improved survival from melanoma, and that activated Wnt/β-catenin signaling was associated with decreased cell proliferation (Chien et al., 2009, *PNAS*, 106:1193-1198).

**[0009]** The focus of cancer drug research is shifting toward targeted therapies aimed at genes, proteins, and pathways involved in human cancer. There is a need for new agents targeting signaling pathways and new combinations of agents that target multiple pathways that could provide therapeutic benefit for cancer patients. Thus, biomolecules (e.g., anti-RSPO antibodies) that disrupt β-catenin signaling are a potential source of new therapeutic agents for cancer, as well as other β-catenin-associated diseases.

## BRIEF SUMMARY OF THE INVENTION

**[0009a]** In one aspect, the present invention provides an isolated monoclonal antibody that specifically binds human R-spondin 1 (RSPO1), which comprises:

(a) a heavy chain CDR1 comprising TGYTMH (SEQ ID NO:12), a heavy chain CDR2 comprising GINPNNGGTTYNQNFKG (SEQ ID NO:13), and a heavy chain CDR3 comprising KEFSDGYYFFAY (SEQ ID NO:14); and

(b) a light chain CDR1 comprising KASQDVIFAVA (SEQ ID NO:15), a light chain CDR2 comprising WASTRHT (SEQ ID NO:16), and a light chain CDR3 comprising QQHYSTPW (SEQ ID NO:17).

**[0009b]** In one aspect, the present invention provides a monoclonal antibody produced by the hybridoma cell line having ATCC deposit number PTA-11970.

**[0009c]** In one aspect, the present invention provides a monoclonal humanized antibody comprising the same heavy chain CDR1, CDR2, CDR3, and light chain CDR1, CDR2, and CDR3 as the antibody as defined herein.

**[0009d]** In one aspect, the present invention provides 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.

[0009e] In one aspect, the present invention provides 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.

[0009f] In one aspect, the present invention provides a cell producing the antibody as defined herein.

[0009g] In one aspect, the present invention provides a hybridoma cell line having ATCC deposit number PTA-11970.

[0009h] In one aspect, the present invention provides an isolated polynucleotide molecule comprising a nucleotide sequence that encodes an antibody as defined herein.

[0009i] In one aspect, the present invention provides a vector comprising the polynucleotide as defined herein.

[0009j] In one aspect, the present invention provides a cell comprising the polynucleotide as defined herein or the vector as defined herein.

[0009k] In one aspect, the present invention provides a pharmaceutical composition comprising the antibody as defined herein and a pharmaceutically acceptable carrier.

[0009l] In one aspect, the present invention provides the antibody as defined herein for use as a medicament.

[0009m] In one aspect, the present invention provides the use of the antibody as defined herein in the manufacture of a medicament for treatment of cancer.

**[0010]** The present ~~invention~~disclosure provides binding agents, such as antibodies, that bind RSPO proteins, as well as compositions, such as pharmaceutical compositions, comprising the binding agents. In certain ~~embodiments~~examples, the RSPO-binding agents are novel polypeptides, such as antibodies, antibody fragments, and other polypeptides related to such antibodies. In certain ~~embodiments~~examples, the binding agents are antibodies that specifically bind human RSPO1, RSPO2, and/or RSPO3. The ~~invention~~disclosure further provides methods of inhibiting the growth of a tumor by administering the RSPO-binding agents to a subject with a tumor. The ~~invention~~disclosure further provides methods of treating cancer by administering the RSPO-binding agents to a subject in need thereof. In some ~~embodiments~~examples, the methods of treating cancer or inhibiting tumor growth comprise targeting cancer stem cells with the RSPO-binding agents. In certain ~~embodiments~~examples, the methods comprise reducing the frequency of cancer stem cells in a tumor, reducing the number of cancer stem cells in a tumor, reducing the tumorigenicity of a tumor, and/or reducing the tumorigenicity of a tumor by reducing the number or frequency of cancer stem cells in the tumor.

**[0011]** Disclosed is~~In one aspect, the invention provides~~ a binding agent, such as an antibody, that specifically binds human RSPO1. In certain ~~embodiments~~examples, the RSPO1-binding agent binds within amino acids 21-263 of human RSPO1. In certain ~~embodiments~~examples, the RSPO1-binding agent binds within amino acids 34-135 of human RSPO1. In certain ~~embodiments~~examples, the RSPO1-binding agent binds within amino acids 91-135 of human RSPO1. In some ~~embodiments~~examples, the RSPO1-binding agent (e.g., an antibody) specifically

binds at least one other human RSPO selected from the group consisting of RSPO2, RSPO3, and RSPO4. In some ~~embodiments~~examples, the RSPO1-binding agent or antibody modulates β-catenin activity, is an antagonist of β-catenin signaling, inhibits β-catenin signaling, and/or inhibits activation of β-catenin. In some ~~embodiments~~examples, the RSPO1-binding agent inhibits RSPO1 signaling. In some ~~embodiments~~examples, the RSPO1-binding agent inhibits or interferes with binding of RSPO1 to one or more LGR protein (e.g., LGR4, LGR5, and/or LGR6). In some ~~embodiments~~examples, the RSPO1-binding agent inhibits binding of RSPO1 to LGR5.

**[0012]** Also disclosed is~~In another aspect, the invention provides~~ a binding agent, such as an antibody, that specifically binds human RSPO2. In certain ~~embodiments~~examples, the RSPO2-binding agent binds within amino acids 22-243 of human RSPO2. In certain ~~embodiments~~examples, the RSPO2-binding agent binds within amino acids 22-205 of human RSPO2. In certain ~~embodiments~~examples, the RSPO2-binding agent binds within amino acids 34-134 of human RSPO2. In certain ~~embodiments~~examples, the RSPO2-binding agent binds within amino acids 90-134 of human RSPO2. In some ~~embodiments~~examples, the RSPO2-binding agent (e.g., an antibody) specifically binds at least one other human RSPO selected from the group consisting of RSPO1, RSPO3, and RSPO4. In some ~~embodiments~~examples, the RSPO2-binding agent or antibody modulates β-catenin activity, is an antagonist of β-catenin signaling, inhibits β-catenin signaling, and/or inhibits activation of β-catenin. In some ~~embodiments~~examples, the RSPO2-binding agent inhibits RSPO2 signaling. In some ~~embodiments~~examples, the RSPO2-binding agent inhibits or interferes with binding of RSPO2 to one or more LGR protein (e.g., LGR4, LGR5, and/or LGR6). In some ~~embodiments~~examples, the RSPO2-binding agent inhibits binding of RSPO2 to LGR5.

**[0013]** In certain ~~embodiments~~examples of each of the aforementioned ~~aspects~~disclosures and ~~embodiments~~examples, as well as other ~~aspects~~disclosures and ~~embodiments~~examples described herein, the RSPO-binding agent is an antibody. In certain ~~embodiments~~examples, the antibody is a monoclonal antibody. In certain ~~embodiments~~examples, the antibody is a humanized antibody. In certain ~~embodiments~~examples, the antibody binds human RSPO1. In certain ~~embodiments~~examples, the antibody binds human RSPO1 and mouse RSPO1. In certain ~~embodiments~~examples, the antibody binds human RSPO1 with a $K_D$ of less than 1nM and mouse RSPO1 with a $K_D$ of less than 1nM.

**[0014]** In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody which comprises a heavy chain CDR1 comprising TGYTMH (SEQ ID NO:12), a heavy chain CDR2 comprising GINPNNGGTTYNQNFKG (SEQ ID NO:13), and a heavy chain CDR3 comprising KEFSDGYYFFAY (SEQ ID NO:14). In some ~~embodiments~~examples, the antibody further comprises a light chain CDR1 comprising KASQDVIFAVA (SEQ ID NO:15), a light chain CDR2 comprising WASTRHT (SEQ ID NO:16), and a light chain CDR3 comprising QQHYSTPW (SEQ ID NO:17). In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody which comprises a light chain CDR1 comprising KASQDVIFAVA (SEQ ID NO:15), a light chain CDR2 comprising WASTRHT (SEQ ID NO:16), and a light chain CDR3 comprising QQHYSTPW (SEQ ID NO:17). In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody which comprises: (a) a heavy chain CDR1 comprising TGYTMH (SEQ ID NO:12), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (b) a heavy chain CDR2 comprising GINPNNGGTTYNQNFKG (SEQ ID NO:13), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (c) a heavy chain CDR3 comprising KEFSDGYYFFAY (SEQ ID NO:14), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (d) a light chain CDR1 comprising KASQDVIFAVA (SEQ ID NO:15), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (e) a light chain CDR2 comprising WASTRHT (SEQ ID NO:16), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and (f) a light chain CDR3 comprising QQHYSTPW (SEQ ID NO:17), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions. In some ~~embodiments~~examples, the amino acid substitutions are conservative amino acid substitutions.

**[0015]** In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody which comprises: (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:10; and/or (b) a light chain variable region having at least 80% sequence identity to SEQ ID NO:11. In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody that comprises: (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:10; and/or (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:11.

**[0016]** In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody which comprises: (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:55; and/or (b) a light chain variable region having at least 80% sequence

identity to SEQ ID NO:59. In certain ~~embodiments~~examples, the RSPO1-binding agent is an antibody that comprises: (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:55; and/or (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:59.

**[0017]** In some ~~embodiments~~examples, the RSPO1-binding agent is monoclonal antibody 89M5 and is produced by the hybridoma cell line 89M5 deposited on June 30, 2011 with ATCC having deposit no. PTA-11970. In some ~~embodiments~~examples, the RSPO1-binding agent is a humanized form of antibody 89M5. In some ~~embodiments~~examples, the RSPO1-binding agent is humanized monoclonal antibody h89M5-H2L2.

**[0018]** In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody which binds human RSPO2. In some ~~embodiments~~examples, the antibody binds human RSPO2 and mouse RSPO2. In certain ~~embodiments~~examples, the antibody comprises 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). In some ~~embodiments~~examples, the antibody further comprises 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). In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody which comprises 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). In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody which comprises: (a) a heavy chain CDR1 comprising SSYAMS (SEQ ID NO:29), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (b) a heavy chain CDR2 comprising SISSGGSTYYPDSVKG (SEQ ID NO:30), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (c) a heavy chain CDR3 comprising RGGDPGVYNGDYEDAMDY (SEQ ID NO:31), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (d) a light chain CDR1 comprising KASQDVSSAVA (SEQ ID NO:32), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (e) a light chain CDR2 comprising WASTRHT (SEQ ID NO:33), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and (f) a light chain CDR3 comprising QQHYSTP (SEQ ID NO:34), or a variant thereof

comprising 1, 2, 3, or 4 amino acid substitutions. In some ~~embodiments~~examples, the amino acid substitutions are conservative amino acid substitutions.

**[0019]** In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody which comprises: (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:27; and/or (b) a light chain variable region having at least 80% sequence identity to SEQ ID NO:28. In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody that comprises: (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:27; and/or (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:28.

**[0020]** In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody which comprises: (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:63; and/or (b) a light chain variable region having at least 80% sequence identity to SEQ ID NO:67. In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody that comprises: (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:63; and/or (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:67.

**[0021]** In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody which comprises: (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO:63; and/or (b) a light chain variable region having at least 80% sequence identity to SEQ ID NO:76. In certain ~~embodiments~~examples, the RSPO2-binding agent is an antibody that comprises: (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:63; and/or (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:76.

**[0022]** In some ~~embodiments~~examples, the RSPO2-binding agent is monoclonal antibody 130M23 and is produced by the hybridoma cell line 130M23 deposited on August 10, 2011 with ATCC having deposit no. PTA-12021. In some ~~embodiments~~examples, the RSPO2-binding agent is a humanized form of antibody 130M23. In some ~~embodiments~~examples, the RSPO2-binding agent is humanized monoclonal antibody h130M23-H1L2. In some ~~embodiments~~examples, the RSPO2-binding agent is humanized monoclonal antibody h130M23-H1L6.

**[0023]** Also disclosed is~~In another aspect, the invention provides~~ a binding agent (e.g., an antibody) that competes for specific binding to a human RSPO protein with an antibody of the ~~invention~~disclosure. In some ~~embodiments~~examples, the binding agent (e.g., an antibody) competes for specific binding to human RSPO1 with an antibody that comprises a heavy chain variable region comprising SEQ ID NO:10, and a light chain variable region comprising SEQ ID NO:11. In some ~~embodiments~~examples, the binding agent (e.g., an antibody) competes for specific binding to human RSPO1 with an antibody that comprises a heavy chain variable region comprising SEQ ID NO:55, and a light chain variable region comprising SEQ ID NO:59. In some ~~embodiments~~examples, the antibody with which the RSPO1-binding agent competes is 89M5 or h89M5-H2L2. In some ~~embodiments~~examples, the binding agent competes for specific binding to RSPO1 with an antibody of the ~~invention~~disclosure in an *in vitro* competitive binding assay.

**[0024]** In certain ~~embodiments~~examples, the antibody binds the same epitope, or essentially the same epitope, on RSPO1 as an antibody of the ~~invention~~disclosure (e.g., 89M5).

**[0025]** In still another ~~aspect~~disclosure, the binding agent is an antibody that binds an epitope on RSPO1 that overlaps with the epitope on RSPO1 bound by an antibody of the ~~invention~~disclosure (e.g., 89M5).

**[0026]** Also disclosed is~~In another aspect, the invention provides~~ a binding agent (e.g., an antibody) that competes for specific binding to human RSPO2 with an antibody of the ~~invention~~disclosure. In some ~~embodiments~~examples, the binding agent (e.g., an antibody) competes for specific binding to human RSPO2 with an antibody that comprises a heavy chain variable region comprising SEQ ID NO:27, and a light chain variable region comprising SEQ ID NO:28. In some ~~embodiments~~examples, the binding agent (e.g., an antibody) competes for specific binding to human RSPO2 with an antibody that comprises a heavy chain variable region comprising SEQ ID NO:63, and a light chain variable region comprising SEQ ID NO:67. In some ~~embodiments~~examples, the binding agent (e.g., an antibody) competes for specific binding to human RSPO2 with an antibody that comprises a heavy chain variable region comprising SEQ ID NO:63, and a light chain variable region comprising SEQ ID NO:76. In some ~~embodiments~~examples, the antibody with which the RSPO2-binding agent competes is 130M23, h130M23-H1L2, or h130M23-H1L6. In some ~~embodiments~~examples, the binding agent competes

for specific binding to RSPO2 with an antibody of the ~~invention~~disclosure in an *in vitro* competitive binding assay.

**[0027]** In certain ~~embodiments~~examples, the antibody binds the same epitope, or essentially the same epitope, on RSPO2 as an antibody of the ~~invention~~disclosure (e.g., 130M23).

**[0028]** In still another ~~aspect~~disclosure, the binding agent is an antibody that binds an epitope on RSPO2 that overlaps with the epitope on RSPO2 bound by an antibody of the ~~invention~~disclosure (e.g., 130M23).

**[0029]** In certain ~~embodiments~~examples of each of the aforementioned ~~aspects~~disclosures, as well as other ~~aspects~~disclosures and/or ~~embodiments~~examples described elsewhere herein, the RSPO-binding agent or antibody is isolated.

**[0030]** Also disclosed is~~In another aspect, the invention provides~~ a polypeptide comprising SEQ ID NO:10 and/or SEQ ID NO:11. Also disclosed is~~In another aspect, the invention provides~~ a polypeptide comprising SEQ ID NO:55 and/or SEQ ID NO:59. Also disclosed is~~In another aspect, the invention provides~~ a polypeptide comprising SEQ ID NO:27 and/or SEQ ID NO:28. Also disclosed is~~In another aspect, the invention provides~~ a polypeptide comprising SEQ ID NO:63 and/or SEQ ID NO:67. Also disclosed is~~In another aspect, the invention provides~~ a polypeptide comprising SEQ ID NO:63 and/or SEQ ID NO:76. In some ~~embodiments~~examples, a polypeptide that binds RSPO1 comprises a polypeptide comprising SEQ ID NO:25 and/or SEQ ID NO:26. In some ~~embodiments~~examples, a polypeptide that binds RSPO1 comprises a polypeptide comprising SEQ ID NO:68 and/or SEQ ID NO:69. In some ~~embodiments~~examples, a polypeptide that binds RSPO2 comprises a polypeptide comprising SEQ ID NO:41 and/or SEQ ID NO:42. In some ~~embodiments~~examples, a polypeptide that binds RSPO2 comprises a polypeptide comprising SEQ ID NO:70 and/or SEQ ID NO:71. In some ~~embodiments~~examples, a polypeptide that binds RSPO2 comprises a polypeptide comprising SEQ ID NO:70 and/or SEQ ID NO:74. In some ~~embodiments~~examples, the polypeptide is isolated. In certain ~~embodiments~~examples, the polypeptide is substantially pure. In certain ~~embodiments~~examples, the polypeptide is an antibody.

**[0031]** Also disclosed is~~In another aspect, the invention provides~~ isolated polynucleotide molecules comprising a polynucleotide that encodes the antibodies and/or polypeptides of each of the aforementioned ~~aspects~~disclosures, as well as other ~~aspects~~disclosures and/or ~~embodiments~~examples described herein. In some ~~embodiments~~examples, the polynucleotide comprises a 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. In some ~~embodiments~~examples, the polynucleotide comprises a 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. The ~~invention~~disclosure further provides expression vectors that comprise the polynucleotides, as well as cells that comprise the expression vectors and/or the polynucleotides. In some ~~embodiments~~examples, the cell is a hybridoma cell line. In certain ~~embodiments~~examples, the cell is a hybridoma cell line having the ATCC deposit number PTA-11970. In certain ~~embodiments~~examples, the cell is a hybridoma cell line having the ATCC deposit number PTA-12021.

**[0032]** Also disclosed are~~In other aspects, the invention provides~~ methods of inhibiting growth of a tumor, comprising contacting the tumor with an effective amount of a RSPO-binding agent or antibody, including each of those described herein.

**[0033]** Also disclosed is~~In another aspect, the invention provides~~ a method of inhibiting the growth of a tumor in a subject, comprising administering to the subject a therapeutically effective amount of a RSPO-binding agent or antibody, including each of those described herein.

**[0034]** Also disclosed is~~In another aspect, the invention provides~~ a method of inhibiting β-catenin signaling in a cell, comprising contacting the cell with an effective amount of a RSPO-binding agent or antibody, including each of those described herein. In some ~~embodiments~~examples, the cell is a tumor cell. In some ~~embodiments~~examples, the tumor is a colorectal tumor. In some ~~embodiments~~examples, the tumor is an ovarian tumor. In some ~~embodiments~~examples, the tumor is a pancreatic tumor. In some ~~embodiments~~examples, the tumor is a lung tumor. In some ~~embodiments~~examples, the tumor expresses elevated levels of at least one RSPO protein. In some ~~embodiments~~examples, the tumor expresses elevated levels of RSPO1. In some ~~embodiments~~examples, the tumor expresses elevated levels of RSPO2. In some ~~embodiments~~examples, the tumor expresses elevated levels of RSPO3. In certain ~~embodiments~~examples, the RSPO-binding agent inhibits growth of the tumor, for example, by reducing the number and/or frequency of cancer stem cells in the tumor.

**[0035]** Also disclosed are~~In another aspect, the invention provides~~ methods of treating cancer in a subject. In some ~~embodiments~~examples, the method comprises administering to a subject a therapeutically

effective amount of any of the RSPO-binding agents or antibodies described above, as well as those described elsewhere herein. In some ~~embodiments~~examples, the cancer is pancreatic cancer. In some ~~embodiments~~examples, the cancer is colorectal cancer. In some ~~embodiments~~examples, the colorectal cancer comprises an inactivating mutation in the adenomatous polyposis coli (APC) gene. In some ~~embodiments~~examples, the colorectal cancer does not comprise an inactivating mutation in the APC gene. In some ~~embodiments~~examples, the colorectal cancer comprises a wild-type APC gene. In some ~~embodiments~~examples, the cancer is ovarian cancer. In some ~~embodiments~~examples, the cancer is breast cancer. In some ~~embodiments~~examples, the cancer is lung cancer. In some ~~embodiments~~examples, the cancer expresses elevated levels of at least one RSPO protein. In some ~~embodiments~~examples, the cancer is an ovarian cancer that expresses elevated levels of RSPO1. In some ~~embodiments~~examples, the cancer is colon cancer that expresses elevated levels of RSPO2. In some ~~embodiments~~examples, the cancer is a pancreatic cancer that expresses elevated levels of RSPO2. In some ~~embodiments~~examples, the cancer is a breast cancer that expresses elevated levels of RSPO2. In some ~~embodiments~~examples, the cancer is a lung cancer that expresses elevated levels of RSPO2.

**[0036]** Also disclosed are~~In another aspect, the invention provides~~ methods of treating a disease in a subject wherein the disease is associated with activation of β-catenin, and/or aberrant β-catenin signaling comprising administering a therapeutically effective amount of a RSPO-binding agent or antibody, including each of those described herein.

**[0037]** In certain ~~embodiments~~examples of each of the aforementioned ~~aspects~~disclosures, as well as other ~~aspects~~disclosures and/or ~~embodiments~~examples described elsewhere herein, the treatment methods comprise administering a RSPO-binding agent in combination with at least one additional therapeutic agent. In some ~~embodiments~~examples, the treatment methods comprise administering a RSPO1-binding agent in combination with a second RSPO-binding agent such as a RSPO2-binding agent, a RSPO3-binding agent, and/or a RSPO4-binding agent. In some ~~embodiments~~examples, the treatment methods comprise administering a RSPO2-binding agent in combination with a second RSPO-binding agent such as a RSPO1-binding agent, a RSPO3-binding agent, and/or a RSPO4-binding agent. In some ~~embodiments~~examples, the treatment methods comprise administering a RSPO1-binding agent in combination with a RSPO2-binding agent. In some ~~embodiments~~examples, the treatment methods comprise administering a combination of a RSPO1-binding agent, a RSPO2-binding agent, and a chemotherapeutic agent.

[0038] In certain ~~embodiments~~examples of each of the aforementioned ~~aspects~~disclosures, as well as other ~~aspects~~disclosures and/or ~~embodiments~~examples described elsewhere herein, the treatment methods further comprise a step of determining the level of at least one RSPO protein expression in the tumor or cancer.

[0039] Also disclosed is~~In another aspect, the invention provides~~ a method of identifying a human subject or selecting a human subject for treatment with a RSPO-binding agent or antibody, including but not limited to, each of those described herein. In some ~~embodiments~~examples, the method comprises determining if the subject has a tumor that has an elevated expression level of a specific RSPO (e.g., RSPO1 or RSPO2) as compared to the expression of the same RSPO protein in normal tissue. In some ~~embodiments~~examples, the method comprises identifying a subject for treatment or selecting a subject for treatment if the tumor has an elevated level of RSPO expression. In some ~~embodiments~~examples, the method comprises determining if the subject has a tumor that comprises an inactivating mutation in the APC gene. In some ~~embodiments~~examples, the method comprises identifying a subject for treatment or selecting a subject for treatment if the tumor comprises an inactivating mutation in the APC gene.

[0040] Pharmaceutical compositions comprising a RSPO-binding agent or antibody described herein and a pharmaceutically acceptable carrier are further provided, as are cell lines that produce the RSPO-binding agents. Methods of treating cancer and/or inhibiting tumor growth in a subject (e.g., a human) comprising administering to the subject an effective amount of a composition comprising the RSPO-binding agents are also provided.

[0041] Where ~~aspects~~disclosures or ~~embodiments~~examples of the ~~invention~~disclosure are described in terms of a Markush group or other grouping of alternatives, the present ~~invention~~disclosure encompasses not only the entire group listed as a whole, but also each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members. The present ~~invention~~disclosure also envisages the explicit exclusion of one or more of any of the group members in the claimed ~~invention~~disclosure.