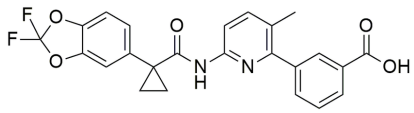
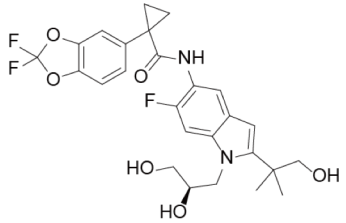
A

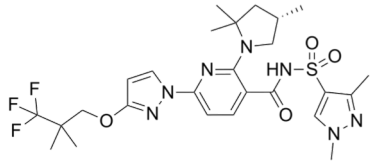
Lumacaftor (VX809)



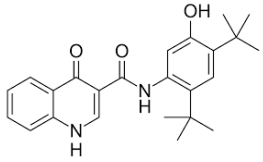
Tezacaftor (VX661)



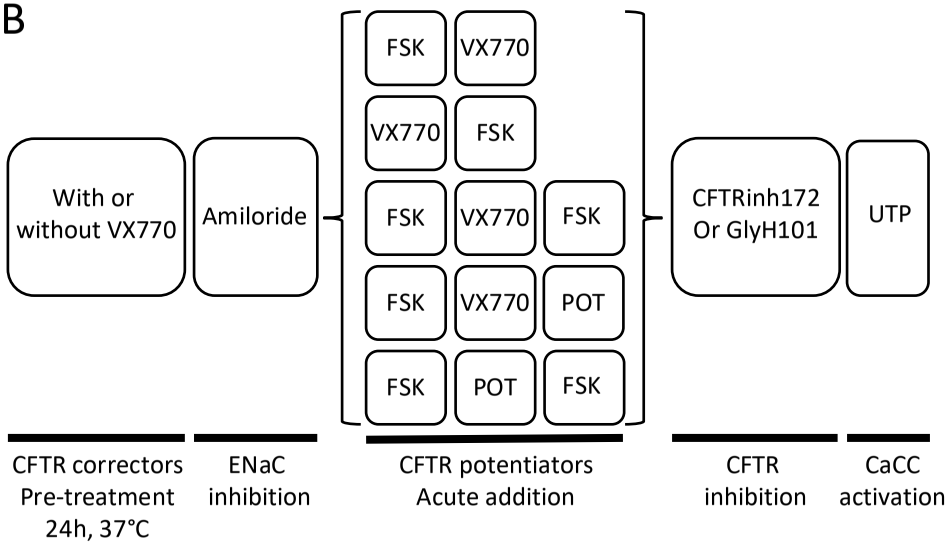
Elexacaftor (VX445)



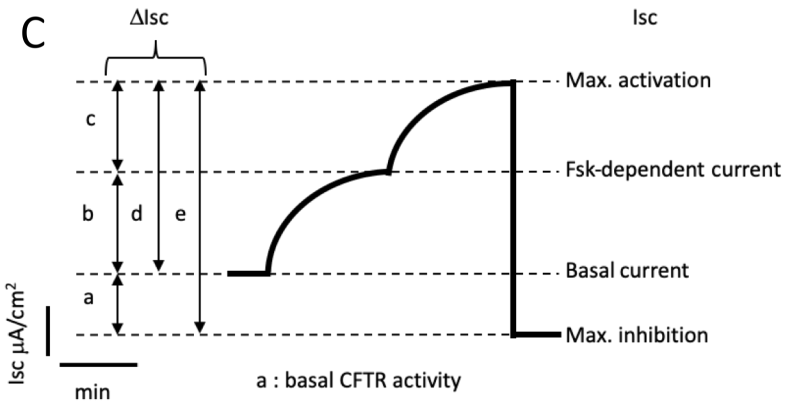
Ivacaftor (VX770)



B



C



a : basal CFTR activity

b : forskolin-dependent CFTR ΔIsc

c : potentiator-dependent CFTR ΔIsc

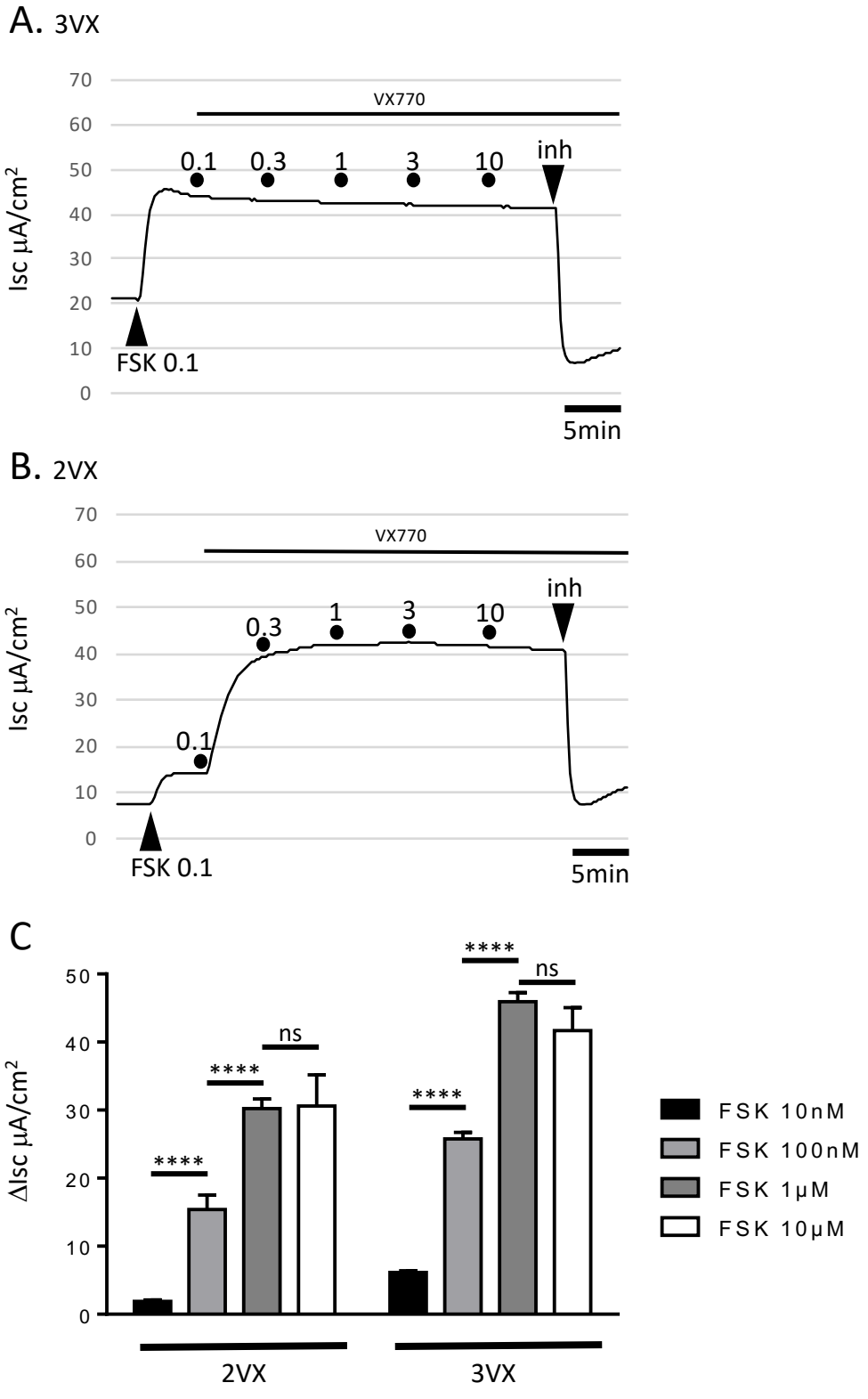
d : activatable CFTR ΔIsc

e : inhibitable CFTR ΔIsc

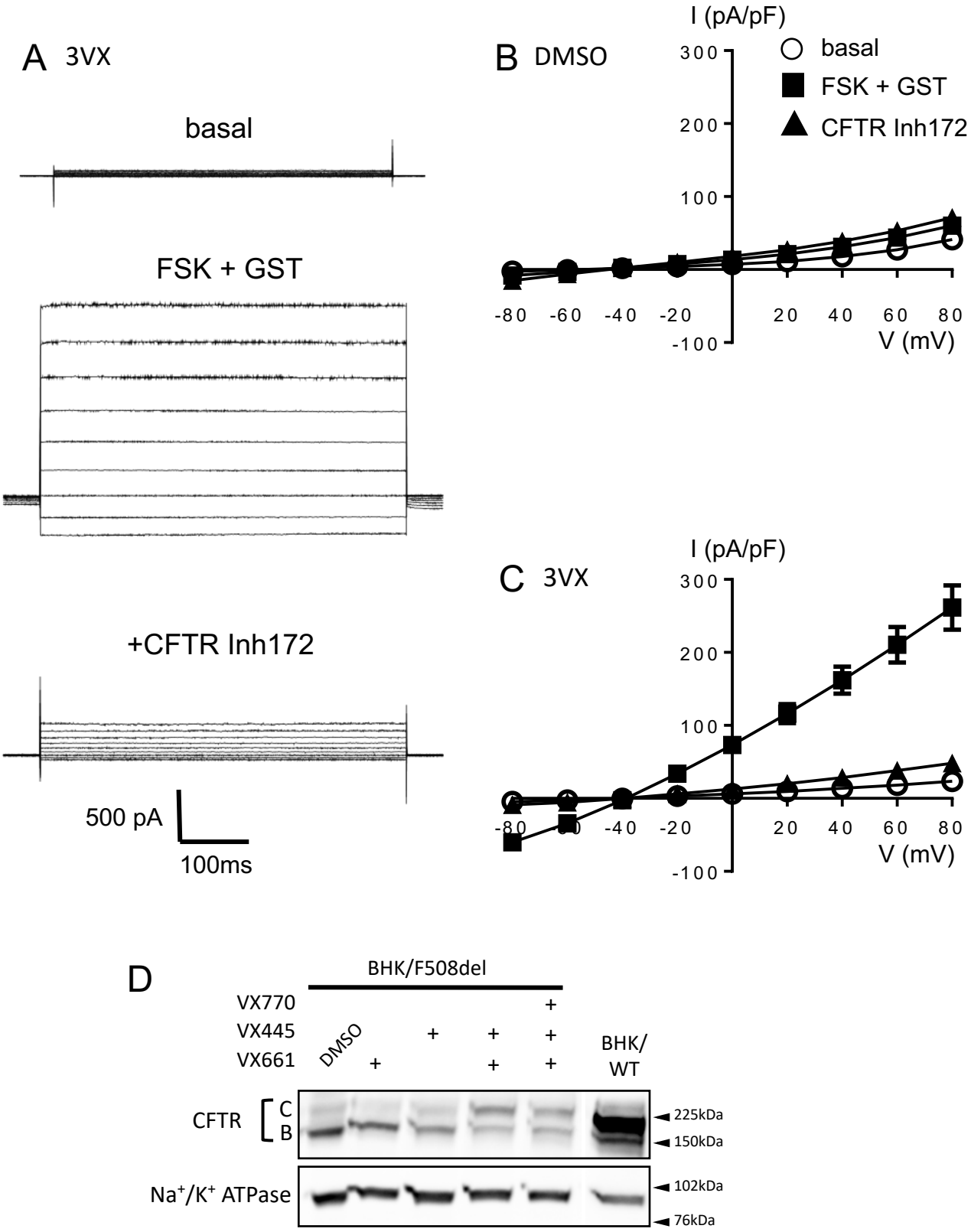
Figure S1

Supplemental Figure S1. Chemicals and protocols A. chemical structures of the therapeutic correctors lumacaftor, tezacaftor and elexacaftor and of the potentiator ivacaftor. B. scheme illustrating the protocols used to record Isc in airway epithelial cells. POT: genistein or Cact-A1. C. scheme showing the analysis of Isc to determine basal Isc (a), forskolin (b) and potentiator (c)-dependent ΔIsc, activatable (d) and inhibitable (e) CFTR ΔIsc.

Figure S2


A. 3VX
VX770
0.1
0.3
1
3
10
inh
Isc µA/cm²
FSK 0.1
5min
B. 2VX
VX770
0.3
1
3
10
inh
0.1
Isc µA/cm²
FSK 0.1
5min
C
ΔIsc µA/cm²
****
ns
****
****
ns
****
2VX
3VX
FSK 10nM
FSK 100nM
FSK 1µM
FSK 10µM

Supplemental Figure S2. Stimulation of F508del-Isc by VX770 and forskolin. a, b) Original tracings showing Isc with CFBE F508del cells incubated by elexacaftor/tezacaftor/ivacaftor (noted 3VX in a) or elexacaftor/tezacaftor (noted 2VX in b). The Isc CFTR current was stimulated by FSK (0.1 µM, arrow) then VX770 (increasing concentrations as indicated by the dot on the traces) then inhibited by 10 µM CFTRinh172 (inh, second arrow). c) Mean ± SEM of ΔIsc in response to increasing concentrations of FSK (n=4-8 for each concentration). ns, no significant difference and ****$P< 0.0001$.


A 3VX
basal
FSK + GST
+CFTR Inh172
500 pA
100ms
B DMSO
I (pA/pF)
basal
FSK + GST
CFTR Inh172
300
200
100
-100
-80 -60 -40 -20 20 40 60 80
V (mV)
C 3VX
I (pA/pF)
300
200
100
-100
-40 -20 20 40 60 80
V (mV)
D
BHK/F508del
VX770
VX445
VX661
DMSO
BHK/
WT
CFTR
C
B
225kDa
150kDa
Na+/K+ ATPase
102kDa
76kDa

Supplemental Figure S3. Whole-cell patch clamp recordings of F508del chloride currents in BHK cells. a) Original tracings of whole-cell F508del-CFTR chloride currents in basal (upper traces), after adding FSK (10 µM) + GST (30 µM) (middle traces) and after adding CFTRinh172 (10 µM) (bottom traces). b, c) Current density/V relationships for non-treated BHK cells (n=14, b) or BHK cells treated by elexacaftor/tezacaftor/ivacaftor (n=15, c). Basal is indicated by circles, FSK+GST by squares and CFTRinh172 by triangles. d) CFTR expression of the total protein fraction from BHK F508del cells after 24h-incubation with VX661 (18 µM), VX445 (3 µM) and VX770 (1 µM) alone or in combination or DMSO control as indicated above blot and of BHK WT cells grown on dish (representative blot of 2 independent experiments). Equal protein loading was controlled via Na^+/K^+ ATPase detection.