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**TARGETING GPCRS FOR TREATING OVARIAN CANCER**

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Introduction: Ovarian cancer is the leading cause of death from gynecologic malignancy in the western world. Genome wide shRNA dropout screening revealed several genes essential for cell survival and proliferation in high-grade serous ovarian cancer cell lines. Our goal is to inhibit the signaling pathway of a GPCR-ligand pair identified as fitness genes, by an antibody-based approach or by nucleic acid drug delivery, to assess its potential as a therapeutic target for ovarian cancer. Methods: A xenograft model of OVCAR8 cells in athymic nude mice was used to assess the efficacy of the GPCR knock-down by lipid nanoparticles (LNPs) encapsulating siRNA. The Bio-distribution of the particles was determined using mRNA-luciferase; the silencing of the GPCR was measured in-vitro and in-vivo by RT-PCR; and tumor burden was monitored by live imaging. Additionally, antibodies targeting the ligand were isolated from a large human synthetic antibody library by yeast display and their ability to neutralize GPCR signaling was assessed in-vitro. Results: When injected intraperitoneally, LNPs showed significant accumulation in the area of the tumor in the ovaries. LNPs encapsulating specific GPCR-siRNA demonstrated silencing of the receptor in the tumors and reduction of tumor burden in the mice. A ligand-specific antibody was isolated and found to neutralize signaling in a reporter cell assay, inhibit cAMP production, and reduced cell proliferation and migration in-vitro. Conclusions: we demonstrate the potential of inhibiting our GPCR of interest as a therapeutic approach for ovarian cancer, either by knock-down of the receptor or by inhibition the ligand.