

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 an ~~an wnt pathway~~R-spondin 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 an ~~an wnt pathway~~R-spondin 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 an ~~an wnt pathway~~R-spondin 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 an ~~an wnt pathway~~R-spondin 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 an ~~an wnt pathway~~R-spondin 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] In one aspect, there is provided a method of identifying an individual with cancer who is more likely or less likely to exhibit benefit from treatment with an anti-cancer therapy comprising an ~~wnt pathway~~ R-spondin 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 ~~R-spondinwnt 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 ~~R-spondinwnt pathway~~ antagonist. In some embodiments, the method further comprises administering an effective amount of the anti-cancer therapy comprising a wnt pathway antagonist.

[0012] In one aspect, there is provided 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 an ~~R-spondinwnt pathway~~ R-spondin 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 ~~R-spondinwnt pathway~~ antagonist and absence of the R-spondin translocation indicates that the individual is less likely to respond effectively to treatment with the ~~R-spondinwnt pathway~~ antagonist. In

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

[0013] In one aspect, there is provided a method of predicting the response or lack of response of an individual with cancer to an anti-cancer therapy comprising an R-spondin-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 R-spondin-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 R-spondin-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

CLAIMS

WHAT IS CLAIMED IS:

- 1) Use of an effective amount of an R-spondina-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) Use of an effective amount of an R-spondina-wnt pathway antagonist in the manufacture of a medicament for treating a cancer cell, wherein the cancer cell comprises an R-spondin translocation.
- 3) Use of an effective amount of an R-spondina-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) Use of an effective amount of an anti-cancer therapy comprising an R-spondina-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.
- 5) Use of an effective amount of an R-spondina-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 an R-spondina-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 R-spondinwnt 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 R-spondinwnt 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 an R-spondina-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 R-spondinwnt pathway antagonist and absence of the R-spondin translocation indicates that the individual is less likely to respond effectively to treatment with the R-spondinwnt pathway antagonist.
- 8) A method of predicting the response or lack of response of an individual with cancer to an anti-cancer therapy comprising an R-spondina-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 R-spondinwnt 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 R-spondinwnt 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 an ~~R-spondin-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.
- 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.
- 12) Use of an effective amount of an R-spondin-translocation antagonist in the manufacture of a medicament for treating cancer in an individual.
- 13) The method of claim 10 or use of claims 11 or 12, wherein the cancer or cancer cell comprises an R-spondin translocation.
- 14) The use of any one of claims 1-5 or method of any one of claims 6-9 or the method or use of claim 13, wherein the R-spondin translocation is a RSPO1 translocation, RSPO2 translocation, RSPO3 translocation and/or RSPO4 translocation.
- 15) The use or method of claim 14, wherein the R-spondin translocation is a RSPO2 translocation.
- 16) The use or method of claim 15, wherein the RSPO2 translocation comprises *EIF3E* and *RSPO2*.
- 17) The use or method of claim 15, wherein the RSPO2 translocation comprises *EIF3E* exon 1 and *RSPO2* exon 2.
- 18) The use or method of claim 15, wherein the RSPO2 translocation comprises *EIF3E* exon 1 and *RSPO2* exon 3.
- 19) The use or method of claim 15, wherein the RSPO2 translocation comprises SEQ ID NO:71.
- 20) The use or method of claim 14, wherein the R-spondin translocation is a RSPO3 translocation.
- 21) The use or method of claim 20, wherein the RSPO3 translocation comprises *PTPRK* and *RSPO3*.
- 22) The use or method of claim 20, wherein the RSPO3 translocation comprises *PTPRK* exon 1 and *RSPO3* exon 2.
- 23) The use or method of claim 20, wherein the RSPO3 translocation comprises *PTPRK* exon 7 and *RSPO3* exon 2.
- 24) The use or method of claim 20, wherein the RSPO3 translocation comprises SEQ ID NO:72 and/or SEQ ID NO:73.
- 25) The use of any one of claims 1-5 or method of any one of claims 6-9 or the use or method of any one of claims 13-24, 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).
- 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 13-25, wherein the cancer or cancer cell is colorectal cancer.
- 27) The use or method of claim 26, wherein the cancer or cancer cell is a colon cancer or rectal cancer.
- 28) The use of any one of claims 1-5 or method of any one of claims 6-9 or the use or method of any one of claims 14-27, wherein the ~~R-spondin-wnt pathway~~ antagonist is an antibody, binding polypeptide, small molecule, or polynucleotide.
- 29) The use of any one of claims 1-5 or method of any one of claims 6-9 or the use or method of any one of claims 14-28, wherein the ~~wnt pathway antagonist~~ is an R-spondin antagonist.
- 30) ~~The use or method of claim 29, wherein the wnt pathway antagonist is an isolated monoclonal antibody which binds R-spondin.~~

~~34)30)~~ The use or method of claim ~~30929~~, wherein the R-spondin is RSPO2 and/or RSPO3.

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

32) The use or method of any one of claims 29-~~34~~~~30~~, wherein the R-spondin antagonist is an R-spondin-translocation antagonist.

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

34) The use or method of claim 32 or antagonist of claim 33, 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.

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

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

37) The use or method or antagonist of claim 35, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 2.

38) The use or method or antagonist of claim 35, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises *EIF3E* exon 1 and *RSPO2* exon 3.

39) The use or method or antagonist of claim 35, wherein the RSPO2-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:71.

40) The use or method or antagonist of claim 34, wherein the R-spondin-translocation fusion polypeptide and/or polynucleotide is a RSPO3-translocation fusion polypeptide and/or polynucleotide.

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

42) The use or method or antagonist of claim 40, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 1 and *RSPO3* exon 2.

43) The use or method or antagonist of claim 40, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises *PTPRK* exon 7 and *RSPO3* exon 2.

44) The use or method or antagonist of claim 40, wherein the RSPO3-translocation fusion polypeptide and/or polynucleotide comprises SEQ ID NO:72 and/or SEQ ID NO:73.

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 34-~~42~~~~44~~, wherein an additional therapeutic agent is to be administered.