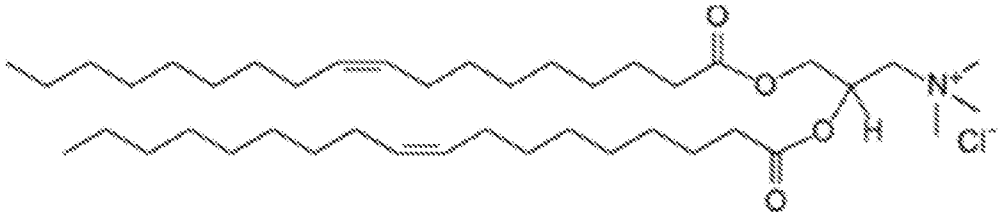
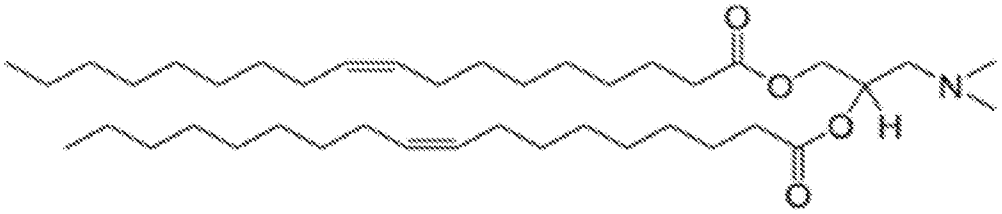
DOTAP



DODAP



EPC

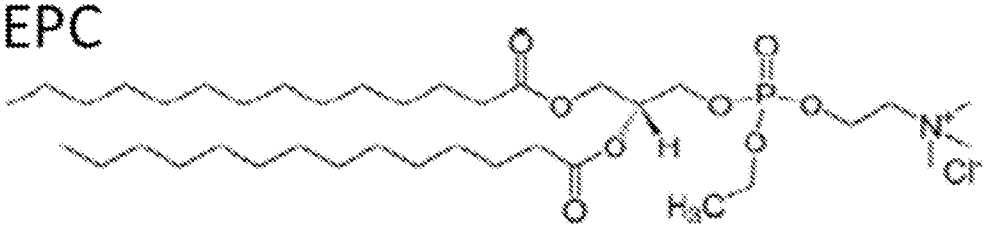


Fig. 1

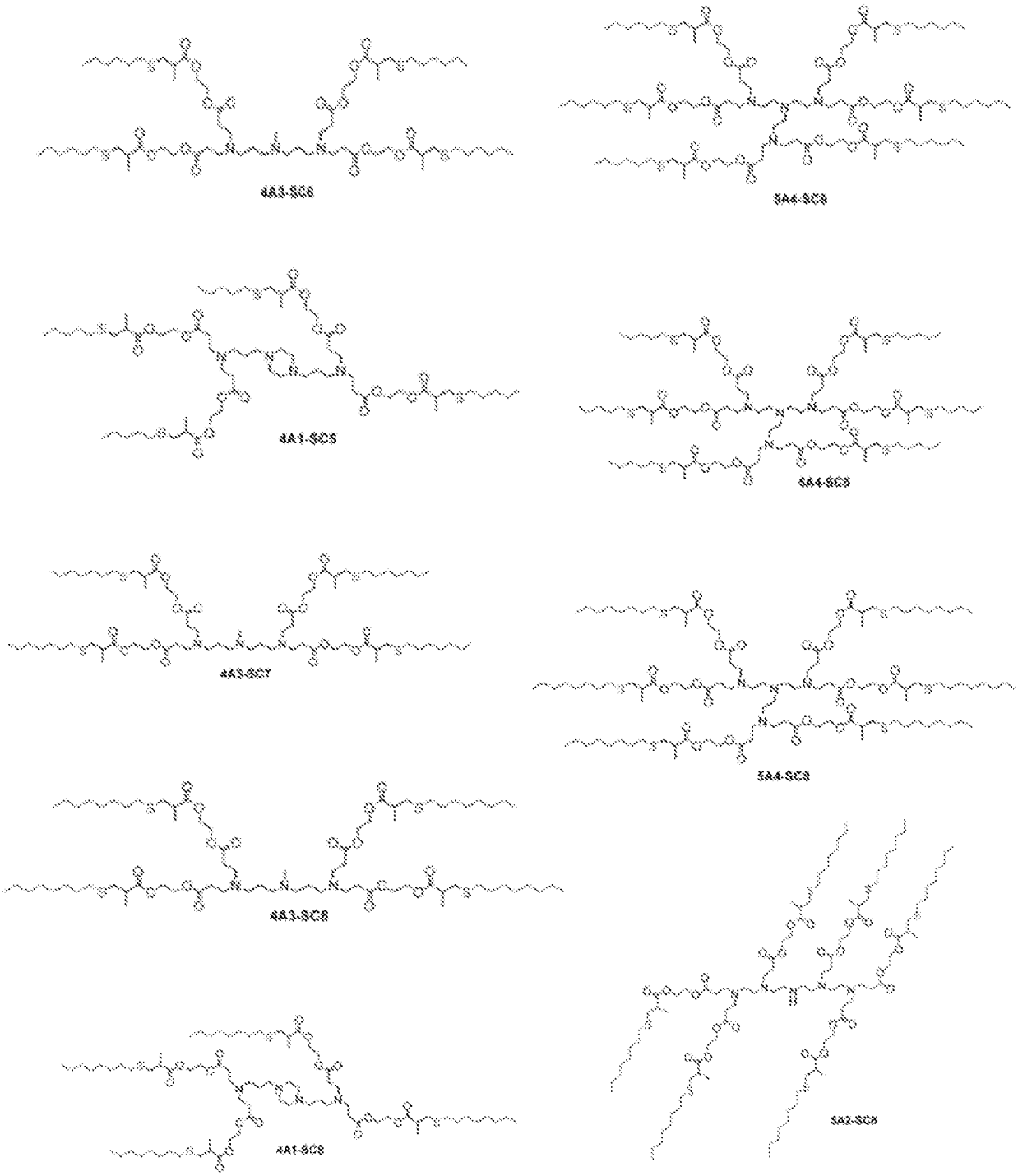
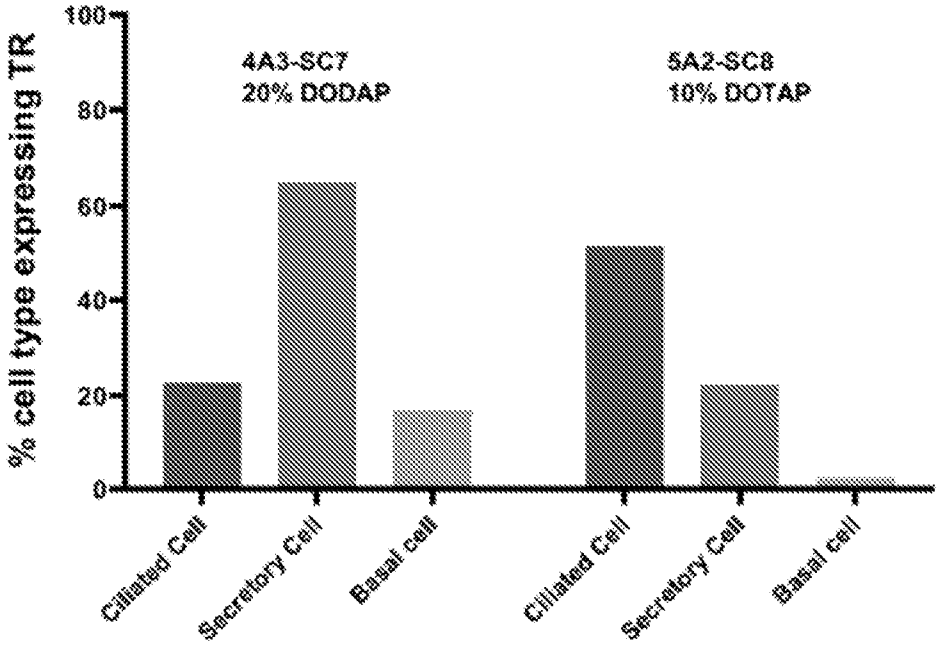

4A3-SC8
5A4-SC8
4A1-SC8
5A4-SC8
4A3-SC7
5A4-SC8
4A3-SC8
5A2-SC8
4A1-SC8

Fig. 2

Apical bolus dosing of well-differentiated human bronchial epithelial cultures with TR mRNA (12 ug)



Aerosol delivery to well-differentiated human bronchial epithelial cultures with TR mRNA (4 ug)

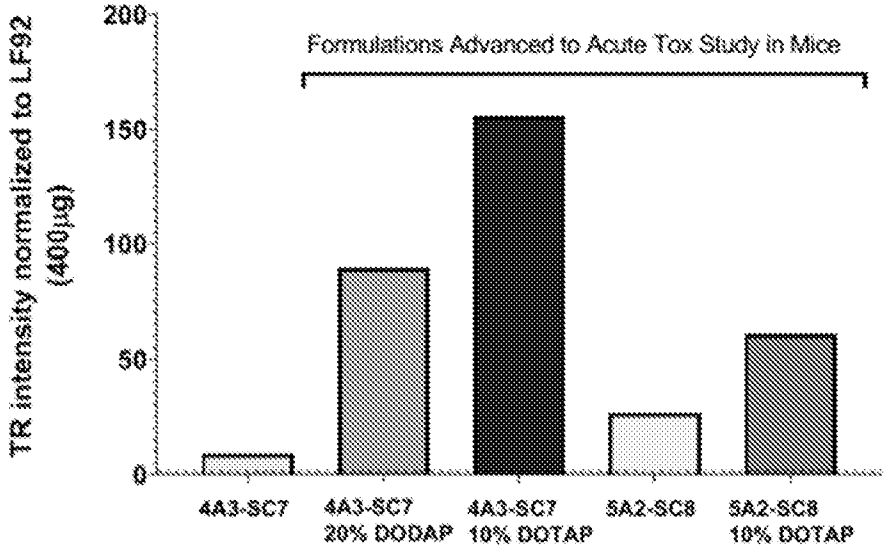


Fig. 3

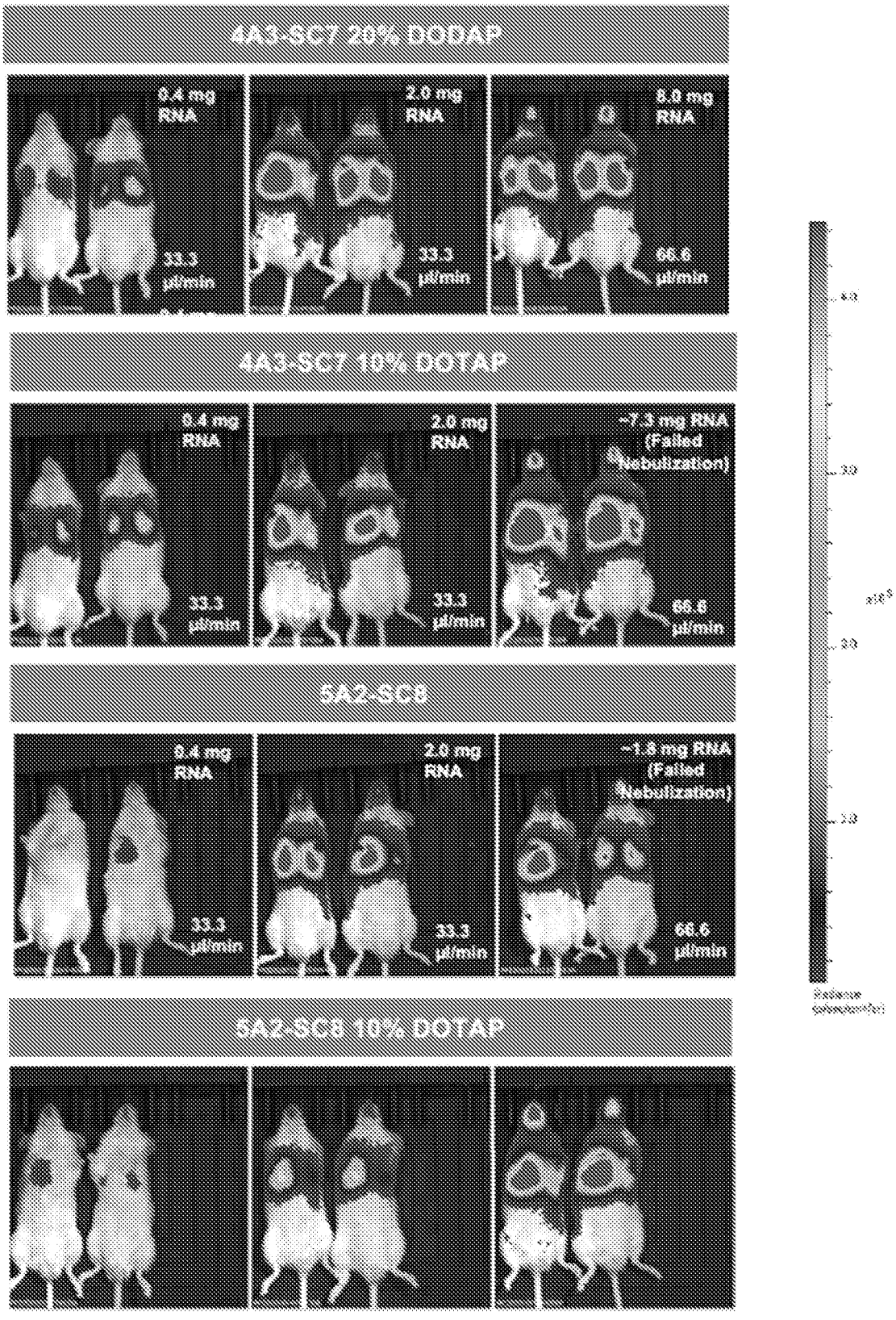

4A3-SC7 20% DODAP
9.4 mg RNA
33.3 µl/min
2.0 mg RNA
33.3 µl/min
8.0 mg RNA
66.6 µl/min
4A3-SC7 10% DOTAP
9.4 mg RNA
33.3 µl/min
2.0 mg RNA
33.3 µl/min
~7.3 mg RNA (Failed Nebulization)
66.6 µl/min
5A2-SC8
9.4 mg RNA
33.3 µl/min
2.0 mg RNA
33.3 µl/min
~1.4 mg RNA (Failed Nebulization)
66.6 µl/min
5A2-SC8 10% DOTAP

Fig. 4

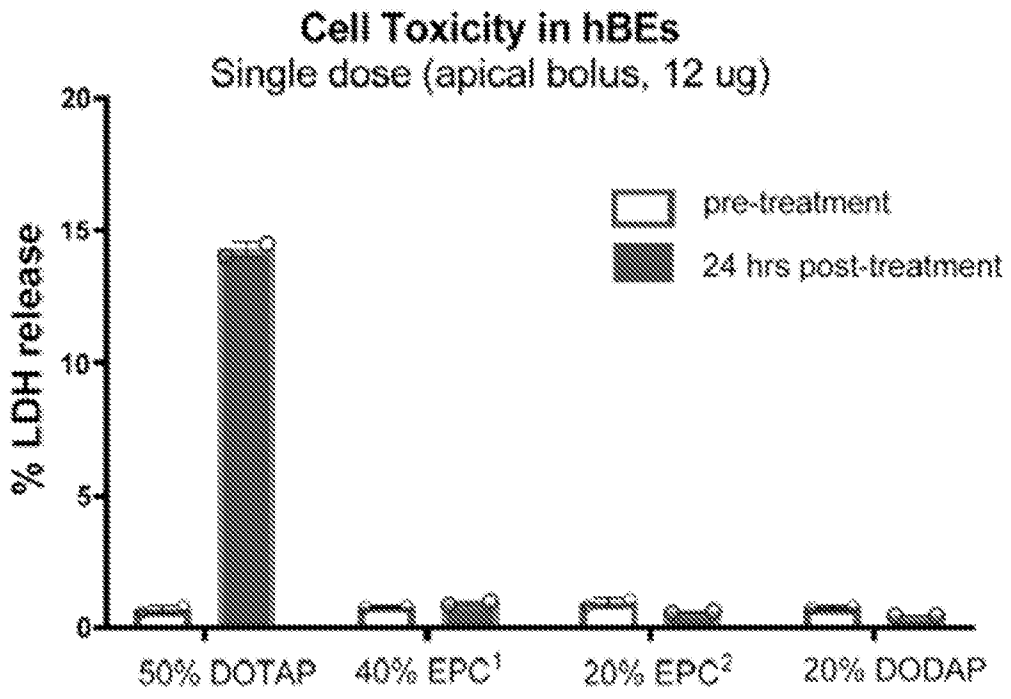

Cell Toxicity in hBEs
Single dose (apical bolus, 12 ug)
% LDH release
20
15
10
5
0
pre-treatment
24 hrs post-treatment
50% DOTAP
40% EPC1
20% EPC2
20% DODAP

FIG. 5

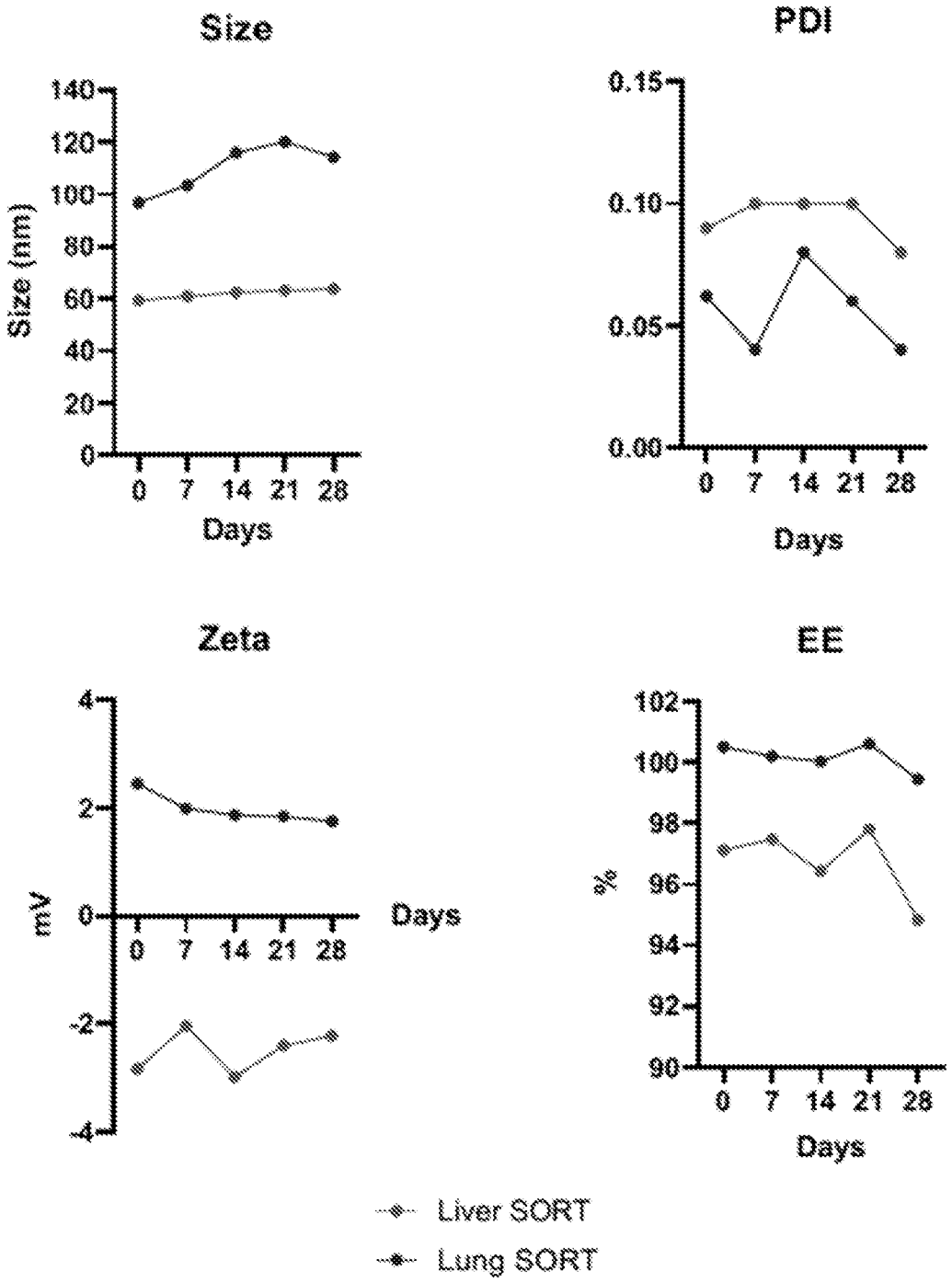

Size
Size (nm)
140
120
100
80
60
40
20
0
0 7 14 21 28
Days
PDI
0.15
0.10
0.05
0.00
0 7 14 21 28
Days
Zeta
mV
4
2
0
-2
-4
0 7 14 21 28
Days
EE
%
102
100
98
96
94
92
90
0 7 14 21 28
Days
Liver SORT
Lung SORT

FIG. 6

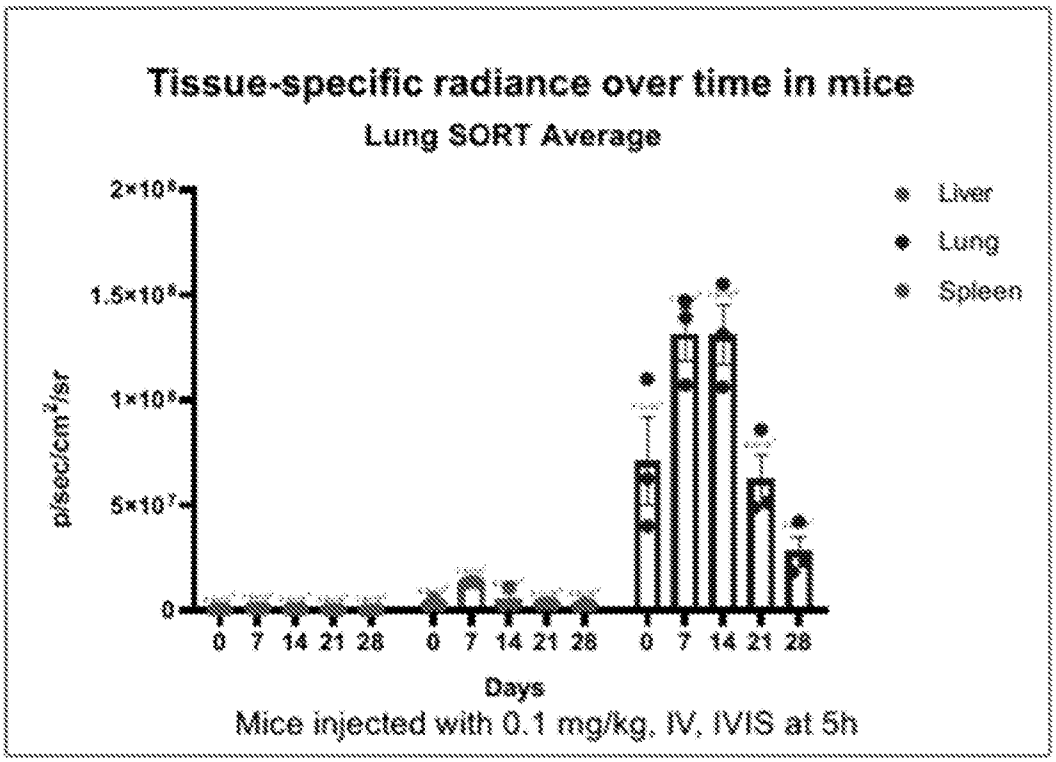

Tissue-specific radiance over time in mice
Lung SORT Average
2×10⁸
1.5×10⁸
1×10⁸
5×10⁷
0
p/sec/cm²/sr
Liver
Lung
Spleen
0 7 14 21 28 0 7 14 21 28 0 7 14 21 28
Days
Mice injected with 0.1 mg/kg, IV, IVIS at 5h

FIG. 7

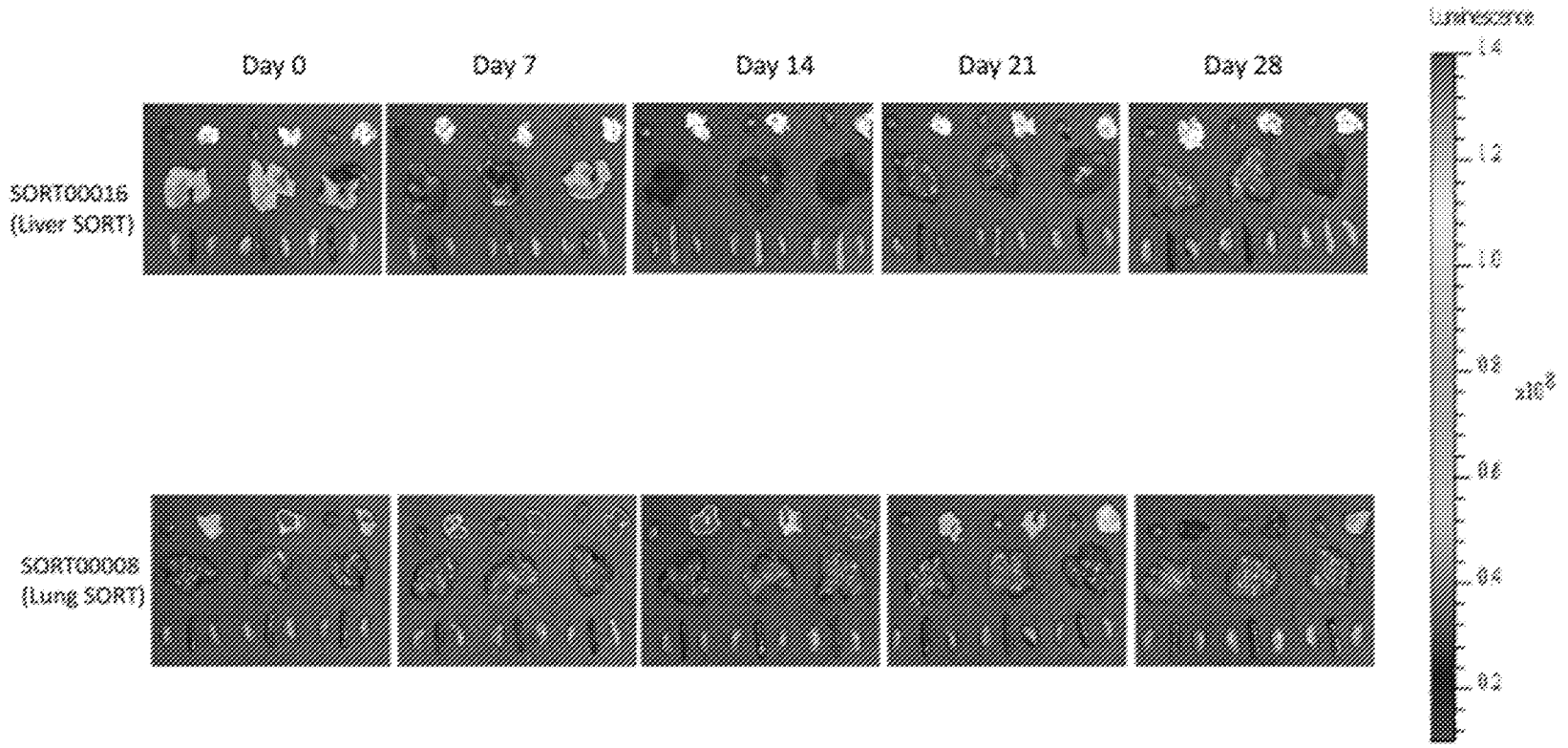

Day 0
Day 7
Day 14
Day 21
Day 28
SORT00016
(Liver SORT)
SORT00008
(Lung SORT)
Luminescence
1.4
1.2
1.0
0.8
0.6
0.4
0.2
x10^8

FIG. 8

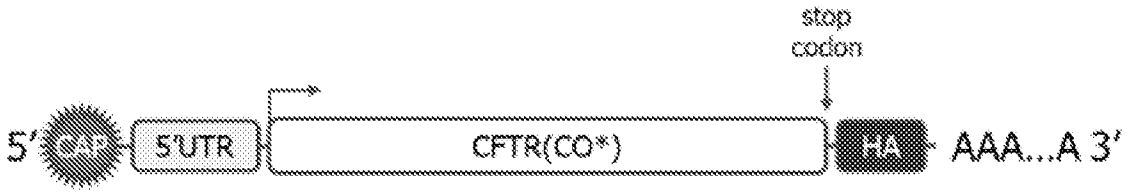

stop
codon
5'
CAP
5'UTR
CFTR(CO*)
HA
AAA...A 3'

FIG. 9A

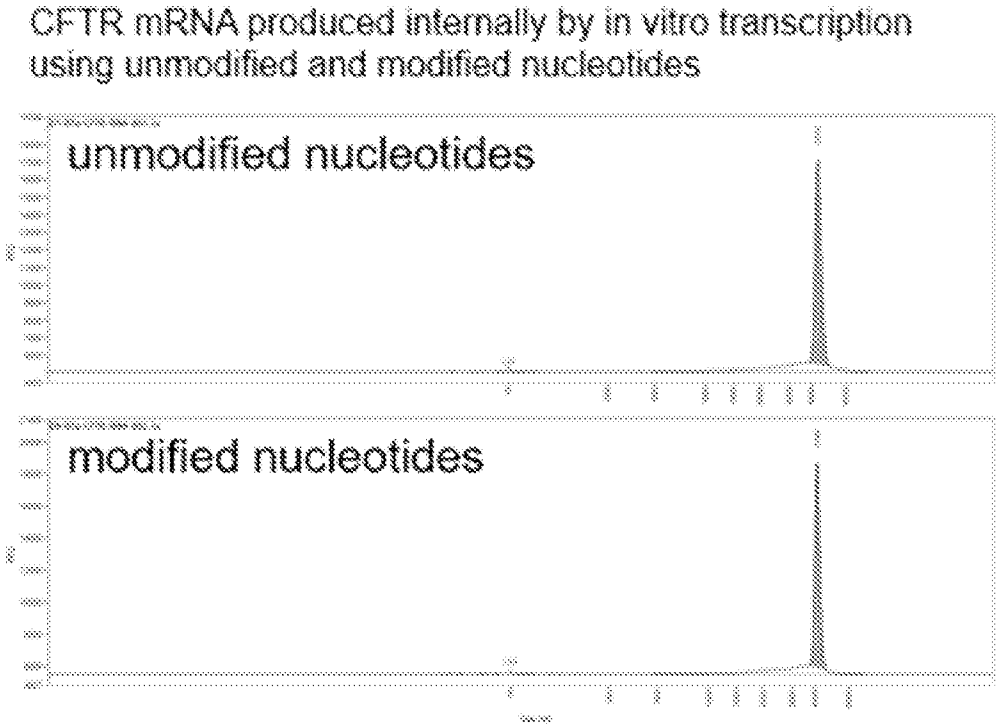

CFTR mRNA produced internally by in vitro transcription
using unmodified and modified nucleotides
unmodified nucleotides
modified nucleotides

FIG. 9B

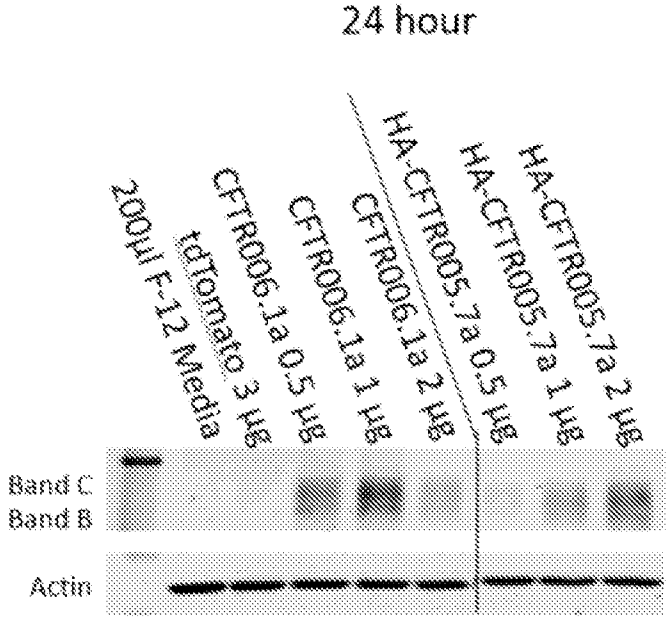


FIG. 10A

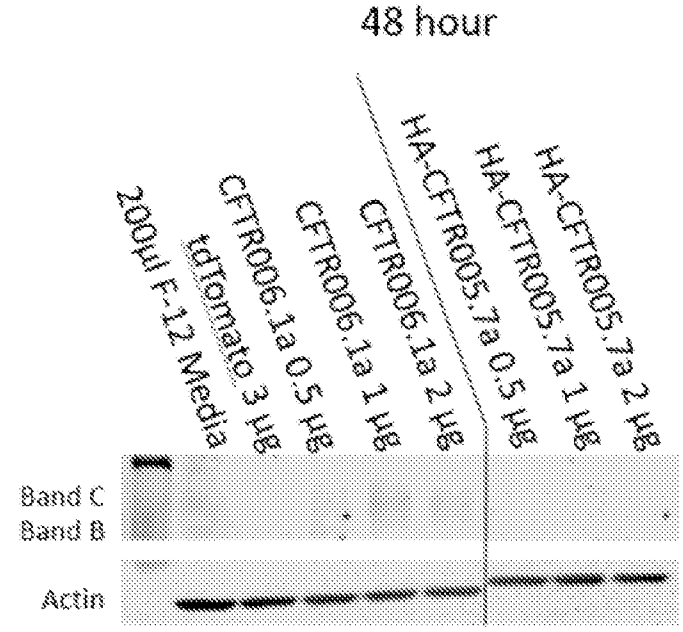


FIG. 10B

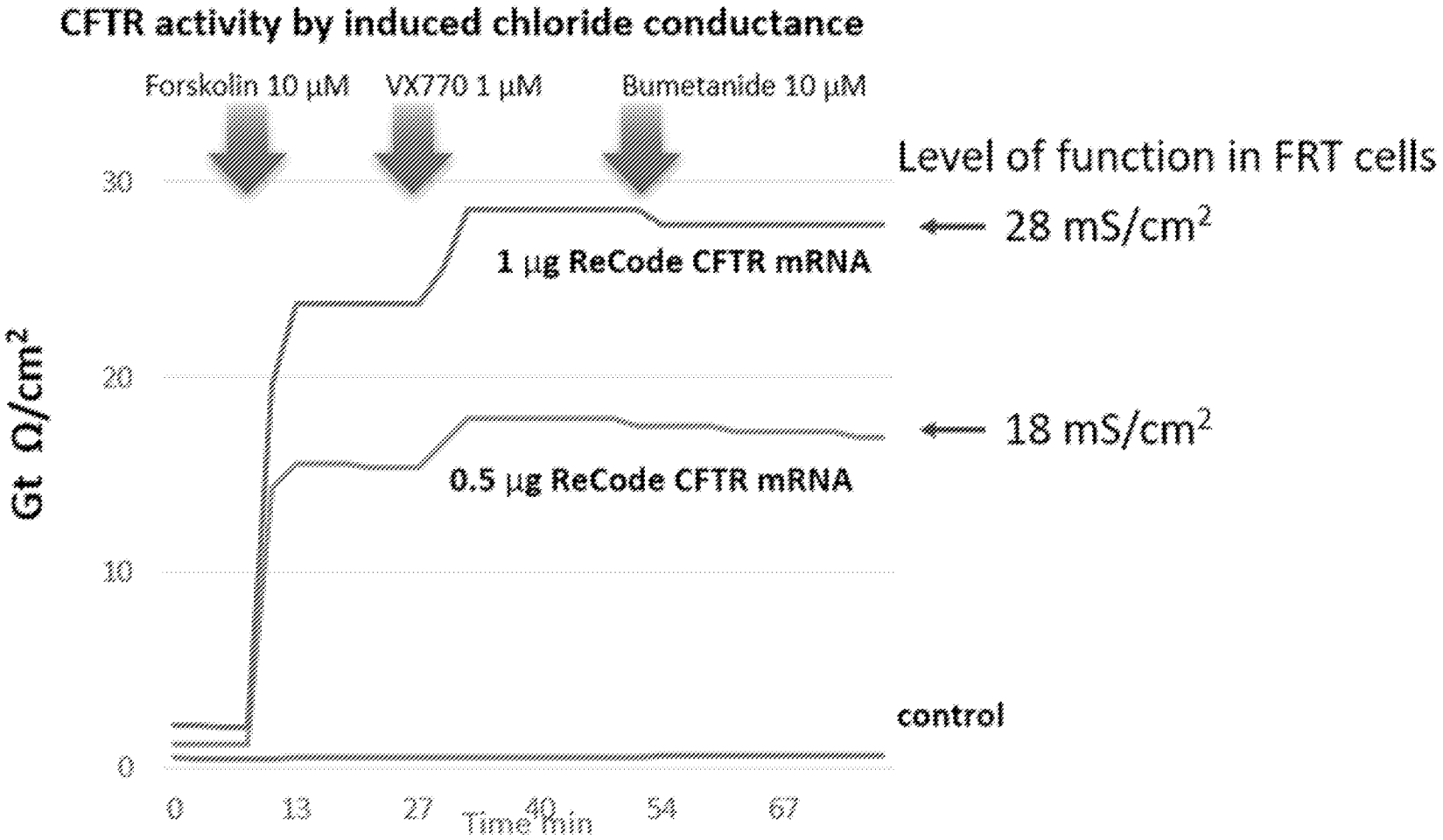

CFTR activity by induced chloride conductance
Forskolin 10 µM
VX770 1 µM
Bumetanide 10 µM
Level of function in FRT cells
30
20
10
0
Gt Q/cm2
1 µg ReCode CFTR mRNA
28 mS/cm2
0.5 µg ReCode CFTR mRNA
18 mS/cm2
control
0
13
27
40
54
67
Time min

FIG. 11A

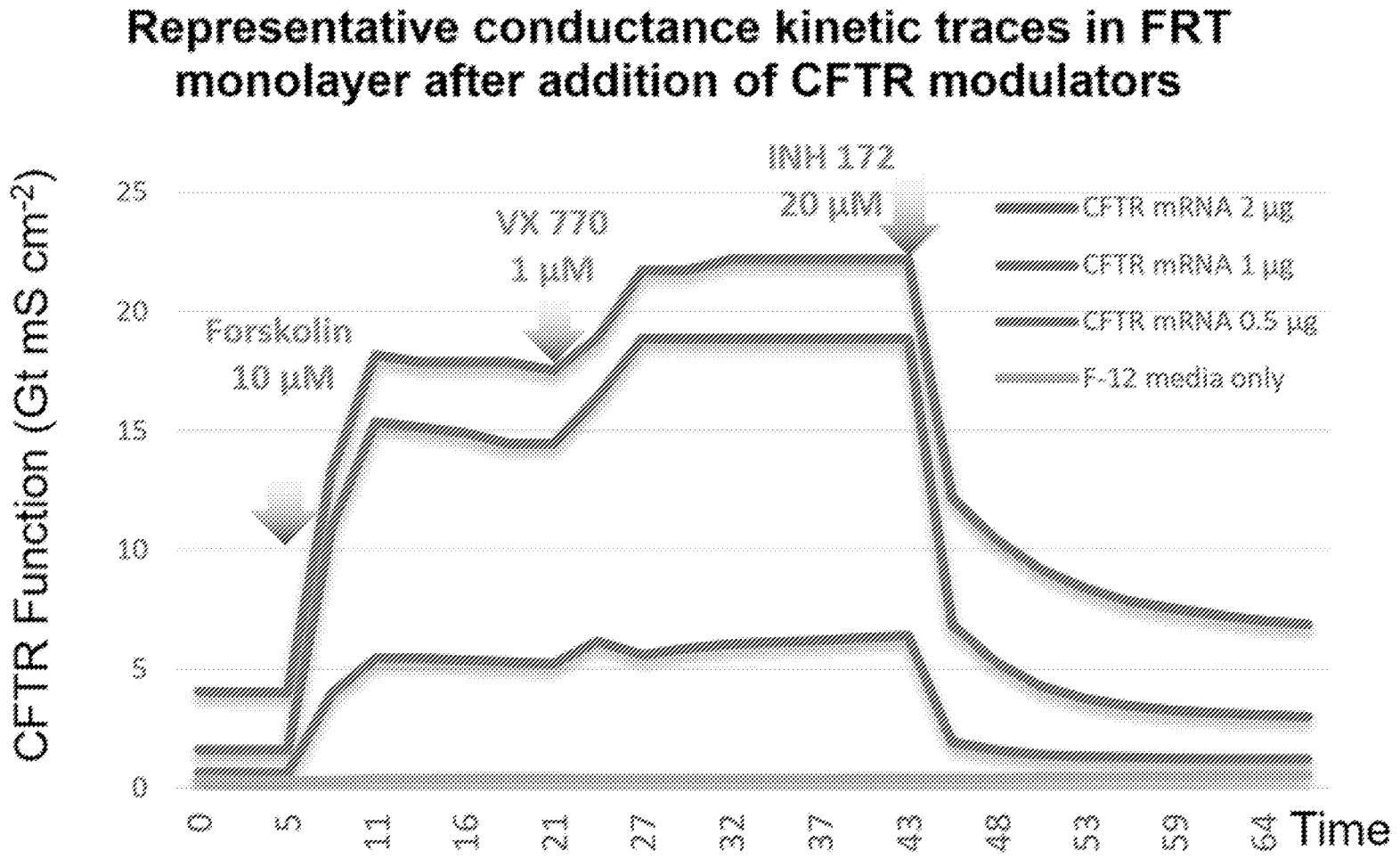

Representative conductance kinetic traces in FRT monolayer after addition of CFTR modulators
CFTR Function (Gt mS cm-2)
25
20
15
10
5
0
Forskolin 10 µM
VX 770 1 µM
INH 172 20 µM
CFTR mRNA 2 µg
CFTR mRNA 1 µg
CFTR mRNA 0.5 µg
F-12 media only
0
5
11
16
21
27
32
37
43
48
53
59
64
Time

FIG. 11B

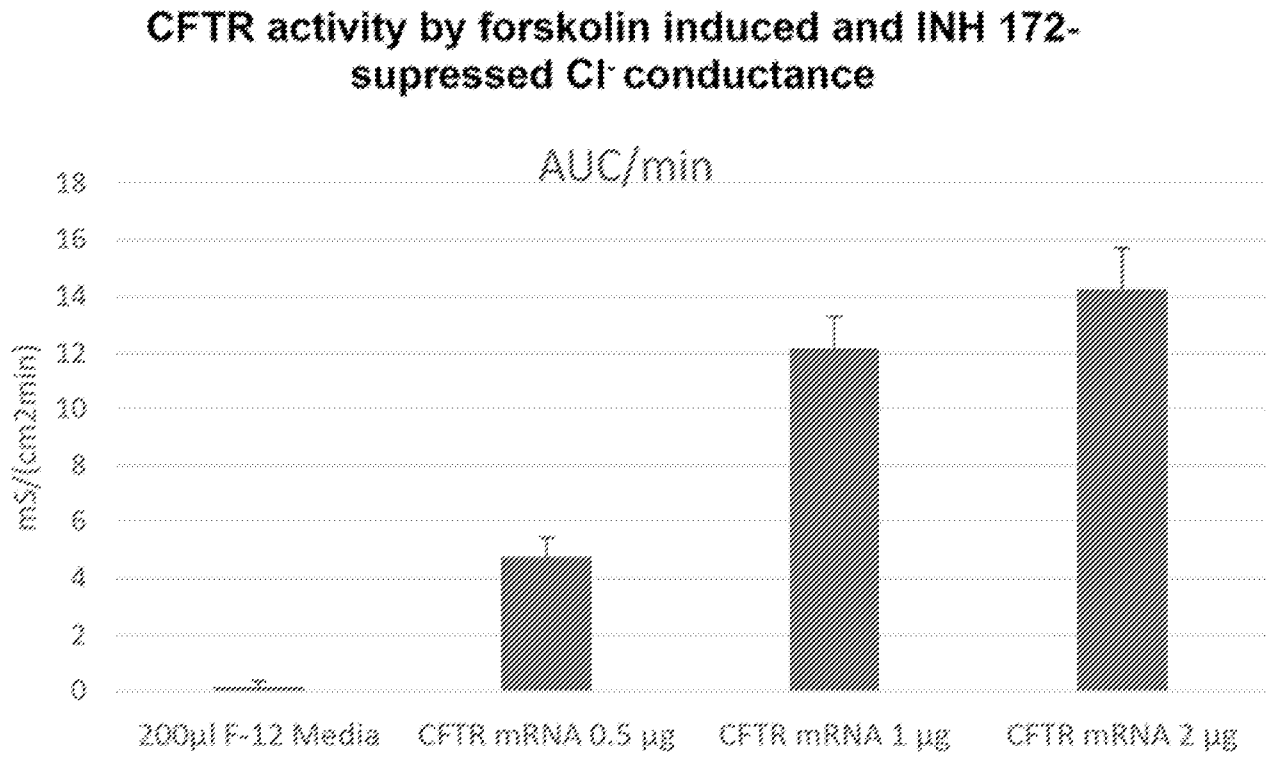

CFTR activity by forskolin induced and INH 172-supressed Cl- conductance
AUC/min
mS/(cm2min)
18
16
14
12
10
8
6
4
2
0
200µl F-12 Media
CFTR mRNA 0.5 µg
CFTR mRNA 1 µg
CFTR mRNA 2 µg

FIG. 11C

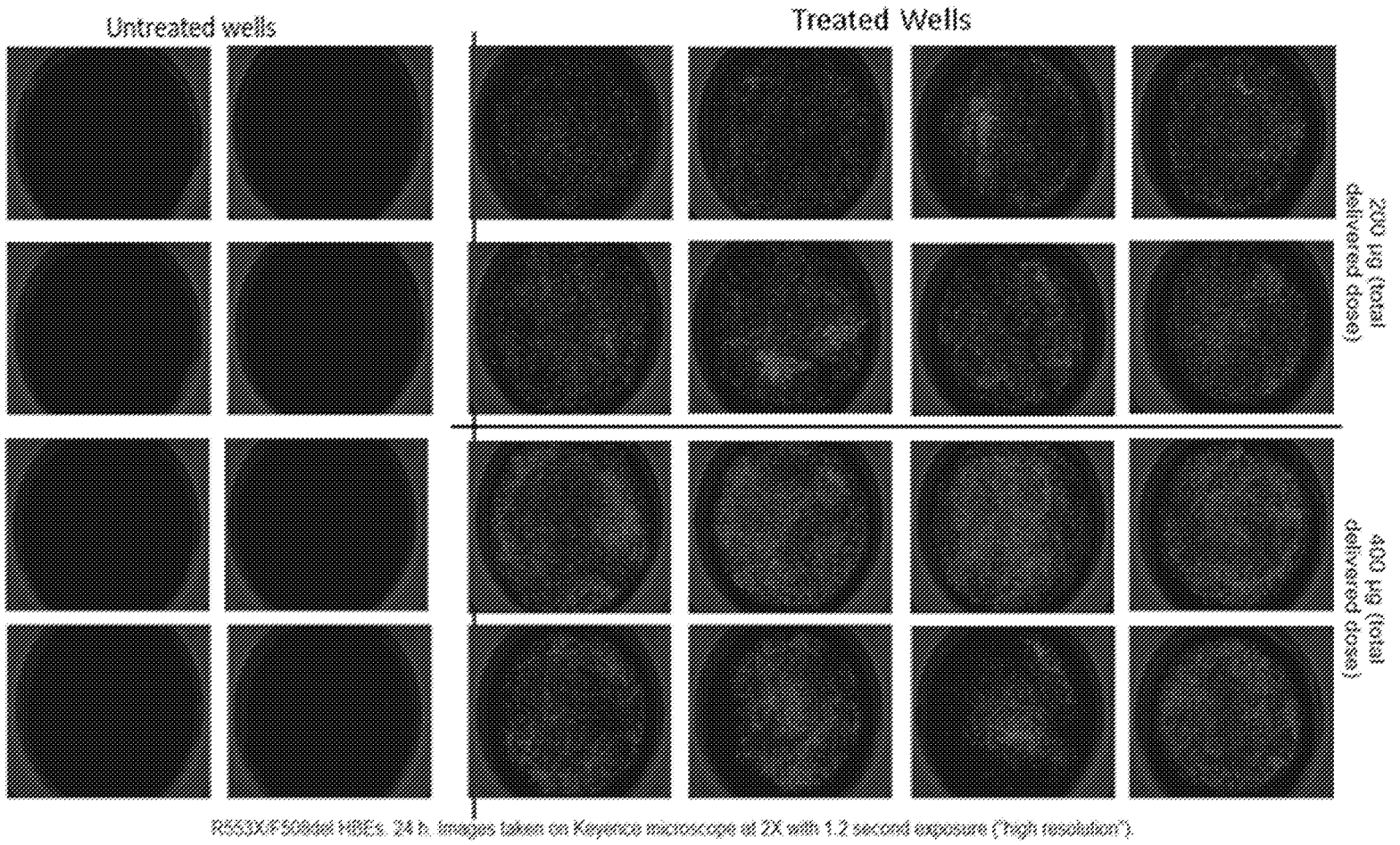

Untreated wells
Treated Wells
200 µg (total delivered dose)
400 µg (total delivered dose)
RSS3X5 Stable HEEs. 24 h. Images taken on Keyence microscope at 2X with 1.2 second exposure ("high resolution").

FIG. 12

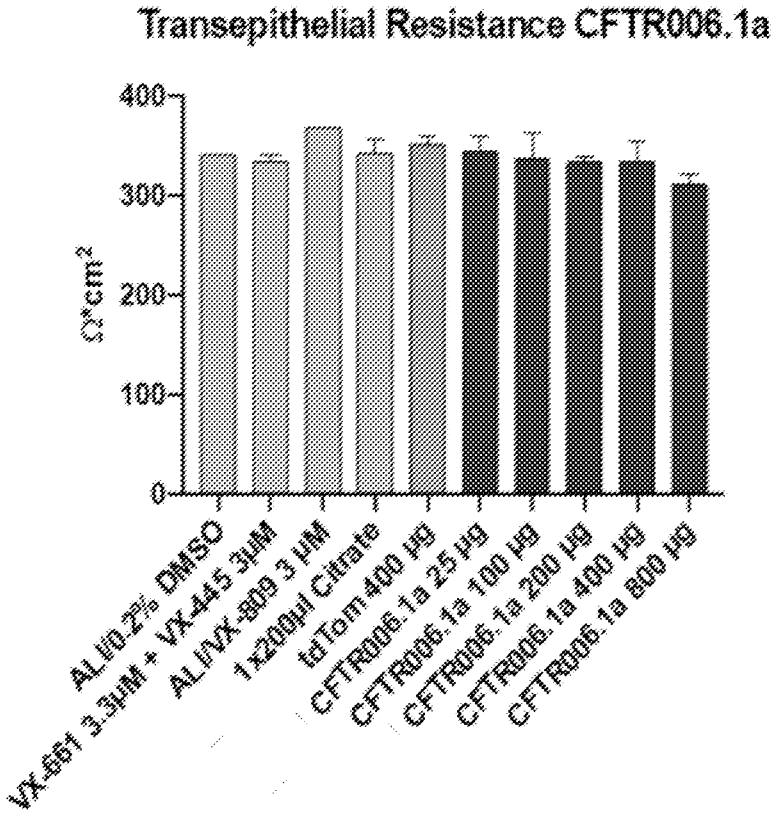


FIG. 13A

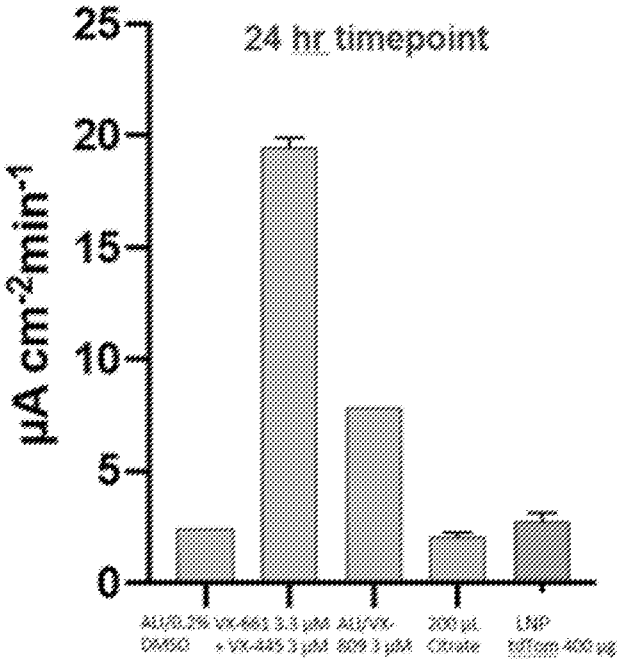


FIG. 13B

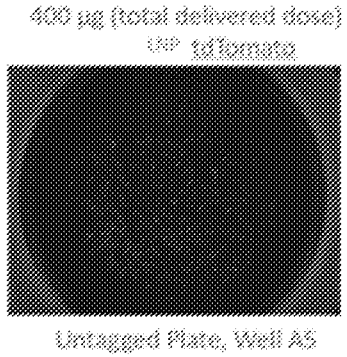


FIG. 13C

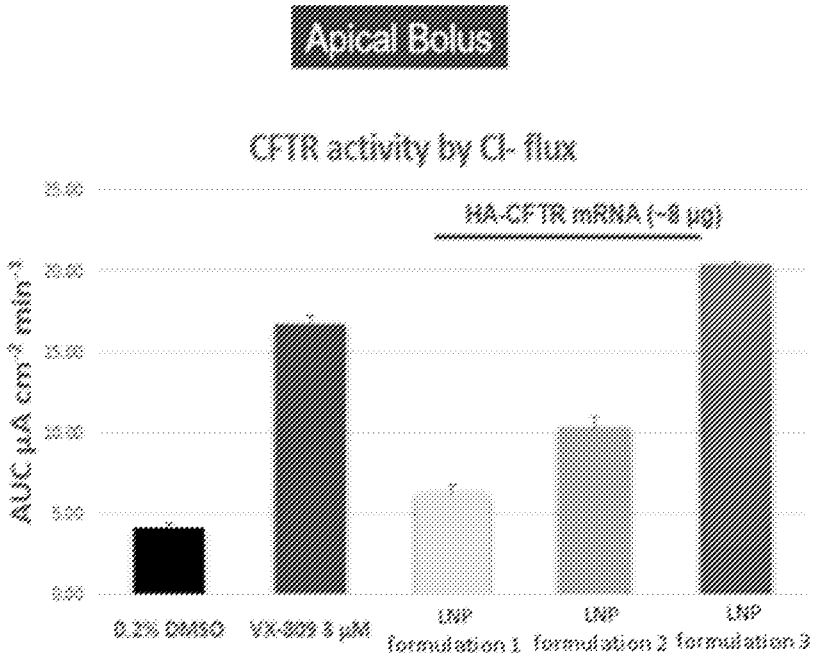


FIG. 14A

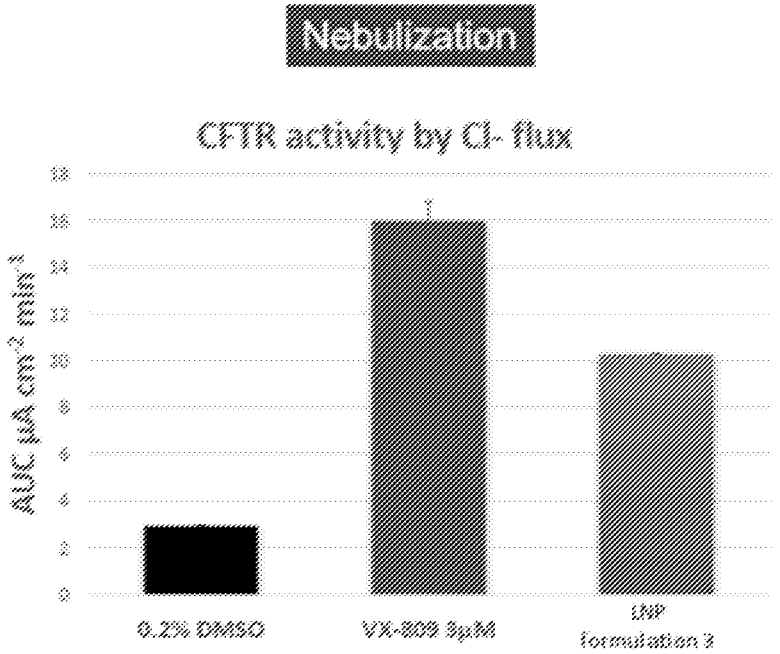


FIG. 14B

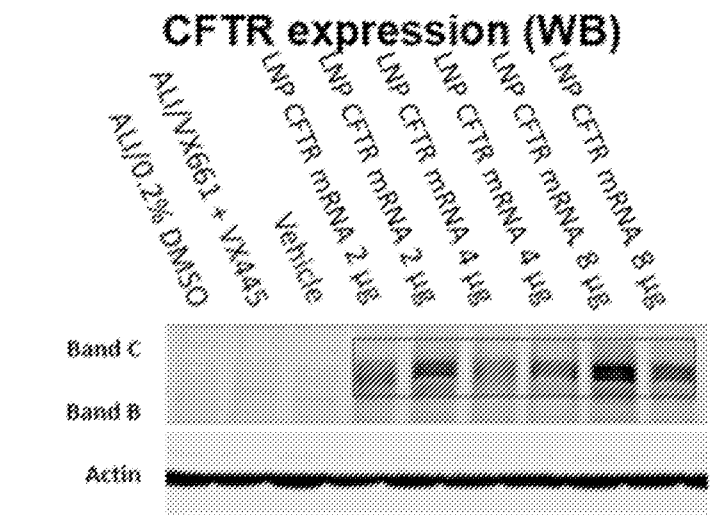


FIG. 15A

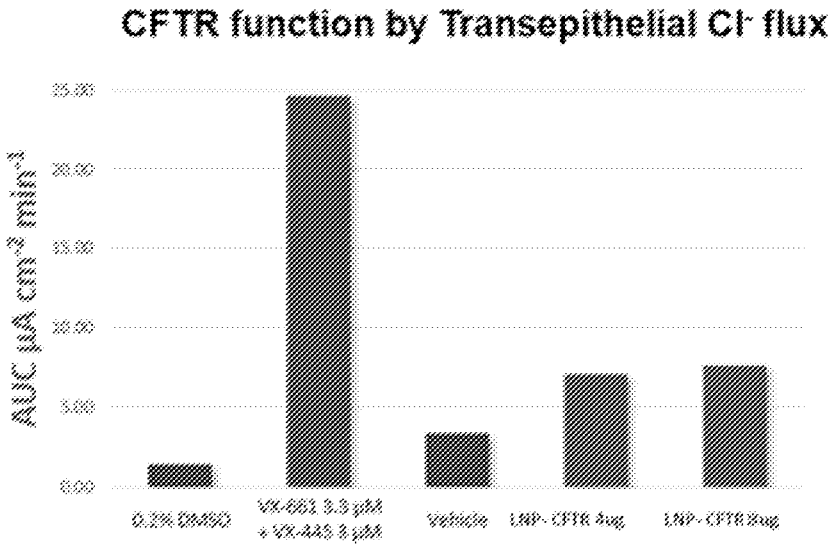


FIG. 15B

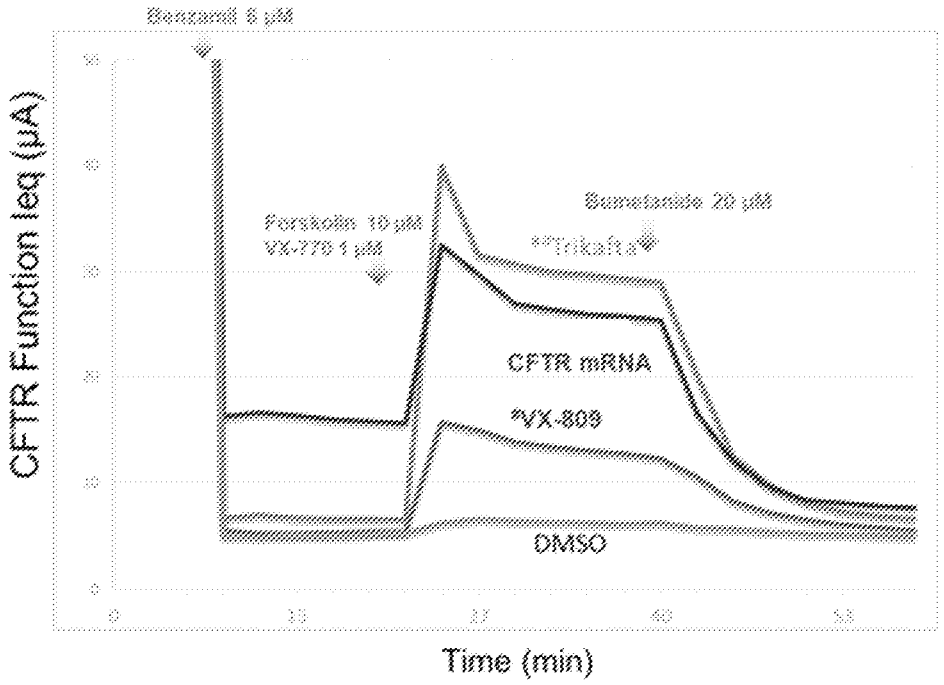


FIG. 16A

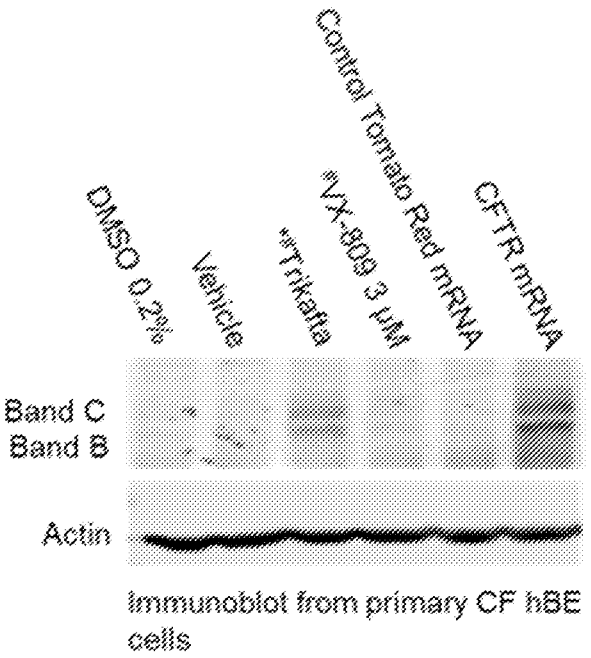


FIG. 16B

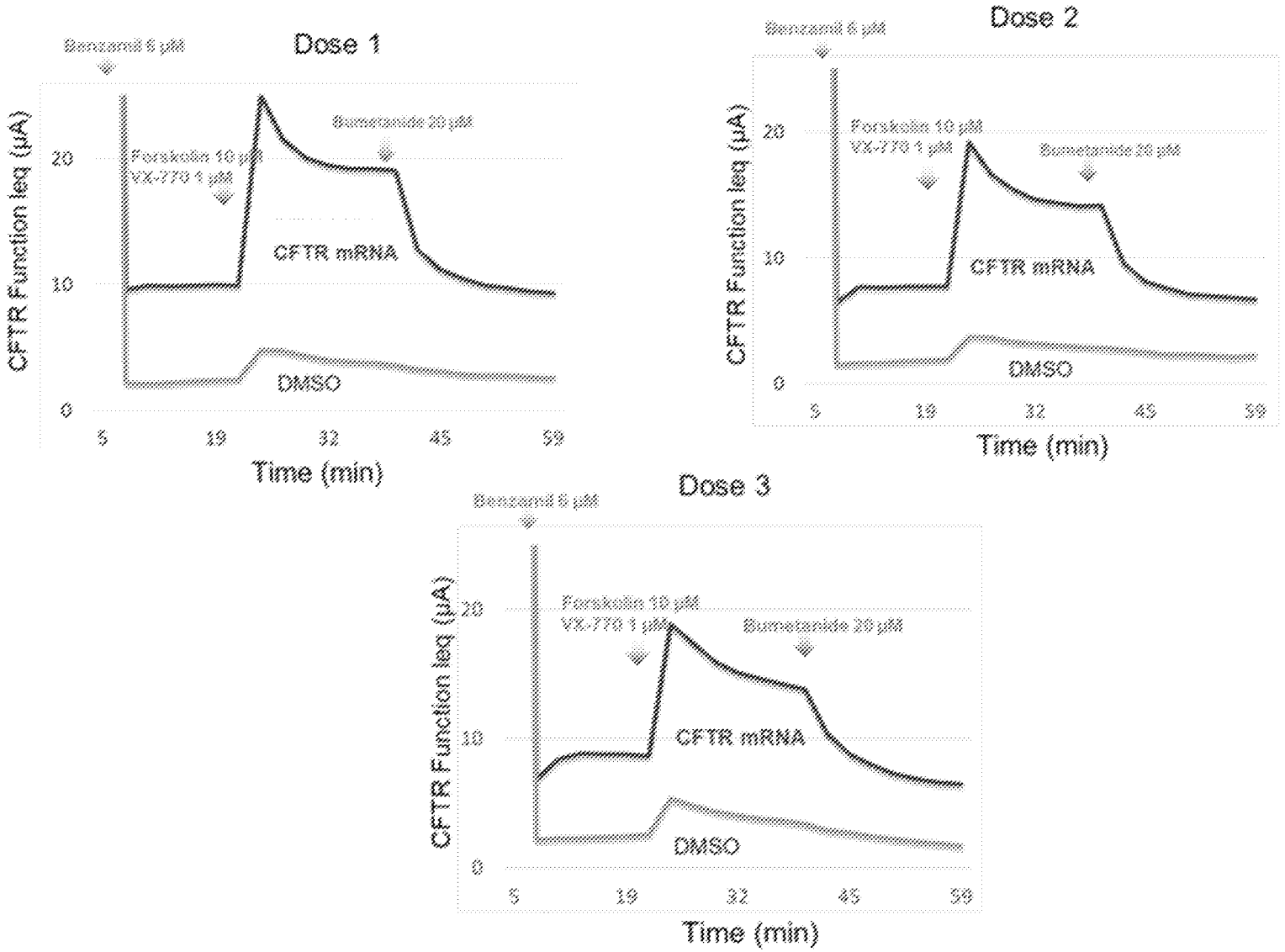
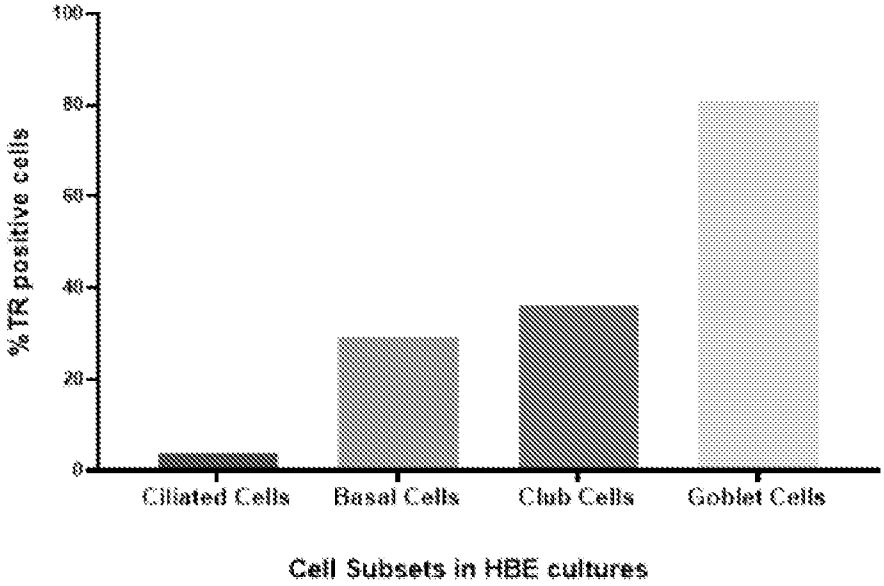

Dose 1
Benzamil 6 μM
Forskolin 10 μM
VX-770 1 μM
Bumetanide 20 μM
CFTR mRNA
DMSO
CFTR Function Ieq (μA)
0
10
20
5
19
32
45
59
Time (min)
Dose 2
Benzamil 6 μM
Forskolin 10 μM
VX-770 1 μM
Bumetanide 20 μM
CFTR mRNA
DMSO
CFTR Function Ieq (μA)
0
10
20
5
19
32
45
59
Time (min)
Dose 3
Benzamil 6 μM
Forskolin 10 μM
VX-770 1 μM
Bumetanide 20 μM
CFTR mRNA
DMSO
CFTR Function Ieq (μA)
0
10
20
5
19
32
45
59
Time (min)

FIG. 17A

FIG. 17B



Ciliated	acetylated-tubulin (AC-Tubulin)
Club	Secretoglobin Family 1A Member 1 (SCGB1A1)
Goblet	Mucin 5AC (MUC5AC)
Basal	Cytokeratin 5 (CK5)
Ciliated	acetylated-tubulin (AC-Tubulin)

FIG. 18

Examples

Indication / Inclusion criteria	Phase 1/2 Study*	Primary Outcome Measures
CF Lead tRNA Program – Adults – CFTR mutation R553X, R1162X, or G542X – FEV1 between 40% and 90%	SAD • MAD (3 mo.) • OLE (9 mo.) Placebo Low Dose High Dose	– Safety and tolerability – Absolute change in percent predicted FEV1

FIG. 19