Supplemental Table 1. *CFTR* mRNA qPCR analysis

Group	Cells	∆CT	Expression Fold Change (%)	*p**
WT	EpCAM^{+} lung	12.7		
CF$^{fl/fl}$	Peritoneal neutrophils	31.4	100	<0.05
CF-LysM	Peritoneal neutrophils	42.3	<1	
CF$^{fl/fl}$	BM megakaryocytes	18.2	100	<0.05
CF-PF4	BM megakaryocytes	20.4	21	

∆CT: Average Ct – GAPDH Ct

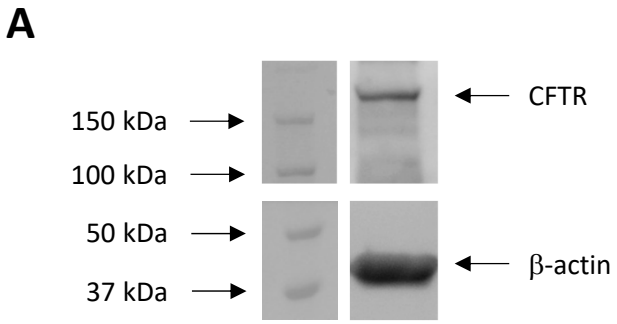
Expression Fold Change (%): 2^-∆∆Ct x 100

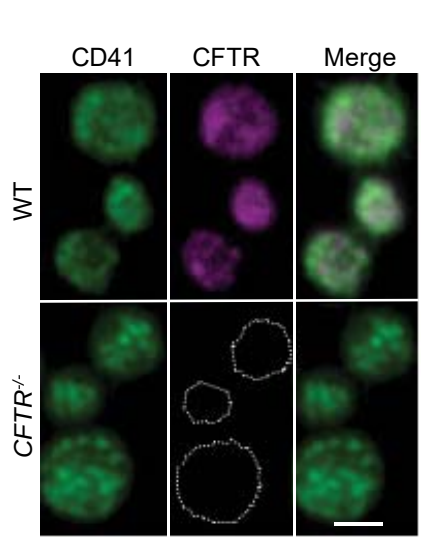
n = 4 - 12 per group

* Student's *t*-test

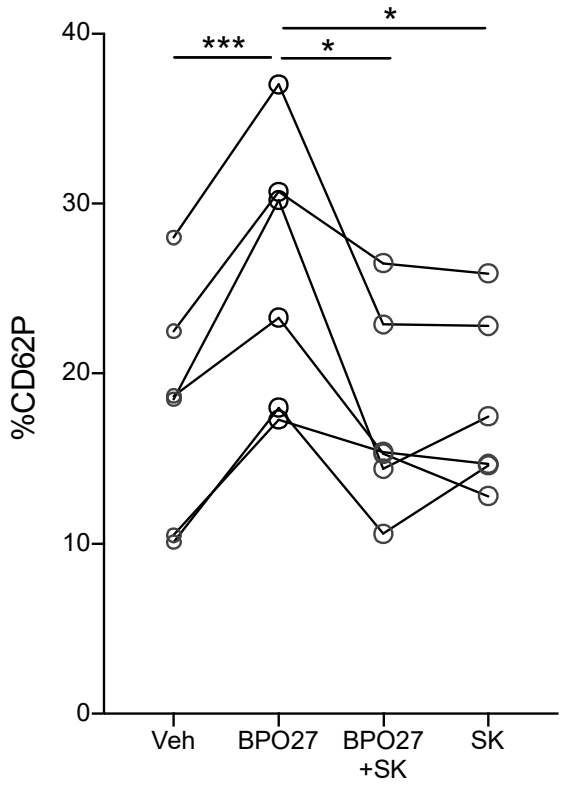
Supplemental Table 2: CF patient demographics.

	CF subjects on Orkambi	CF subjects (no modulators)
Number	6	9
Age (years)	35	29
Female (%)	33	57
BMI	21.8	22.9
FEV1 (baseline)	61%	58%
FEV1 (after Orkambi)	75%	n/a
FVC (baseline)	84%	83%
FVC (after Orkambi)	94%	n/a
Inhaled antibiotics	100%	55%
Vest (>daily)	75%	67%
Pancreatic Insufficiency	100%	100%
Genotype	DelF508/DelF508 (all)	DelF508/DelF508 (5), DelF508/DelI507, DelF508/G542X, DelF508/2657+6G>A, DelF508/398DelTT
Exacerbations/yr (baseline)	6	2
Exacerbations/yr (after Orkambi)	2	n/a
Pseudomonas aeruginosa colonization	100%	67%

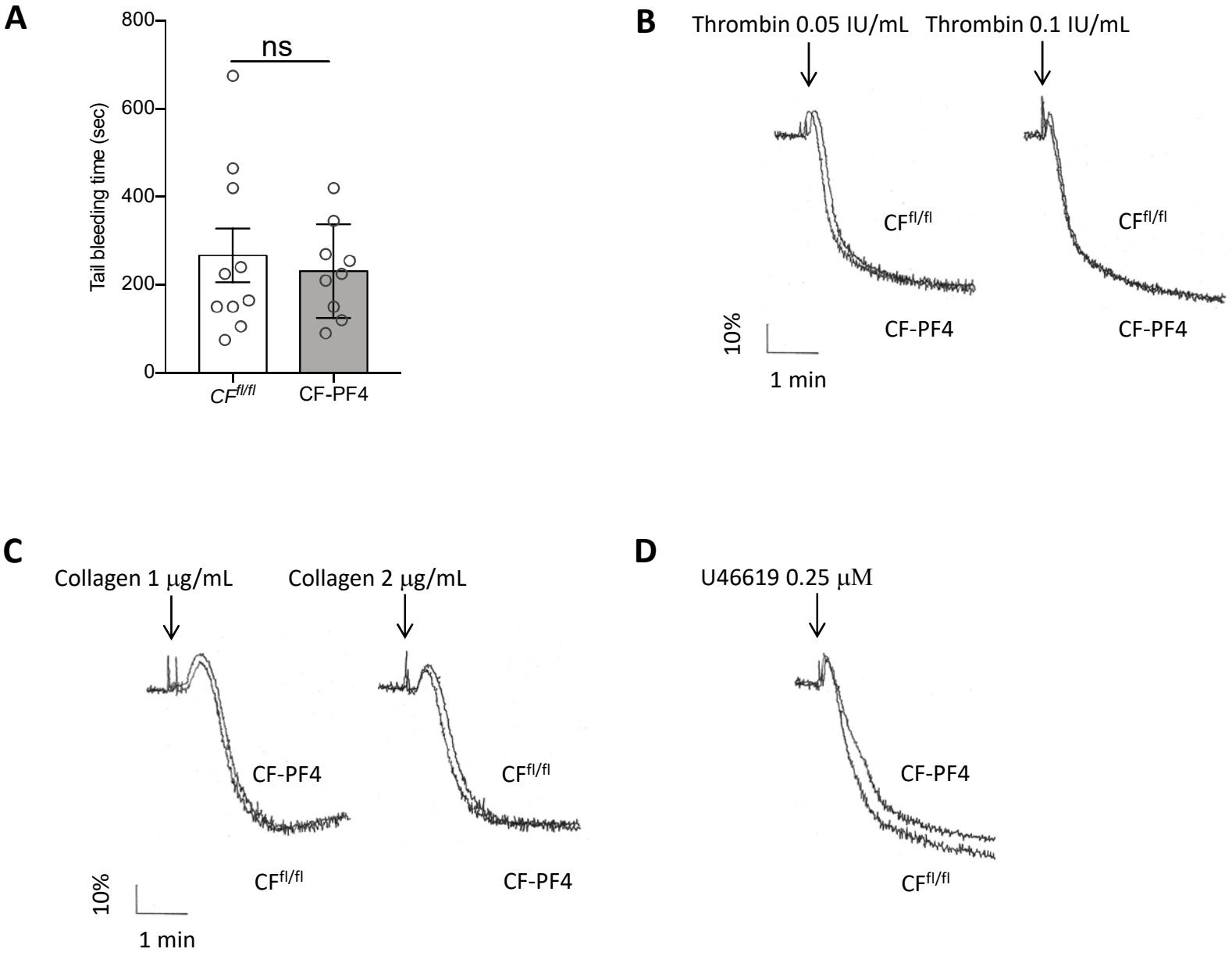




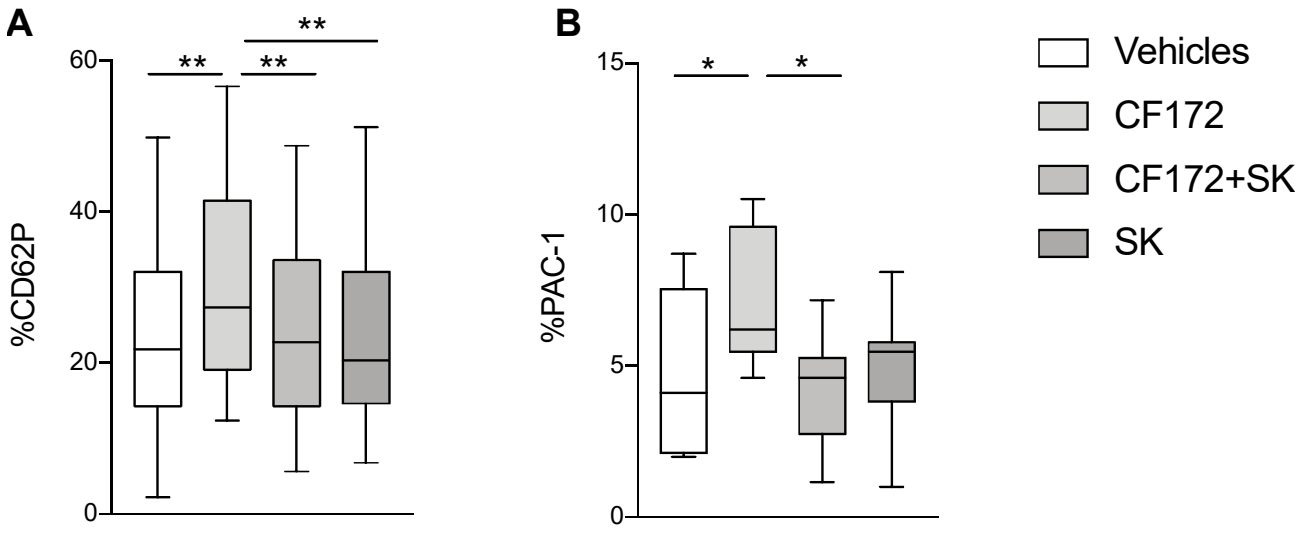
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4

Supplemental Table 1. *CFTR* mRNA qPCR analysis in cells isolated from WT and CF mice. $EpCAM^+$ cells obtained from the lungs of WT mice were used as a positive control for this assay. Peritoneal neutrophils were obtained 24 hours after Casein i.p. injection in $CF^{fl/fl}$ and CF-LysM mice. Bone marrow megakaryocytes were obtained from $CF^{fl/fl}$ and CF-PF4 mice. ΔCT: Average Ct – GAPDH Ct. Expression Fold Change (%): 2^-ΔΔCt x 100. *n* = 4 - 12 per group. * Student's *t*-test

Supplemental Table 2. CF patient demographics with variables that reflect lung disease severity including body mass index (BMI), forced expiratory volume at 1 sec (FEV1), and forced vital capacity (FVC), exacerbations per year, and colonization with *Pseudomonas aeruginosa*. Extrapulmonary manifestations are noted by pancreatic insufficiency, which all patients have. Genotypes are all homozygous ΔF508 in the CF group treated with Orkambi and either homozygous or heterozygous ΔF508 with the second allele belonging to Class I-II in the CF group not treated with Orkambi. Enrolling homozygous ΔF508 subjects not on Orkambi was difficult as it is an evolving standard of care for this genotype.

Supplemental Figure 1. CFTR expression in human and mouse platelets. (**A**) CFTR Western blot analysis from platelets obtained from normal human volunteers. A representative blot is shown from 3 independent experiments. The lanes were run on the same gel but were noncontiguous. (**B**) CD41 and CFTR immunofluorescence staining on platelets isolated from WT and $CFTR^{-/-}$ mice (representative of 4 independent experiments). A negative control stained with only the secondary antibody showed no fluorescence in either the WT or $CFTR^{-/-}$ platelets. Scale bar = 2.5 μm.

Supplemental Figure 2. CD62P expression on WT mouse platelets incubated with an alternative CFTR inhibitor, BPO27, under thrombin-stimulated conditions. Platelets

incubated with BPO27 show increased CD62P expression, which was decreased by incubation with SKF-96365 (SK). Data are mean ± SEM of 5 animals per group. *p≤ 0.05.

Supplemental Figure 3. Tail bleeding and platelet aggregation responses in CF mice. (**A**) Tail bleeding times (sec) in $CF^{fl/fl}$ and CF-PF4 mice. (**B**) Platelet aggregation responses to thrombin (0.5 IU/mL, 0.1 IU/mL), (c) collagen (1 μg/mL, 2 μg/mL), and (d) U46619 (0.25 μM) in $CF^{fl/fl}$ and CF-PF4 mice.

Supplemental Figure 4. Human CF platelet activation after thrombin challenge in modified assay with tezacaftor/ivacaftor incubation. Isolated platelets from CF subjects (DelF508 and one other residual function mutation on tezacaftor/ivacaftor) were incubated with 3 μM VX-661 (tezacaftor) and 5 μM VX-770 (ivacaftor) throughout the assay described in Figure 5D-E. Platelets were incubated with vehicles, CF172, CF172 + SK, or SK alone, challenged with thrombin, and stained for CD62P (**A**) and PAC-1 expression (**B**). Data are presented as min-to-max whiskers and box plots showing the median and interquartile ranges. *n* = 10 subjects. Data were analyzed by 2-way ANOVA. *p≤ 0.05, **p≤ 0.01.