~~14)~~15) The use or method of claim 1~~4~~3, wherein the R-spondin translocation is a RSPO2 translocation.

~~15)~~16) The use or method of claim 1~~5~~4, wherein the RSPO2 translocation comprises *EIF3E* and *RSPO2*.

~~16)~~17) The use or method of claim 1~~5~~4, wherein the RSPO2 translocation comprises *EIF3E* exon 1 and *RSPO2* exon 2.

~~17)~~18) The use or method of claim 1~~5~~4, wherein the RSPO2 translocation comprises *EIF3E* exon 1 and *RSPO2* exon 3.

~~18)~~19) The use or method of claim 1~~5~~4, wherein the RSPO2 translocation comprises SEQ ID NO:71.

~~19)~~20) The use or method of claim 1~~4~~3, wherein the R-spondin translocation is a RSPO3 translocation.

~~20)~~21) The use or method of claim 20~~19~~, wherein the RSPO3 translocation comprises *PTPRK* and *RSPO3*.

~~21)~~22) The use or method of claim 20~~19~~, wherein the RSPO3 translocation comprises *PTPRK* exon 1 and *RSPO3* exon 2.

~~22)~~23) The use or method of claim 20~~19~~, wherein the RSPO3 translocation comprises *PTPRK* exon 7 and *RSPO3* exon 2.

~~23)~~24) The use or method of claim 20~~19~~, wherein the RSPO3 translocation comprises SEQ ID NO:72 and/or SEQ ID NO:73.

~~24)~~25) The use of any one of claims 1-5 or method of any one of claims ~~1~~6-9 ~~and~~or the use or method of any one of claims 13~~2~~-24~~3~~, wherein the R-spondin translocation is detected at the chromosomal level (e.g., FISH), DNA level, RNA level (*e.g.*, RSPO1-translocation fusion transcript), and/or protein level (*e.g.*, RSPO1-translocation fusion polypeptide).

~~25)~~26) The use of any one of claims 1-5 or 11-12 or method of any one of claims 6-10 or the use or method of any one of claims ~~1~~13-25~~4~~, wherein the cancer or cancer cell is colorectal cancer.

~~26)~~27) The use or method of claim 26~~5~~, wherein the cancer or cancer cell is a colon cancer or rectal cancer.

~~27)~~28) The use of any one of claims 1-5 or method of any one of claims ~~1~~6-9 ~~and~~ or the use or method of any one of claims 14~~3~~-27~~6~~, wherein the wnt pathway antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

~~28)~~29) The use of any one of claims 1-5 or method of any one of claims ~~6~~1-9 ~~and~~ or the use or method of any one of claims 14~~3~~-28~~7~~, wherein the wnt pathway antagonist is an R-spondin antagonist.

~~29)~~30) The use or method of claim 29~~8~~, wherein the wnt pathway antagonist is an isolated monoclonal antibody which binds R-spondin.

~~30)~~31) The use or method of claim 30-~~29~~, wherein the R-spondin is RSPO2 and/or RSPO3.

~~31)~~32) The use or method of any one of claims 2~~9~~8-3~~1~~0, wherein the R-spondin antagonist is an R-spondin-translocation antagonist.

~~32)~~33) An isolated R-spondin-translocation antagonist, wherein the R-spondin-translocation antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.

~~33)~~34) The use or method of claim 3~~2~~1 or antagonist of claim 3~~3~~2, wherein the R-spondin-translocation antagonist binds a RSPO1-translocation fusion polypeptide and/or polynucleotide, RSPO2-translocation fusion polypeptide and/or polynucleotide, RSPO3-translocation fusion polypeptide and/or polynucleotide and/or RSPO4-translocation fusion polypeptide and/or polynucleotide.

~~34)~~35) The use or method or antagonist of claim 3~~4~~3, wherein the R-spondin-translocation antagonist binds a RSPO2-translocation fusion polypeptide and/or polynucleotide.

~~35)~~36) The use or method or antagonist of claim 3~~5~~4, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* and *RSPO2*.

~~36)~~37) The use or method or antagonist of claim 3~~5~~4, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 2.

~~37)~~38) The use or method or antagonist of claim 3~~5~~4, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 3.

~~38)~~39) The use or method or antagonist of claim 3~~5~~4, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:71.

~~39)~~40) The use or method or antagonist of claim 3~~4~~3, wherein the R-spondin-translocation fusion polypeptide and/or polynucleotide is a RSPO3-translocation fusion polypeptide and/or polynucleotide.

~~40)~~41) The use or method or antagonist of claim 4~~0~~39, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* and *RSPO3*.

~~41)~~42) The use or method or antagonist of claim 4~~0~~39, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 1 and *RSPO3* exon 2.

~~42)~~43) The use or method or antagonist of claim 4~~0~~39, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 7 and *RSPO3* exon 2.

~~43)~~44) The use or method or antagonist of claim 4~~0~~39, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:72 and/or SEQ ID NO:73.

~~44)~~45) The use of any one of claims 1-5 or 11-12, or method of any one of claims 6-10, or the use or method of any one of claims 13-32, or the antagonist of claim 33, or the use or method or antagonist of any one of claims ~~1~~34-4~~2~~1, wherein ~~the method further comprises administering~~ an additional therapeutic agent is to be administered.