FIG. 1A

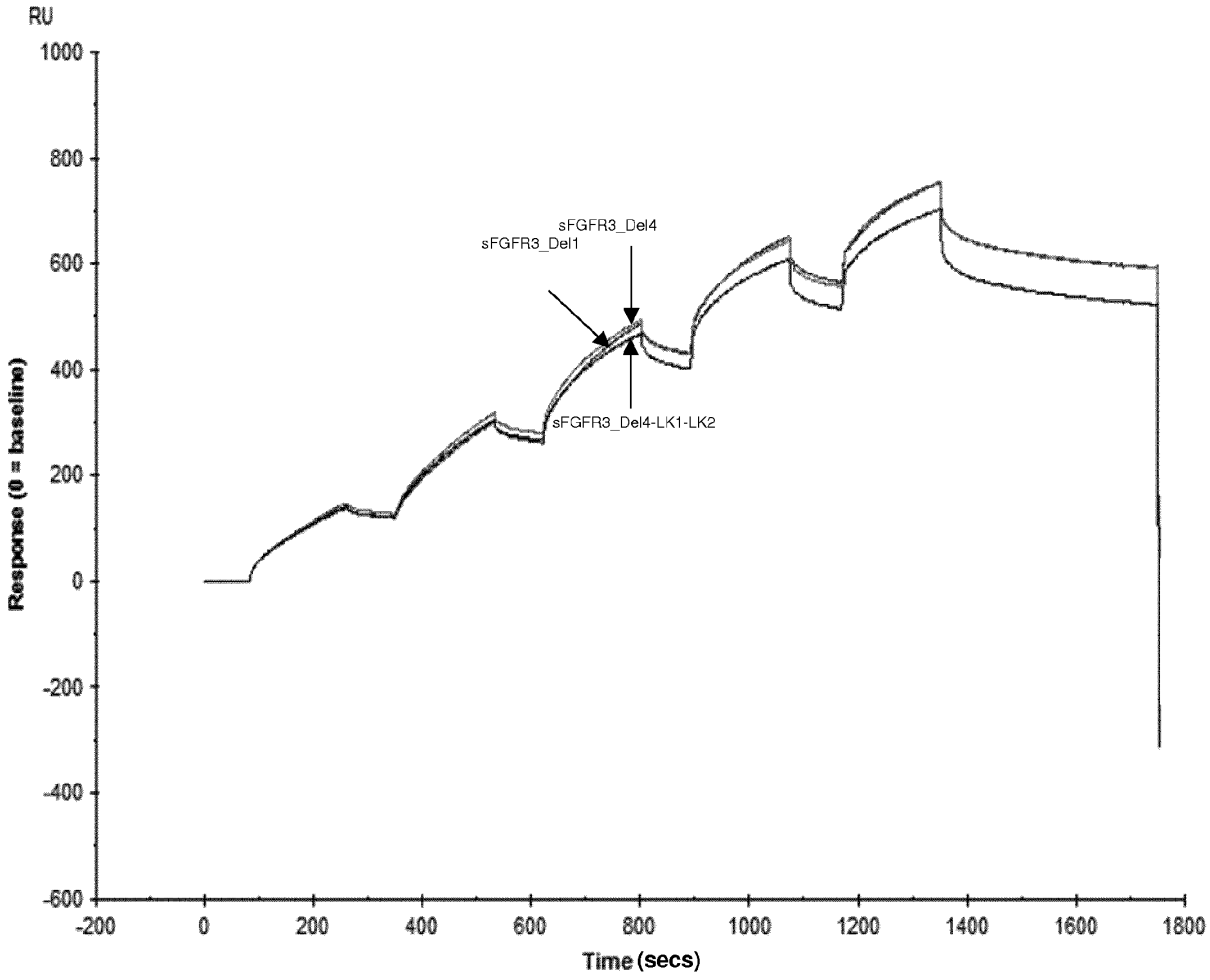

RU
1000
800
600
400
200
0
-200
-400
-600
Response (0 = baseline)
-200
0
200
400
600
800
1000
1200
1400
1600
1800
Time (secs)
sFGFR3_Del4
sFGFR3_Del1
sFGFR3_Del4-LK1-LK2

FIG. 1B

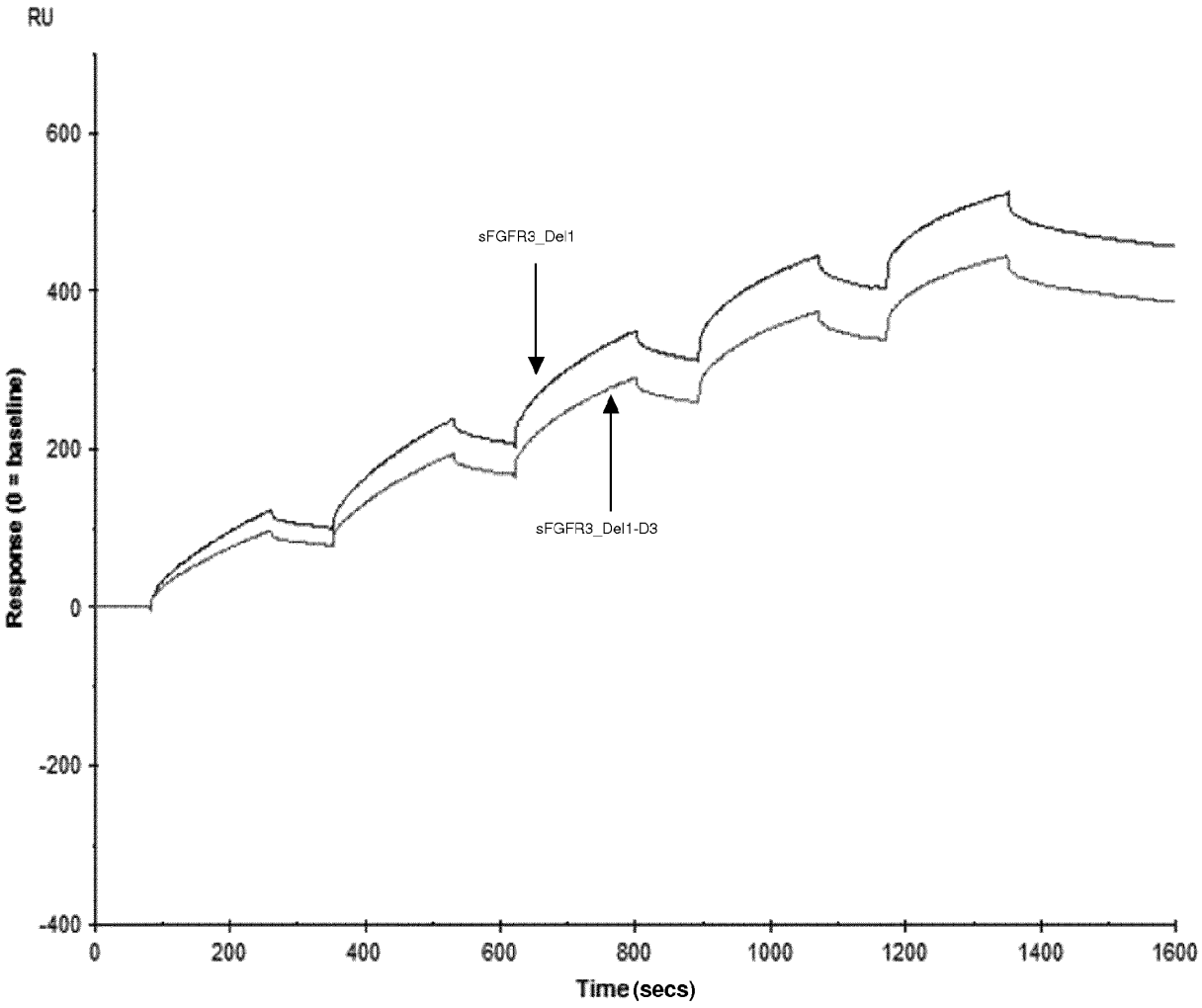

RU
600
400
200
0
-200
-400
Response (0 = baseline)
sFGFR3_Del1
sFGFR3_Del1-D3
0
200
400
600
800
1000
1200
1400
1600
Time (secs)

FIG. 1C

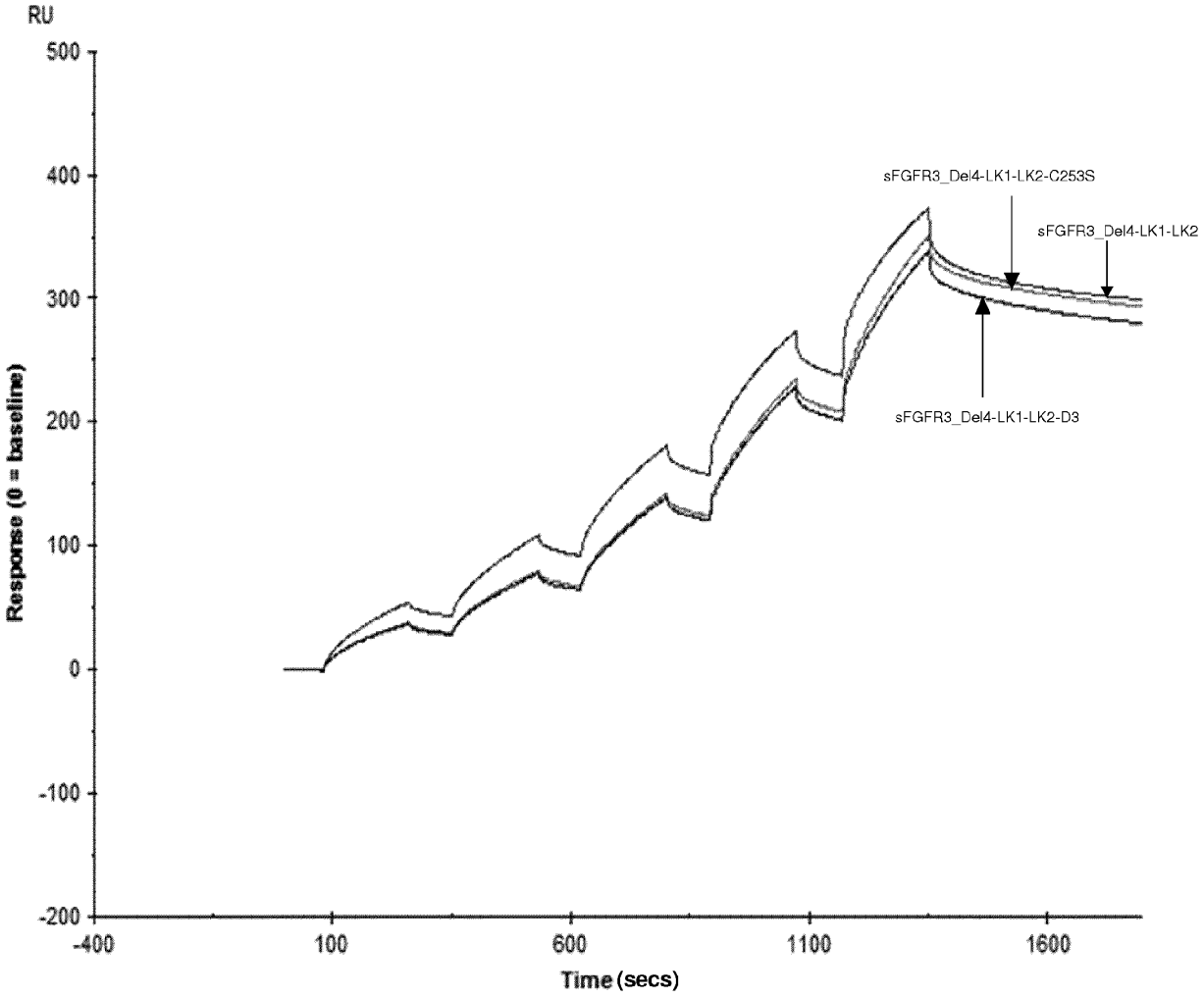

RU
500
400
300
200
100
0
-100
-200
Response (0 = baseline)
-400
100
600
1100
1600
Time (secs)
sFGFR3_Del4-LK1-LK2-C253S
sFGFR3_Del4-LK1-LK2
sFGFR3_Del4-LK1-LK2-D3

FIG. 1D

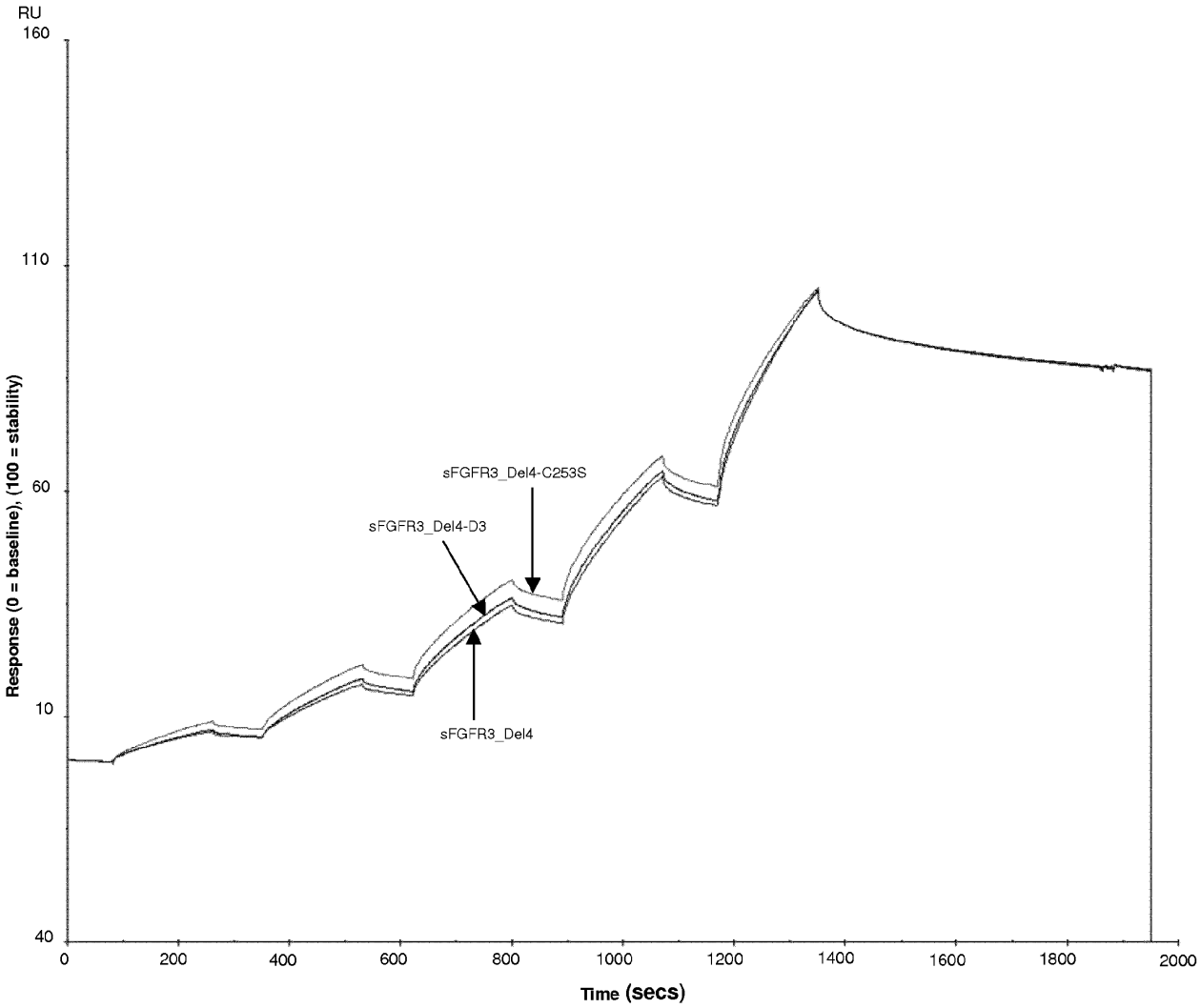

RU
160
110
60
10
40
Response (0 = baseline), (100 = stability)
sFGFR3_Del4-C253S
sFGFR3_Del4-D3
sFGFR3_Del4
0
200
400
600
800
1000
1200
1400
1600
1800
2000
Time (secs)

FIG. 2A

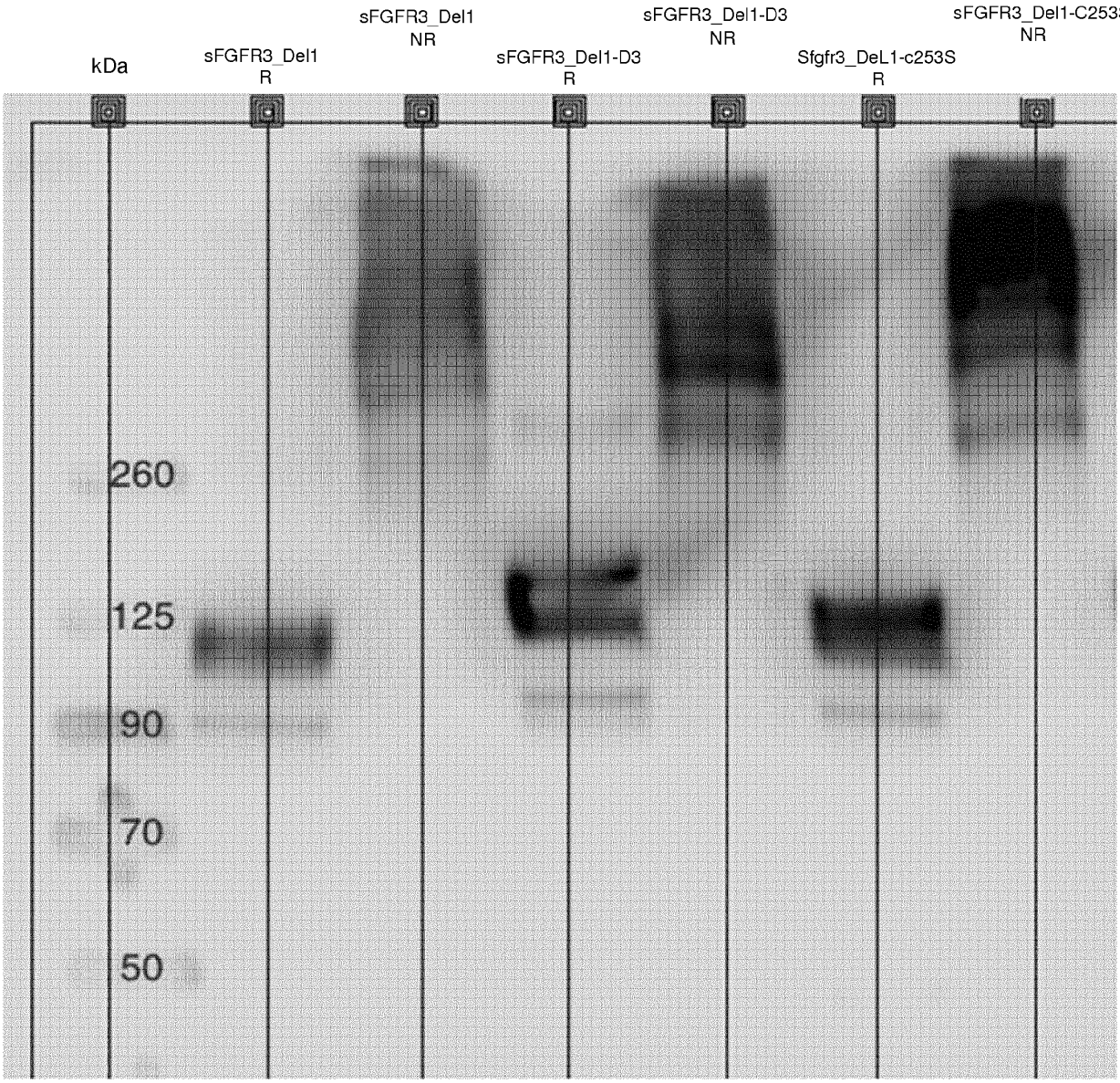

kDa
sFGFR3_Del1 R
sFGFR3_Del1 NR
sFGFR3_Del1-D3 R
sFGFR3_Del1-D3 NR
Sfgfr3_DeL1-c253S R
sFGFR3_Del1-C253S NR
260
125
90
70
50

FIG. 2B

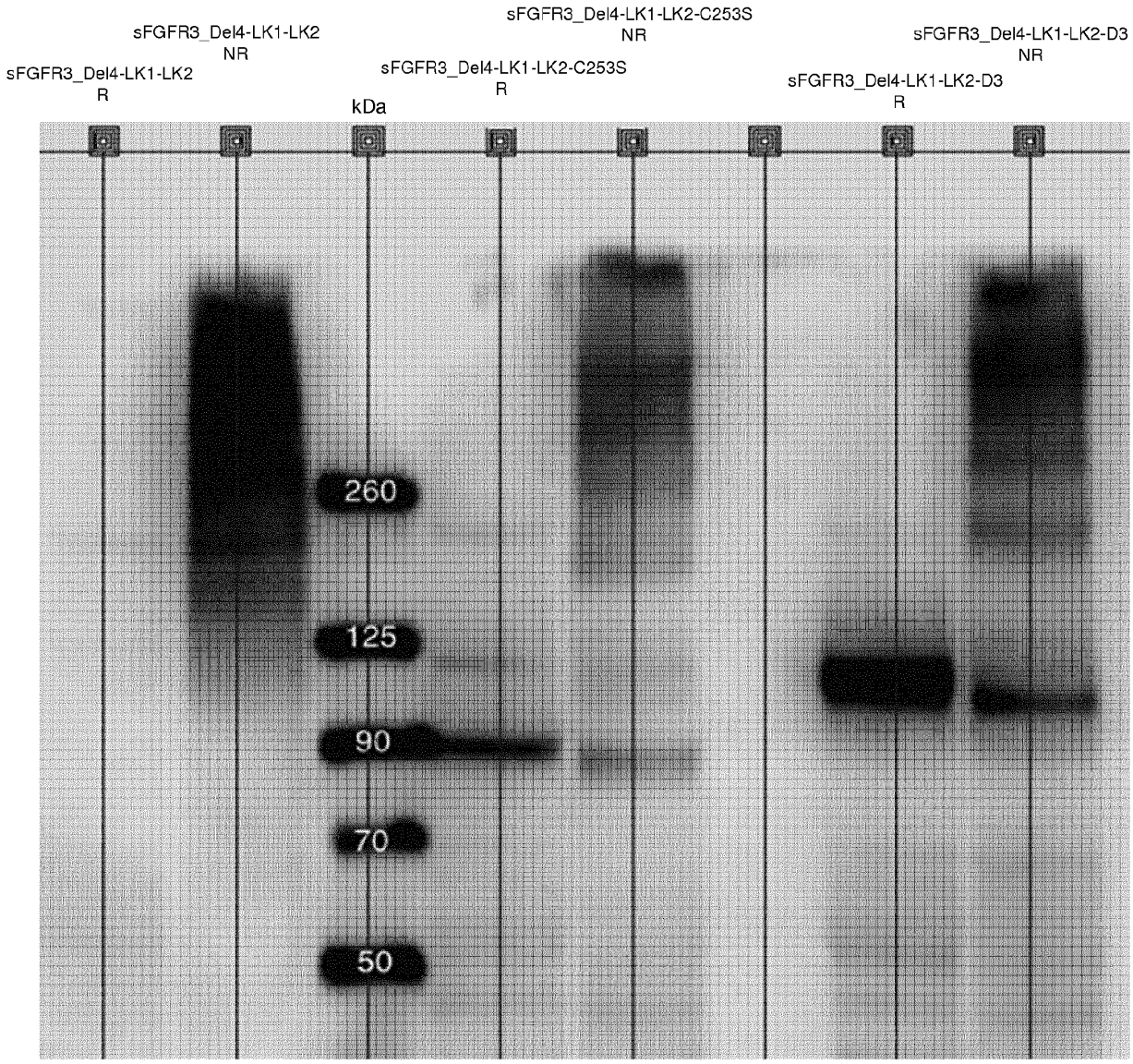

sFGFR3_Del4-LK1-LK2
R
sFGFR3_Del4-LK1-LK2
NR
kDa
sFGFR3_Del4-LK1-LK2-C253S
R
sFGFR3_Del4-LK1-LK2-C253S
NR
sFGFR3_Del4-LK1-LK2-D3
R
sFGFR3_Del4-LK1-LK2-D3
NR
260
125
90
70
50

FIG. 2C

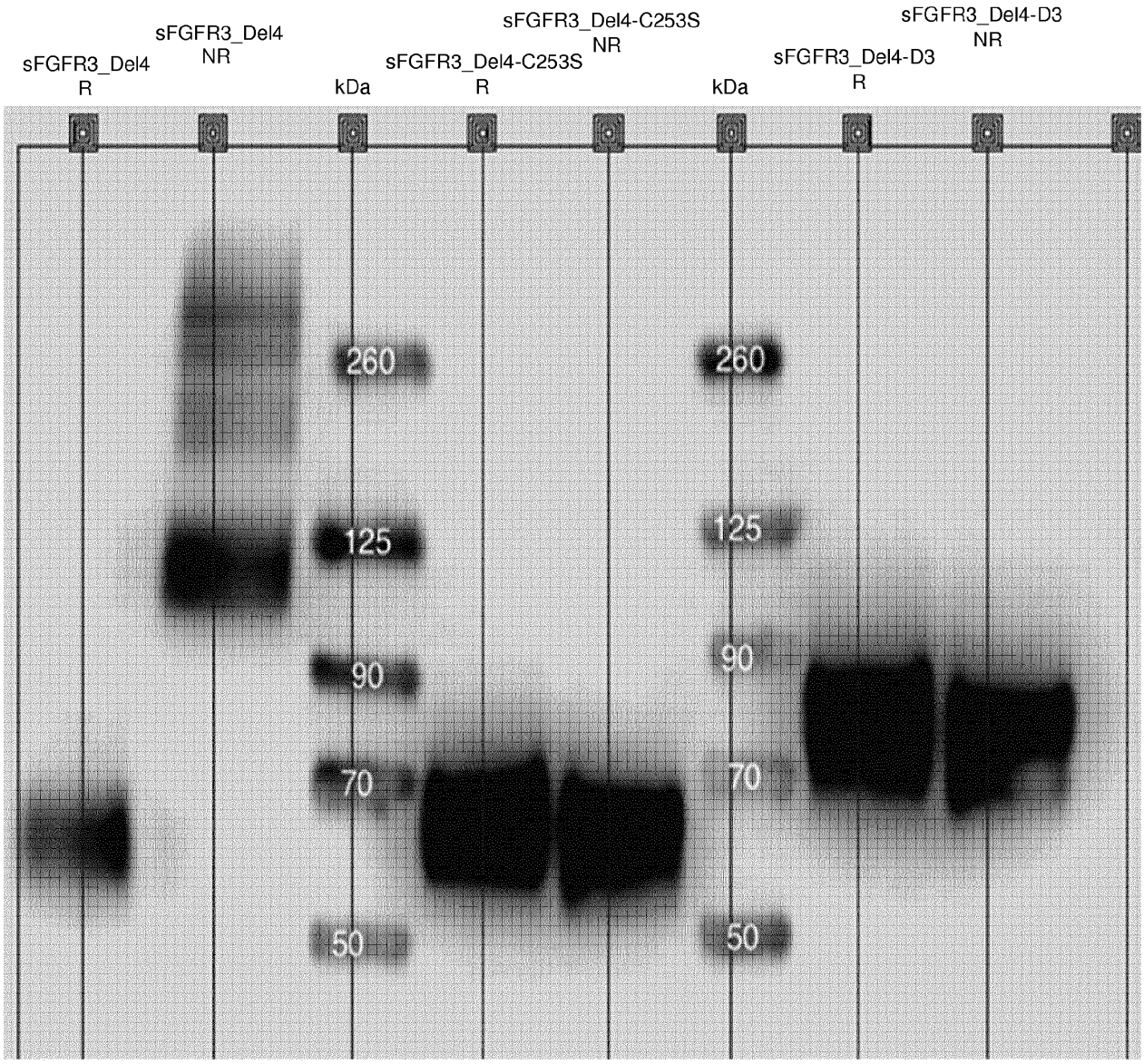
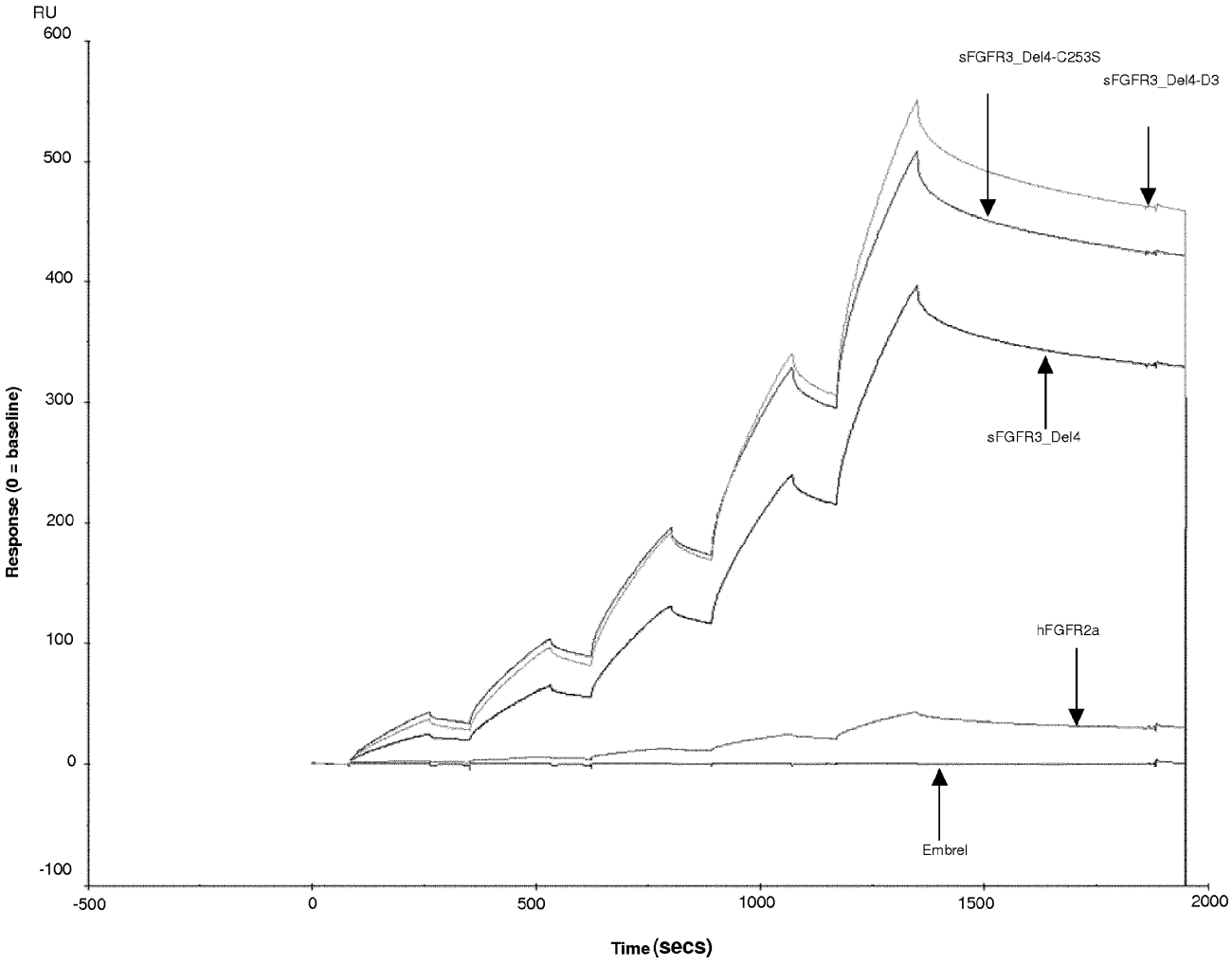

sFGFR3_Del4
R
sFGFR3_Del4
NR
kDa
260
125
90
70
50
sFGFR3_Del4-C253S
R
sFGFR3_Del4-C253S
NR
kDa
260
125
90
70
50
sFGFR3_Del4-D3
R
sFGFR3_Del4-D3
NR

FIG. 3A


RU
600
500
400
300
200
100
0
-100
Response (0 = baseline)
-500
0
500
1000
1500
2000
Time (secs)
sFGFR3_Del4-C253S
sFGFR3_Del4-D3
sFGFR3_Del4
hFGFR2a
Embrel

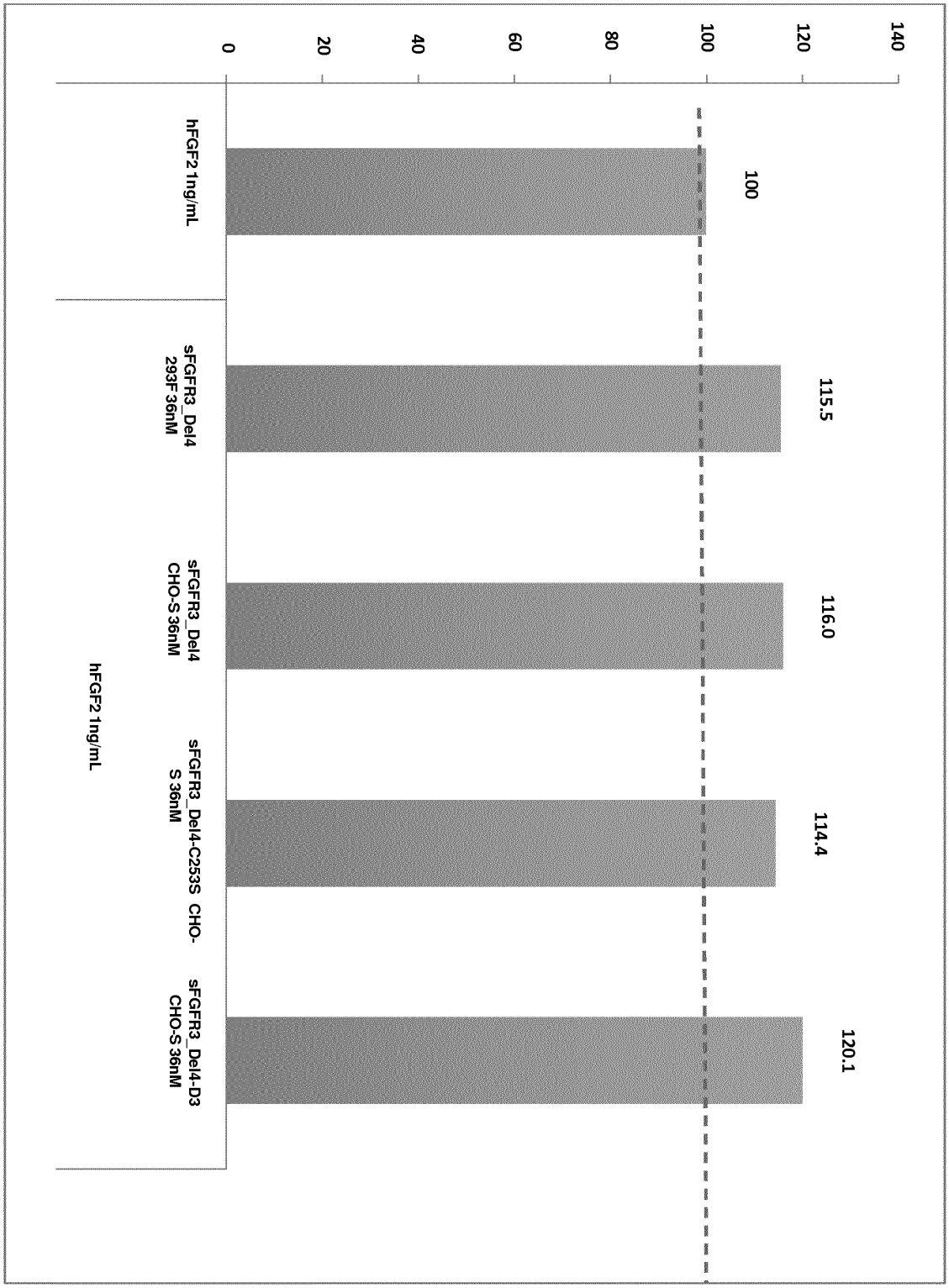

140
120
100
80
60
40
20
0
100
115.5
116.0
114.4
120.1
hFGF2 1ng/mL
sFGFR3_Del4 293F 36nM
sFGFR3_Del4 CHO-S 36nM
sFGFR3_Del4-C253S CHO-S 36nM
sFGFR3_Del4-D3 CHO-S 36nM
hFGF2 1ng/mL

FIG. 3B

FIG. 4

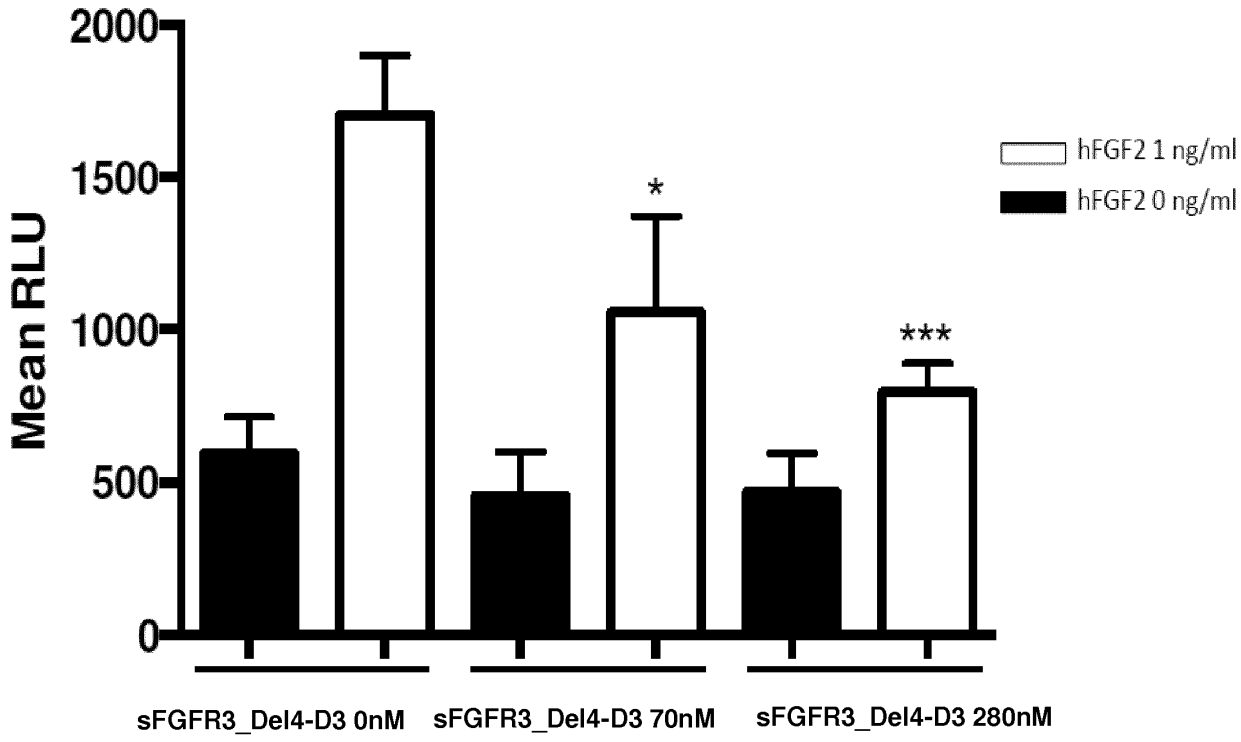

2000
1500
1000
500
0
Mean RLU
*
***
hFGF2 1 ng/ml
hFGF2 0 ng/ml
sFGFR3_Del4-D3 0nM
sFGFR3_Del4-D3 70nM
sFGFR3_Del4-D3 280nM

FIG. 5

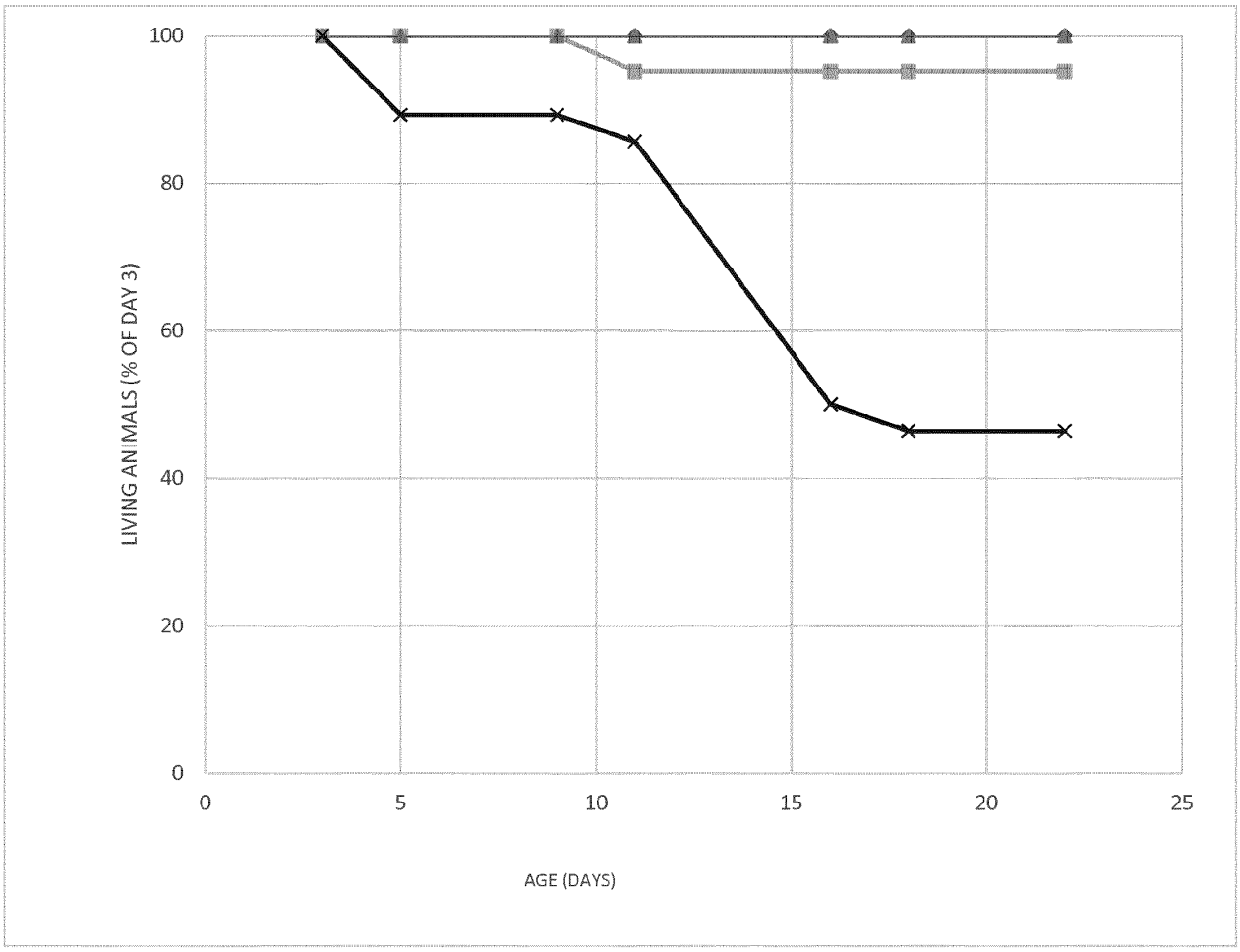

100
80
60
40
20
0
LIVING ANIMALS (% OF DAY 3)
0
5
10
15
20
25
AGE (DAYS)
Fgfr3ach/+ sFGFR3_Del4-D3 0.25 mg/kg
WT PBS
Fgfr3ach/+ PBS

FIG. 6

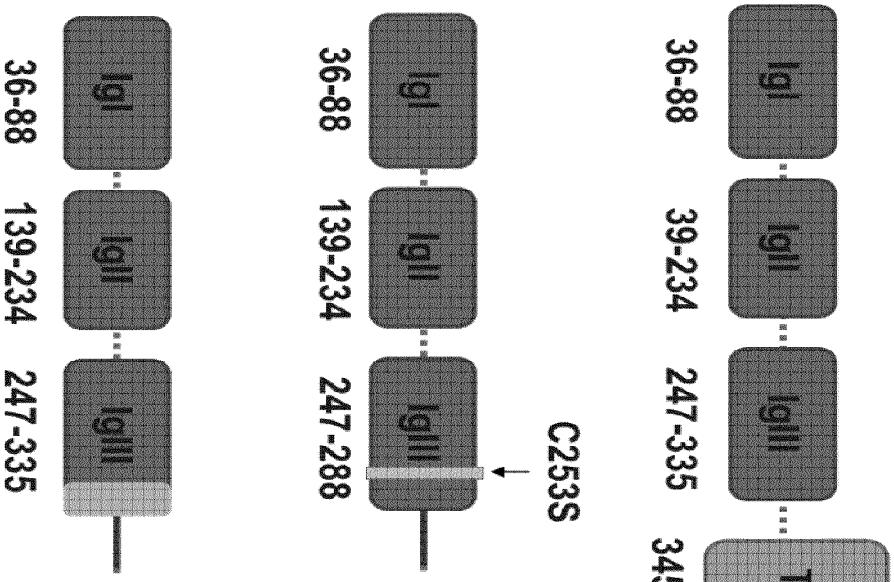

Extracellular
Intracellular
Wildtype FGFR3
(SEQ ID NO: 5)
IgI
IgII
IgIII
TM
TK
TK
36-88
39-234
247-335
345-377
378-784
sFGFR3_Del4-C253S
(SEQ ID NO: 2)
C253S
IgI
IgII
IgIII
36-88
139-234
247-288
sFGFR3_Del4-D3
(SEQ ID NO: 33)
IgI
IgII
IgIII
36-88
139-234
247-335

FIG. 7A

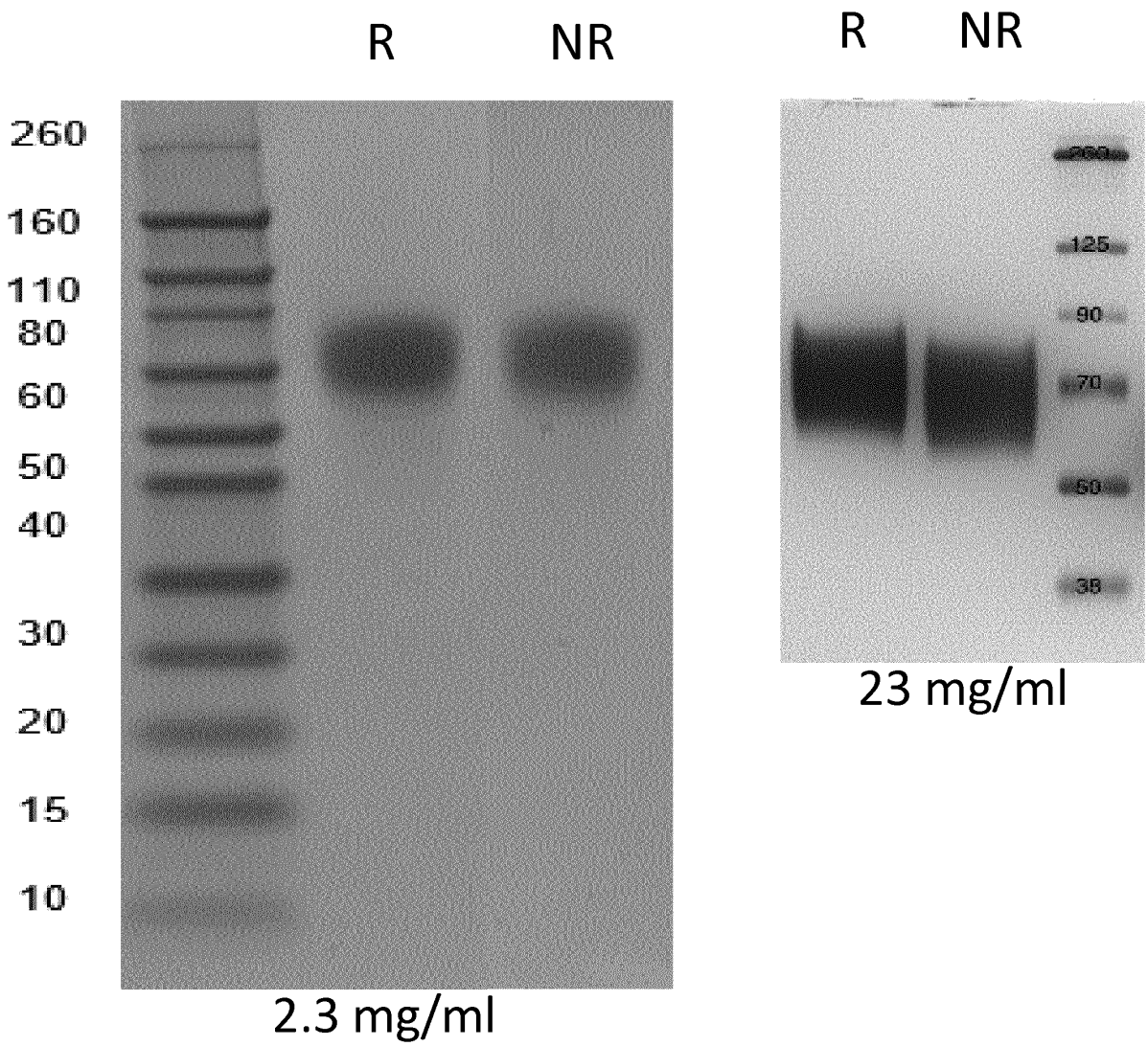
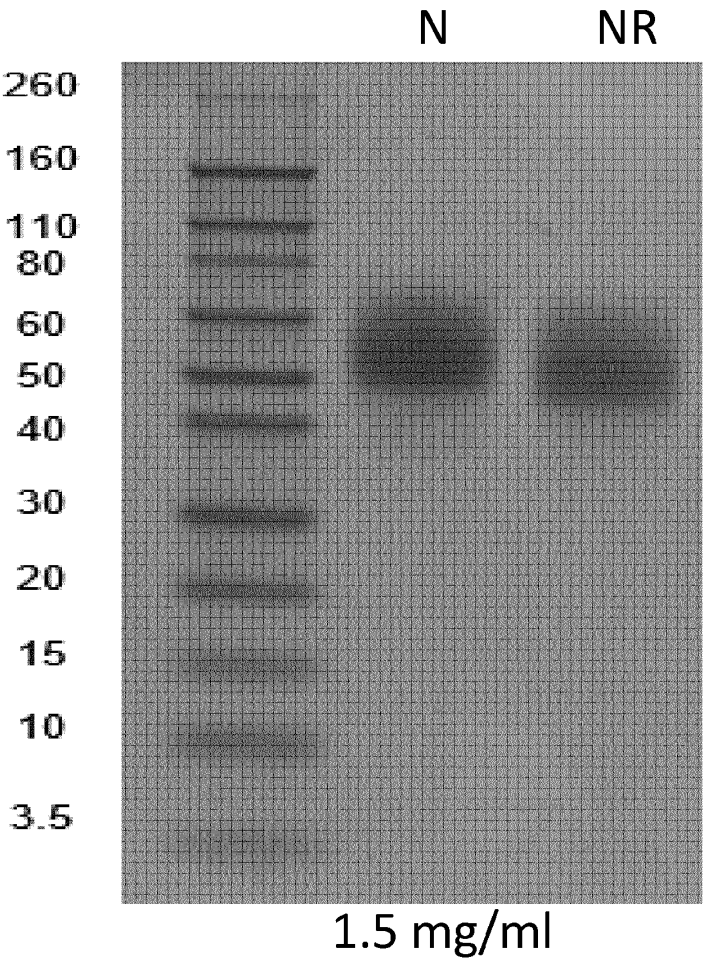
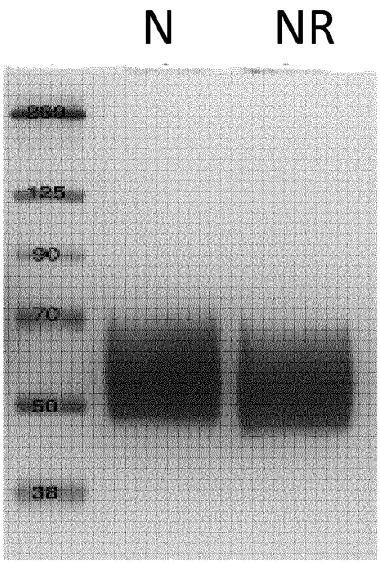

R
NR
260
160
110
80
60
50
40
30
20
15
10
2.3 mg/ml
R
NR
125
90
70
50
35
23 mg/ml

FIG. 7B



1.5 mg/ml



15 mg/ml

FIG. 8A

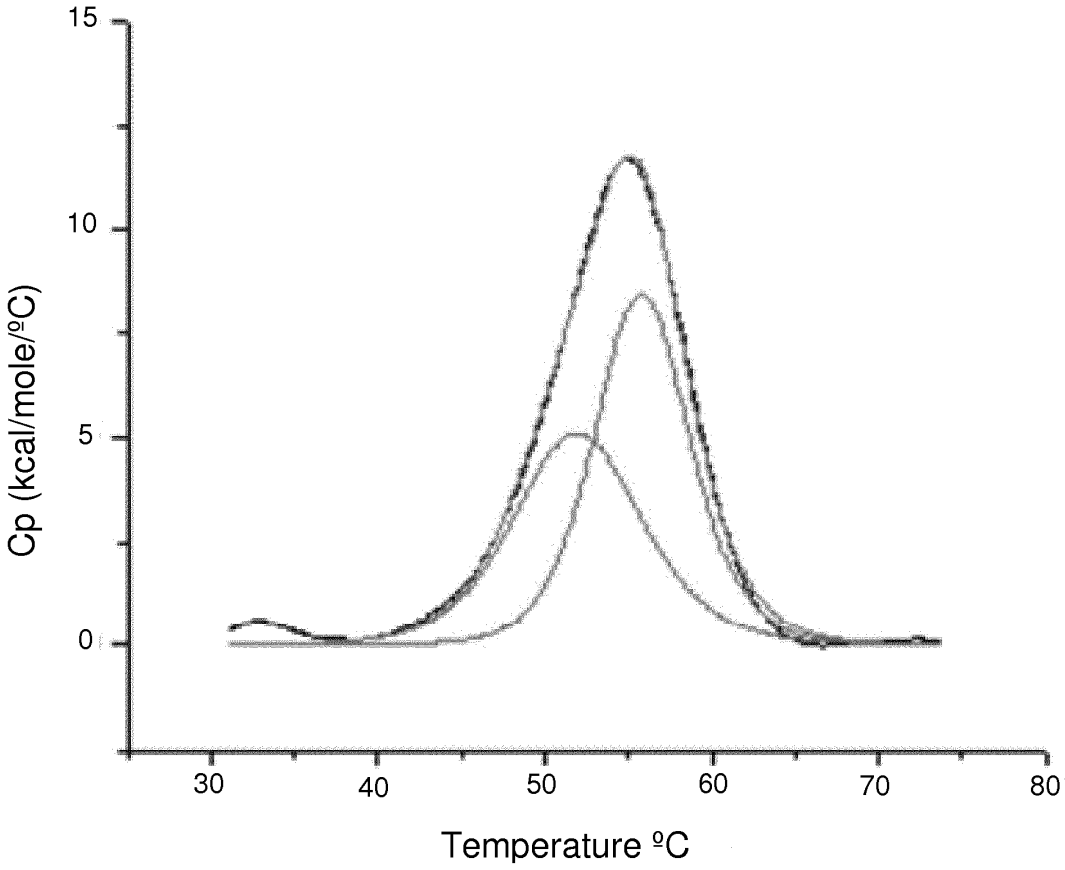
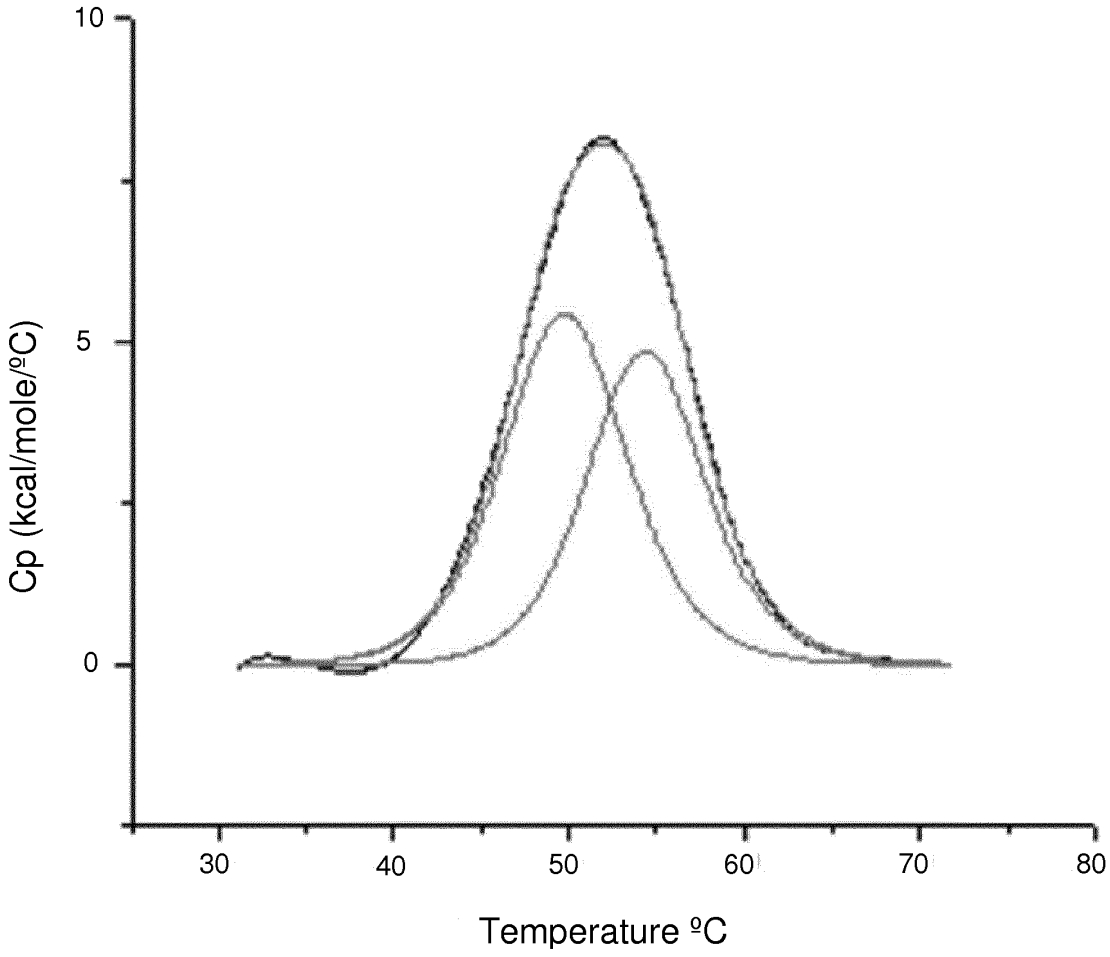


FIG. 8B



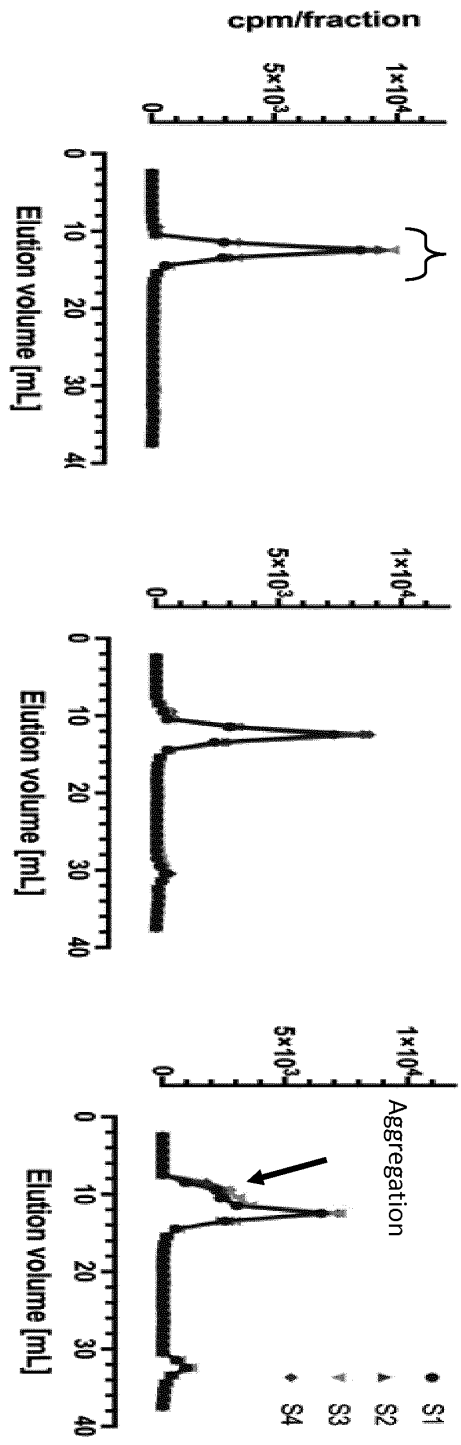

cpm/fraction
1×10^4
5×10^3
0
Elution volume [mL]
0
10
20
30
40
0 min; 95%
2 hr; 95%
24 hr; ~92%
Aggregation
S1
S2
S3
S4

FIG. 9A

FIG. 9B

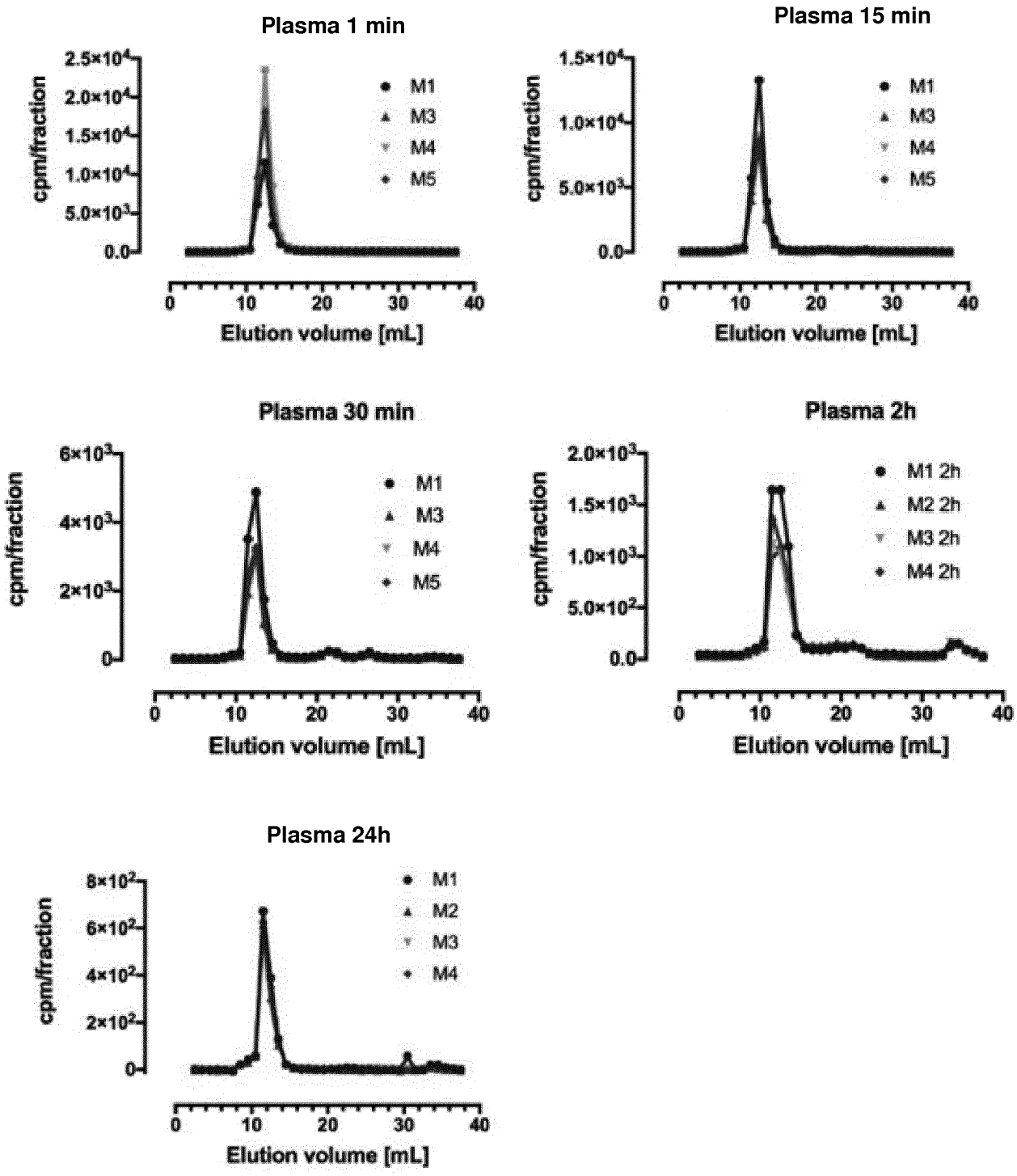
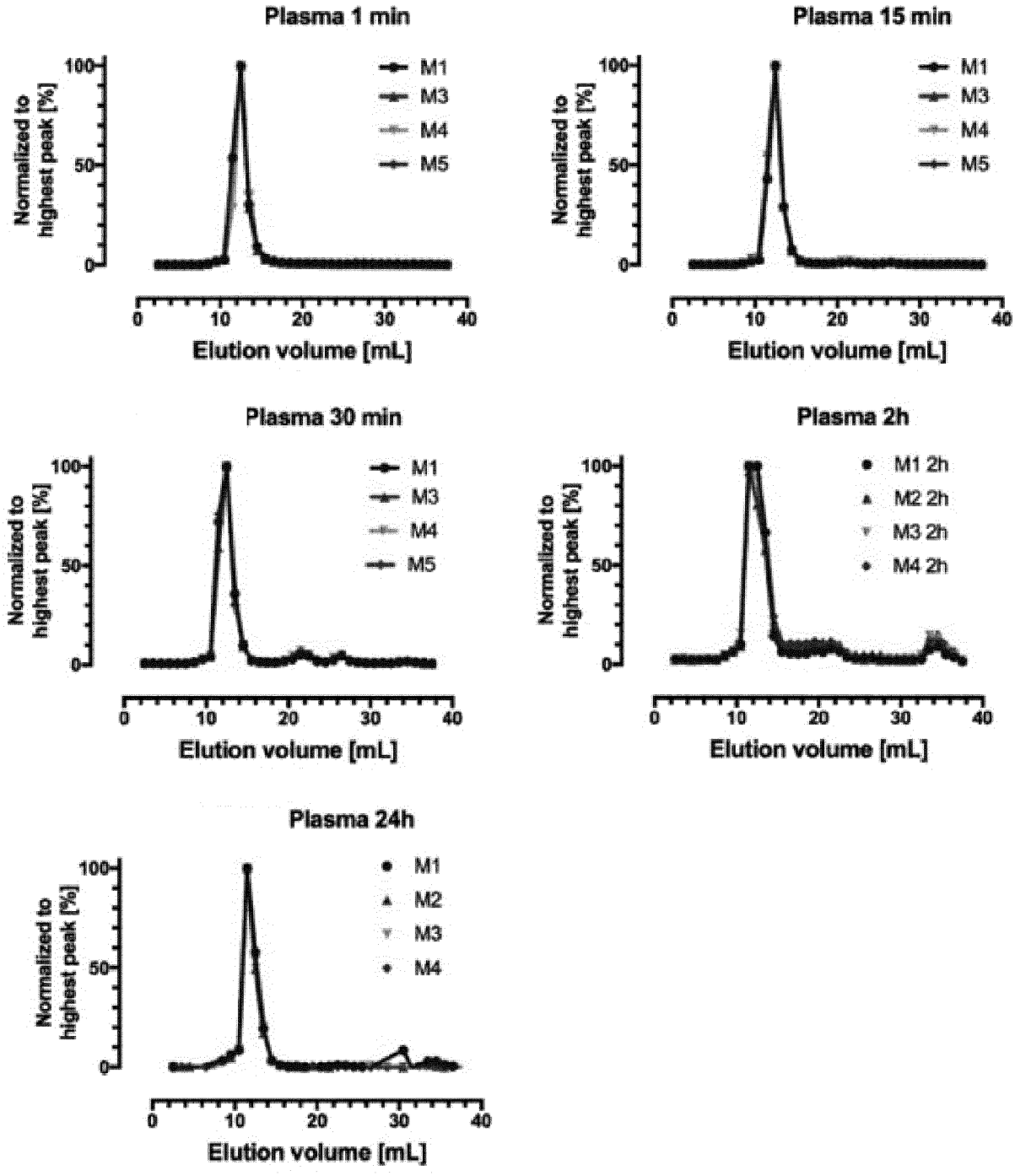

Plasma 1 min
cpm/fraction
2.5×10^4
2.0×10^4
1.5×10^4
1.0×10^4
5.0×10^3
0.0
M1
M3
M4
M5
0
10
20
30
40
Elution volume [mL]
Plasma 15 min
cpm/fraction
1.5×10^4
1.0×10^4
5.0×10^3
0.0
M1
M3
M4
M5
0
10
20
30
40
Elution volume [mL]
Plasma 30 min
cpm/fraction
6×10^3
4×10^3
2×10^3
0
M1
M3
M4
M5
0
10
20
30
40
Elution volume [mL]
Plasma 2h
cpm/fraction
2.0×10^3
1.5×10^3
1.0×10^3
5.0×10^2
0.0
M1 2h
M2 2h
M3 2h
M4 2h
0
10
20
30
40
Elution volume [mL]
Plasma 24h
cpm/fraction
8×10^2
6×10^2
4×10^2
2×10^2
0
M1
M2
M3
M4
0
10
20
30
40
Elution volume [mL]

FIG. 9B cont.


Plasma 1 min
Normalized to highest peak [%]
100
50
0
M1
M3
M4
M5
0
10
20
30
40
Elution volume [mL]
Plasma 15 min
Normalized to highest peak [%]
100
50
0
M1
M3
M4
M5
0
10
20
30
40
Elution volume [mL]
Plasma 30 min
Normalized to highest peak [%]
100
50
0
M1
M3
M4
M5
0
10
20
30
40
Elution volume [mL]
Plasma 2h
Normalized to highest peak [%]
100
50
0
M1 2h
M2 2h
M3 2h
M4 2h
0
10
20
30
40
Elution volume [mL]
Plasma 24h
Normalized to highest peak [%]
100
50
0
M1
M2
M3
M4
0
10
20
30
40
Elution volume [mL]

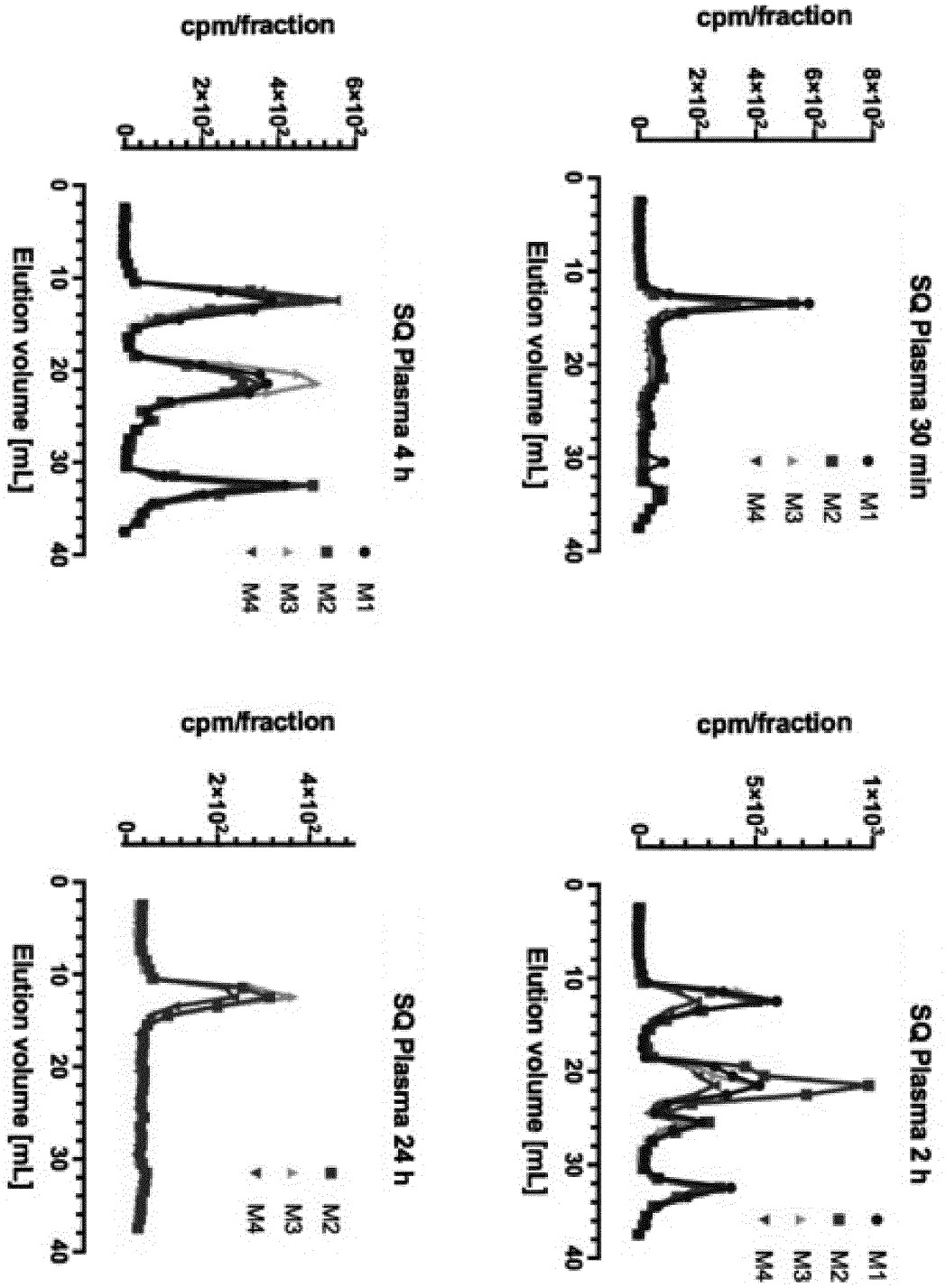

SQ Plasma 30 min
SQ Plasma 2 h
SQ Plasma 4 h
SQ Plasma 24 h
cpm/fraction
Elution volume [mL]
M1
M2
M3
M4

FIG. 9C

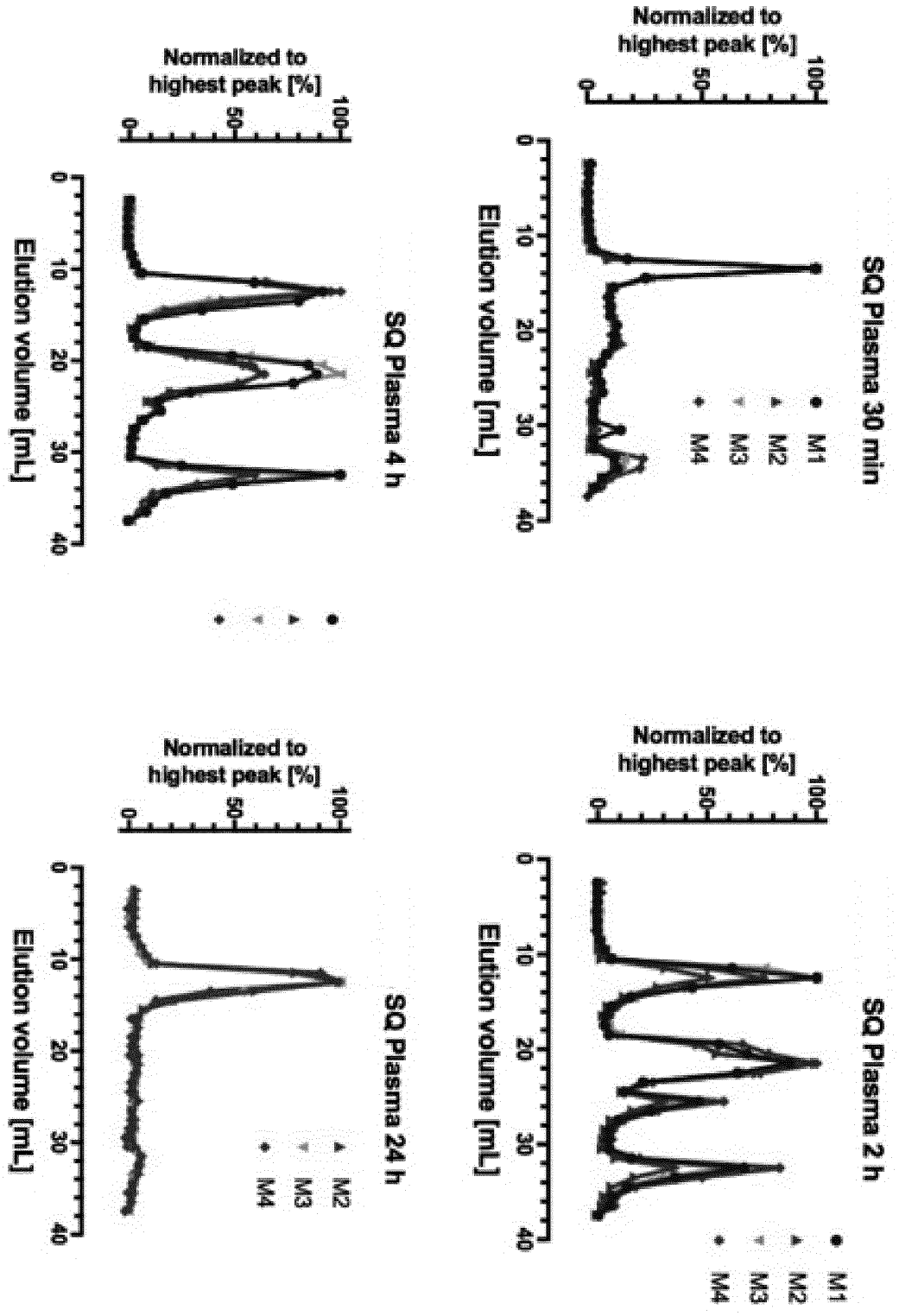

SQ Plasma 30 min
SQ Plasma 4 h
SQ Plasma 2 h
SQ Plasma 24 h
Normalized to highest peak [%]
Elution volume [mL]
M1
M2
M3
M4

FIG. 9C cont.

FIG. 10A

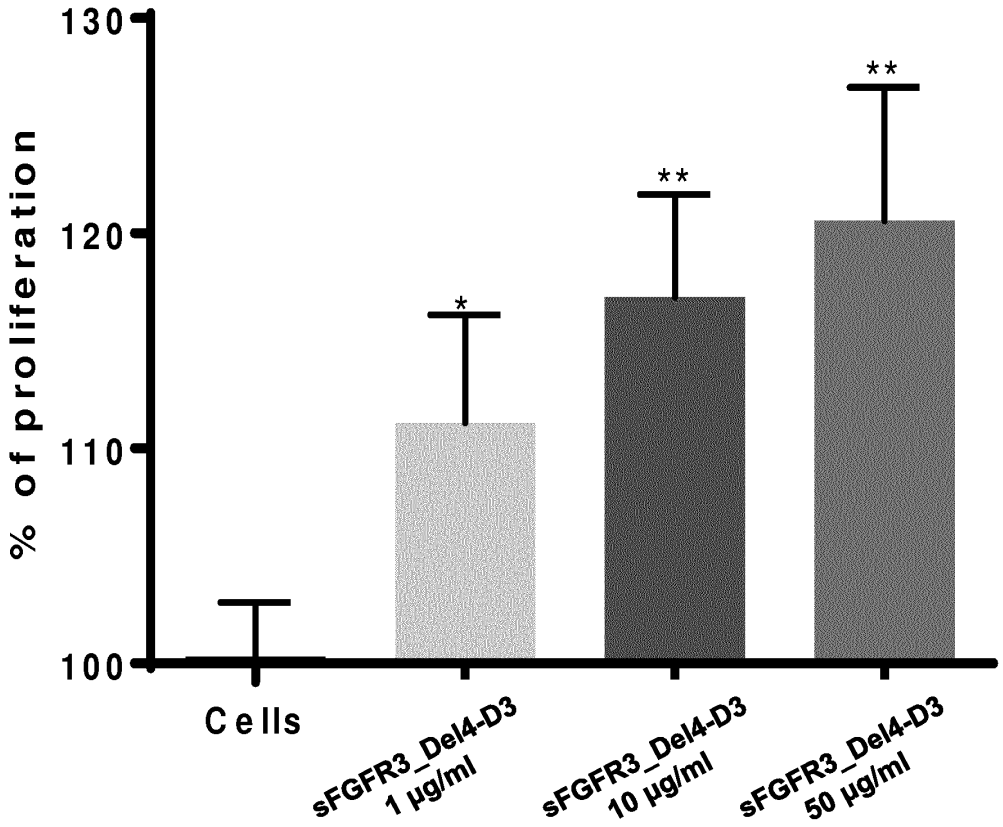
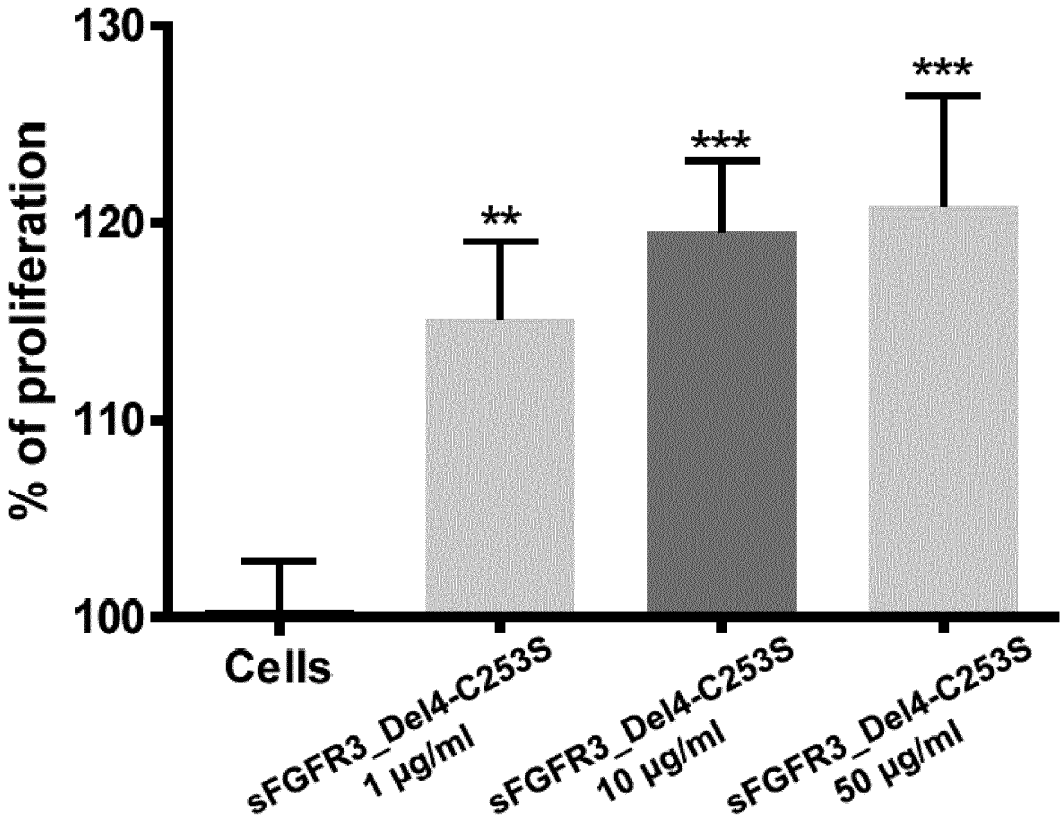

130
120
110
100
% of proliferation
*
**
**
Cells
sFGFR3_Del4-D3 1 µg/ml
sFGFR3_Del4-D3 10 µg/ml
sFGFR3_Del4-D3 50 µg/ml

FIG. 10B


130
120
110
100
% of proliferation
**
***
***
Cells
sFGFR3_Del4-C253S 1 µg/ml
sFGFR3_Del4-C253S 10 µg/ml
sFGFR3_Del4-C253S 50 µg/ml

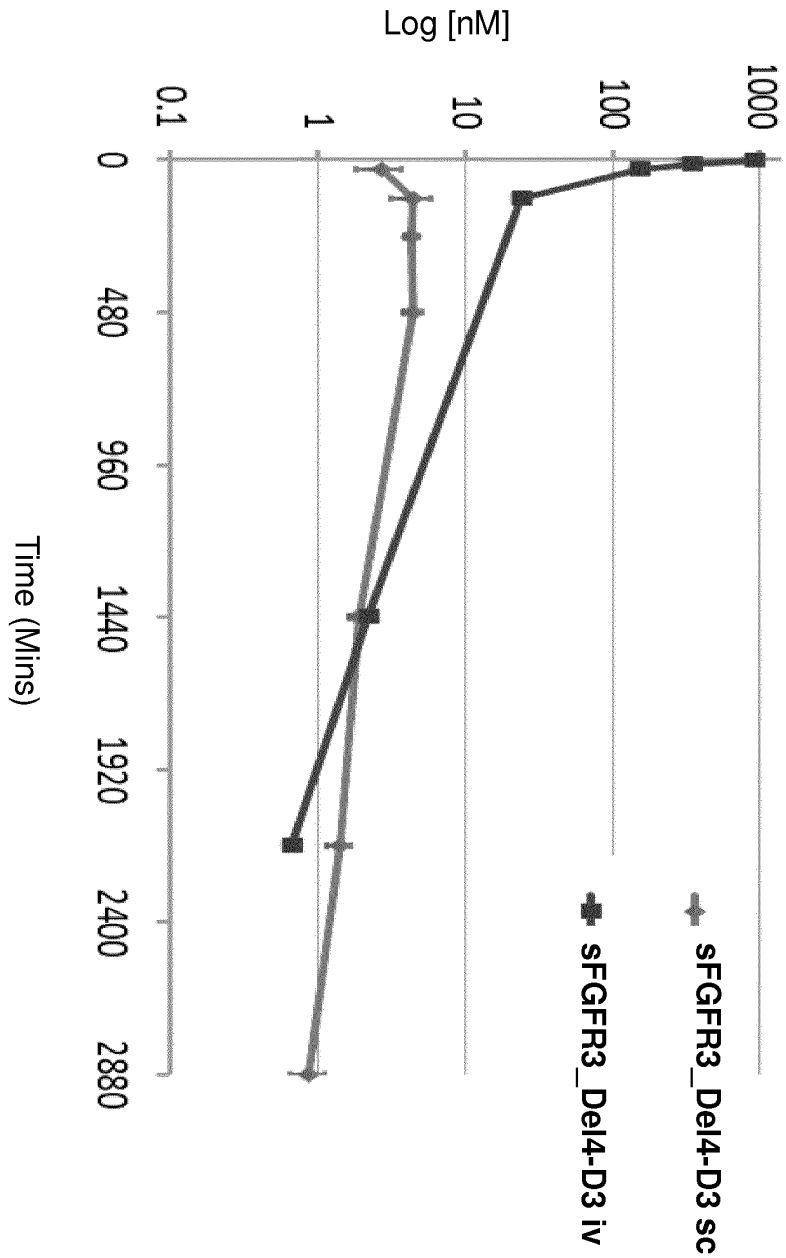

Log [nM]
1000
100
10
1
0.1
0
480
960
1440
1920
2400
2880
Time (Mins)
sFGFR3_Del4-D3 sc
sFGFR3_Del4-D3 iv

FIG. 11

FIG. 12

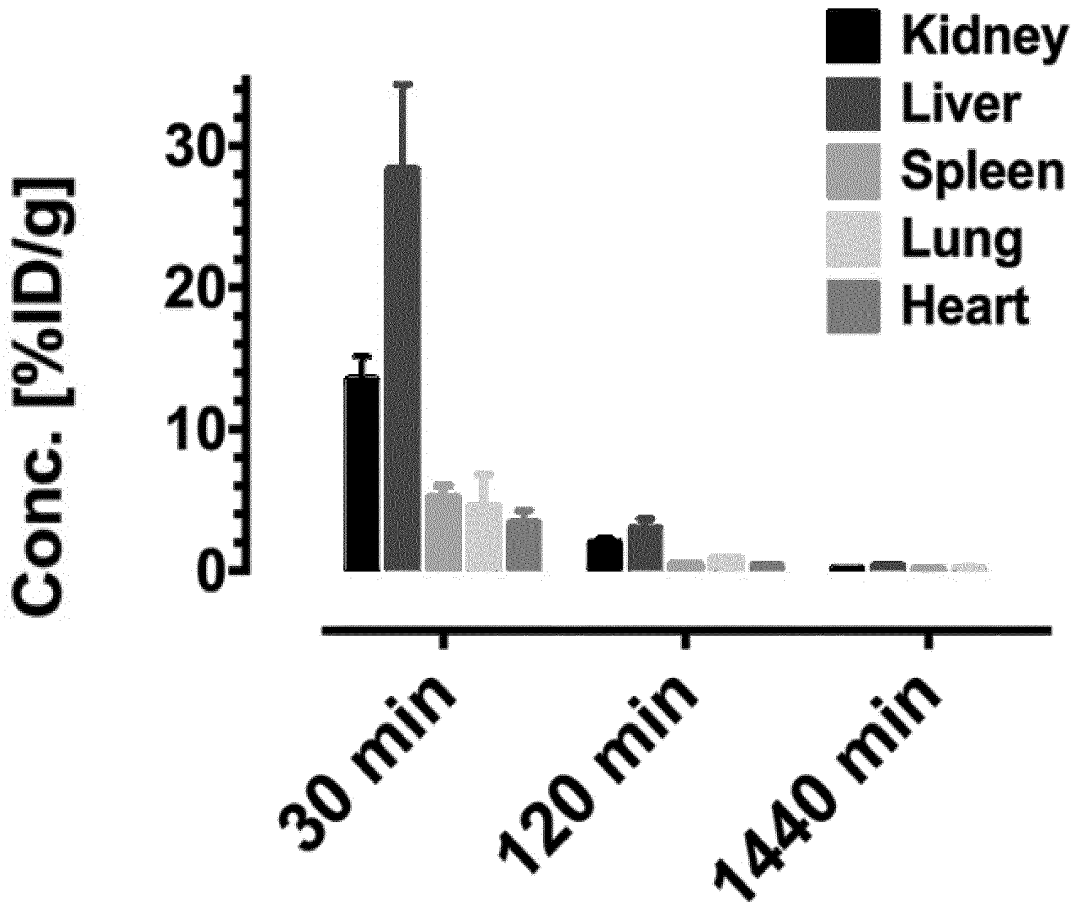
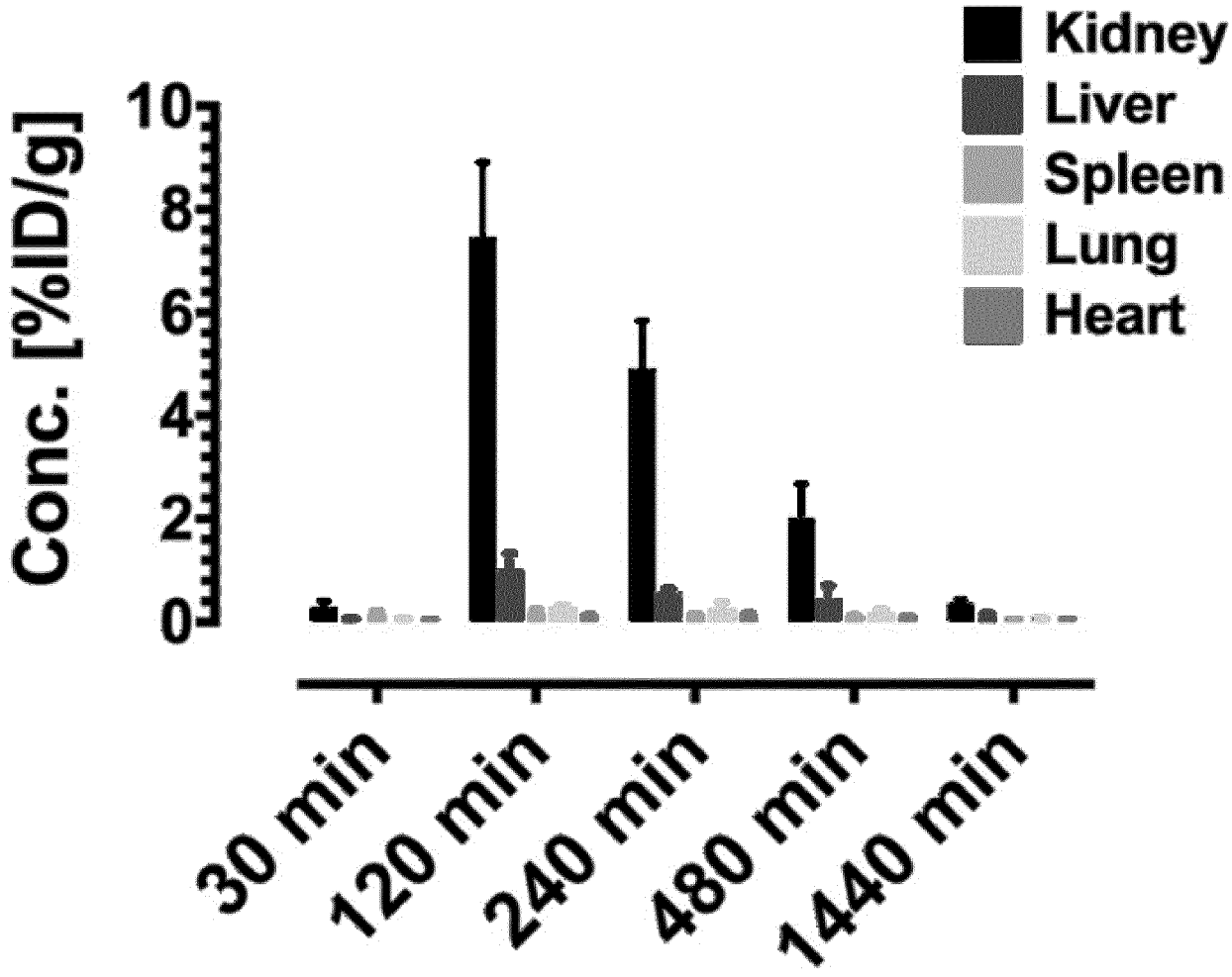

Kidney
Liver
Spleen
Lung
Heart
Conc. [%ID/g]
0
10
20
30
30 min
120 min
1440 min

FIG. 13


Kidney
Liver
Spleen
Lung
Heart
Conc. [%ID/g]
10
8
6
4
2
0
30 min
120 min
240 min
480 min
1440 min

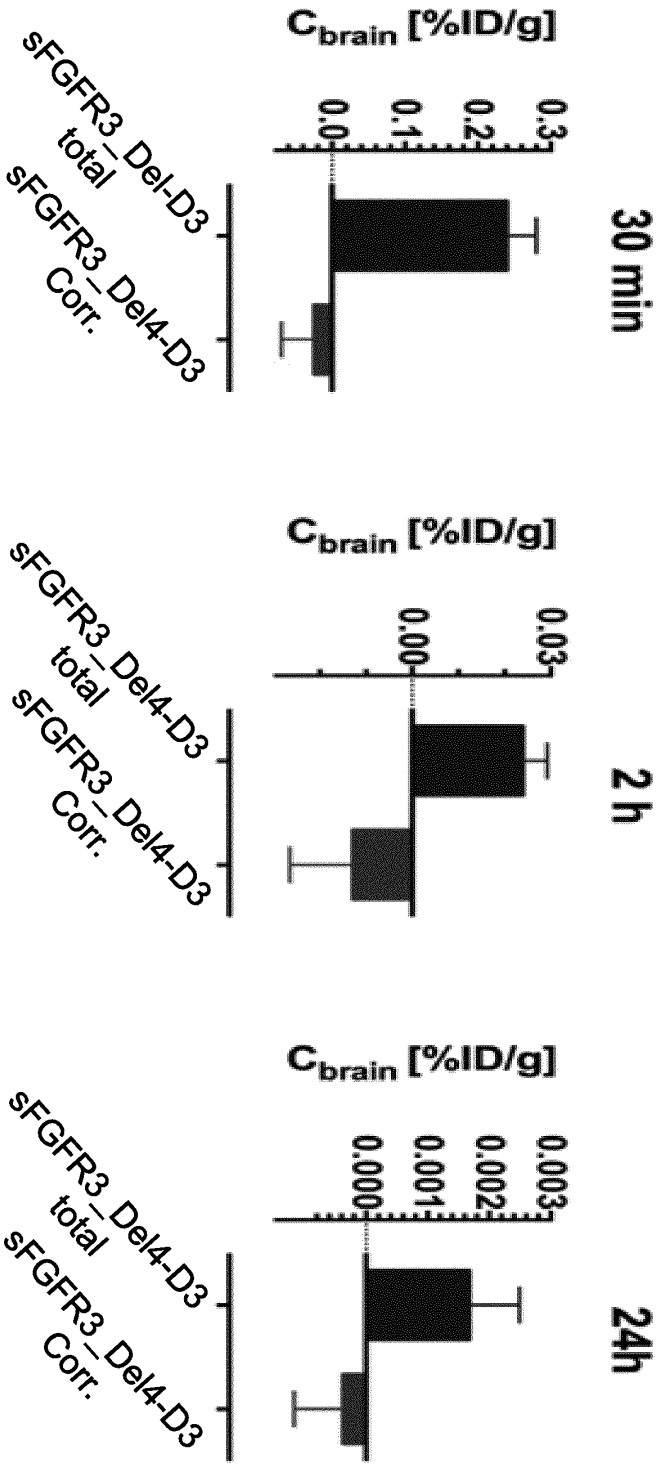

30 min
C_{brain} [%ID/g]
0.0
0.1
0.2
0.3
sFGFR3_Del-D3 total
sFGFR3_Del4-D3 Corr.
2 h
C_{brain} [%ID/g]
0.00
0.03
sFGFR3_Del4-D3 total
sFGFR3_Del4-D3 Corr.
24h
C_{brain} [%ID/g]
0.000
0.001
0.002
0.003
sFGFR3_Del4-D3 total
sFGFR3_Del4-D3 Corr.

FIG. 14A

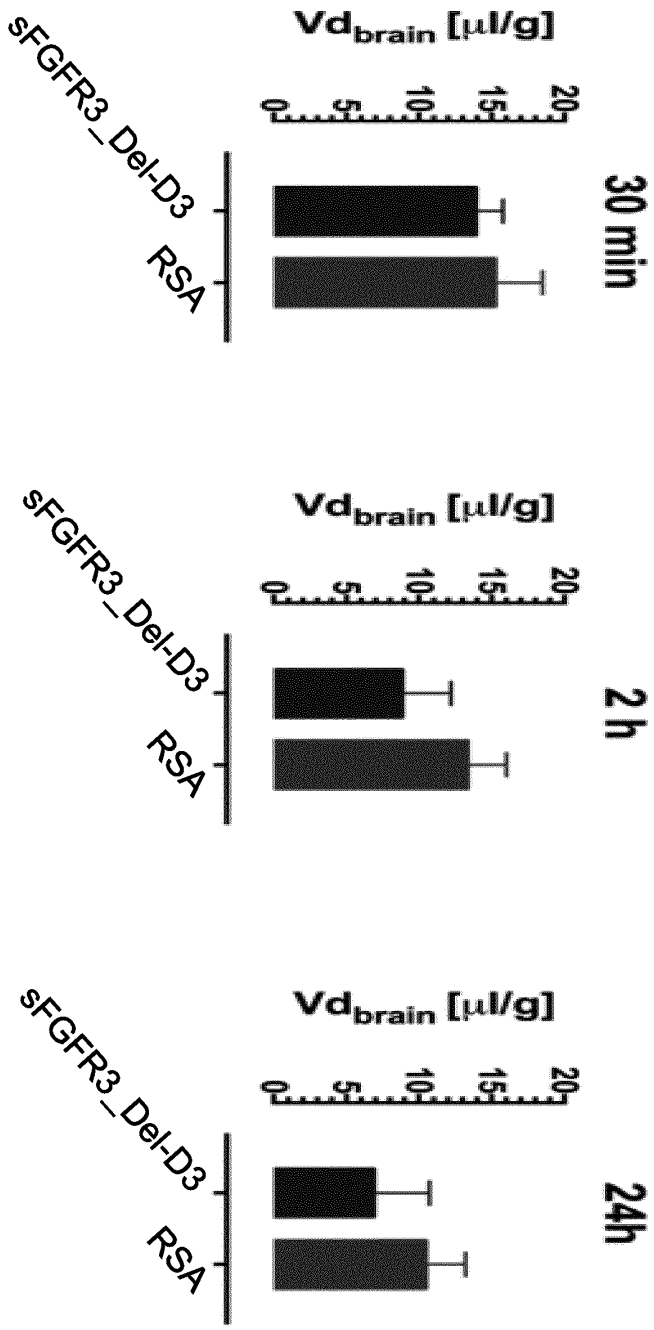

Vd brain [µl/g]
0
5
10
15
20
sFGFR3_Del-D3
RSA
30 min
Vd brain [µl/g]
0
5
10
15
20
sFGFR3_Del-D3
RSA
2 h
Vd brain [µl/g]
0
5
10
15
20
sFGFR3_Del-D3
RSA
24h

FIG. 14B

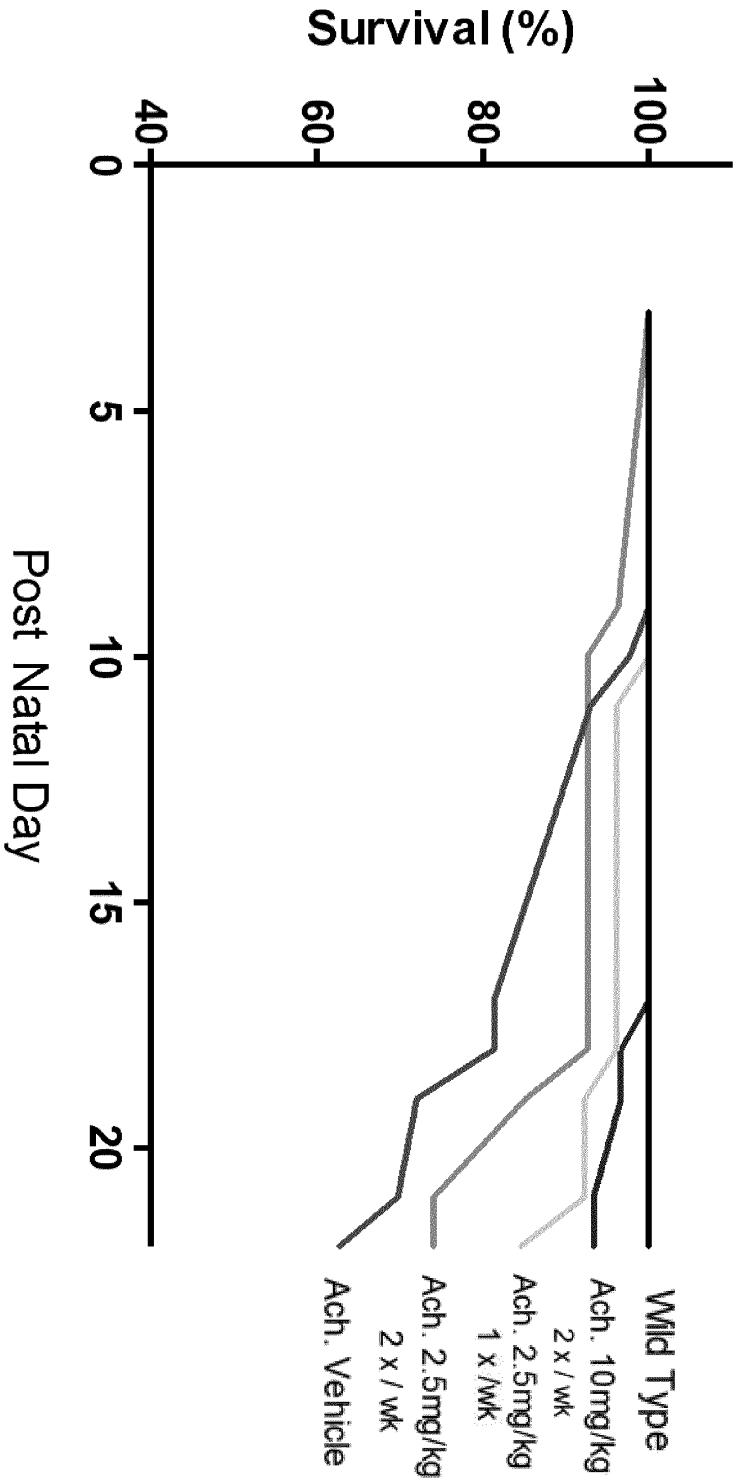
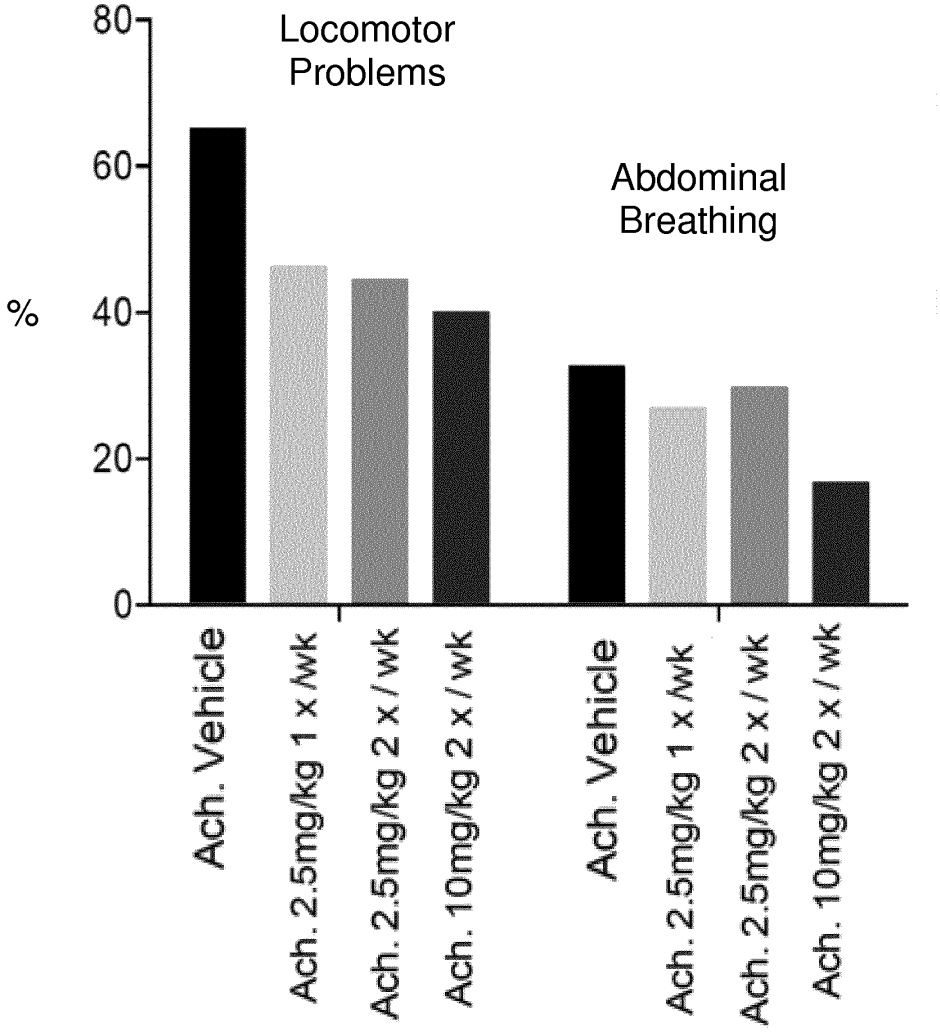

Survival Analysis
Survival (%)
100
80
60
40
0
5
10
15
20
Post Natal Day
Wild Type
Ach. 10mg/kg
2 x / wk
Ach. 2.5mg/kg
1 x /wk
Ach. 2.5mg/kg
2 x / wk
Ach. Vehicle

FIG. 15

FIG. 16


80
60
40
20
0
%
Locomotor Problems
Abdominal Breathing
Ach. Vehicle
Ach. 2.5mg/kg 1 x /wk
Ach. 2.5mg/kg 2 x / wk
Ach. 10mg/kg 2 x / wk
Ach. Vehicle
Ach. 2.5mg/kg 1 x /wk
Ach. 2.5mg/kg 2 x / wk
Ach. 10mg/kg 2 x / wk

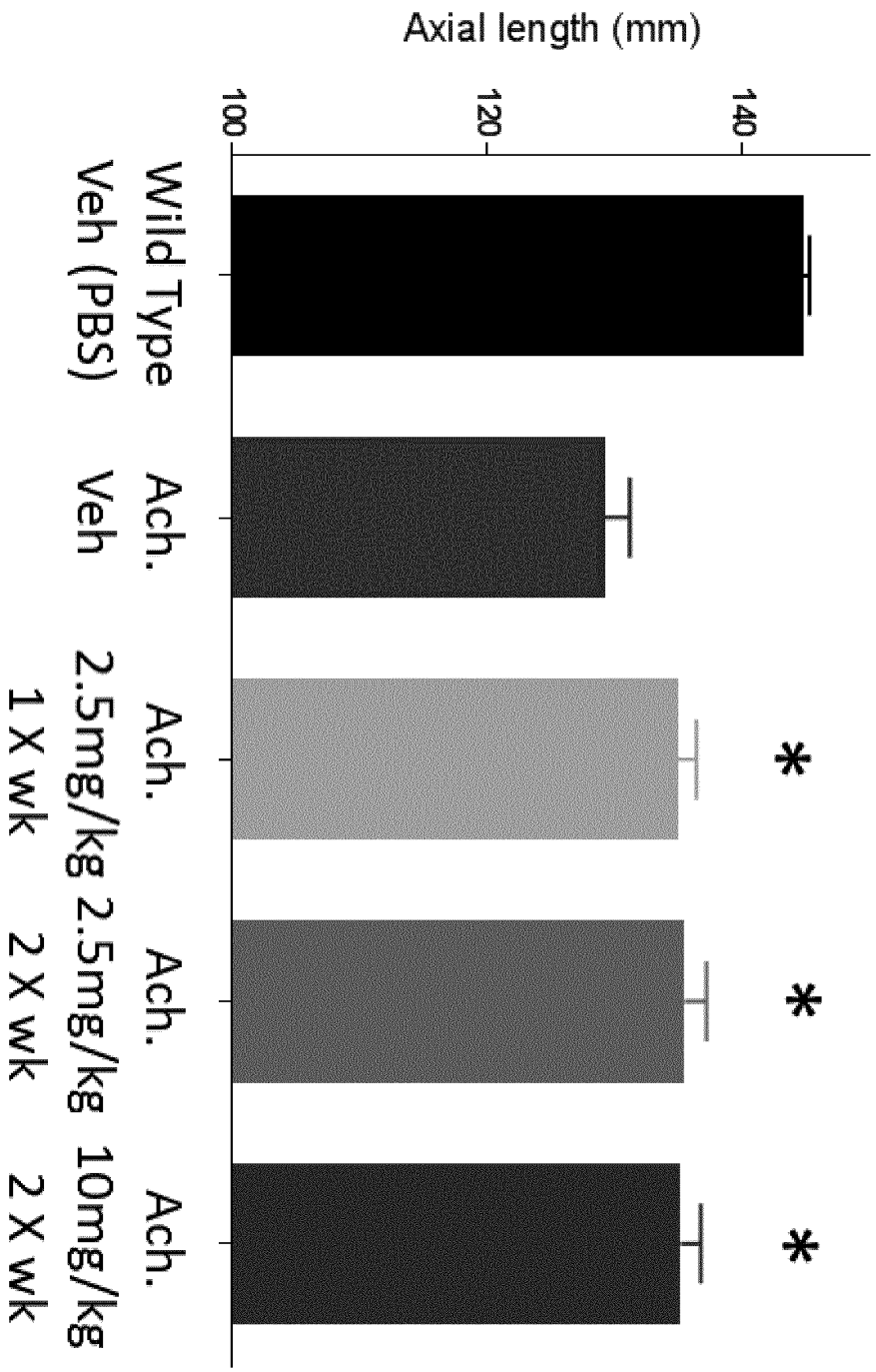

Axial length (mm)
100
120
140
Wild Type
Veh (PBS)
Ach.
Veh
Ach.
2.5mg/kg
1 X wk
Ach.
2.5mg/kg
2 X wk
Ach.
10mg/kg
2 X wk
*
*
*

FIG. 17A

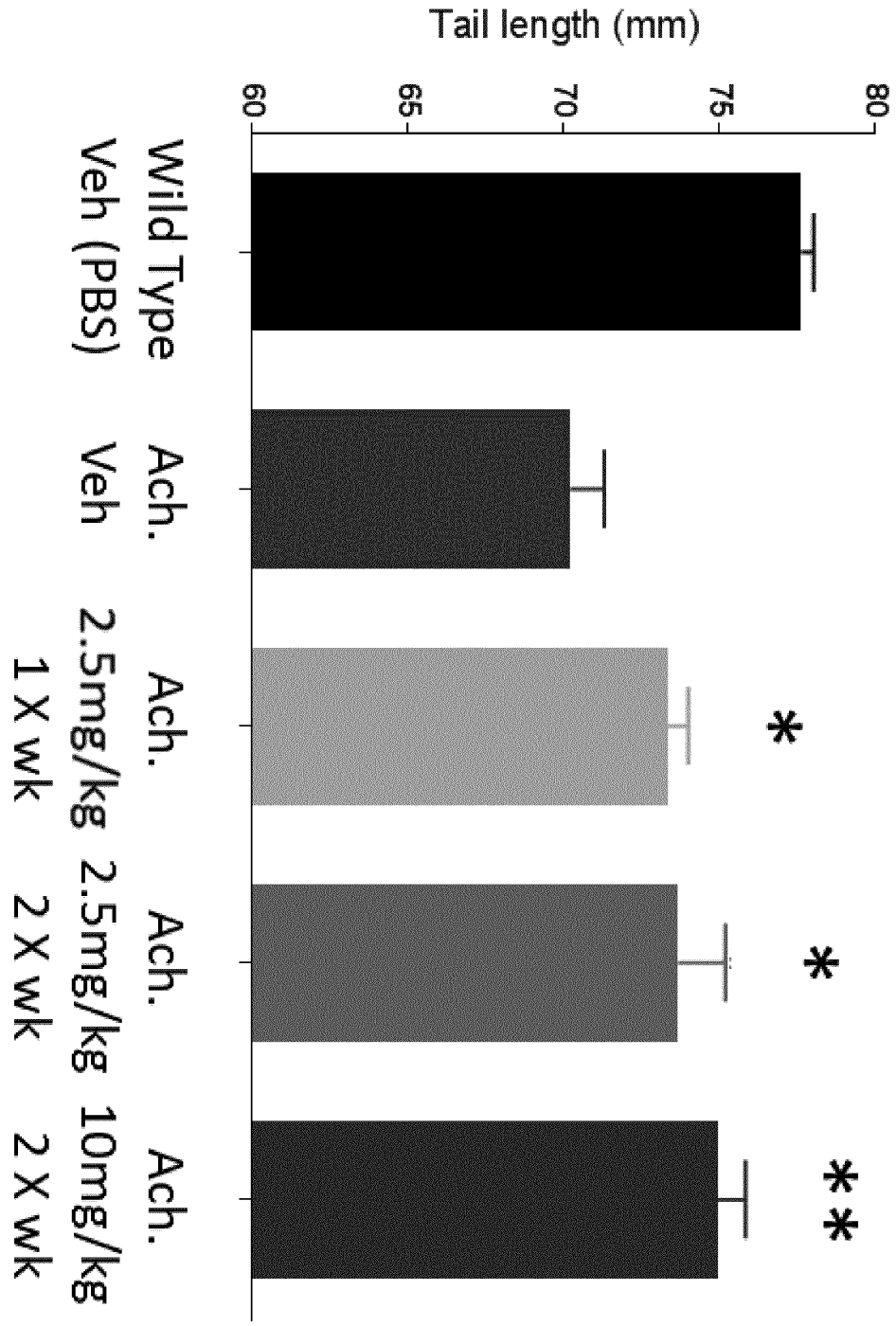

Tail length (mm)
60
65
70
75
80
Wild Type
Veh (PBS)
Ach.
Veh
Ach.
2.5mg/kg
1 X wk
Ach.
2.5mg/kg
2 X wk
Ach.
10mg/kg
2 X wk
*
*
**

FIG. 17B

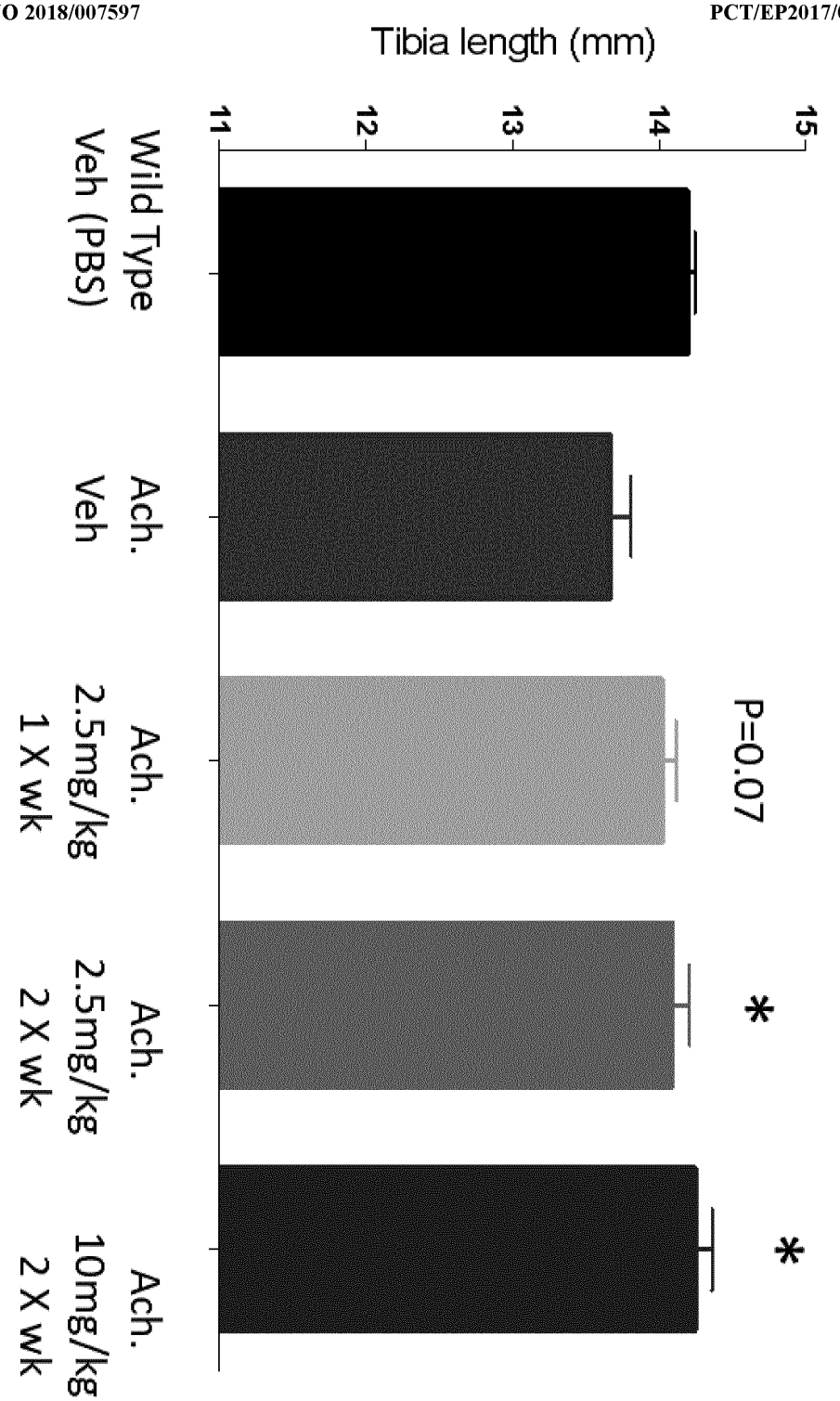
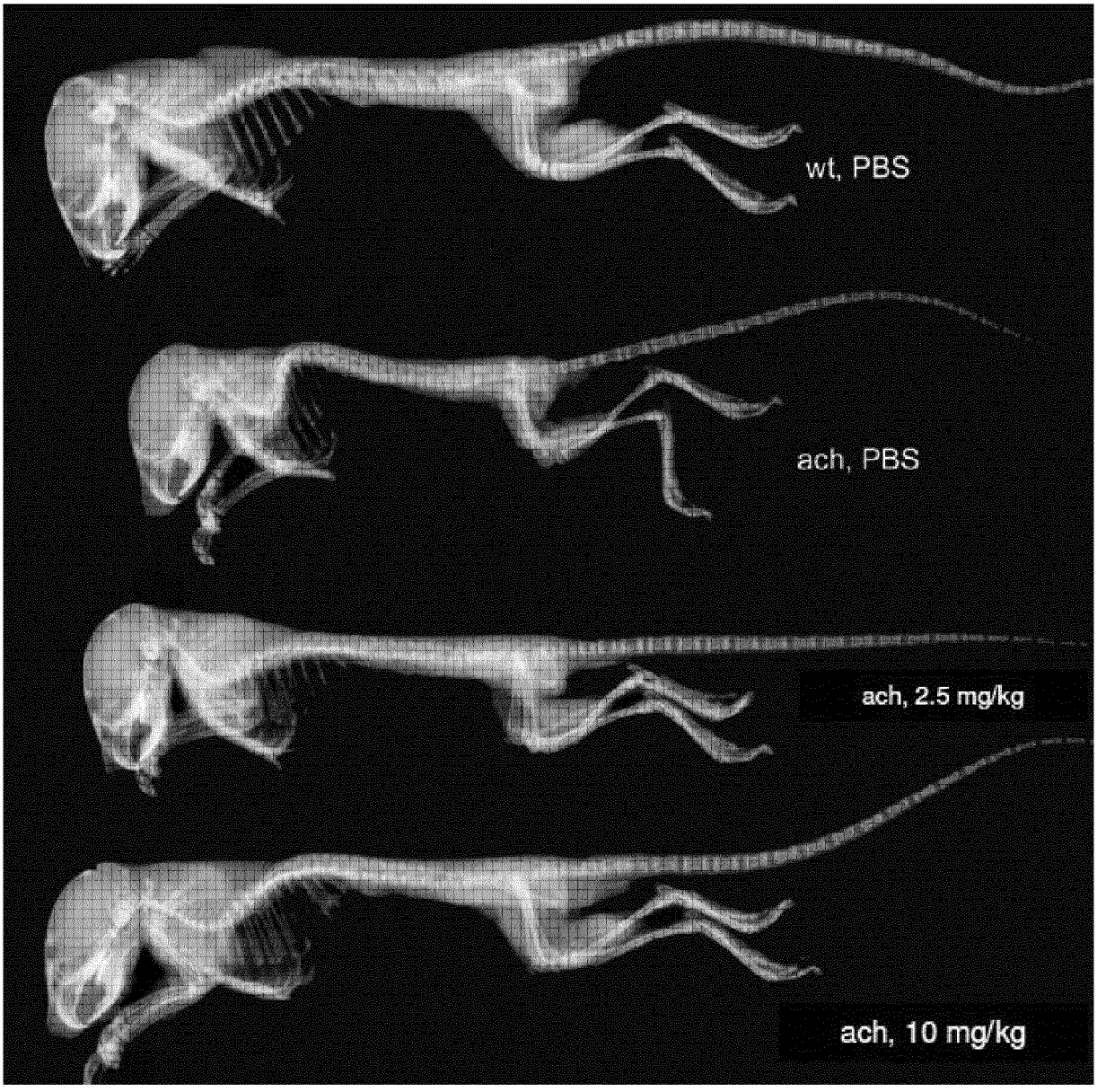

Tibia length (mm)
11
12
13
14
15
Wild Type Veh (PBS)
Ach. Veh
Ach. 2.5mg/kg 1 X wk
Ach. 2.5mg/kg 2 X wk
Ach. 10mg/kg 2 X wk
P=0.07
*
*

FIG. 17C

FIG. 17D



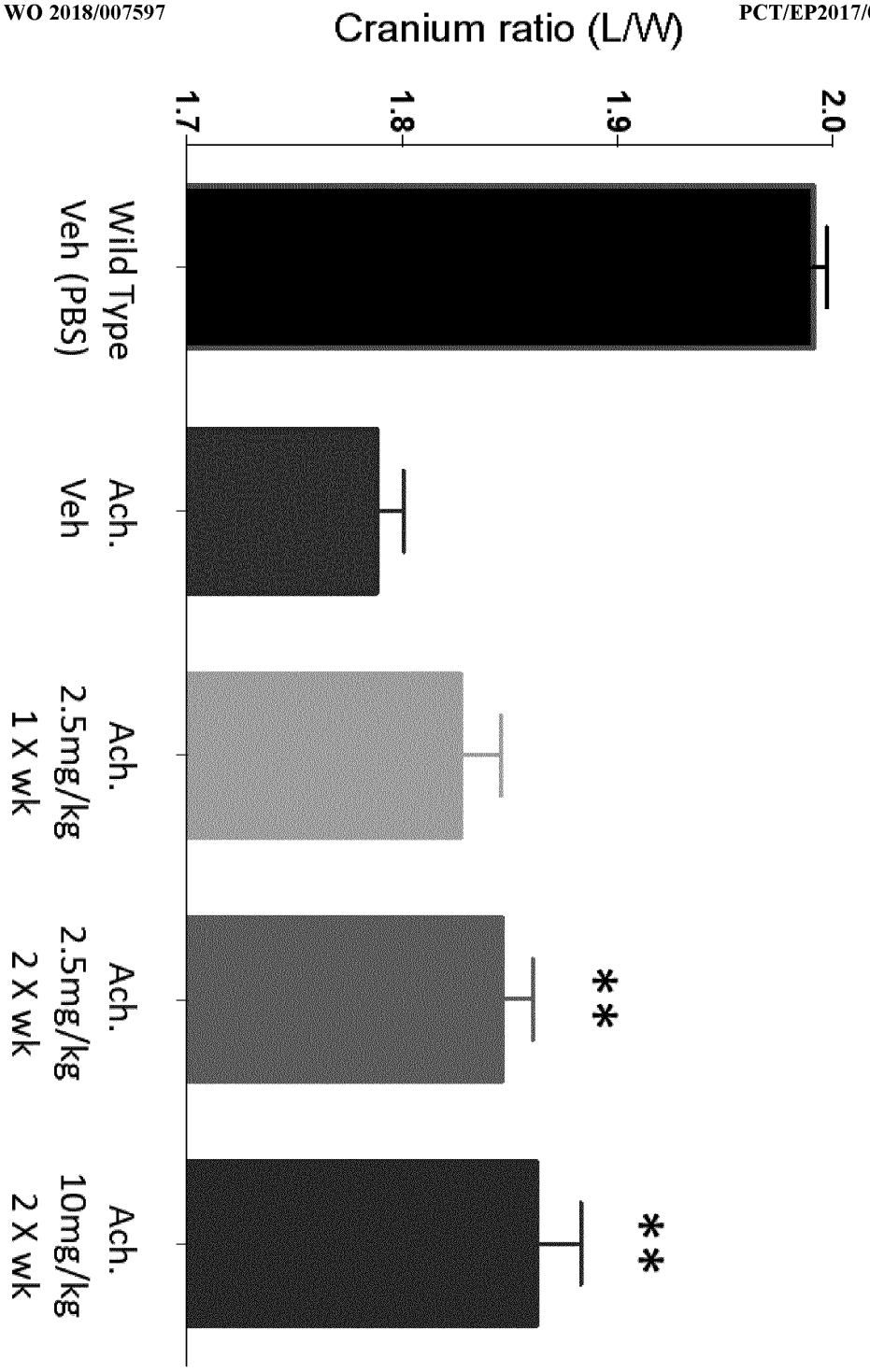
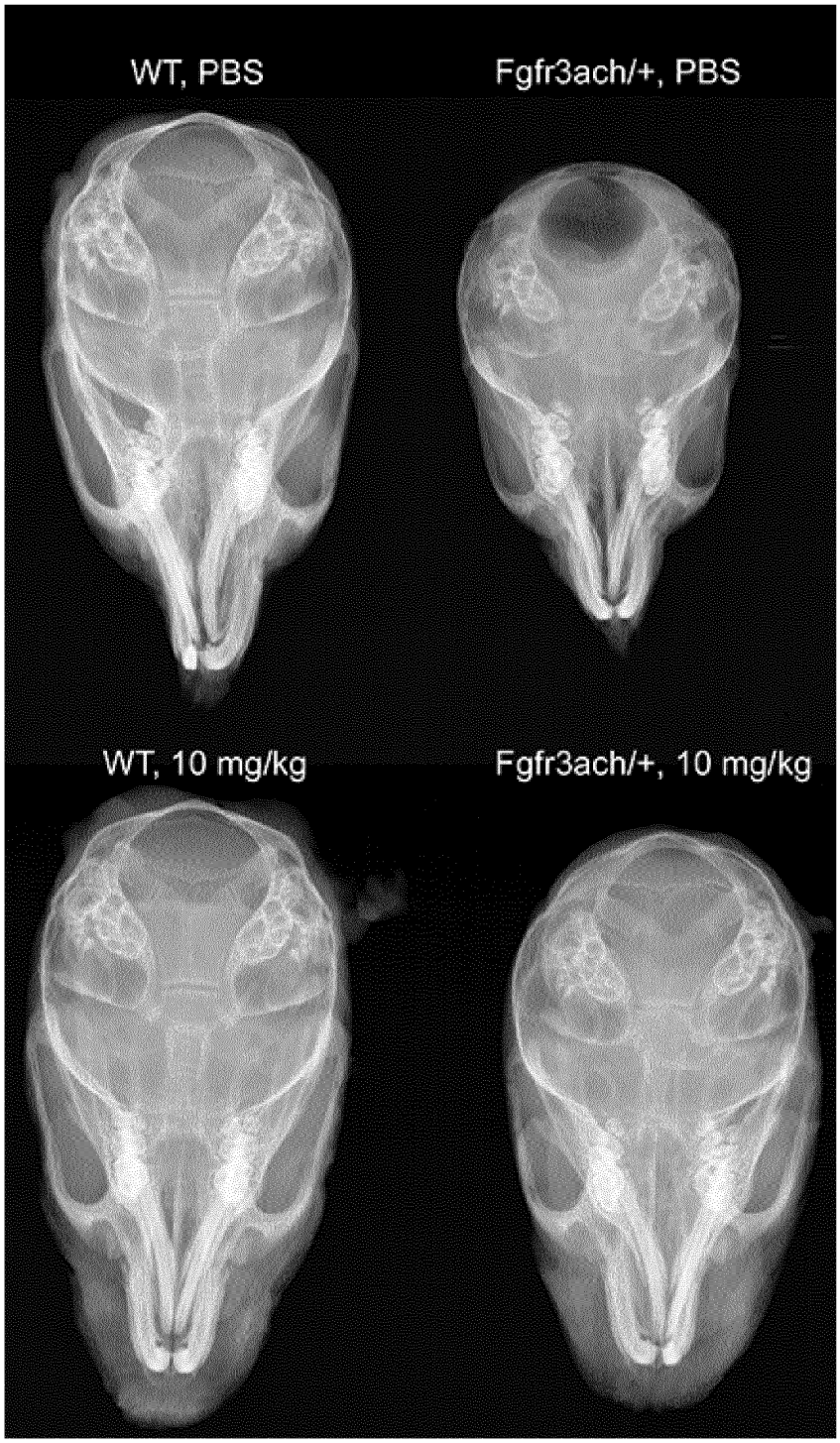

Cranium ratio (L/W)
1.7
1.8
1.9
2.0
Wild Type Veh (PBS)
Ach. Veh
Ach. 2.5mg/kg 1 X wk
Ach. 2.5mg/kg 2 X wk
Ach. 10mg/kg 2 X wk
**
**

FIG. 18A

FIG. 18B



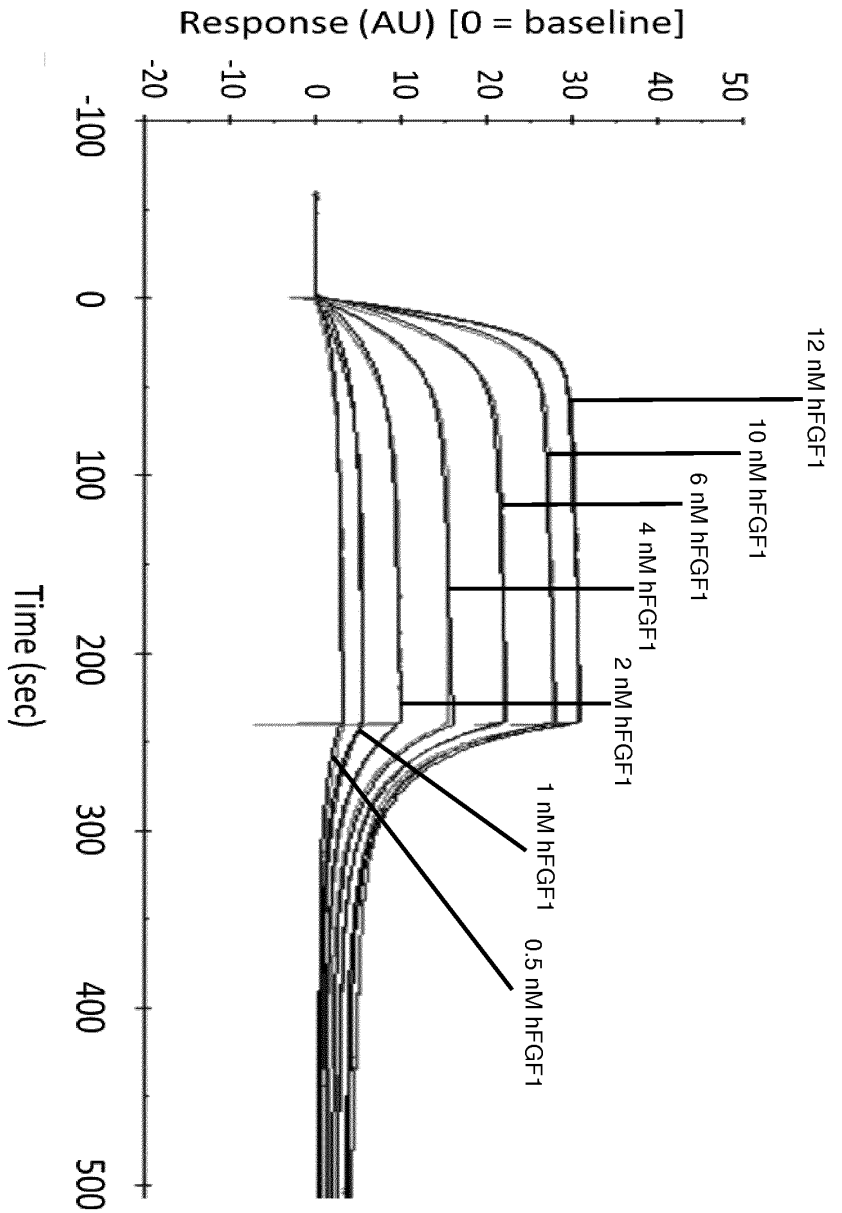

Response (AU) [0 = baseline]
-20
-10
0
10
20
30
40
50
-100
0
100
200
300
400
500
Time (sec)
12 nM hFGF1
10 nM hFGF1
6 nM hFGF1
4 nM hFGF1
2 nM hFGF1
1 nM hFGF1
0.5 nM hFGF1

FIG. 19A

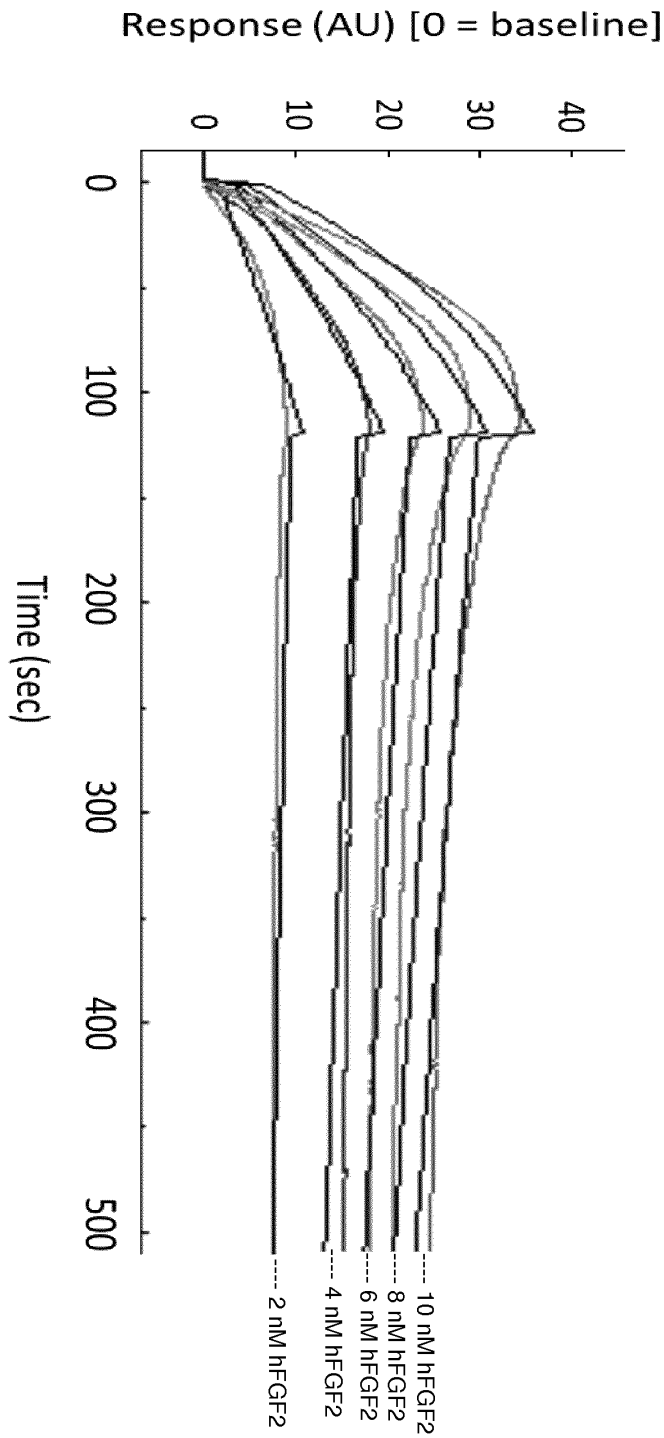

Response (AU) [0 = baseline]
0
10
20
30
40
Time (sec)
0
100
200
300
400
500
10 nM hFGF2
8 nM hFGF2
6 nM hFGF2
4 nM hFGF2
2 nM hFGF2

FIG. 19B

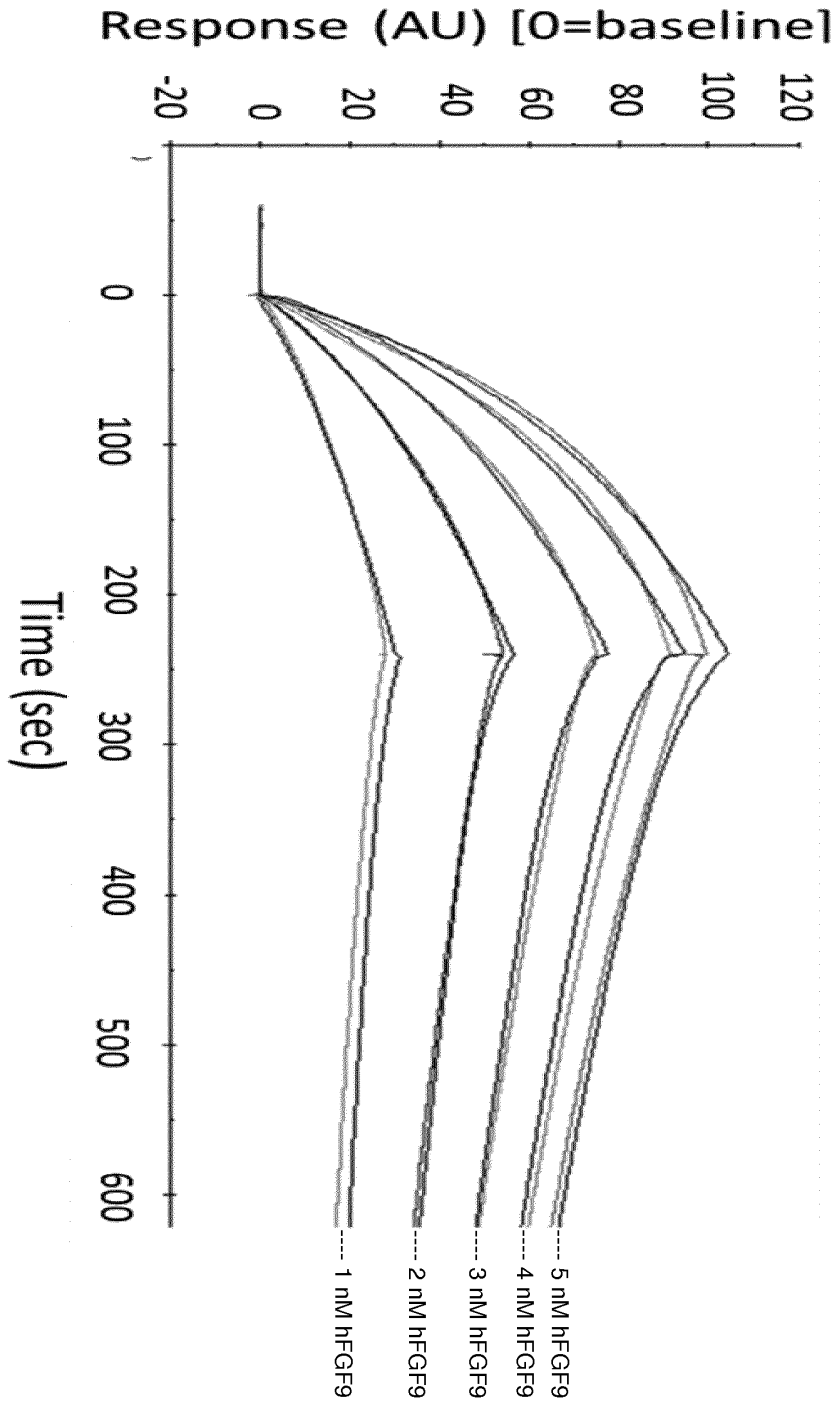

Response (AU) [0=baseline]
-20
0
20
40
60
80
100
120
Time (sec)
0
100
200
300
400
500
600
1 nM hFGF9
2 nM hFGF9
3 nM hFGF9
4 nM hFGF9
5 nM hFGF9

FIG. 19C

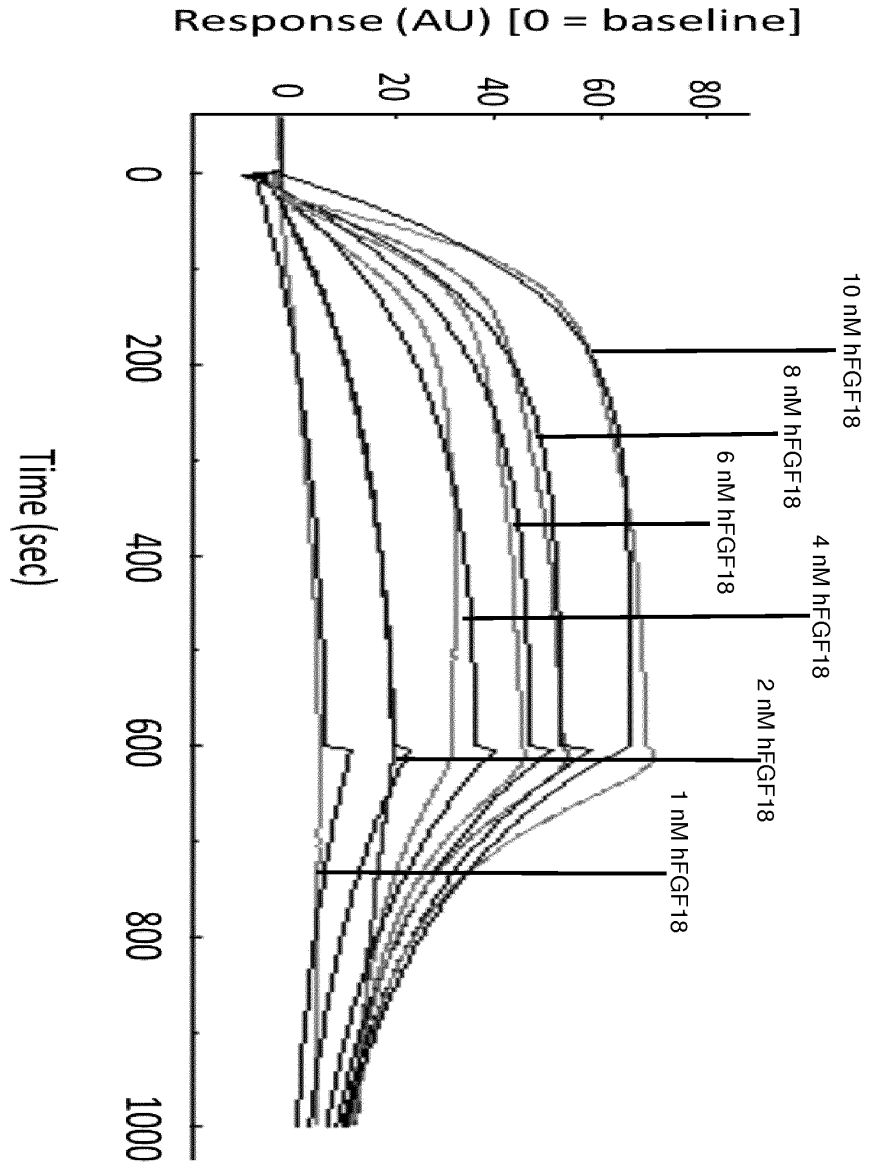

Response (AU) [0 = baseline]
0
20
40
60
80
Time (sec)
0
200
400
600
800
1000
10 nM hFGF18
8 nM hFGF18
6 nM hFGF18
4 nM hFGF18
2 nM hFGF18
1 nM hFGF18

FIG. 19D

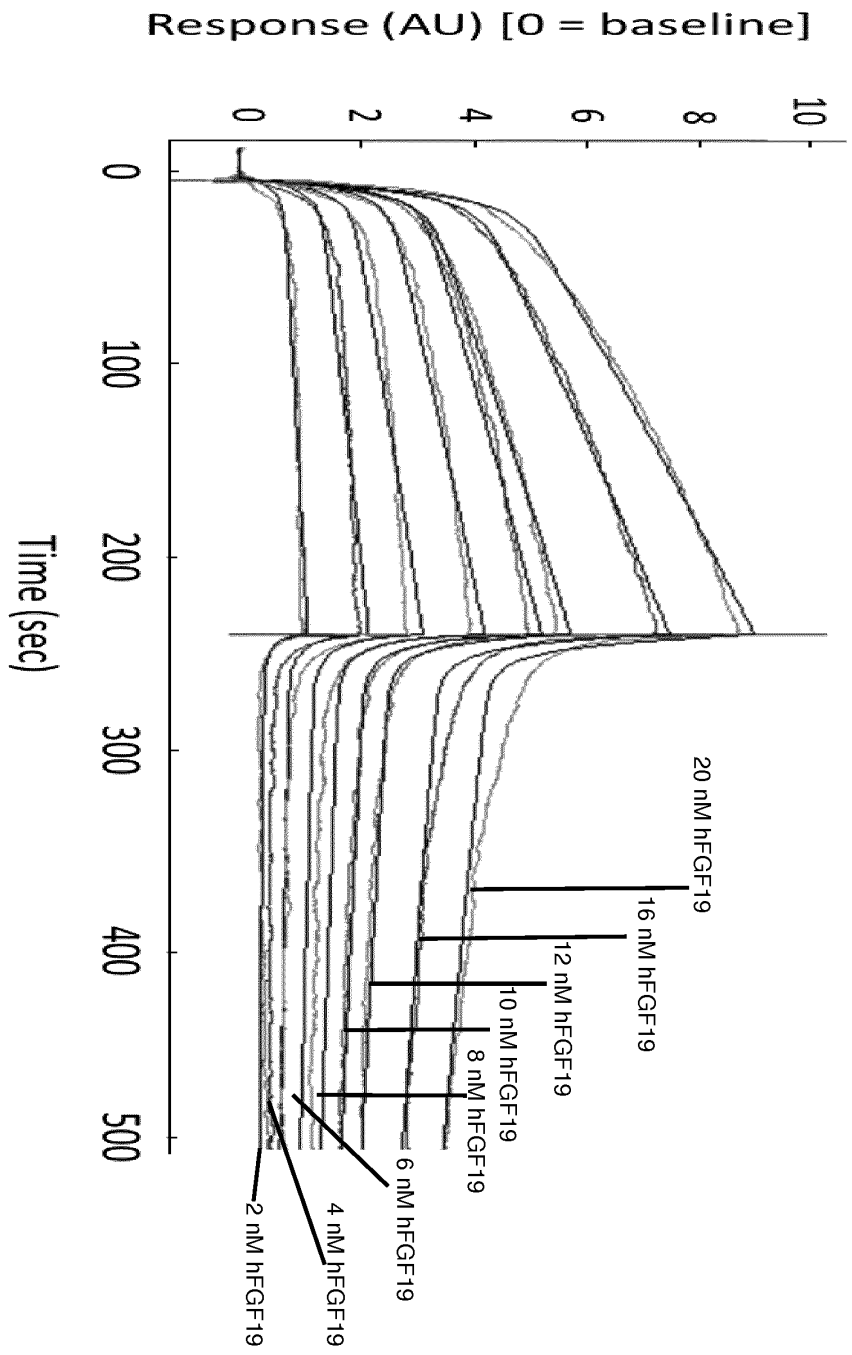

Response (AU) [0 = baseline]
0
2
4
6
8
10
Time (sec)
0
100
200
300
400
500
20 nM hFGF19
16 nM hFGF19
12 nM hFGF19
10 nM hFGF19
8 nM hFGF19
6 nM hFGF19
4 nM hFGF19
2 nM hFGF19

FIG. 19E

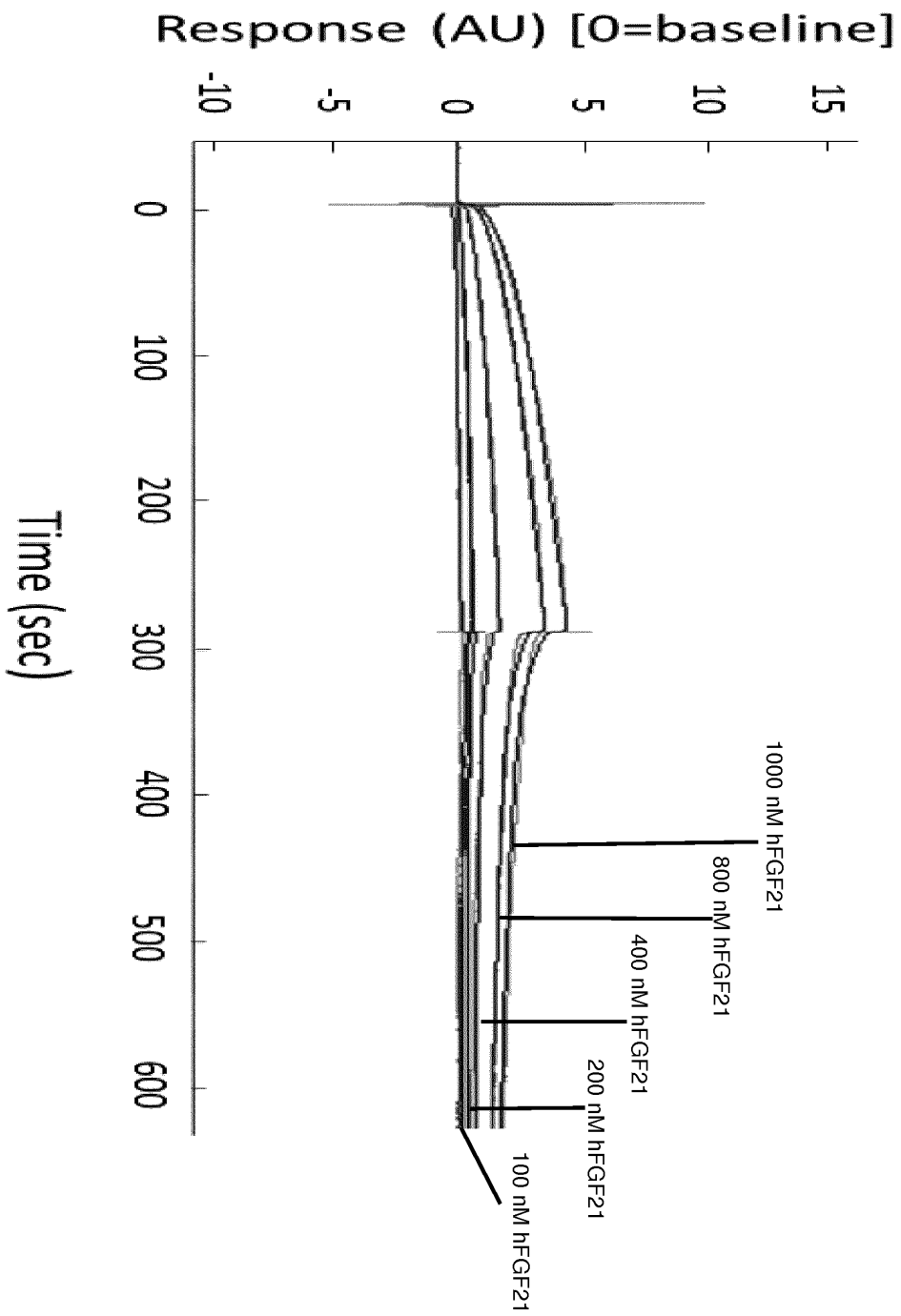

Response (AU) [0=baseline]
-10
-5
0
5
10
15
Time (sec)
0
100
200
300
400
500
600
1000 nM hFGF21
800 nM hFGF21
400 nM hFGF21
200 nM hFGF21
100 nM hFGF21

FIG. 19F

FIG. 20

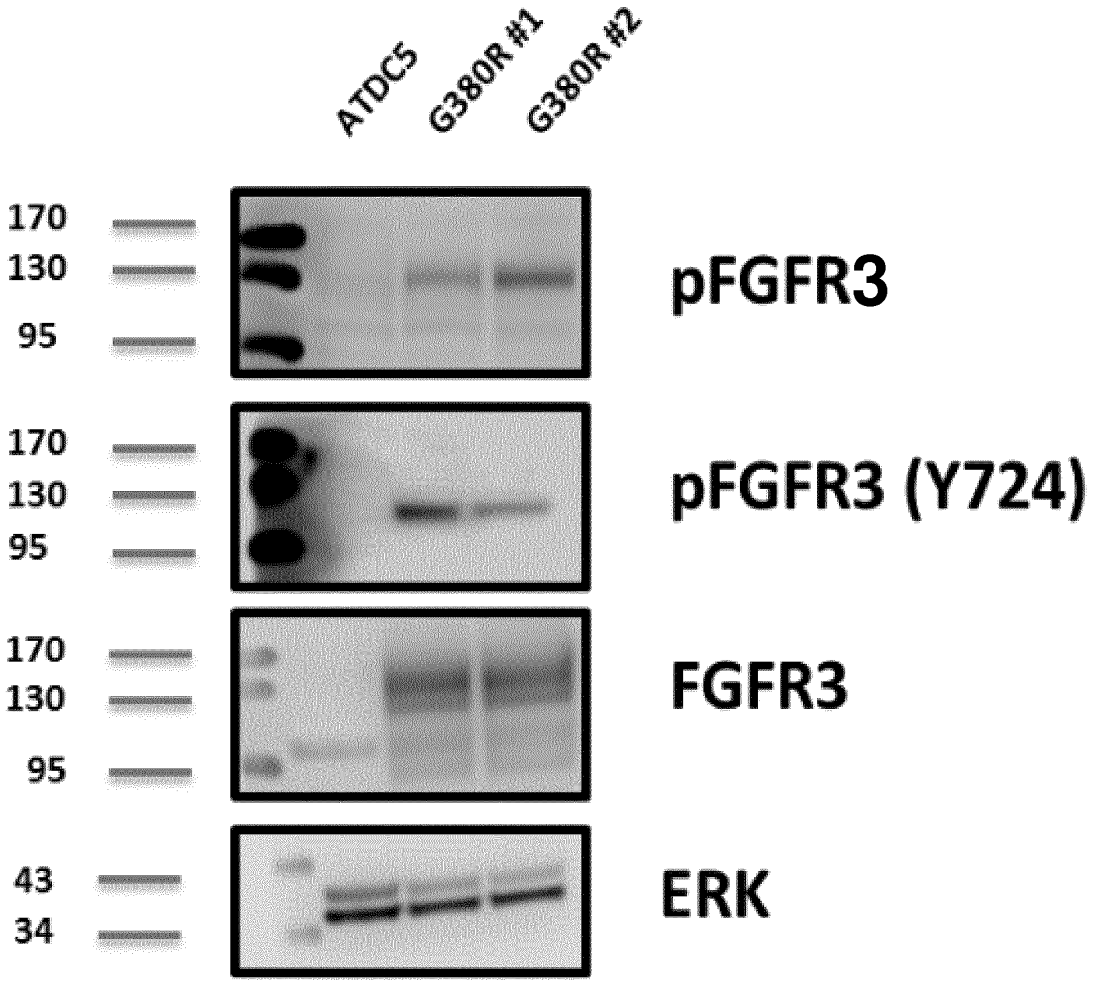
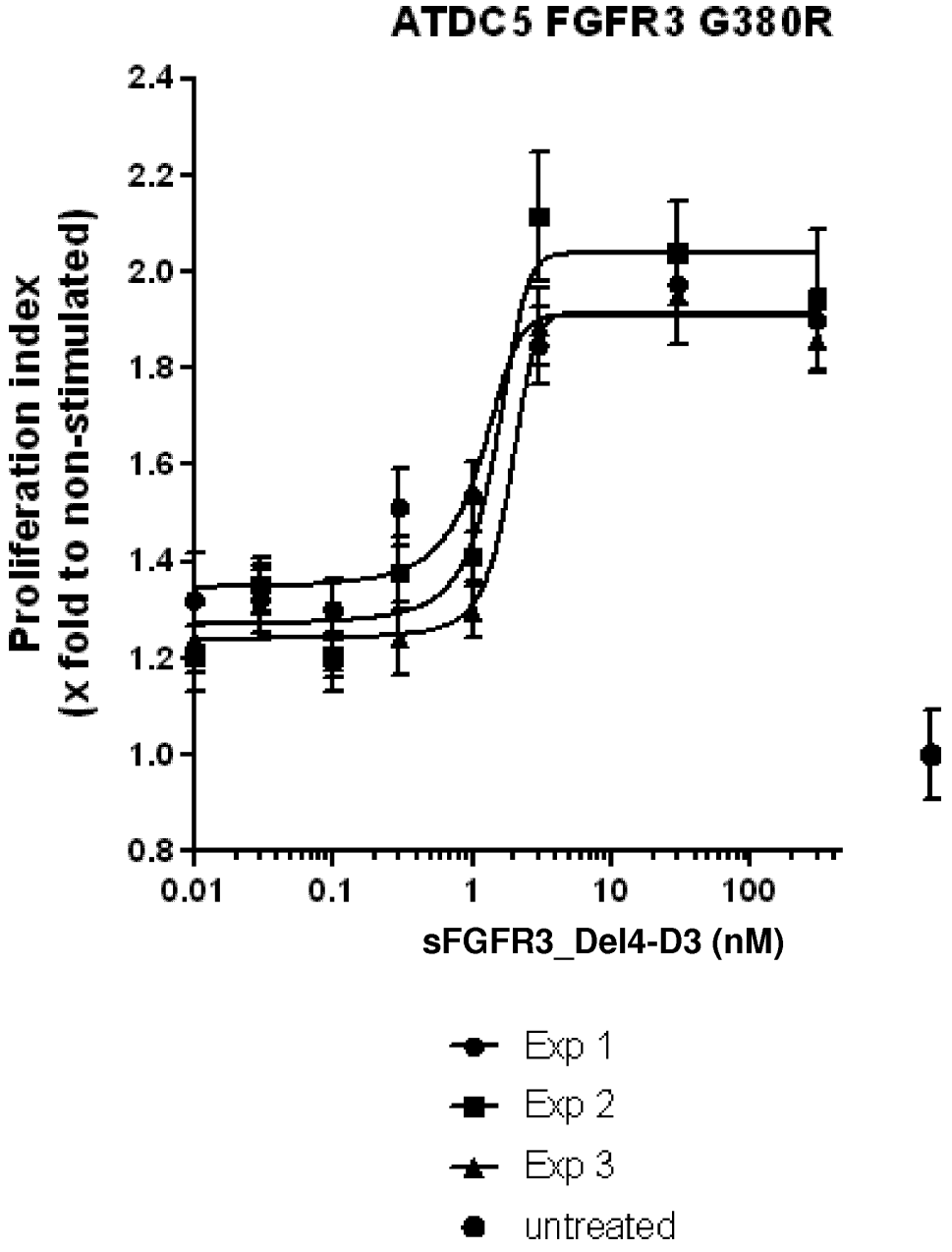

ATDC5
G380R #1
G380R #2
170
130
95
pFGFR3
170
130
95
pFGFR3 (Y724)
170
130
95
FGFR3
43
34
ERK

FIG. 21


ATDC5 FGFR3 G380R
Proliferation index
(x fold to non-stimulated)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.01
0.1
1
10
100
sFGFR3_Del4-D3 (nM)
Exp 1
Exp 2
Exp 3
untreated