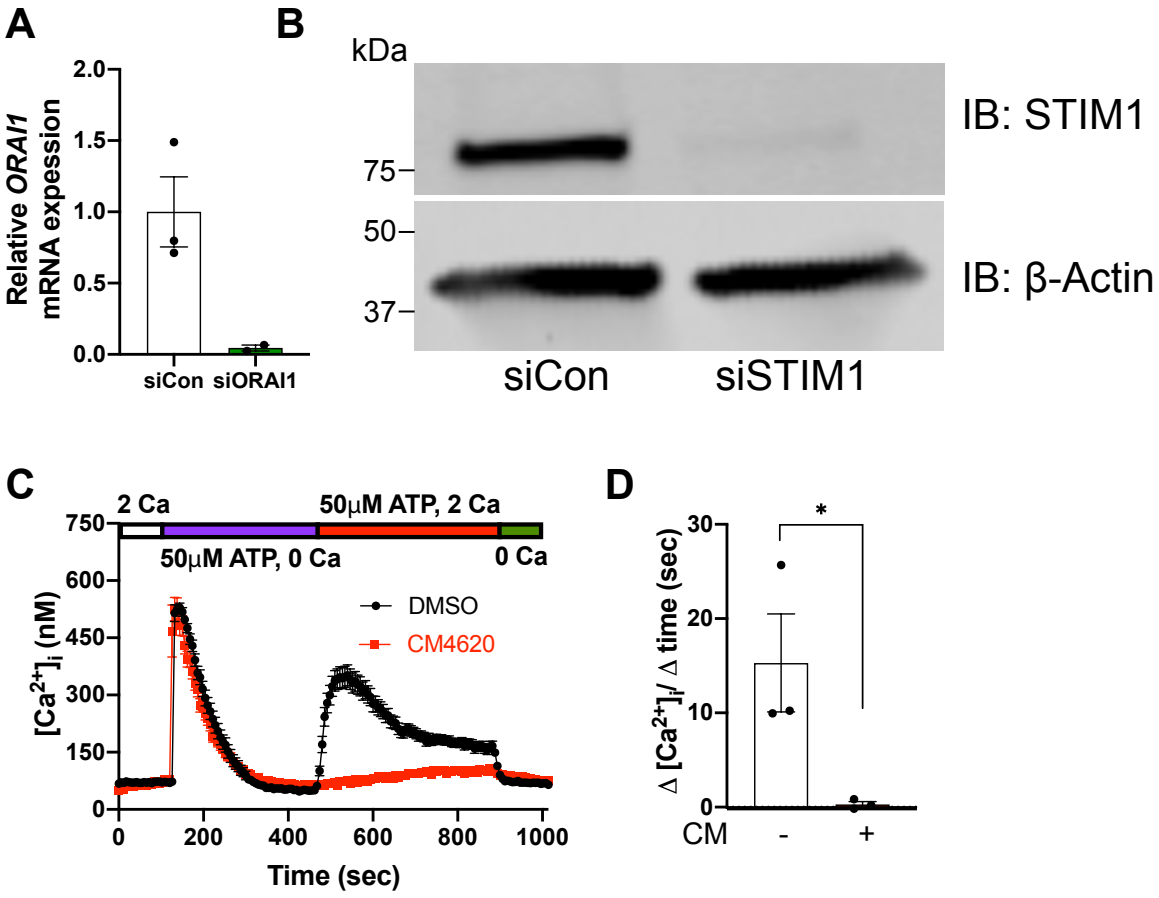
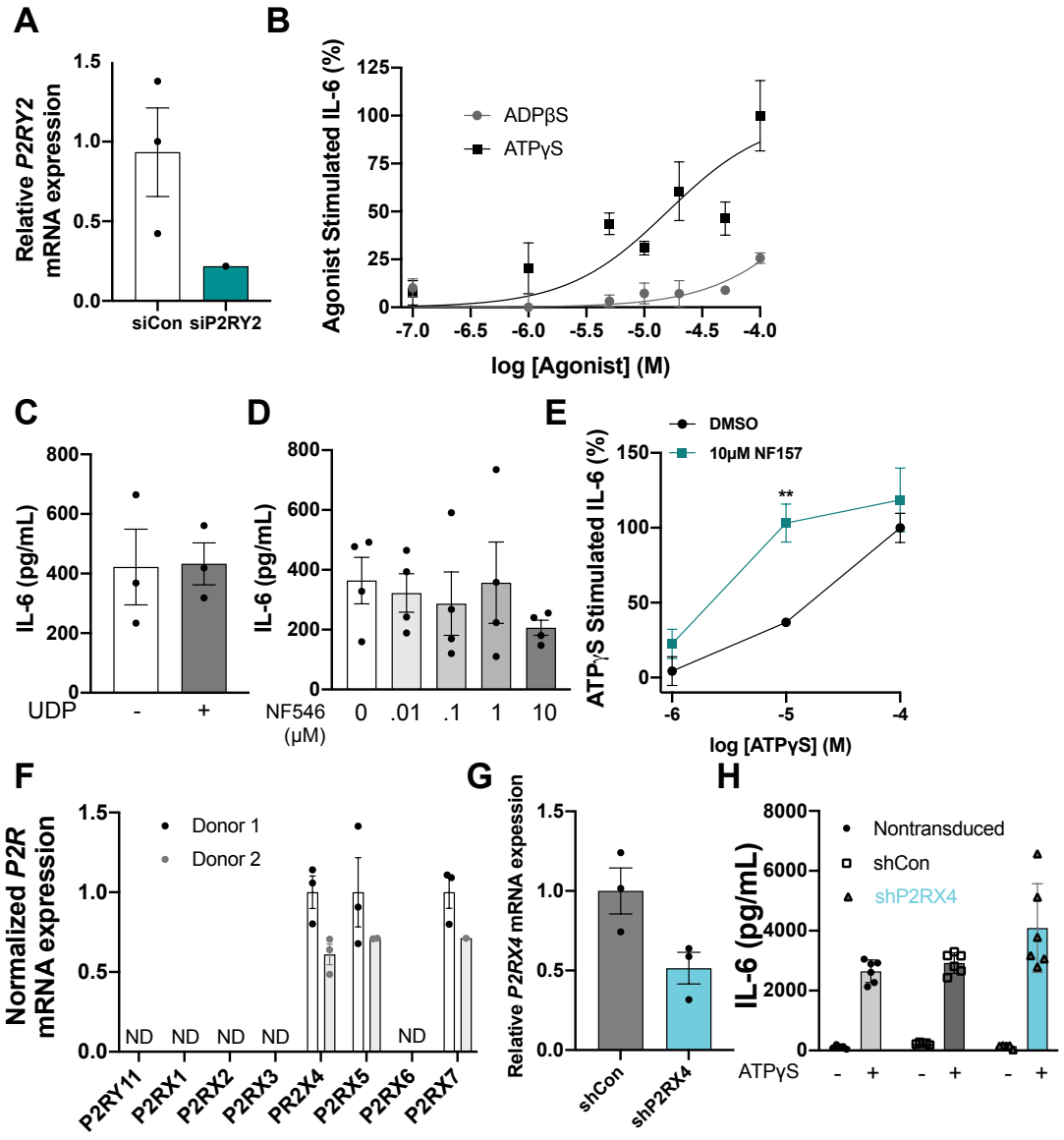
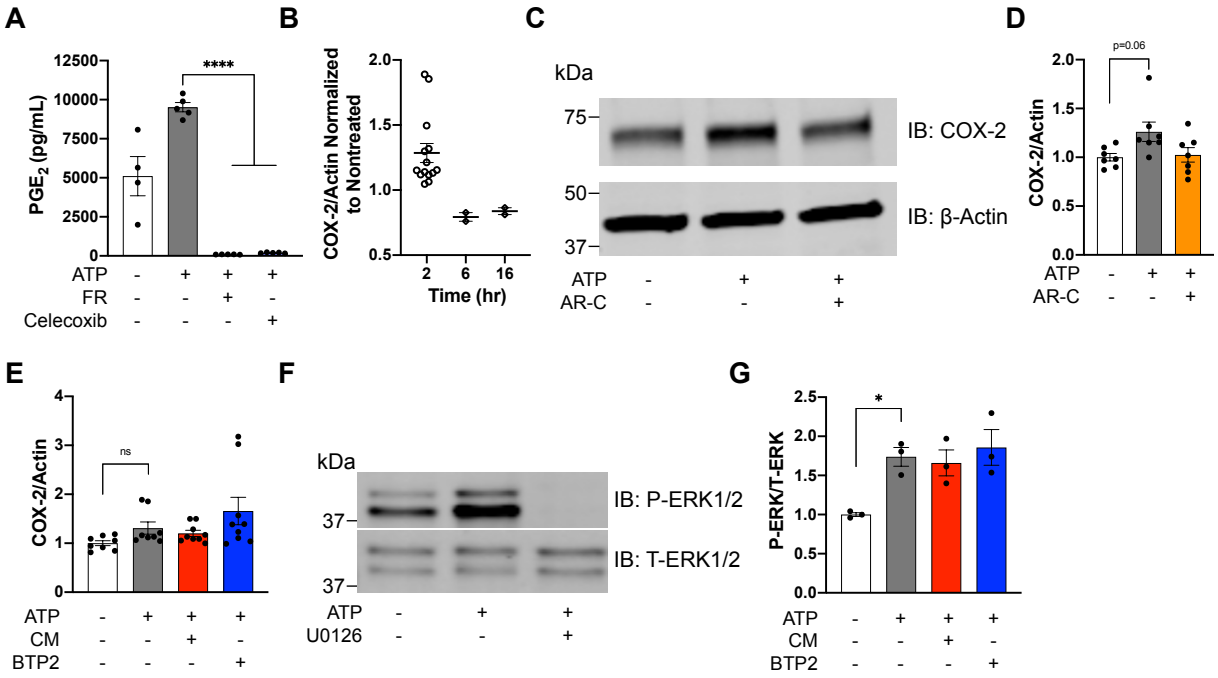


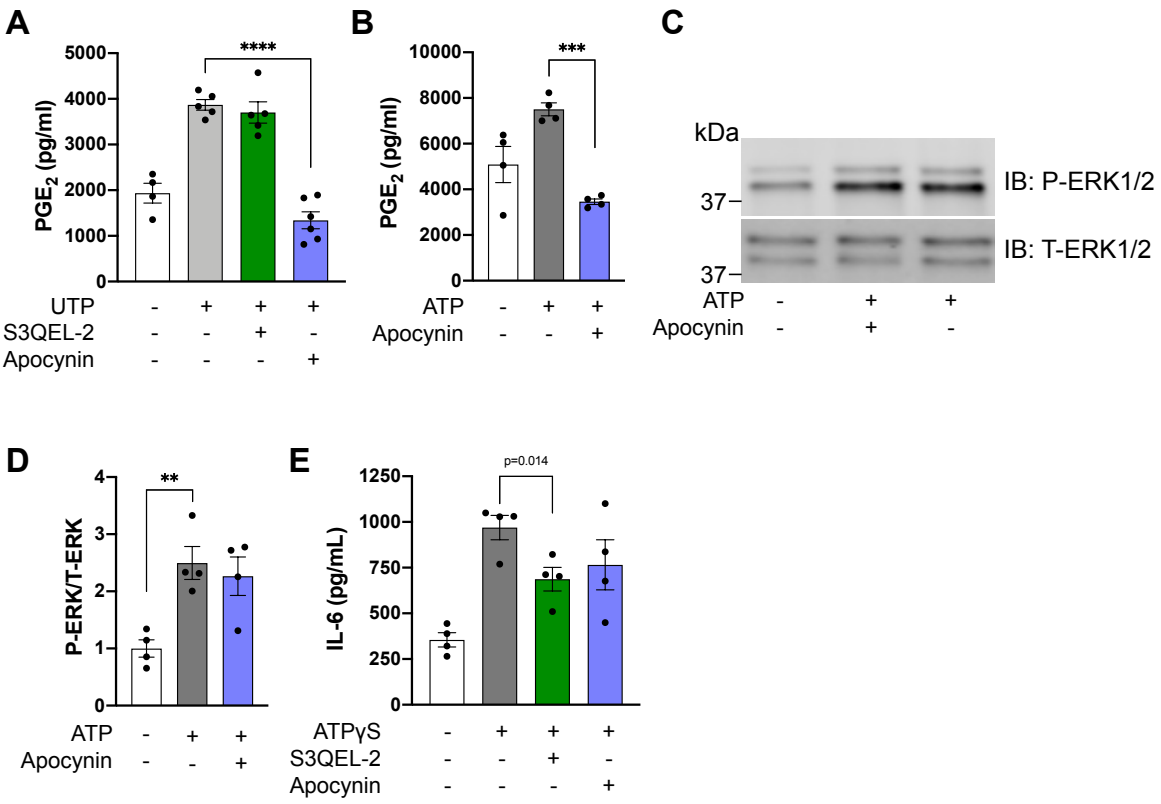
Supplemental Figure 1. Extracellular ATP evokes Ca^{2+} influx through CRAC channels. A) *siORAI1* decreases *ORAI1* mRNA expression. Expression was normalized to the three housekeeping genes *RPLP0*, *PPIA*, *HPRT1*. Data are mean ± SEM of n = 2-3 samples. **B)** *siSTIM1* decreases STIM1 protein expression. STIM1 protein was detected using a polyclonal antibody (See Methods). **C)** ATP-induced Ca^{2+} influx is inhibited by pretreatment (2hrs) with the ORAI1 inhibitor CM4620 (1 μM). Cells were treated with ATP (50 μM) in Ca^{2+}-free Ringer's solution to allow for store release followed by perfusion of Ringers containing 2 mM Ca^{2+}. Data are mean ± SEM of n = 14-21 cells. **D)** Quantification of the rate of Ca^{2+} influx in *C*. Rate of influx was calculated for the 24 seconds immediately following extracellular Ca^{2+} addition. Each data point is the mean Ca^{2+} influx rate for a given experiment (one dish) and graph is mean ± SEM of n = 3 independent tests. *p<0.05.



Supplemental Figure 2. P2Y receptor activation fails to elicit IL-6 release from AECs. A) *siP2RY2* decreases *P2RY2* mRNA expression. Expression was normalized to the housekeeping gene *RPLP0*. Data are mean ± SEM of n = 1-3 samples. **B)** Dose-response for ATPγS versus ADPβS induced IL-6 secretion measured in cell culture supernatant 16 hrs following agonist addition. Data are mean ± SEM of n = 4-6 samples. **C)** UDP (a $P2Y_6$ receptor agonist) does not elicit IL-6 secretion. Data are mean ± SEM of n = 3 samples. **D)** NF546 ($P2Y_{11}$ receptor agonist) fails to elicit IL-6 secretion. Data are mean ± SEM of n = 4 samples. **E)** NF157 (an antagonist of $P2Y_{11}$ and $P2X_1$ receptors) enhances low dose ATPγS-induced IL-6 secretion. Data are mean ± SEM of n = 3 samples. **F)** Two independent donors (NHBE cells) were examined for P2R expression via RT-qPCR. P2RX4,5,7 transcripts were detected while P2RY11, P2RX1-3,6 were not seen. **G)** *P2RX4* mRNA knockdown using shRNA quantified via RT-qpCR. Expression was normalized to the housekeeping gene *RPLP0*. Data are mean ± SEM of n = 3 samples. **H)** Knockdown of *P2RX4* does not affect ATPγS-evoked IL-6 synthesis. Data are mean ± SEM of n = 5-6 samples. **p<0.01



Supplemental Figure 3. P2Y$_2$ receptor-mediated PGE$_2$ synthesis requires COX-2 activity but not increase in COX-2 expression A) PGE$_2$ synthesis induced by ATP (100 μM) is abolished with the COX-1 inhibitor FR122047 (1μM) and the by the COX-2 inhibitor Celecoxib (1μM). Cells were pretreated for 1 hr prior to agonist stimulation. Data are mean ± SEM of n = 4-5 samples. **B)** Time course for ATP (100μM)-mediated COX-2 upregulation. Data are mean ± SEM of n = 2-14 samples. **C)** ATP (100μM, 2hrs) induces only a small extent of COX-2 upregulation which is inhibited by AR-C 118925XX (10μM). **D)** Summary of COX-2 upregulation using densitometry analysis. Data are mean ± SEM of n = 7 samples. **E)** CRAC channel inhibitors CM4620 (1μM) and BTP2 (1μM) do not alter ATP (100μM) induced COX-2 upregulation (2hr stimulation duration). Data are mean ± SEM of n = 7-9 samples and densitometry was performed for quantification. **F)** Pretreatment of cells with the MEK1/2 inhibitor U0126 (20μM) inhibits ATP (100μM) induced ERK1/2 phosphorylation. **G)** CRAC channel inhibitors CM4620 (1μM) and BTP2 (1μM) do not alter ATP induced ERK1/2 activation (100 μM, 15min stimulation). Data are mean ± SEM of n = 3 samples and densitometry was performed for quantification. *p<0.05, ****p<0.0001



Supplemental Figure 4. Inhibition of NADPH oxidase occludes ATP- and UTP- induced synthesis of PGE_2. A) Apocynin (200μM), an inhibitor of NADPH oxidase, abrogates UTP (50μM) induced PGE_2 synthesis. By contrast, the mitochondrial complex III inhibitor S3QEL-2 (20μM) does not affect the UTP (50μM)- induced PGE_2 response. Data are mean ± SEM of n = 4-6 samples. **B)** Likewise, apocynin (200μM) abrogates ATP (50μM)-induced PGE_2 synthesis. Data from the first two bars are the same as the control responses shown in Figure 5B. Data are mean ± SEM of n = 4 samples. **C)** Pretreatment of cells with the apocynin (200μM) does not inhibit ATP (100μM)-induced ERK1/2 phosphorylation (15min stimulation). **D)** Densitometry to quantify experiments shown in *C*. Data are mean ± SEM of n = 4 samples. **E)** Inhibition of NADPH oxidase with apocynin (200μM) or the mitochondrial complex III inhibitor S3QEL-2 (20μM) have only modest effects on ATPγS (100μM) induced IL-6 synthesis. Data are mean ± SEM of n = 4 samples. **p<0.01, ***p<0.001, ****p<0.0001.