Colorectal cancer (CRC) is the third most common cancer diagnosed in both men and women. Dysregulation of the WNT/β-catenin pathway is the most commonly mutated pathway in CRC. Mutations in APC or β-catenin are present in approximately 90% of CRC cases. R-spondins (RSPO), a family of secreted proteins, are enhancers of WNT signaling complex is stabilized and subsequent WNT induced signaling is promoted.

RSPO3, has demonstrated efficacy in human RSPO3 high, APC pathway activating mutations in APC or β-catenin and lack tumor-cell derived RSPO3. Inhibition of RSPO3 with OMP-131R10, a clinical stage therapeutic antibody which binds to human and murine RSPO3 antagonism sensitizes colorectal cancer to taxane treatment.

RSPO3 antagonism enhances mitotic arrest in combination with nab-paclitaxel and promotes expansion of terminally differentiated secretory cells.

CONCLUSION
1. Anti-RSPO3 (OMP-131R10) inhibits tumor growth in combination with nab-paclitaxel in CRC models with RSPO3 translocations and RSPO3 overexpression.
2. The combination of OMP-131R10 and taxane treatment resulted in synergistic inhibition of tumor growth in 8/10 Patient Derived Xenograft (PDX) models. These models contain WNT pathway activating mutations in APC or β-catenin and lack tumor-cell derived RSPO3.
3. The tumor microenvironment is a source of Rs30 and Wnt.
4. The combination of OMP-131R10 with nab-paclitaxel potentiated mitotic arrest, enhanced terminal differentiation and reduced the tumorigenic cell frequency.
5. OMP-131R10 is currently in phase 1B clinical trials.
6. The synergistic activity of OMP-131R10 with nab-paclitaxel provides an opportunity to provide clinical benefit for CRC patients with either overexpression of RSPO3 or WNT pathway activating mutations.