Supplementary Figures:

Supplementary Figure 1. A. Sensitivity of human colon cancer cell lines to DR5 agonist antibody Lexatumumab *in vitro*. HT29, SW480, HCT116, and COLO205 were sensitive to Lexatumumab, as measured by Sub-G1 apoptotic population. Upper panel shows control samples, and bottom panel shows Lexatumumab-treated samples. The percent values show apoptotic cell population in each sample. **B.** Insensitivity of human colon cancer cell lines to 3TSR *in vitro*. HT29, SW480, HCT116, and COLO205 were not sensitive to 3TSR treatment, as measured by Sub-G1 apoptotic population. Upper panel shows control samples, and bottom panel shows 3TSR-treated samples. The percent values show apoptotic cell population in each sample. **C.** Histology examination on tissues from treated mice bearing SW480 xenograft tumors. Major organs were prepared for histology study as described in Materials and Methods. Similar results were observed from samples of 3 mice from each treatment group. Original photos were taken at 200× magnification.

Supplementary Figure 2. Caspase-8, -3, and -9 activity assays. HDMEC in EBM-2 containing 0.5% FBS were treated with buffer (CTL), 3TSR and the caspase-8, -3, or -9-specific inhibitor. Caspase-8 activity was detected using the Apo Alert^{TM} caspase fluorescent assay kit (left). Caspase-3 activity was detected using the Apo Alert^{TM} caspase colorimetric assay kit. Caspase-9 activity was detected using the Apo Alert^{TM} caspase fluorescent assay kit. Jurkat cells treated with TRAIL in the presence or absence of z-IETD-fmk were used as controls.

Supplementary Figure 3. 3TSR-induced p38 activation does not affect DR5 expression. **Top:** 3TSR-stimulated phosphorylation of p38MAPK in HDMEC was inhibited by treatment

with SB203580, a selective inhibitor of p38MAPK. **Bottom:** 3TSR treatment of HDMEC for 4 h upregulated DR5 expression; treatment of these cells with S SB203580 did not have any effect on DR5 expression.