embodiments, the antibody binds RSPO3, RSPO2, and RSPO4. In some embodiments, the antibody binds both human RSPO3 and mouse RSPO3.

[0191] In some embodiments, the antibody generated by the methods described herein is a RSPO antagonist. In some embodiments, the antibody generated by the methods described herein inhibits β-catenin signaling.

[0192] In some embodiments, a method of producing an antibody to at least one human RSPO protein comprises identifying an antibody using a membrane-bound heterodimeric molecule comprising a single antigen-binding site. In some non-limiting embodiments, the antibody is identified using methods and polypeptides described in International Publication WO 2011/100566~~, which is incorporated by reference herein in its entirety~~.

[0193] In some embodiments, a method of producing an antibody to at least one human RSPO protein comprises screening an antibody-expressing library for antibodies that bind a human RSPO protein. In some embodiments, the antibody-expressing library is a phage library. In some embodiments, the screening comprises panning. In some embodiments, the antibody-expressing library (e.g., phage library) is screened using at least a portion of amino acids 21-263 of human RSPO1. In some embodiments, antibodies identified in the first screening, are screened again using a different RSPO protein thereby identifying an antibody that binds RSPO1 and a second RSPO protein. In certain embodiments, the polypeptide used for screening comprises at least a portion of amino acids 21-263 of human RSPO1 selected from the group consisting of SEQ ID NOs:5-9. In some embodiments, the antibody identified in the screening binds RSPO1 and at least one other RSPO protein. In certain embodiments, the at least one other RSPO protein is selected from the group consisting of RSPO2, RSPO3 and RSPO4. In certain embodiments, the antibody identified in the screening binds RSPO1 and RSPO2. In certain embodiments, the antibody identified in the screening binds RSPO1 and RSPO3. In certain embodiments, the antibody identified in the screening binds RSPO1 and RSPO4. In some embodiments, the antibody identified in the screening binds both human RSPO1 and mouse RSPO1. In some embodiments, the antibody identified in the screening is a RSPO1 antagonist. In some embodiments, the antibody identified in the screening inhibits β-catenin signaling induced by RSPO1. In some embodiments, the antibody-expressing library (e.g., phage library) is screened using at least a portion of amino acids 22-205 of human RSPO2. In some embodiments, antibodies identified in the first

agents can be found in U.S. Patent No. 7,982,013, which is incorporated by reference herein in its entirety. FZD-binding agents may include, but are not limited to, anti-FZD antibodies. In some embodiments, a method comprises administering a RSPO-binding agent in combination with an anti-FZD antibody. In some embodiments, a method comprises administering a RSPO-binding agent in combination with the anti-FZD antibody 18R5. In some embodiments, the Wnt pathway inhibitors are Wnt protein binding agents, "Wnt-binding agents". Nonlimiting examples of Wnt-binding agents can be found in U.S. Patent Nos. 7,723,477 and 7,947,277; and International Publications WO 2011/088127 and WO 2011/088123, which are incorporated by reference herein in their entirety. Wnt-binding agents may include, but are not limited to, anti-Wnt antibodies and FZD-Fc soluble receptors. In some embodiments, a method comprises administering a RSPO-binding agent in combination with a FZD-Fc soluble receptor. In some embodiments, a method comprises administering a RSPO-binding agent in combination with a FZD8-Fc soluble receptor. In some embodiments, a method comprises administering a RSPO1-binding agent in combination with an anti-FZD antibody. In some embodiments, a method comprises administering anti-RSPO1 antibody 89M5 or h89M5-H2L2 in combination with an anti-FZD antibody. In some embodiments, a method comprises administering anti-RSPO1 antibody 89M5 or h89M5H2L2 in combination with anti-FZD antibody 18R5. In some embodiments, a method comprises administering anti-RSPO1 antibody 89M5 or h89M5-H2L2 in combination with a FZD-Fc soluble receptor. In some embodiments, a method comprises administering anti-RSPO1 antibody 89M5 or h89M5-H2L2 in combination with a FZD8-Fc soluble receptor. In some embodiments, a method comprises administering a RSPO2-binding agent in combination with an anti-FZD antibody. In some embodiments, a method comprises administering anti-RSPO2 antibody 130M23 or h130M23-H1L2 in combination with an anti-FZD antibody. In some embodiments, a method comprises administering anti-RSPO2 antibody 130M23, h130M23-H1L2, or h130M23-H1L6 in combination with anti-FZD antibody 18R5. In some embodiments, a method comprises administering anti-RSPO2 antibody 130M23, h130M23-H1L2, or h130M23-H1L6 in combination with a FZD-Fc soluble receptor. In some embodiments, a method comprises administering anti-RSPO2 antibody 130M23, h130M23-H1L2, or h130M23-H1L6 in combination with a FZD8-Fc soluble receptor.

into the intraperitoneal cavity. Tumor growth was monitored and tumor volumes were measured with electronic calipers on the indicated days. Data are expressed as mean ± S.E.M.

[0351] As shown in Figure 18, a combination of anti-RSPO1antibody 89M5 and anti-RSPO2 antibody 130M23 with cisplatin inhibited tumor growth better than cisplatin alone ($p = 0.04$, combination group vs cisplatin alone). The triple combination had a significant effect, despite the fact that the combination of antibodies 89M5 and 130M25 without cisplatin had only a minimal effect on this tumor.

[0352] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to person skilled in the art and are to be included within the spirit and purview of this application.

~~[0353] All publications, patents, patent applications, internet sites, and accession numbers/database sequences including both polynucleotide and polypeptide sequences cited herein are hereby incorporated by reference herein in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, internet site, or accession number/database sequence were specifically and individually indicated to be so incorporated by reference.~~