31. The polypeptide of claim 30, which is an antibody.

32. A cell comprising or producing the antibody or polypeptide according to any one of claims 1-31.

33. A hybridoma cell line having ATCC deposit number PTA-11970.

34. An isolated polynucleotide molecule comprising a polynucleotide that encodes an antibody or polypeptide according to any one of claims 1-31.

35. An isolated polynucleotide molecule comprising a polynucleotide sequence selected from the group consisting of: SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, and SEQ ID NO:58.

36. A vector comprising the polynucleotide of claim 34 or claim 35.

37. A cell comprising the polynucleotide of claim 34 or claim 35 or the vector of claim 36.

38. A pharmaceutical composition comprising the antibody or polypeptide according to any one of claims 1-31 and a pharmaceutically acceptable carrier.

39. ~~A method of inhibiting growth of a tumor, wherein the method comprises contacting the tumor with~~ Use of an effective amount of an antibody according to any of claims 1-29 in the manufacture of a medicament for inhibiting growth of a tumor, wherein the medicament is to be contacted to the tumor.

40. ~~A method of inhibiting growth of a tumor in a subject, wherein the method comprises administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any of claims 1-29 in the manufacture of a medicament for inhibiting growth of a tumor in a subject, wherein the medicament is to be administered to the subject.

41. ~~A method of inducing differentiation of tumor cells in a subject, comprising administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any one of claims 1-29 in the manufacture of a medicament for inducing differentiation of tumor cells in a subject, wherein the medicament is to be administered to the subject.

42. ~~A method of reducing the frequency of cancer stem cells in a tumor in a subject, comprising administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any one of claims 1-29 in the manufacture of a medicament for reducing the frequency of cancer stem cells in a tumor in a subject, wherein the medicament is to be administered to the subject.

43. ~~A method of inhibiting β-catenin signaling in a cell, comprising contacting the cell with~~ Use of an effective amount of an antibody according to any one of claims 1-29 in the manufacture of a medicament for inhibiting β-catenin signaling in a cell, wherein said medicament is to be contacted to the cell.

44. The ~~method~~use of claim 43, wherein the cell is a tumor cell.

45. The ~~method~~use according to any one of claims 39-42 or 44, wherein the tumor is selected from the group consisting of colorectal tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor.

46. The ~~method~~use of claim 45, wherein the tumor is a pancreatic tumor.

47. The ~~method~~use of claim 45, wherein the tumor is an ovarian tumor.

48. ~~A method of treating cancer in a subject, wherein the method comprises administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any of claims 1-29 in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is to be administered to the subject.

49. The ~~method~~use of claim 48, wherein the cancer is selected from the group consisting of colorectal cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer.

50. The ~~method~~use of claim 49, wherein the cancer is colorectal cancer or pancreatic cancer.

51. The ~~method~~use of claim 50, wherein the colorectal cancer comprises an inactivating mutation in the adenomatous polyposis coli (APC) gene.

52. The ~~method~~use of claim 50, wherein the colorectal cancer does not comprise an inactivating mutation in the APC gene.

53. The ~~method~~use of claim 50, wherein the colorectal cancer comprises a wild-type APC gene.

54. The ~~method~~use of claim 50, wherein the colorectal cancer does not comprise an activating mutation in the β-catenin gene.

55. The ~~method~~use of claim 49, wherein the cancer is ovarian cancer.

56. The ~~method~~use according to any one of claims 39-42 or 44-55, wherein the tumor or the cancer expresses elevated levels of RSPO1 as compared to levels of RSPO1 in normal tissue.

57. The ~~method~~use according to any one of claims 40-42 or 45-56, wherein the subject has had a tumor or a cancer removed.

58. The ~~method~~use according to any one of claims 39-42 or 44-57, further comprising a step of determining the level of RSPO1 expression in the tumor or cancer.

59. The ~~method~~use according to any one of claims 39-42 or 44-58, further comprising a step of determining if the tumor or cancer has an inactivating mutation in the APC gene.

60. The ~~method~~use according to any one of claims 39-42 or 44-59, further comprising a step of determining if the tumor or cancer has an activating mutation in the β-catenin gene.

61. The ~~method~~use of claim 58, wherein determining the level of RSPO1 expression is done prior to treatment or contact with the antibody.

62. The ~~method~~use of claim 61, wherein if the tumor or cancer has an elevated level of RSPO1 expression, the antibody is:

(a) to be administered to the subject; or

(b) to be contacted with the tumor or tumor cell.

63. ~~A method of treating a disease in a subject wherein the disease is associated with activation of β-catenin, comprising administering~~ Use of a therapeutically effective amount of an antibody according to any one of claims 1-29 in the manufacture of a medicament for treating a disease in a subject wherein the disease is associated with activation of β-catenin.

64. The ~~method~~use according to any one of claims 39-63, which further comprises ~~administering~~ the administration of at least one additional therapeutic agent.

65. The ~~method~~use of claim 64, wherein the additional therapeutic agent is a chemotherapeutic agent.

66. The ~~method~~use of claim 64, wherein the additional therapeutic agent is an angiogenesis inhibitor.

67. The ~~method~~use according to any one of claims 39-42 or 45-66, wherein the subject is human.

68. ~~A~~An *in vitro* method of selecting a human subject for treatment with an antibody that binds RSPO1, comprising: determining if the subject has a tumor that has an elevated expression level of

RSPO1, wherein if the tumor has an elevated expression level of RSPO1 the subject is selected for treatment with an antibody that specifically binds RSPO1.

69. The method of claim 68, wherein the tumor is an ovarian tumor.

70. The method according to any one of claims 58, 68, or 69, wherein the expression level of RSPO1 is determined in a sample by a PCR-based assay, microarray analysis, or nucleotide sequencing.

71. ~~A~~ An *in vitro* method of selecting a human subject for treatment with an antibody that binds RSPO1, comprising: determining if the subject has a tumor that comprises an inactivating mutation in the APC gene, wherein if the tumor has an inactivating mutation in the APC gene the subject is selected for treatment with an antibody that specifically binds RSPO1.

72. The method of claim 71, wherein the tumor is a colorectal tumor.

73. The method according to any one of claims 59, 71, or 72, wherein an inactivating mutation in the APC gene is determined in a sample by a PCR-based assay, hybridization assay, microarray analysis, or nucleotide sequencing.

74. The method of claim 70 or claim 73, wherein the sample is a fresh tumor sample, a frozen tumor sample, or a formalin-fixed paraffin-embedded sample.

75. The method according to any one of claims 68-74, wherein the antibody is an antibody according to any one of claims 1-29.

76. An isolated antibody that specifically binds human R-spondin2 (RSPO2), which comprises:

(a) a heavy chain CDR1 comprising SSYAMS (SEQ ID NO:29), a heavy chain CDR2 comprising SISSGGSTYYPDSVKG (SEQ ID NO:30), and a heavy chain CDR3 comprising RGGDPGVYNGDYEDAMDY (SEQ ID NO:31); and/or

(b) a light chain CDR1 comprising KASQDVSSAVA (SEQ ID NO:32), a light chain CDR2 comprising WASTRHT (SEQ ID NO:33), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:34).

77. An isolated antibody that specifically binds human RSPO2, which comprises:

111. An isolated polynucleotide molecule comprising a polynucleotide sequence selected from the group consisting of: SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:72, and SEQ ID NO:75.

112. A vector comprising the polynucleotide of claim 110 or claim 111.

113. A cell comprising the polynucleotide of claim 110 or claim 111 or the vector of claim 112.

114. A pharmaceutical composition comprising the antibody or polypeptide according to any one of claims 76-107 and a pharmaceutically acceptable carrier.

115. ~~A method of inhibiting growth of a tumor, wherein the method comprises contacting the tumor with~~ Use of an effective amount of an antibody according to any of claims 76-105 in the manufacture of a medicament for inhibiting growth of a tumor, wherein the medicament is to be contacted to the tumor.

116. ~~A method of inhibiting growth of a tumor in a subject, wherein the method comprises administering to the subject~~Use of a therapeutically effective amount of an antibody according to any of claims 76-105 in the manufacture of a medicament for inhibiting growth of a tumor in a subject, wherein the medicament is to be administered to the subject.

117. ~~A method of inducing differentiation of tumor cells in a subject, comprising administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any one of claims 76-105 in the manufacture of a medicament for inducing differentiation of tumor cells in a subject.

118. ~~A method of reducing the frequency of cancer stem cells in a tumor in a subject, comprising administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any one of claims 76-105 in the manufacture of a medicament for reducing the frequency of cancer stem cells in a tumor in a subject.

119. ~~A method of inhibiting β-catenin signaling in a cell, comprising contacting the cell with~~ Use of an effective amount of an antibody according to any one of claims 76-105 in the manufacture of a medicament for inhibiting β-catenin signaling in a cell, comprising contacting the cell with the medicament.

120. The ~~method~~use of claim 119, wherein the cell is a tumor cell.

121. The ~~method~~use according to any one of claims 115-118 or 120, wherein the tumor is selected from the group consisting of colorectal tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor.

122. The ~~method~~use of claim 121, wherein the tumor is a pancreatic tumor.

123. The ~~method~~use of claim 121, wherein the tumor is an ovarian tumor.

124. ~~A method of treating cancer in a subject, wherein the method comprises administering to the subject~~ Use of a therapeutically effective amount of an antibody according to any of claims 76-105 in the manufacture of a medicament for treating cancer in a subject.

125. The ~~method~~use of claim 124, wherein the cancer is selected from the group consisting of colorectal cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer.

126. The ~~method~~use of claim 125, wherein the cancer is colorectal cancer.

127. The ~~method~~use of claim 126, wherein the colorectal cancer comprises an inactivating mutation in the adenomatous polyposis coli (APC) gene.

128. The ~~method~~use of claim 126, wherein the colorectal cancer does not comprise an inactivating mutation in the APC gene.

129. The ~~method~~use of claim 126, wherein the colorectal cancer comprises a wild-type APC gene.

130. The ~~method~~use of claim 126, wherein the colorectal cancer does not comprise an activating mutation in the β-catenin gene.

131. The ~~method~~use of claim 125, wherein the cancer is pancreatic cancer.

132. The ~~method~~use according to any one of claims 115-118 or 120-131, wherein the tumor or the cancer expresses elevated levels of RSPO2 as compared to levels of RSPO2 in normal tissue.

133. The ~~method~~use according to any one of claims 116-118 or 121-132, wherein the subject has had a tumor or a cancer removed.

134. The ~~method~~use according to any one of claims 115-118 or 120-133, further comprising a step of determining the level of RSPO2 expression in the tumor or cancer.

135. The ~~method~~use according to any one of claims 115-118 or 120-134, further comprising a step of determining if the tumor or cancer has an inactivating mutation in the APC gene.

136. The ~~method~~use according to any one of claims 115-118 or 120-135, further comprising a step of determining if the tumor or cancer has an activating mutation in the β-catenin gene.

137. The ~~method~~use of claim 134, wherein determining the level of RSPO2 expression is done prior to treatment or contact with the antibody.

138. The ~~method~~use of claim 137, wherein if the tumor or cancer has an elevated expression level of RSPO2, the antibody is:

(a) to be administered to the subject; or

(b) to be contacted with the tumor or tumor cell.

139. ~~A method of treating a disease in a subject wherein the disease is associated with activation of β-catenin, comprising administering~~ Use of a therapeutically effective amount of an antibody according to any one of claims 76-105 in the manufacture of a medicament for treating a disease in a subject wherein the disease is associated with activation of β-catenin.

140. The ~~method~~use according to any one of claims 115-139, which further comprises ~~administering~~ administration of at least one additional therapeutic agent.

141. The ~~method~~use of claim 140, wherein the additional therapeutic agent is a chemotherapeutic agent.

142. The ~~method~~use of claim 140, wherein the additional therapeutic agent is a Wnt pathway inhibitor.

143. The ~~method~~use according to any one of claims 116-118 or 121-142, wherein the subject is human.

144. ~~A~~An *in vitro* method of selecting a human subject for treatment with an antibody that binds RSPO2, comprising: determining if the subject has a tumor that has an elevated expression level of RSPO2, wherein if the tumor has an elevated expression level of RSPO2 the subject is selected for treatment with an antibody that specifically binds RSPO2.

145. The method of claim 144, wherein the tumor is a pancreatic tumor.

146. The method of claim 144, wherein the tumor is a breast tumor.

147. The method of claim 144, wherein the tumor is a lung tumor.

148. The method of claim 144, wherein the tumor is a melanoma tumor.

149. The method of claim 144, wherein the tumor is a colorectal tumor.

150. The method according to any one of claims 134 or 144-149, wherein the expression level of RSPO2 is determined in a sample by a PCR-based assay, microarray analysis, or nucleotide sequencing.

151. ~~A~~An *in vitro* method of selecting a human subject for treatment with an antibody that binds RSPO2, comprising: determining if the subject has a tumor that comprises an inactivating mutation in the APC gene, wherein if the tumor has an inactivating mutation in the APC gene the subject is selected for treatment with an antibody that specifically binds RSPO2.

152. The method of claim 151, wherein the tumor is a colorectal tumor.

153. The method according to any one of claims 135, 151, or 152, wherein an inactivating mutation in the APC gene is determined in a sample by a PCR-based assay, hybridization assay, microarray analysis, or nucleotide sequencing.

154. The method of claim 150 or claim 153, wherein the sample is a fresh tumor sample, a frozen tumor sample, or a formalin-fixed paraffin-embedded sample.

155. The method according to any one of claims 144-154, wherein the antibody is an antibody according to any one of claims 76-105.

156. An antibody comprising a heavy chain amino acid sequence of SEQ ID NO:25 and a light chain amino acid sequence of SEQ ID NO:26.

157. An antibody comprising a heavy chain amino acid sequence of SEQ ID NO:41, and a light chain amino acid sequence of SEQ ID NO:42.

158. An antibody comprising a heavy chain amino acid sequence of SEQ ID NO:68 and a light chain amino acid sequence of SEQ ID NO:69.

159. An antibody comprising a heavy chain amino acid sequence of SEQ ID NO:70, and a light chain amino acid sequence of SEQ ID NO:71.

160. An antibody comprising a heavy chain amino acid sequence of SEQ ID NO:70, and a light chain amino acid sequence of SEQ ID NO:74.

161. ~~A~~An *in vitro* method of selecting a human subject for treatment with an antibody that binds RSPO3, comprising: determining if the subject has a tumor that has an elevated expression level of RSPO3, wherein if the tumor has an elevated expression level of RSPO3 the subject is selected for treatment with an antibody that specifically binds RSPO3.

162. The method of claim 161, wherein the tumor is a lung tumor.

163. The method of claim 161, wherein the tumor is a breast tumor.

164. The method of claim 161, wherein the tumor is an ovarian tumor.

165. The method of claim 161, wherein the tumor is a colorectal tumor.

166. The method according to any one of claims 161-165, wherein the expression level of RSPO3 is determined in a sample by a PCR-based assay, microarray analysis, or nucleotide sequencing.

167. The method of claim 166, wherein the sample is a fresh tumor sample, a frozen tumor sample, or a formalin-fixed paraffin-embedded sample.

168. ~~A~~An *in vitro* method of selecting a human subject for treatment with an antibody that binds RSPO4, comprising: determining if the subject has a tumor that has an elevated expression level of RSPO4, wherein if the tumor has an elevated expression level of RSPO4 the subject is selected for treatment with an antibody that specifically binds RSPO4.

169. The method of claim 168, wherein the tumor is a lung tumor.

170. The method of claim 168, wherein the tumor is a breast tumor.

171. The method of claim 168, wherein the tumor is an ovarian tumor.