**Supplementary Figures:**

**SF 1.** **(A)** QPCR for NPTX2 expression in an array of normal (n=4) and ccRCC (n=7) cell lines. All samples are normalized to a water negative control. Four shRNA lentiviral constructs (sh804, sh855, sh1316, sh1623) against NPTX2 were used to infect A498 cells. (**B**) Description of ccRCC cell line VHL mutational status. **(C)** QPCR for NPTX2 mRNA in each of the A498 NT vs. target lentiviral clones. **(D)** Western blot analysis for NPTX2 protein expression in all four A498 NPTX2 shRNA clones compared to NT control. Protein expression level quantitation is normalized to β-actin. **(E)** Proliferation (7 day) rescue assay of A498 cells transfected with either a human NPTX2 expression vector (+NPTX2) plasmid or empty vector (EV) control, and infected with NT control, sh1316 or sh1623 NPTX2 targeting lentivirus.

**SF 2.**  **(A)** IF of non-permeabilized KIJ265T cells for NPTX2 expression.(**B**) Relative NPTX2 expression values of patient gene array data sorted into low versus high NPTX2 expression groups. **(C)** IF for NPTX2 (far left panel) and Fibronectin (far right panel) in A498 NT vs. sh1316 NPTX2 knockdown cells. 60x magnification of regions highlighted in 20x images are shown (central panels).

**SF 3. (A)** QPCR for GluR4 mRNA in A498 cells infected with one of four lentiviral constructs against GluR4 (sh925, sh1676, sh2145, sh2285) as compared to NT control. **(B)** Western blot analysis for GluR4 expression in all four A498 GluR4 shRNA clones compared to NT control. Protein expression level quantitation is normalized to β-actin. **(C)** Proliferation of A498 GluR4 shRNA clones compared to NT control.

**SF 4.** Measurement of intracellular calcium influx into **(A)** empty vector or **(B)** GluR4 transfected Caki1 cells treated with 1ng/µL R-NPTX2 and DMSO or CFM-2 (10µM) over time using the cell permeable fluorescently labeled calcium indicator Calcium GreenTM-1, AM. Results are calculated as change in fluorescence over time (min)**.** (\*) Denotes significant change in fluorescence as compared to DMSO control per time point, and (\*\*) denotes a significant change between R-NPTX2 +/- CFM-2 treated cells. **(C)** Intracellular Ca2+ levels of NPTX2 and NPTX2-GluR4 transfected Caki1 cells pretreated for 1 hour with DMSO or specified doses of CFM-2.(\*) Denotes a significant change in fluorescence of NPTX2 and NPTX2-GluR4 as compared to EV control, and (\*\*) indicates significant changes in fluorescence between DMSO and CFM-2 treated groups