**Supplementary Figure Legends**

**Supplementary Figure S1. C-tail phosphorylation of SST2 mutants.** HEK293 cells were transiently transfected with HA-tagged SST2, SST2 ΔTSI, or SST2 358T and stimulated with SS14 (100 nM) for 15 min. Lysates were probed with antibodies specific for the phosphorylation sites shown, and then reprobed for HA-epitope.

**Supplementary Figure S2. Rab4 and Rab11 dominant negative mutants block recycling of the µOR.** HEK293 cells were transiently transfected with HA-tagged µOR and either GFP, GFP-Rab4 S22N, or GFP-Rab11 S25N. Cells were treated for 30 min with the µOR agonist DAMGO (100 nM), washed, and then incubated with the µOR antagonist naloxone (1 µM) for 30 min. Cell surface receptor was measured by ELISA and compared to untreated controls. Data are shown as the average ± SEM from 3 independent experiments. B) Confocal images of HEK293 cells transfected with the GFP-Rab4 and GFP-Rab11 plasmids shown. Scale bars = 10 µM.

**Supplementary Figure S3. Lower magnification examples of co-localization of SST2, SST2 ΔTSI, and SST2 358T with Rab4.** HEK293 cells transiently transfected with SST2, SST2 ΔTSI, or SST2 358T plus GFP-Rab4. Cells were treated for 30 min with SS14 (100 nM), washed, fresh media with PRL2915 (100 nM) was added, and the cells were incubated for 15 min before being fixed and stained for immunofluorescence analysis. HA-SST2 proteins, GFP-Rab4, and DNA are shown in red, green, and blue, respectively. Scale bars are 10 µM.

**Supplementary Figure S4. Lower magnification examples of co-localization of SST2, SST2 ΔTSI, and SST2 358T with Rab11.** HEK293 cells transiently transfected with SST2, SST2 ΔTSI, or SST2 358T plus GFP-Rab11. Cells were treated for 30 min with SS14 (100 nM), washed, fresh media with PRL2915 (100 nM) was added, and the cells were incubated for 15 min before being fixed and stained for immunofluorescence analysis. HA-SST2 proteins, GFP-Rab4, and DNA are shown in red, green, and blue, respectively. Scale bars are 10 µM.

**Supplementary Figure S5. Co-purification of SST2 with EEA1 and LAMP1 after ligand stimulation.** HEK293 cells were transiently transfected with HA-SST2 and treated for 2, 5 or 30 min with SS14 (100 nM) to induce receptor internalization. Cells were lysed and endosome fractions were separated by centrifugation on a continuous gradient. Fractions were collected and analyzed by western blot. EEA1 is a marker for early endosomes and LAMP1 is a marker of late endosomes. Shown are representative examples.

**Supplementary Figure S6. Lower magnification examples of SST2 and δOR localization after ligand stimulation.** HEK293 cells were transiently transfected with HA-SST2 and FLAG-δOR and treated for 30 min with both SS14 (100 nM) and DADLE (1 µM) to induce internalization. Cells were fixed and stained for immunofluorescence. SST2, δOR, and DNA are shown in red, green, and blue, respectively.

**Supplementary Figure S7. Lower magnification examples of co-localization of SST2 proteins with CI-M6PR.** HEK293 cells were transiently transfected with HA-tagged SST2, SST2 ΔTSI, or SST2 358T, treated with SS14 (100 nM) for 30 min, and fixed. Cells were co-stained for HA-epitope (green) and CI-M6PR (red) to mark the trans-golgi network. DNA is in blue. Scale bars are 10 μm.