

Supplementary Information

Supplementary figure legends

Supplementary Figure 1. Δ F508 CFTR exhibits less functional decline at the plasma membrane in the presence of VX-809. Bar-graphs representing maximal short-circuit currents (maximum increase from the baseline value) for the data points corresponding to 0 h, 2 h and 4 h of incubation at 37°C following temperature rescue of (A) Δ F508 CFTR and (B) Δ F508 CFTR His 10 at the plasma membrane at 37°C in CFBEo⁻ cells pretreated with DMSO or VX-809 (5 μ M, 48 h). Data at each time-point is represented relative to the function at 0 h. Data represents means of three to four independent experiments. Δ F508 CFTR retained more function in the presence of VX-809 compared to DMSO which was found to be statistically significant (** $p < 0.01$). However, no such statistical significance (ns) was observed for the functional profile of Δ F508 CFTR His 10 with and without VX-809.

Supplementary Figure 2. VX-809 increases surface levels of Δ F508 CFTR and Δ F508 CFTR His 10 molecules

Surface expression of Flag-tagged WT, Δ F508 CFTR and Δ F508 CFTR His 10 molecules in HEK-293 cells detected using HRP-based ELISA. Surface levels of Δ F508 CFTR are enhanced in the presence of VX-809; * $p < 0.05$, ** $p < 0.01$.

Supplementary Figure 3. VX-809 potentiates Δ F508 CFTR function in HEK 293 cells

Representative line graph to show iodide efflux measurements depicting CFTR function in HEK-293 cells. VX-809 potentiates function of Flag- Δ F508 CFTR maintained at 37°C or in the temperature rescue condition. Bar-graph represents the maximal increase in iodide efflux rate

(maximum increase from the baseline value). Par refers to the cells that express no CFTR. Data represents mean of three experiments; $**p < 0.01$.

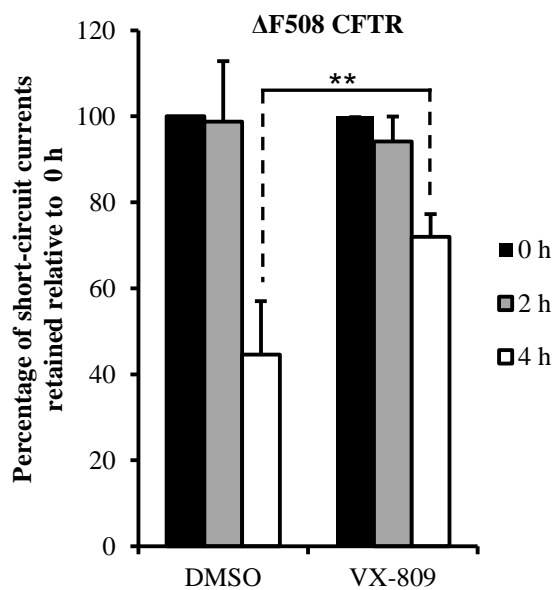
Supplementary Figure 4. VX-809 potentiates $\Delta F508$ CFTR function in CFBEo⁻ cells

Representative traces of short-circuit current showing $\Delta F508$ CFTR function in CFBEo⁻ cells pretreated with DMSO or VX-809 and maintained at (A) 37°C and (B) in the temperature rescue condition (28°C). Bar-graph shows the maximal increase in short-circuit currents (maximum increase from the baseline value). Cocktail refers to the mix of cAMP-elevating reagents composed of 10 μM Fsk and 100 μM IBMX added to the apical side of the cells. Data represents mean of three experiments; $*p < 0.05$.

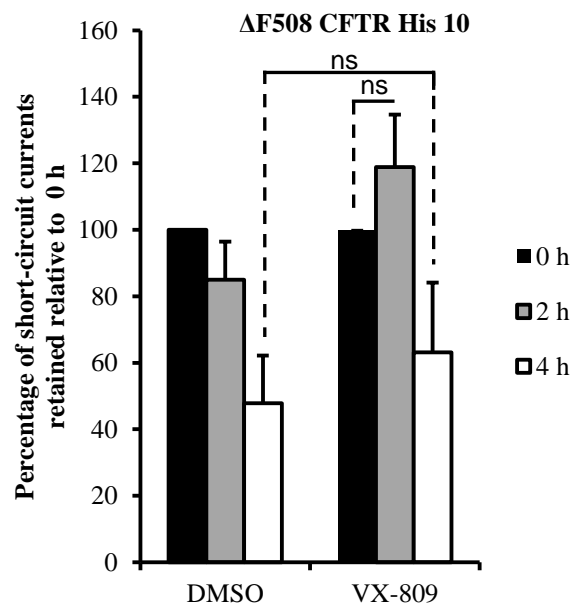
Supplementary Figure 5. Luminal secretions in the intestinal organoids are CFTR-mediated

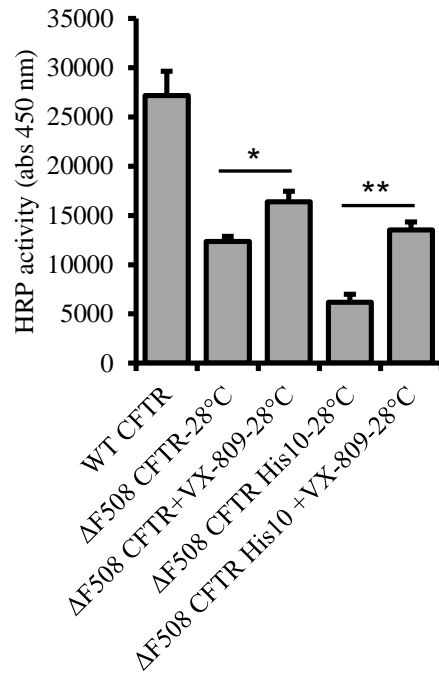
Representative images of the intestinal organoids depicting extent of luminal secretions in response to various reagents [(DMSO/Fsk (10 μM)/Fsk (10 μM) + CFTR_{inh}-172 (50 μM)] after 30 min of treatment. Bar-graph represents change in the luminal secretions at 30 min from the base-line values at 0 min (images not shown). Data represents mean of three experiments; $**p < 0.01$, ns=non-significant.

A



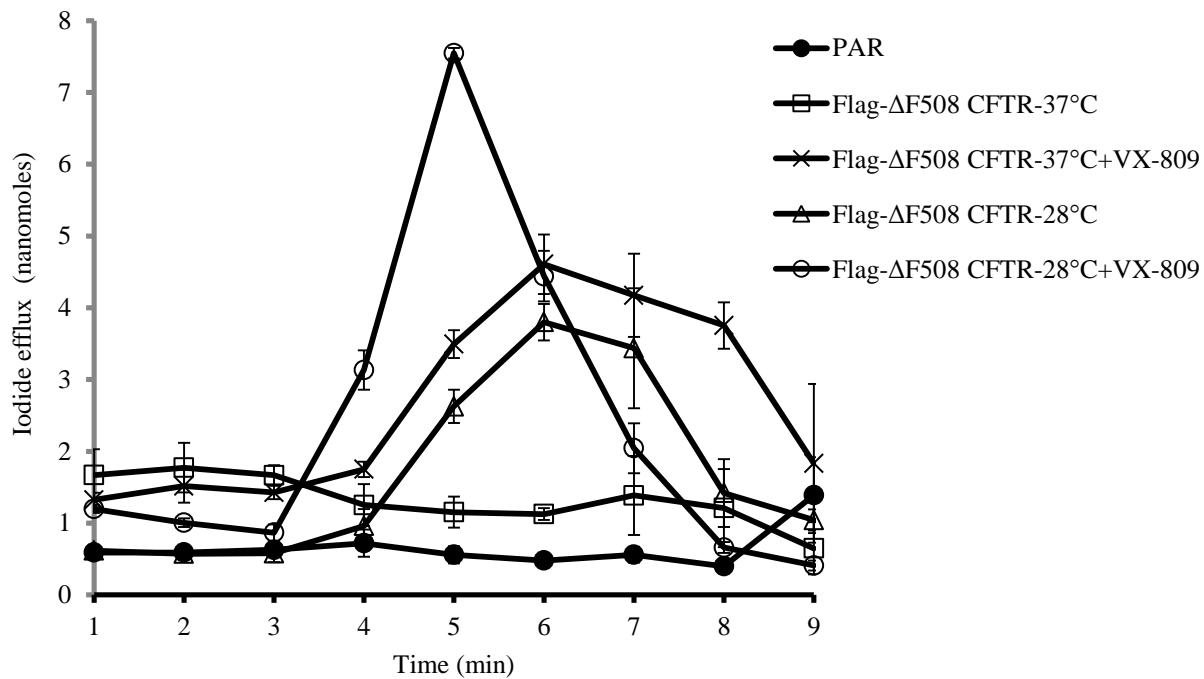
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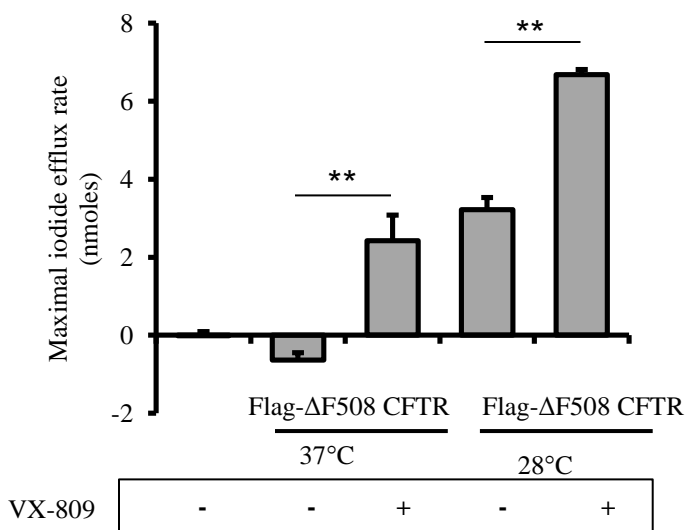


Supplementary figure 2

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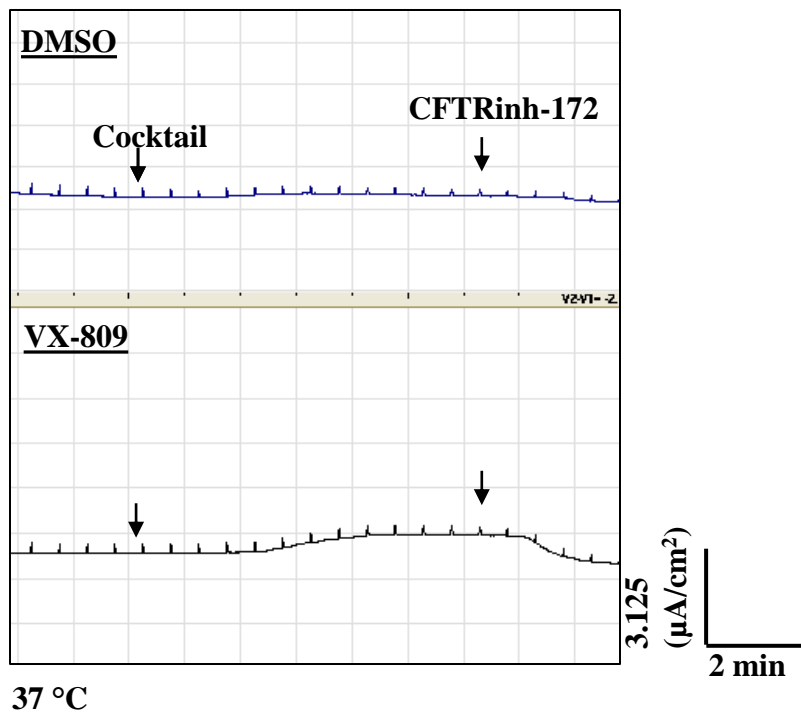


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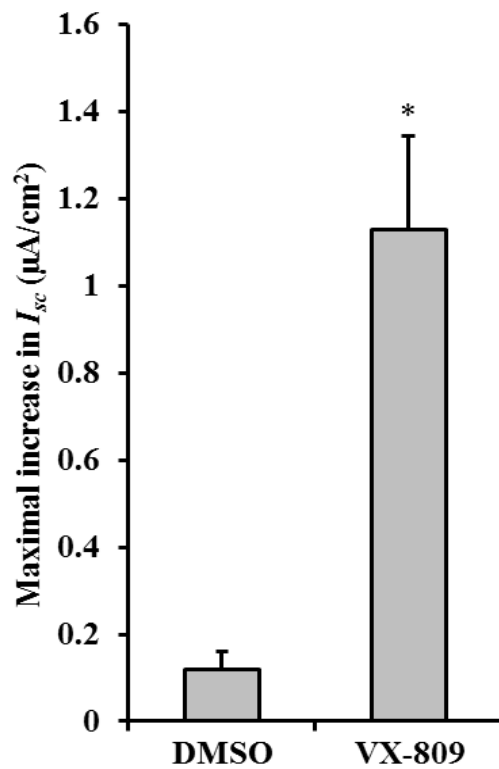


Supplementary figure 3

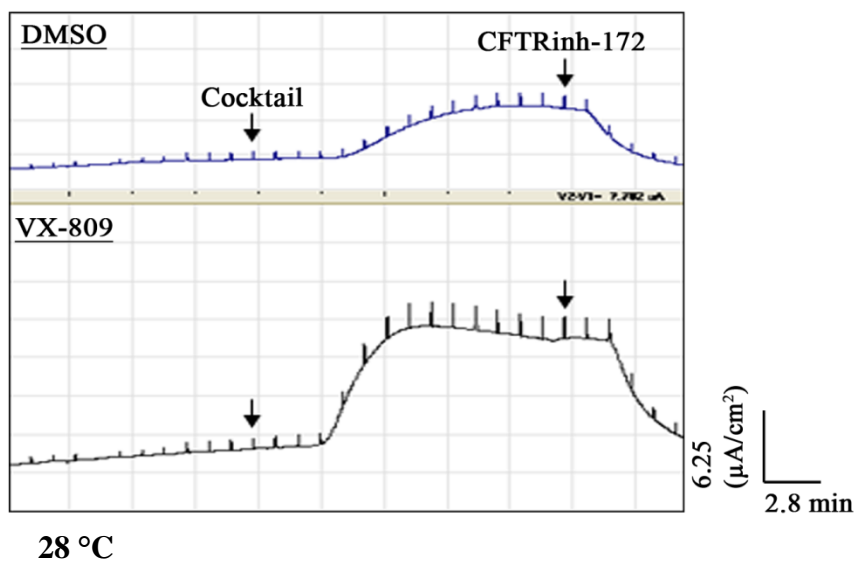
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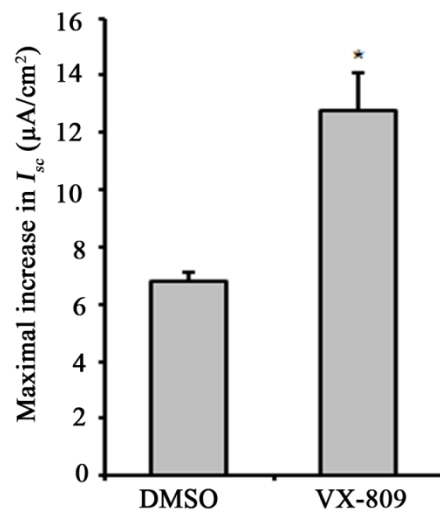
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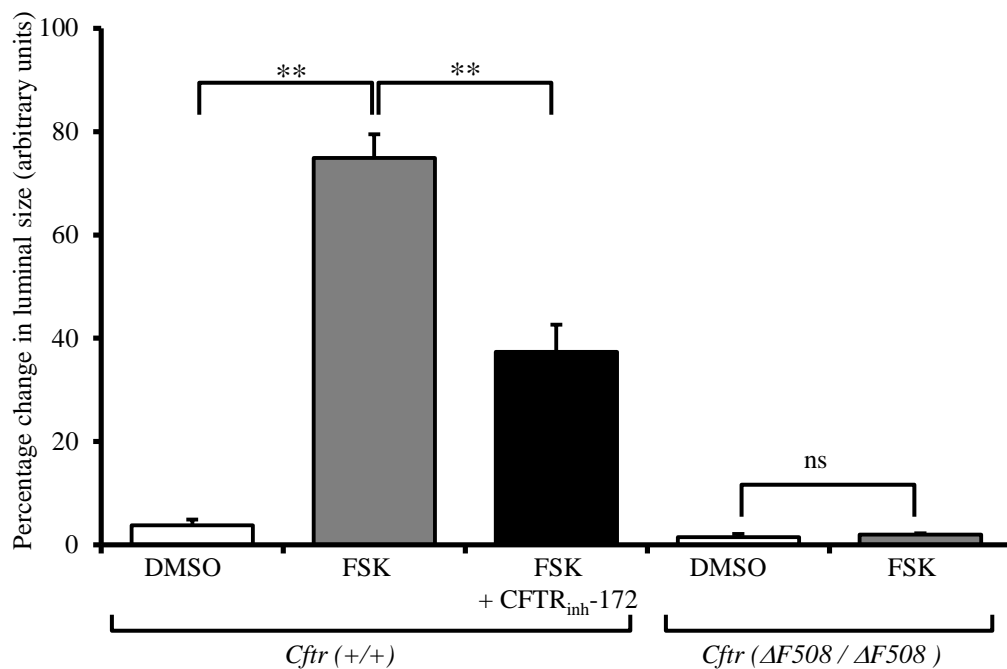
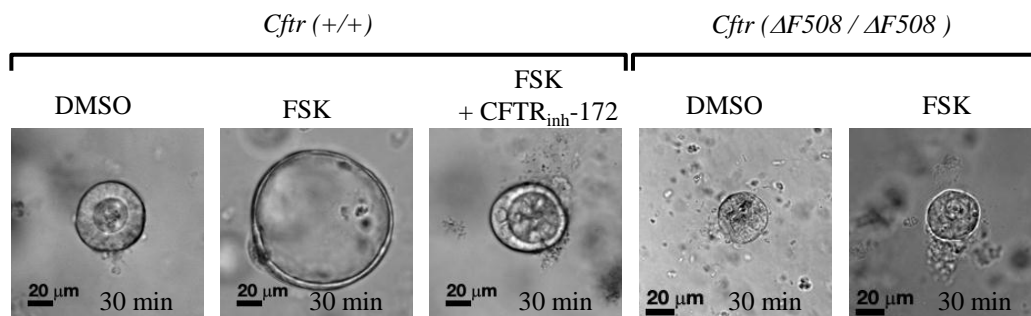


C



D





Supplementary figure 5