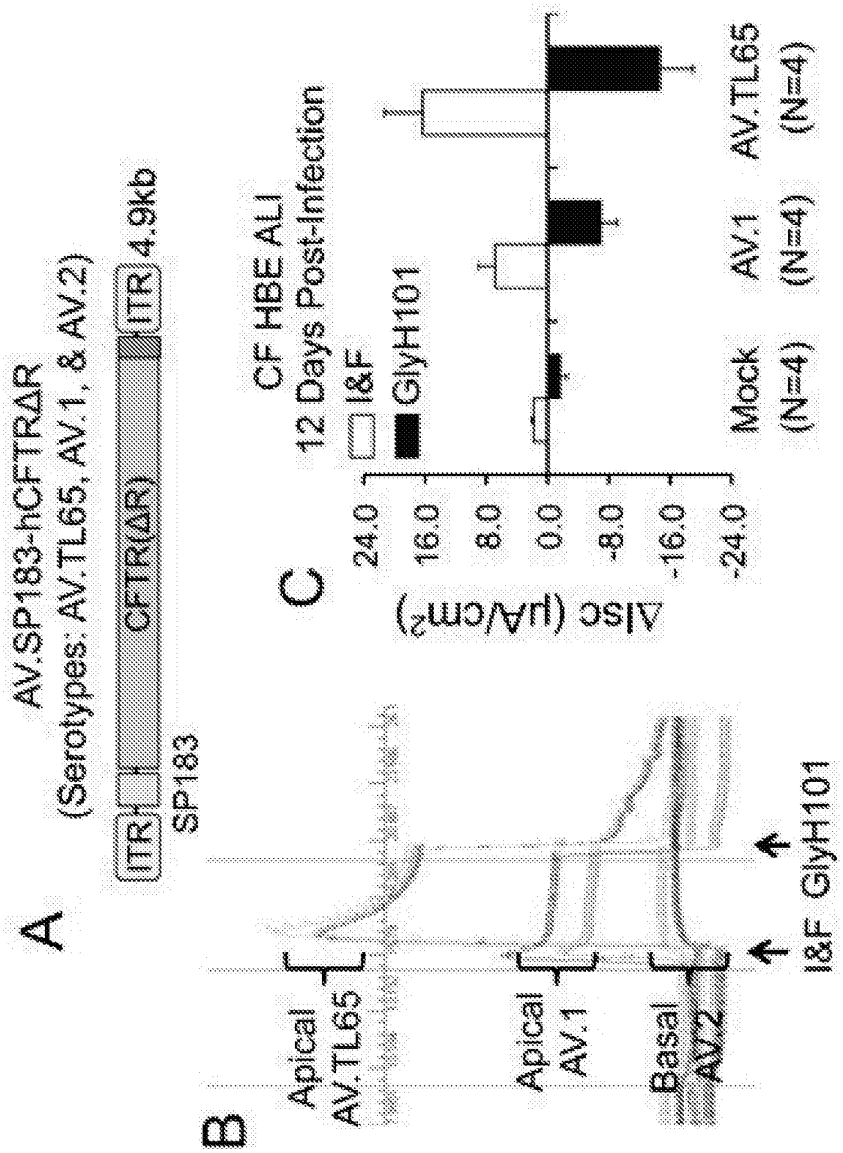
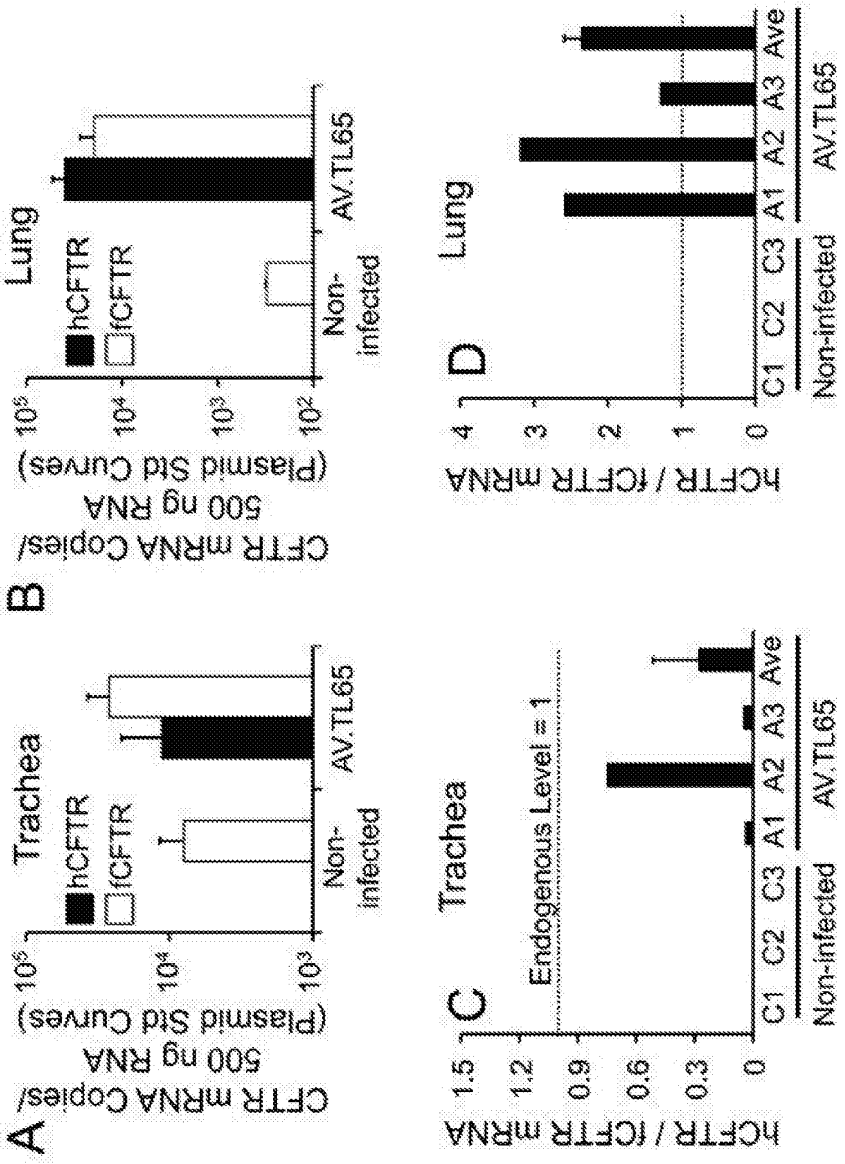
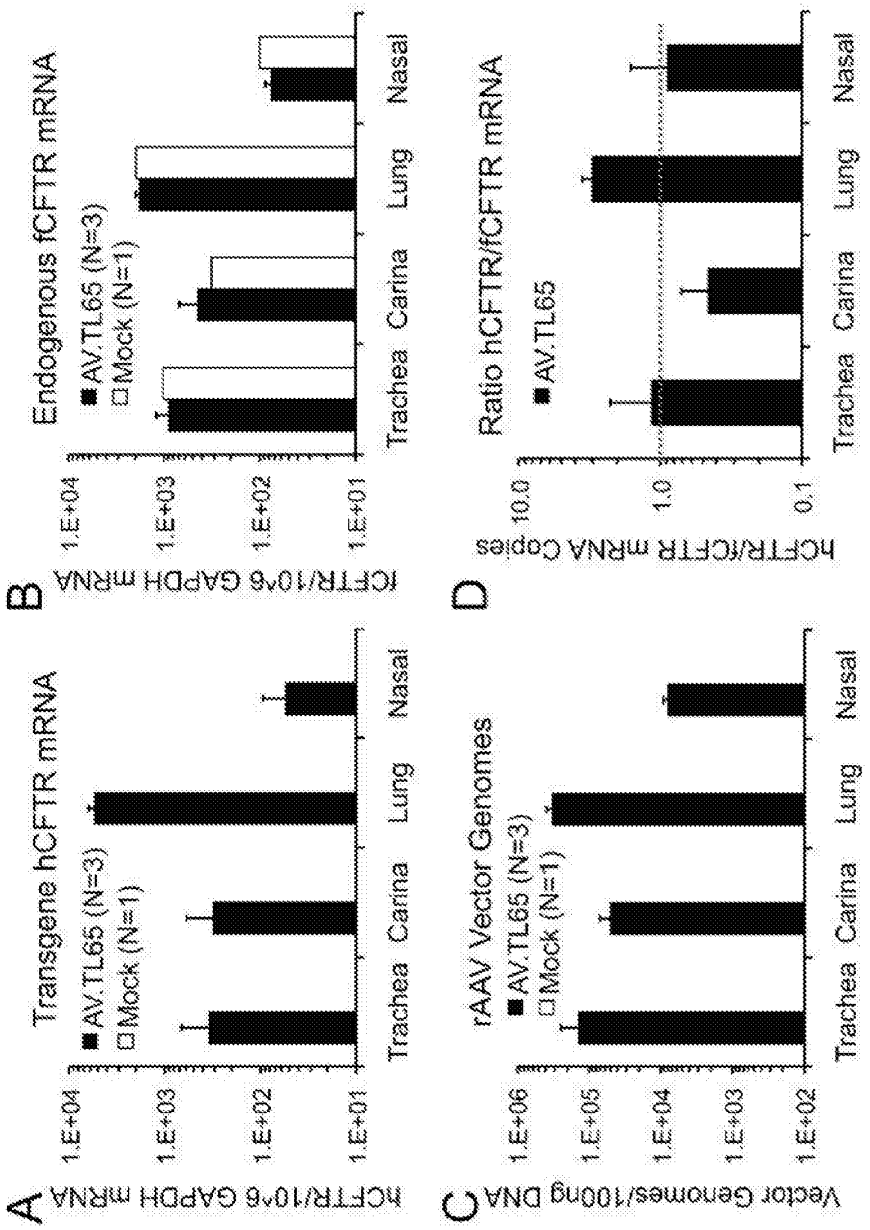

A
AV.SP183-hCFTRΔR
(Serotypes: AV.TL65, AV.1, & AV.2)
ITR
CFTR(ΔR)
ITR 4.9kb
SP183
B
Apical
AV.TL65
Apical
AV.1
Basal
AV.2
I&F GlyH101
C
CF HBE ALI
12 Days Post-Infection
I&F
GlyH101
Δlsc (μA/cm²)
24.0
16.0
8.0
0.0
-8.0
-16.0
-24.0
Mock
(N=4)
AV.1
(N=4)
AV.TL65
(N=4)

FIGS. 1A-1C


A
Trachea
hCFTR
fCFTR
Non-infected
AV.TL65
CFTR mRNA Copies/ 500 ng RNA (Plasmid Std Curves)
B
Lung
C
Trachea
Endogenous Level = 1
hCFTR / fCFTR mRNA
C1 C2 C3 A1 A2 A3 Ave
Non-infected
AV.TL65
D
Lung

FIGS. 2A-2D


A
Transgene hCFTR mRNA
hCFTR/10^6 GAPDH mRNA
AV.TL65 (N=3)
Mock (N=1)
1.E+04
1.E+03
1.E+02
1.E+01
Trachea
Carina
Lung
Nasal
B
Endogenous fCFTR mRNA
fCFTR/10^6 GAPDH mRNA
AV.TL65 (N=3)
Mock (N=1)
1.E+04
1.E+03
1.E+02
1.E+01
Trachea
Carina
Lung
Nasal
C
rAAV Vector Genomes
Vector Genomes/100ng DNA
AV.TL65 (N=3)
Mock (N=1)
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
Trachea
Carina
Lung
Nasal
D
Ratio hCFTR/fCFTR mRNA
hCFTR/fCFTR mRNA Copies
AV.TL65
10.0
1.0
0.1
Trachea
Carina
Lung
Nasal

FIGS. 3A-3D

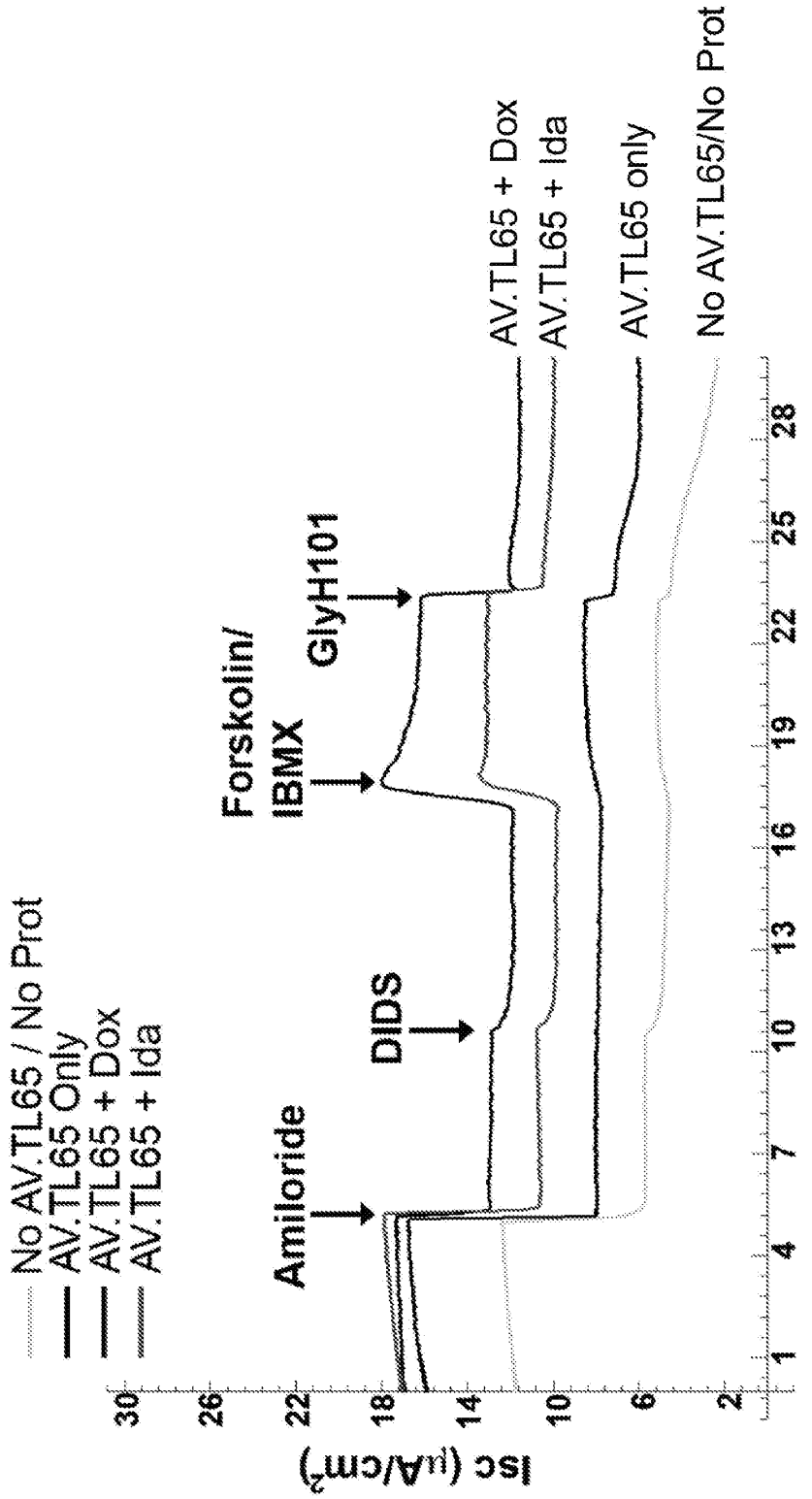

No AV.TL65 / No Prot
AV.TL65 Only
AV.TL65 + Dox
AV.TL65 + Ida
Amiloride
DIDS
Forskolin/
IBMX
GlyH101
AV.TL65 + Dox
AV.TL65 + Ida
AV.TL65 only
No AV.TL65/No Prot
Isc (μA/cm²)
30
26
22
18
14
10
6
2
1
4
7
10
13
16
19
22
25
28
Time (min)

FIG. 4

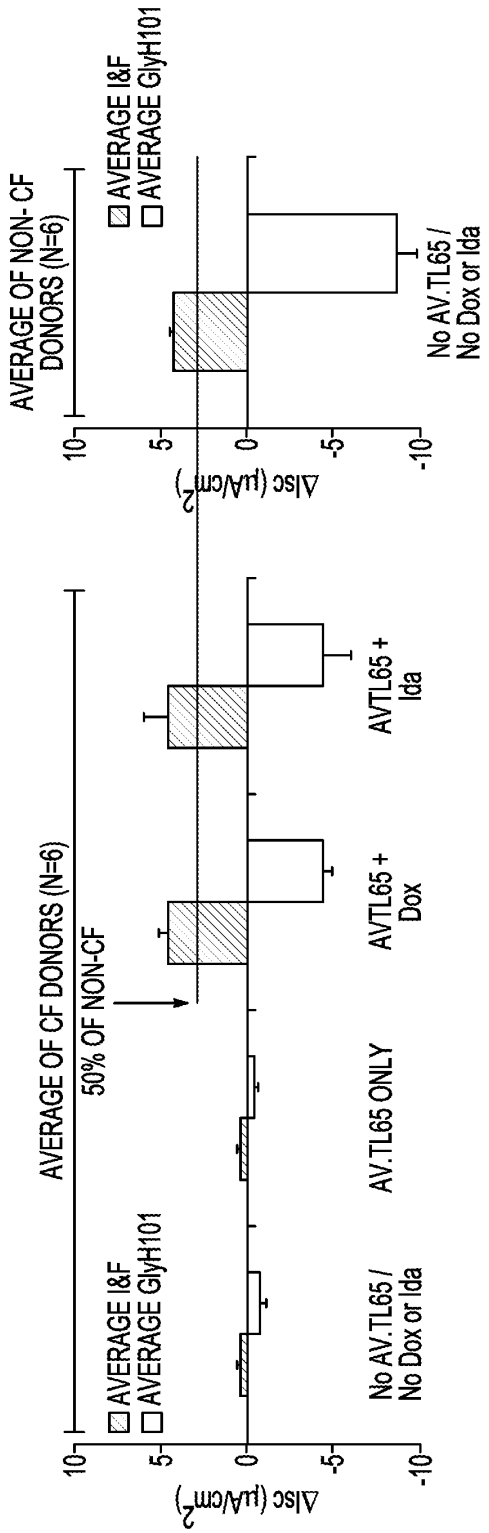

AVERAGE OF NON- CF DONORS (N=6)
AVERAGE I&F
AVERAGE GlyH101
No AV.TL65 / No Dox or Ida
ΔIsc (μA/cm²)
10
5
0
-5
-10
AVERAGE OF CF DONORS (N=6)
50% OF NON-CF
AVERAGE I&F
AVERAGE GlyH101
No AV.TL65 / No Dox or Ida
AV.TL65 ONLY
AVTL65 + Dox
AVTL65 + Ida

FIG. 5

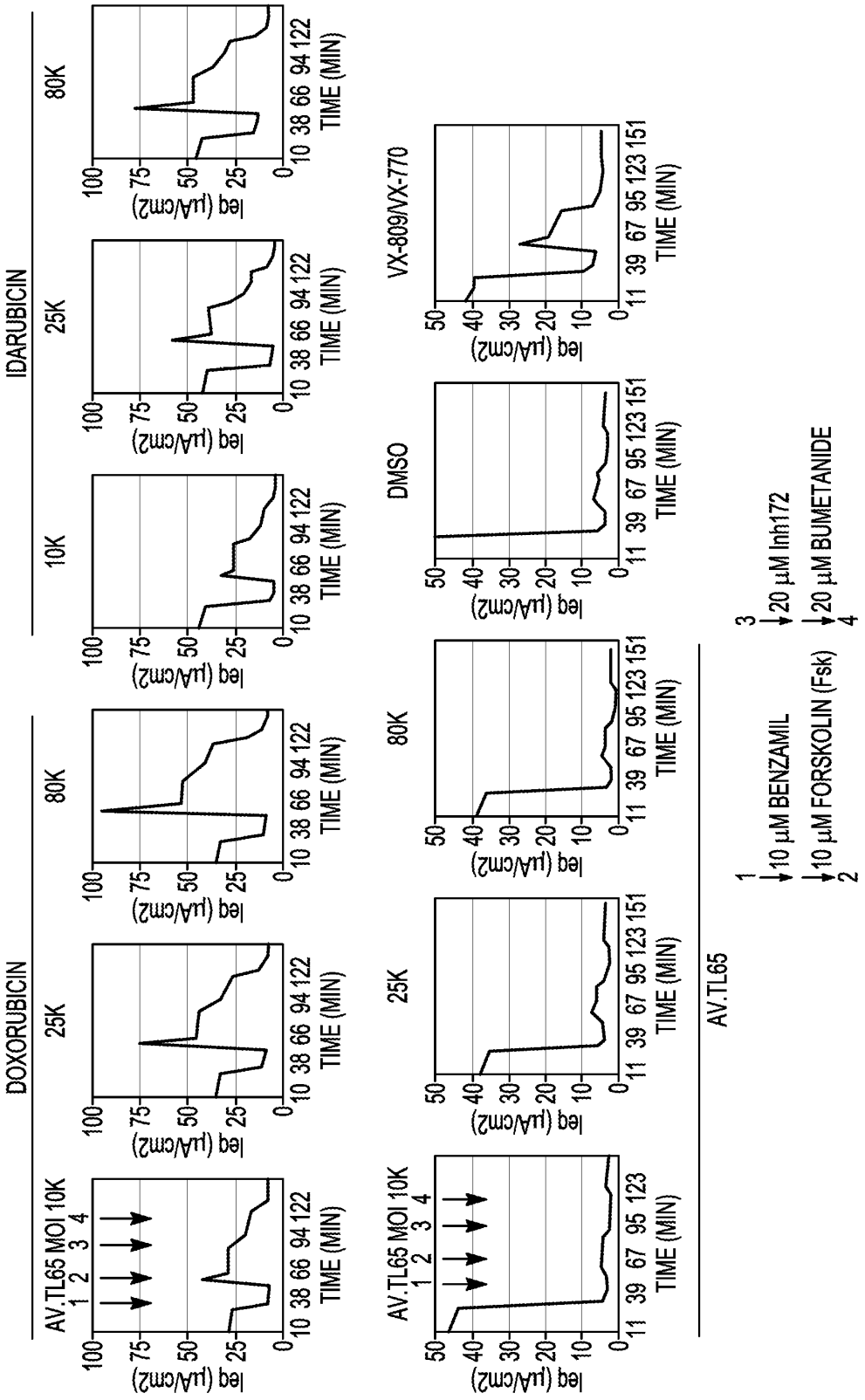

DOXORUBICIN
IDARUBICIN
AV.TL65 MOI 10K
1 2 3 4
25K
80K
10K
DMSO
VX-809/VX-770
Ieq (μA/cm2)
TIME (MIN)
AV.TL65
1
10 μM BENZAMIL
2
10 μM FORSKOLIN (Fsk)
3
20 μM Inh172
4
20 μM BUMETANIDE

FIG. 6

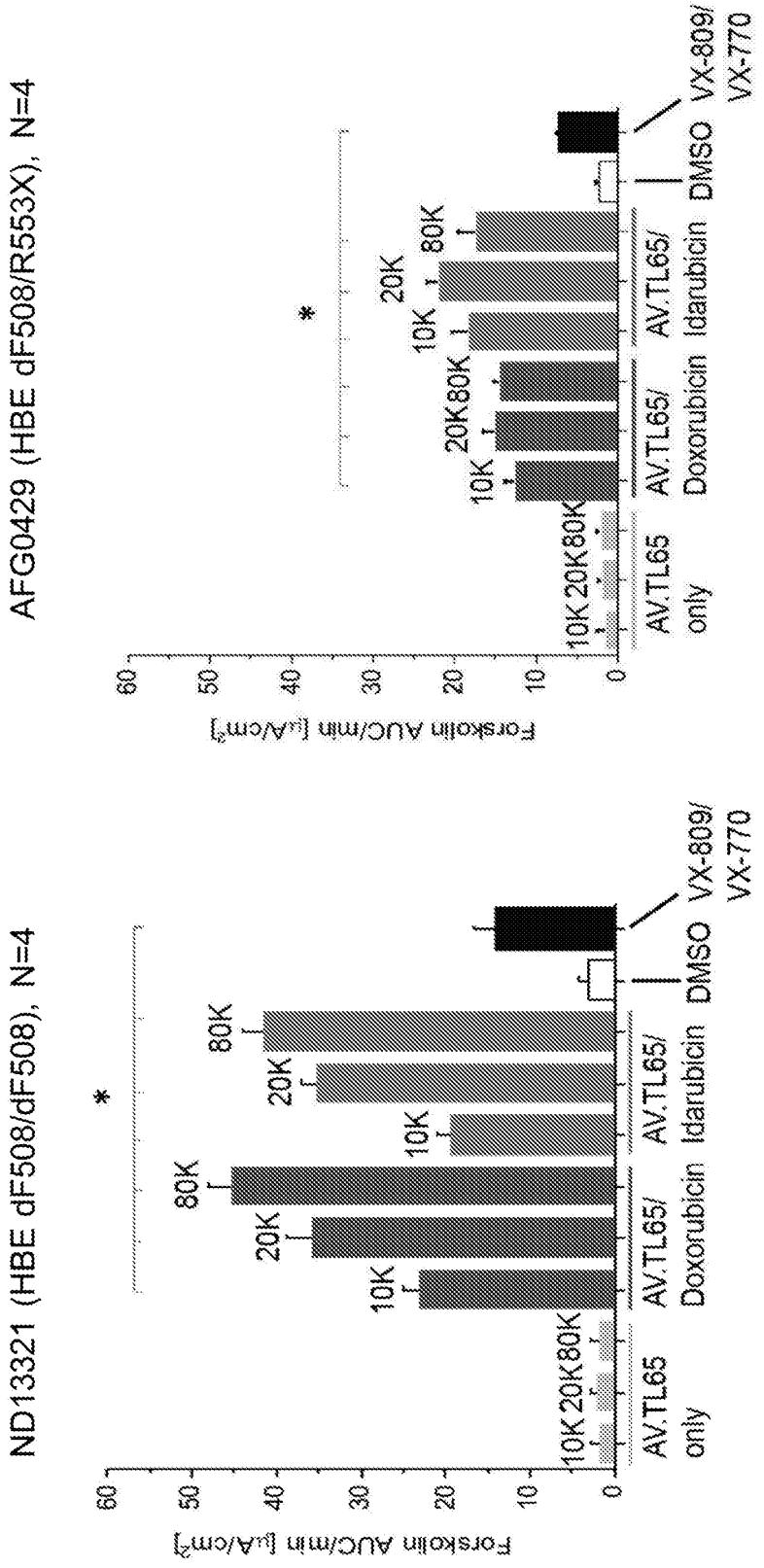

AFG0429 (HBE dF508/R553X), N=4
Forskolin AUC/min [μA/cm²]
0
10
20
30
40
50
60
*
10K
20K
80K
AV.TL65 only
AV.TL65/ Doxorubicin
AV.TL65/ Idarubicin
DMSO
VX-809/ VX-770
ND13321 (HBE dF508/dF508), N=4
Forskolin AUC/min [μA/cm²]
0
10
20
30
40
50
60
*
10K
20K
80K
AV.TL65 only
AV.TL65/ Doxorubicin
AV.TL65/ Idarubicin
DMSO
VX-809/ VX-770

FIG. 7

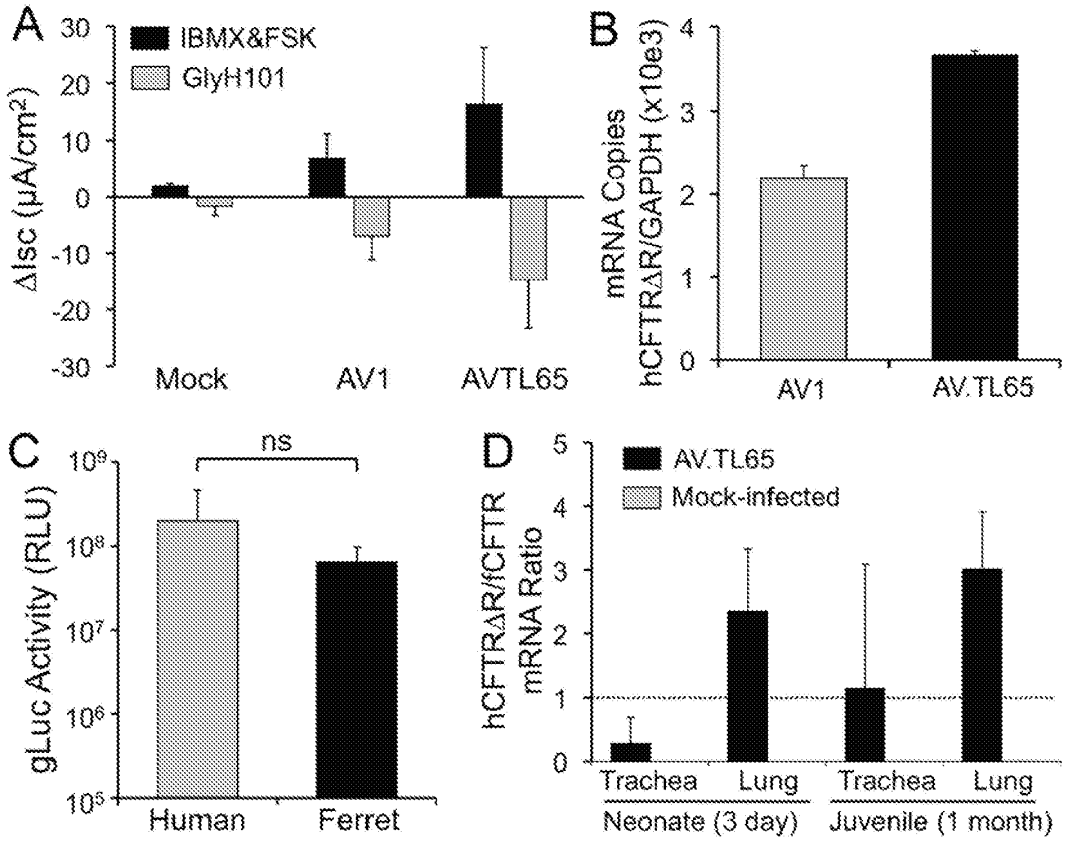

A
IBMX&FSK
GlyH101
ΔIsc (μA/cm²)
30
20
10
0
-10
-20
-30
Mock
AV1
AVTL65
B
mRNA Copies
hCFTRΔR/GAPDH (x10e3)
4
3
2
1
0
AV1
AV.TL65
C
gLuc Activity (RLU)
10⁹
10⁸
10⁷
10⁶
10⁵
ns
Human
Ferret
D
hCFTRΔR/fCFTR
mRNA Ratio
5
4
3
2
1
0
AV.TL65
Mock-infected
Trachea
Lung
Trachea
Lung
Neonate (3 day)
Juvenile (1 month)

FIG. 8

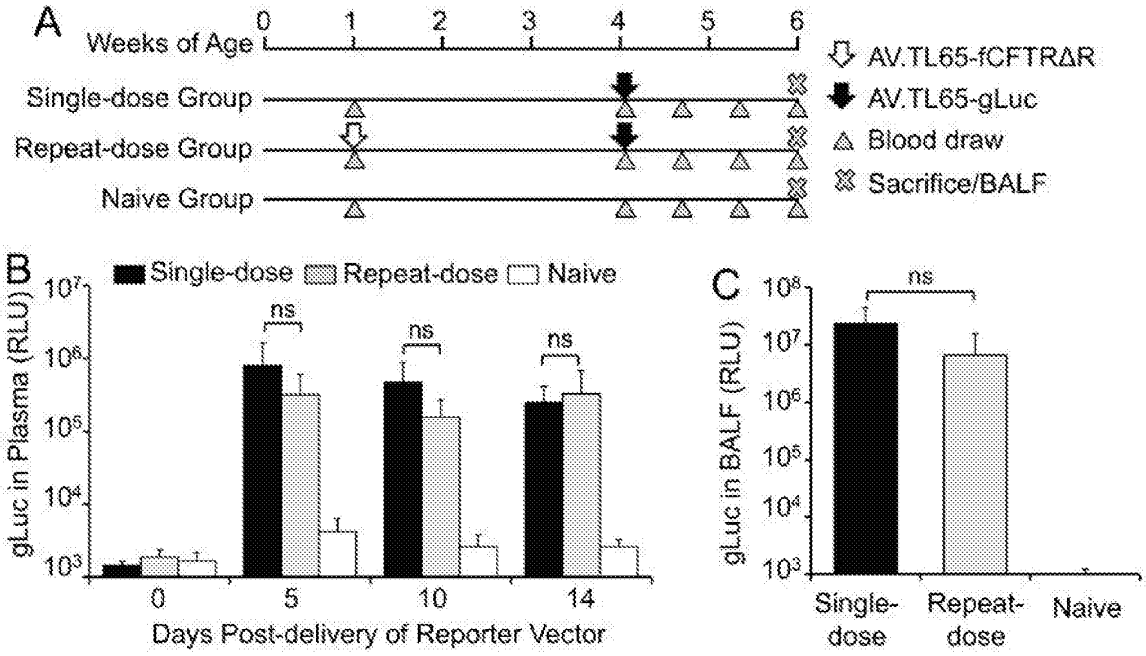

A
Weeks of Age
0
1
2
3
4
5
6
Single-dose Group
Repeat-dose Group
Naive Group
AV.TL65-fCFTRΔR
AV.TL65-gLuc
Blood draw
Sacrifice/BALF
B
Single-dose
Repeat-dose
Naive
gLuc in Plasma (RLU)
ns
Days Post-delivery of Reporter Vector
C
gLuc in BALF (RLU)
Single-dose
Repeat-dose
Naive

FIG. 9

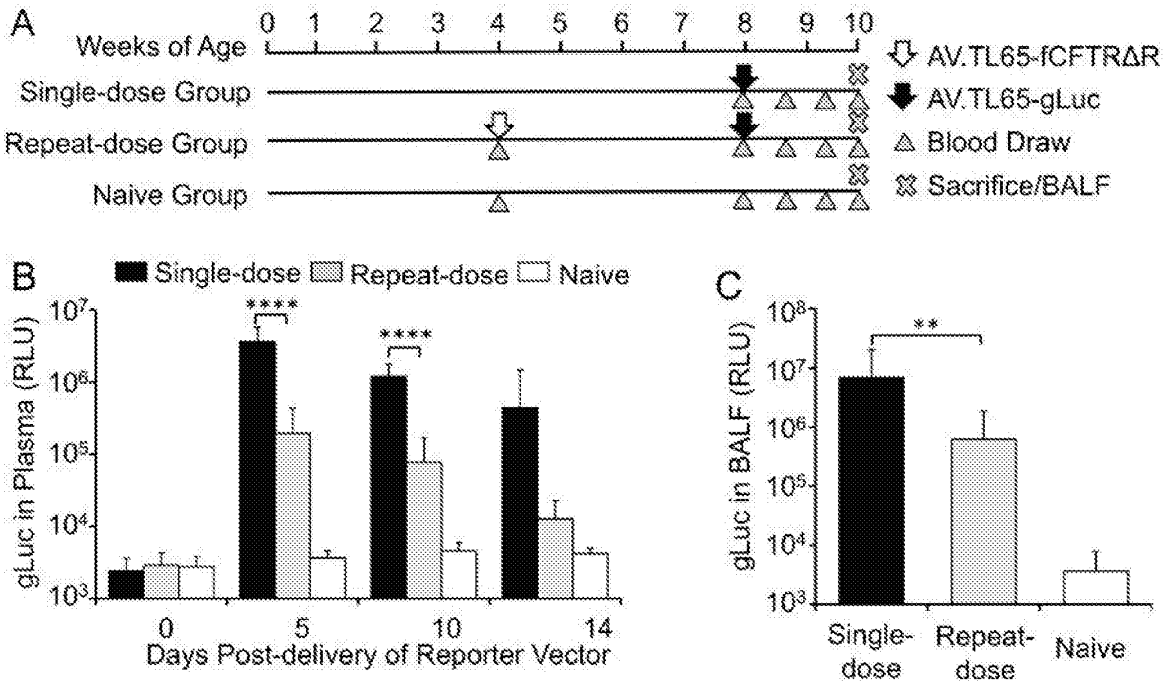

A
Weeks of Age
0 1 2 3 4 5 6 7 8 9 10
Single-dose Group
Repeat-dose Group
Naive Group
AV.TL65-fCFTRΔR
AV.TL65-gLuc
Blood Draw
Sacrifice/BALF
B
Single-dose
Repeat-dose
Naive
gLuc in Plasma (RLU)
Days Post-delivery of Reporter Vector
****
****
C
gLuc in BALF (RLU)
**
Single-dose
Repeat-dose
Naive

FIG. 10

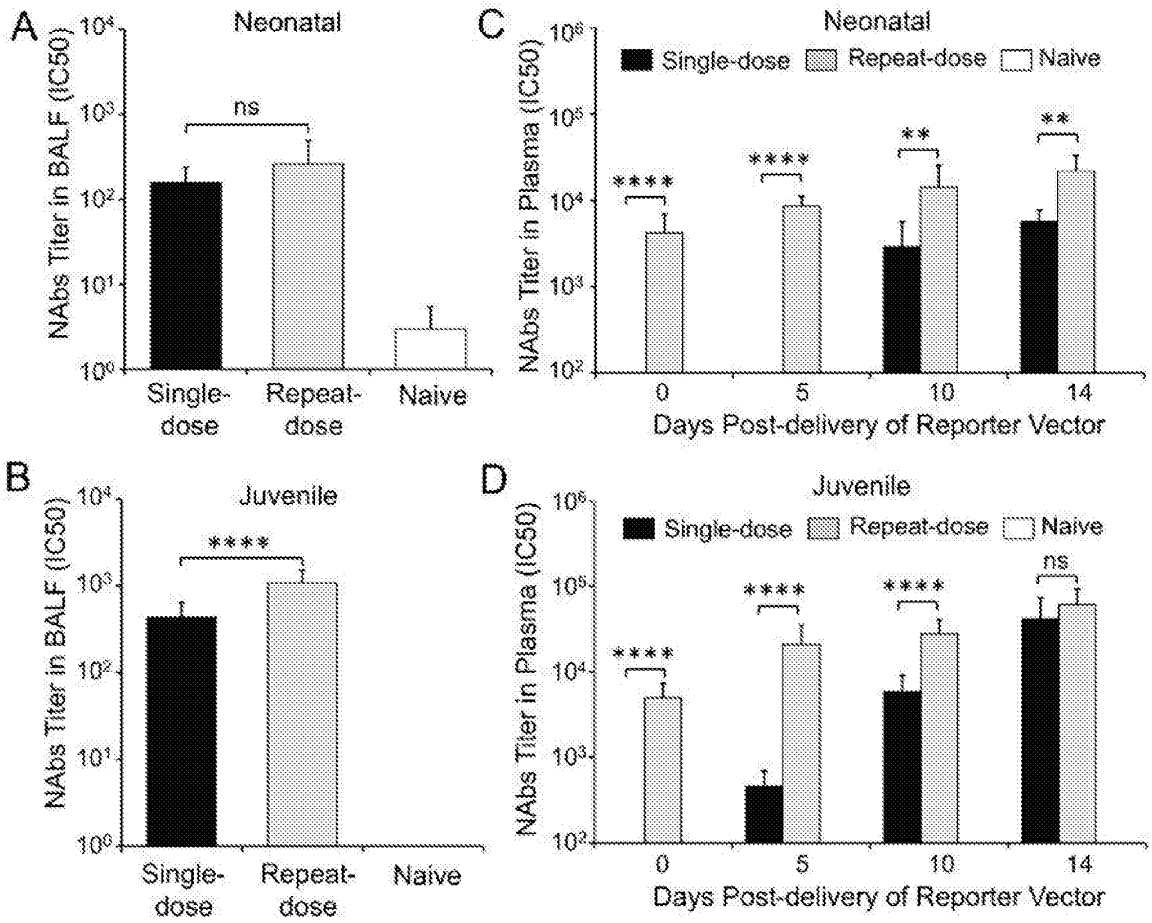

A
Neonatal
NAbs Titer in BALF (IC50)
ns
Single-dose
Repeat-dose
Naive
B
Juvenile
****
C
Neonatal
Single-dose
Repeat-dose
Naive
NAbs Titer in Plasma (IC50)
Days Post-delivery of Reporter Vector
D
Juvenile

FIG. 11

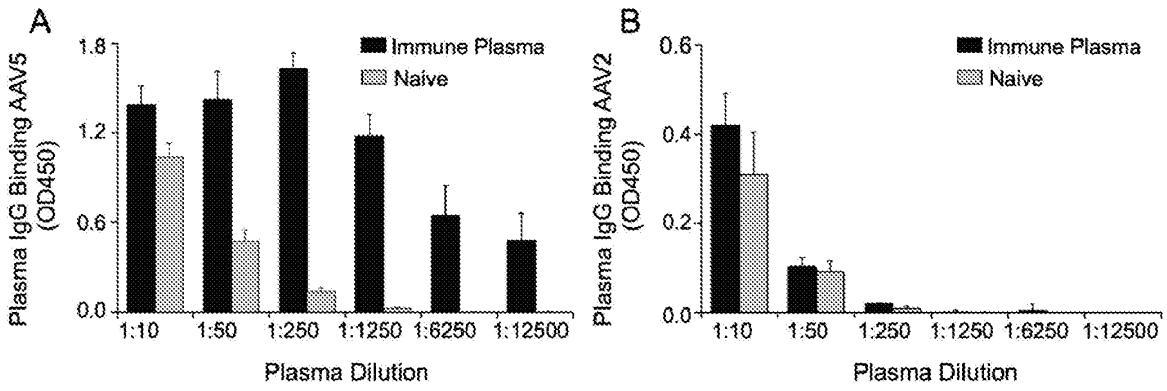

A
Plasma IgG Binding AAV5 (OD450)
1.8
1.2
0.6
0.0
Immune Plasma
Naive
1:10
1:50
1:250
1:1250
1:6250
1:12500
Plasma Dilution
B
Plasma IgG Binding AAV2 (OD450)
0.6
0.4
0.2
0.0
Immune Plasma
Naive
1:10
1:50
1:250
1:1250
1:6250
1:12500
Plasma Dilution

FIG. 12

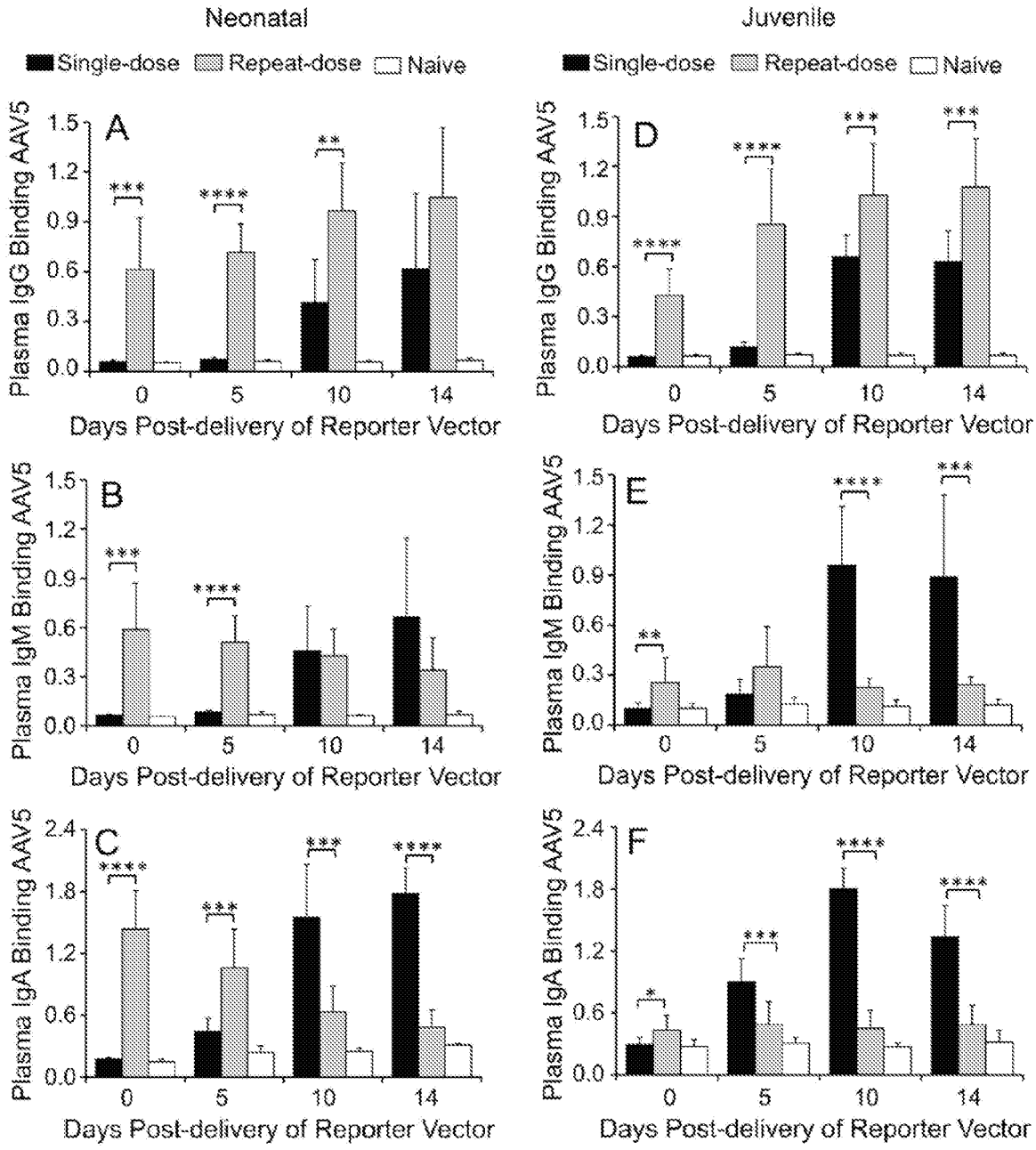

Neonatal
Juvenile
Single-dose
Repeat-dose
Naive
A
B
C
D
E
F
Plasma IgG Binding AAV5
Plasma IgM Binding AAV5
Plasma IgA Binding AAV5
Days Post-delivery of Reporter Vector
0
5
10
14

FIG. 13

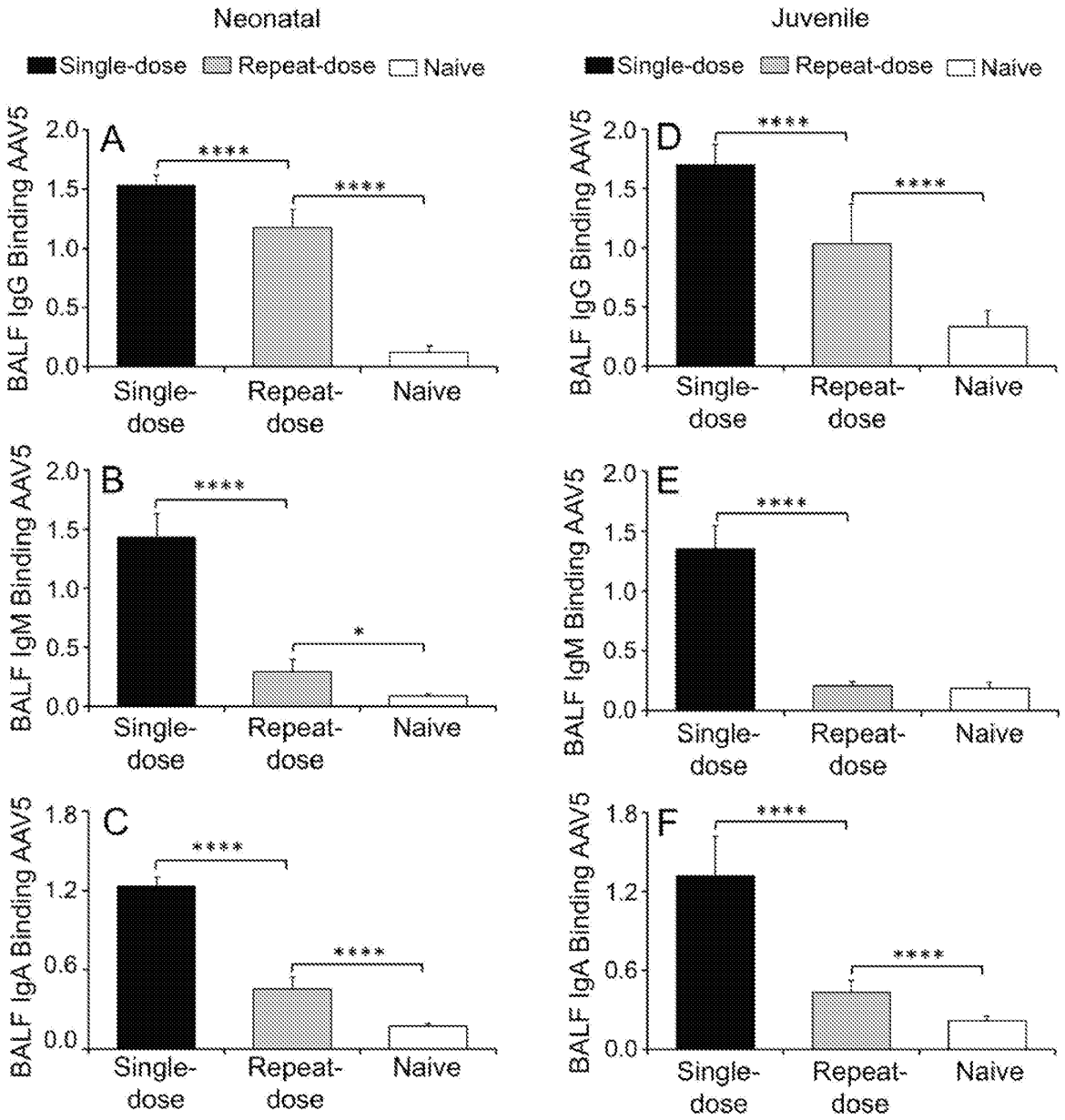

Neonatal
Juvenile
Single-dose
Repeat-dose
Naive
A
B
C
D
E
F
BALF IgG Binding AAV5
BALF IgM Binding AAV5
BALF IgA Binding AAV5
****
*
Single-dose
Repeat-dose
Naive

FIG. 14