WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody that specifically binds human R-spondin 3 (RSPO3), which comprises:

   (a) a heavy chain CDR1 comprising DYSIH (SEQ ID NO:78), KASGYTFTDYS (SEQ ID NO:9), or KASGYTFTSYTF (SEQ ID NO:34), a heavy chain CDR2 comprising YIYPSNGDSGYNQKFK (SQ ID NO:79) or IYPSNGDS (SEQ ID NO:10), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80), ATYFANYFDY (SEQ ID NO:11), or ATYFANNFDY (SEQ ID NO:35); and

   (b) a light chain CDR1 comprising KASQSVDYDGDSYMN (SEQ ID NO:81) or QSVDYDGDSYM (SEQ ID NO:12), a light chain CDR2 comprising AASNLES (SEQ ID NO:82) or AAS (SEQ ID NO:13), and a light chain CDR3 comprising QQSNEDPLTF (SEQ ID NO:83) or QQSNEDPLT (SEQ ID NO:14).

2. The antibody of claim 1, which comprises:

   (a) a heavy chain CDR1 comprising DYSIH (SEQ ID NO:78), a heavy chain CDR2 comprising YIYPSNGDSGYNQKFK (SQ ID NO:79), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80); and

   (b) a light chain CDR1 comprising KASQSVDYDGDSYMN (SEQ ID NO:81), a light chain CDR2 comprising AASNLES (SEQ ID NO:82), and a light chain CDR3 comprising QQSNEDPLTF (SEQ ID NO:83).

3. The antibody of claim 1, which comprises:

   (a) a heavy chain CDR1 comprising DYSIH (SEQ ID NO:78) or KASGYTFTDYS (SEQ ID NO:9), a heavy chain CDR2 comprising YIYPSNGDSGYNQKFK (SQ ID NO:79), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80); and a light chain CDR1 comprising KASQSVDYDGDSYMN (SEQ ID NO:81), a light chain CDR2 comprising AASNLES (SEQ ID NO:82), and a light chain CDR3 comprising QQSNEDPLTF (SEQ ID NO:83);

   (b) a heavy chain CDR1 comprising KASGYTFTDYS (SEQ ID NO:9) or KASGYTFTSYTF (SEQ ID NO:34), a heavy chain CDR2 comprising IYPSNGDS (SEQ ID NO:10), and a heavy chain CDR3 comprising

ATYFANYFDY (SEQ ID NO:11) or ATYFANNFDY (SEQ ID NO:35), and a light chain CDR1 comprising QSVDYDGDSYM (SEQ ID NO:12), a light chain CDR2 comprising AAS (SEQ ID NO:13), and a light chain CDR3 comprising QQSNEDPLT (SEQ ID NO:14);

or

(c) a heavy chain CDR1 comprising KASGYTFTDYS (SEQ ID NO:9) or DYSIH (SEQ ID NO:78), a heavy chain CDR2 comprising IYPSNGDS (SEQ ID NO:10), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80); and a light chain CDR1 comprising QSVDYDGDSYM (SEQ ID NO:12), a light chain CDR2 comprising AAS (SEQ ID NO:13), and a light chain CDR3 comprising QQSNEDPLT (SEQ ID NO:14).

4. The antibody of claim 1, which comprises:

(a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:44, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:45, or SEQ ID NO:62; and

(b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:86, SEQ ID NO:17, or SEQ ID NO:72.

5. The antibody of claim 4, which comprises:

(a) a heavy chain variable region comprising SEQ ID NO:44 and a light chain variable region comprising SEQ ID NO:86, SEQ ID NO:72, or SEQ ID NO:17;

(b) a heavy chain variable region comprising SEQ ID NO:15 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(c) a heavy chain variable region comprising SEQ ID NO:16 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(d) a heavy chain variable region comprising SEQ ID NO:36 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(e) a heavy chain variable region comprising SEQ ID NO:37 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(f) a heavy chain variable region comprising SEQ ID NO:45 and a light chain variable region comprising SEQ ID NO:17, SEQ ID NO:72, or SEQ ID NO:86; or

(g) a heavy chain variable region comprising SEQ ID NO:62 and a light chain variable region comprising SEQ ID NO:17, SEQ ID NO:72, or SEQ ID NO:86.

6. The antibody of claim 5, which comprises a heavy chain variable region comprising SEQ ID NO:44 and a light chain variable region comprising SEQ ID NO:86.

7. A monoclonal antibody that competes for specific binding to RSPO3 with a reference antibody comprising a heavy chain variable region comprising SEQ ID NO:44 and a light chain variable region comprising SEQ ID NO:86.

8. The antibody according to any one of claims 1-7, which is a recombinant antibody, a chimeric antibody, a bispecific antibody, a humanized antibody, a human antibody, an IgG1 antibody, an IgG2 antibody, or an antibody fragment comprising an antigen binding site.

9. An antibody that specifically binds human R-spondin 3 (RSPO3) and comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-120420 and the light chain variable region encoded by the plasmid deposited with ATCC as PTA-120421.

10. The antibody according to any one of claims 1-9, which inhibits binding of RSPO3 to at least one leucine-rich repeat containing G protein coupled receptor (LGR).

11. The antibody of claim 10, wherein the LGR is selected from the group consisting of LGR5, LGR4, and LGR6.

12. The antibody according to any one of claims 1-11, which

(a) inhibits RSPO3 signaling;

(b) inhibits activation of β-catenin;

(c) inhibits β-catenin signaling;

(d) inhibits tumor growth;

(e) induces expression of differentiation markers in a tumor;

(f) induces cells in a tumor to differentiate; or

(g) reduces the frequency of cancer stem cells in a tumor.

13. A pharmaceutical composition comprising the antibody according to any one of claims 1-9 and a pharmaceutically acceptable carrier.

14. An isolated polynucleotide comprising a nucleotide sequence that encodes the antibody according to any one of claims 1-9.

15. An isolated cell comprising:

(a) the antibody according to any one of claims 1-9; or

(b) the polynucleotide of claim 14.

16. The antibody according to any one of claims 1-9, for use in one of selected from the group consisting of inhibiting tumor growth, inducing differentiation of tumor cells, and inhibiting β-catenin signaling in a cell.

17. The antibody of claim 16, wherein the cell is a tumor cell.

18. antibody according to claim 16, or claim 17, wherein the tumor is a pancreatic tumor, lung tumor, colorectal tumor, or ovarian tumor.

19. The use of the antibody according to any one of claims 1-9, in the manufacture of a medicament for the treatment of cancer.

20. The use of claim 19, wherein the cancer is colorectal cancer, pancreatic cancer, lung cancer, or ovarian cancer.

21. The antibody according to any one of claims 16-18 or the use according to claim 19 or claim 20, wherein the tumor or the cancer comprises a RSPO gene fusion.

22. The antibody according to any one of claims 16-18 or the use according to claim 19 or claim 20, wherein the inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, and treatment of cancer comprises determining if the tumor or cancer comprises a RSPO gene fusion.

23. The antibody according to any one of claims 16-18 or the use according to claim 19 or claim 20, wherein the tumor or the cancer has an elevated expression or a high expression level of RSPO3.

24. The antibody according to any one of claims 16-18 or the use according to claim 19 or claim 20, wherein the inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, and treatment of cancer comprises determining if the tumor or cancer has an elevated expression or a high expression level of RSPO3.

25. The antibody according to any one of claims 1-9 for use in treating a disease associated with activation of β-catenin.

26. The antibody according to any one of claims 16-18 and 21-25 or the use according to any one claims 19-24, wherein the inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, treatment of cancer, and treating a disease associated with activation of β-catenin comprises administration of the antibody and at least one additional therapeutic agent.

27. The antibody or the use of claim 26, wherein the at least one additional therapeutic agent is a chemotherapeutic agent, an angiogenesis inhibitor, or an additional antibody.

28. An *in vitro* method of identifying a tumor for treatment with an antibody according to any one of claims 1-9 comprising: determining if the tumor that has an elevated expression or a high expression level of RSPO3.

29. The method according to claim 28, wherein the expression level of RSPO3 is determined by a PCR-based assay, microarray analysis, or nucleotide sequencing.

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody that specifically binds human R-spondin 3 (RSPO3), which comprises:

(a) a heavy chain CDR1 comprising DYSIH (SEQ ID NO:78), KASGYTFTDYS (SEQ ID NO:9), or KASGYTFTSYTF (SEQ ID NO:34), a heavy chain CDR2 comprising YIYPSNGDSGYNQKFK (SQ ID NO:79) or IYPSNGDS (SEQ ID NO:10), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80), ATYFANYFDY (SEQ ID NO:11), or ATYFANNFDY (SEQ ID NO:35); and

(b) a light chain CDR1 comprising KASQSVDYDGDSYMN (SEQ ID NO:81) or QSVDYDGDSYM (SEQ ID NO:12), a light chain CDR2 comprising AASNLES (SEQ ID NO:82) or AAS (SEQ ID NO:13), and a light chain CDR3 comprising QQSNEDPLTF (SEQ ID NO:83) or QQSNEDPLT (SEQ ID NO:14).

2. The antibody of claim 1, which comprises:

(a) a heavy chain CDR1 comprising DYSIH (SEQ ID NO:78), a heavy chain CDR2 comprising YIYPSNGDSGYNQKFK (SEQ ID NO:79), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80); and

(b) a light chain CDR1 comprising KASQSVDYDGDSYMN (SEQ ID NO:81), a light chain CDR2 comprising AASNLES (SEQ ID NO:82), and a light chain CDR3 comprising QQSNEDPLTF (SEQ ID NO:83).

3. The antibody of claim 1, which comprises:

(a) a heavy chain CDR1 comprising DYSIH (SEQ ID NO:78) or KASGYTFTDYS (SEQ ID NO:9), a heavy chain CDR2 comprising YIYPSNGDSGYNQKFK (SEQ ID NO:79), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80); and a light chain CDR1 comprising KASQSVDYDGDSYMN (SEQ ID NO:81), a light chain CDR2 comprising AASNLES (SEQ ID NO:82), and a light chain CDR3 comprising QQSNEDPLTF (SEQ ID NO:83);

(b) a heavy chain CDR1 comprising KASGYTFTDYS (SEQ ID NO:9) or KASGYTFTSYTF (SEQ ID NO:34), a heavy chain CDR2 comprising IYPSNGDS (SEQ ID NO:10), and a heavy chain CDR3 comprising ATYFANYFDY (SEQ ID NO:11) or ATYFANNFDY (SEQ ID NO:35), and a

light chain CDR1 comprising QSVDYDGDSYM (SEQ ID NO:12), a light chain CDR2 comprising AAS (SEQ ID NO:13), and a light chain CDR3 comprising QQSNEDPLT (SEQ ID NO:14);

or

(c) a heavy chain CDR1 comprising KASGYTFTDYS (SEQ ID NO:9) or DYSIH (SEQ ID NO:78), a heavy chain CDR2 comprising IYPSNGDS (SEQ ID NO:10), and a heavy chain CDR3 comprising TYFANNFD (SEQ ID NO:80); and a light chain CDR1 comprising QSVDYDGDSYM (SEQ ID NO:12), a light chain CDR2 comprising AAS (SEQ ID NO:13), and a light chain CDR3 comprising QQSNEDPLT (SEQ ID NO:14).

4. The antibody of claim 1, which comprises:

(a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:44, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:45, or SEQ ID NO:62; and

(b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:86, SEQ ID NO:17, or SEQ ID NO:72.

5. The antibody of claim 4, which comprises:

(a) a heavy chain variable region comprising SEQ ID NO:44 and a light chain variable region comprising SEQ ID NO:86, SEQ ID NO:72, or SEQ ID NO:17;

(b) a heavy chain variable region comprising SEQ ID NO:15 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(c) a heavy chain variable region comprising SEQ ID NO:16 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(d) a heavy chain variable region comprising SEQ ID NO:36 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(e) a heavy chain variable region comprising SEQ ID NO:37 and a light chain variable region comprising SEQ ID NO:17 or SEQ ID NO:72;

(f) a heavy chain variable region comprising SEQ ID NO:45 and a light chain variable region comprising SEQ ID NO:17, SEQ ID NO:72, or SEQ ID NO:86; or

(g) a heavy chain variable region comprising SEQ ID NO:62 and a light chain variable region comprising SEQ ID NO:17, SEQ ID NO:72, or SEQ ID NO:86.

6. The antibody of claim 5, which comprises a heavy chain variable region comprising SEQ ID NO:44 and a light chain variable region comprising SEQ ID NO:86.

7. The antibody according to any one of claims 1-6, which is a recombinant antibody, a chimeric antibody, a bispecific antibody, a humanized antibody, a human antibody, an IgG1 antibody, an IgG2 antibody, or an antibody fragment comprising an antigen binding site.

8. An antibody that specifically binds human R-spondin 3 (RSPO3) and comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-120420 and the light chain variable region encoded by the plasmid deposited with ATCC as PTA-120421.

9. The antibody according to any one of claims 1-8, which inhibits binding of RSPO3 to at least one leucine-rich repeat containing G protein coupled receptor (LGR).

10. The antibody of claim 9, wherein the LGR is selected from the group consisting of LGR5, LGR4, and LGR6.

11. The antibody according to any one of claims 1-10, which
(a) inhibits RSPO3 signaling;
(b) inhibits activation of β-catenin;
(c) inhibits β-catenin signaling;
(d) inhibits tumor growth;
(e) induces expression of differentiation markers in a tumor;
(f) induces cells in a tumor to differentiate; or
(g) reduces the frequency of cancer stem cells in a tumor.

12. A pharmaceutical composition comprising the antibody according to any one of claims 1-8 and a pharmaceutically acceptable carrier.

13. An isolated polynucleotide comprising a nucleotide sequence that encodes the antibody according to any one of claims 1-8.

14. An isolated cell comprising:

(a) the antibody according to any one of claims 1-8; or

(b) the polynucleotide of claim 13.

15. The antibody according to any one of claims 1-8, for use in inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, or treating a disease associated with activation of β-catenin signaling.

16. The antibody for use according to claim 15, wherein the cell is a tumor cell.

17. The antibody for use according to claim 15, or claim 16, wherein the tumor is, or the tumor cell is from, a tumor selected from the group consisting of a pancreatic tumor, lung tumor, colorectal tumor, or ovarian tumor.

18. The use of the antibody according to any one of claims 1-8, in the manufacture of a medicament for the treatment of cancer.

19. The use of claim 18, wherein the cancer is colorectal cancer, pancreatic cancer, lung cancer, or ovarian cancer.

20. The antibody for use according to any one of claims 15-17 or the use according to claim 18 or claim 19, wherein the tumor or the cancer comprises a RSPO gene fusion.

21. The antibody for use according to any one of claims 15-17 or the use according to claim 18 or claim 19, wherein the inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, treatment of a disease associated with

activation of β-catenin signaling, and treatment of cancer comprises determining if the tumor or cancer comprises a RSPO gene fusion.

22. The antibody for use according to any one of claims 15-17 or the use according to claim 18 or claim 19, wherein the tumor or the cancer has an elevated expression or a high expression level of RSPO3.

23. The antibody for use according to any one of claims 15-17 or the use according to claim 18 or claim 19, wherein the inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, treatment of a disease associated with activation of β-catenin signaling, and treatment of cancer comprises determining if the tumor or cancer has an elevated expression or a high expression level of RSPO3.

24. The antibody for use according to any one of claims 15-17 and 20-23 or the use according to claim 18 or claim 19, wherein the inhibiting tumor growth, inducing differentiation of tumor cells, inhibiting β-catenin signaling in a cell, treatment of cancer, and treating a disease associated with activation of β-catenin comprises administration of the antibody and at least one additional therapeutic agent.

25. The antibody for use according to or the use of claim 24, wherein the at least one additional therapeutic agent is a chemotherapeutic agent, an angiogenesis inhibitor, or an additional antibody.

26. An *in vitro* method of identifying a tumor for treatment with an antibody according to any one of claims 1-8 comprising: determining if the tumor that has an elevated expression or a high expression level of RSPO3.

27. The method according to claim 26, wherein the expression level of RSPO3 is determined by a PCR-based assay, microarray analysis, or nucleotide sequencing.