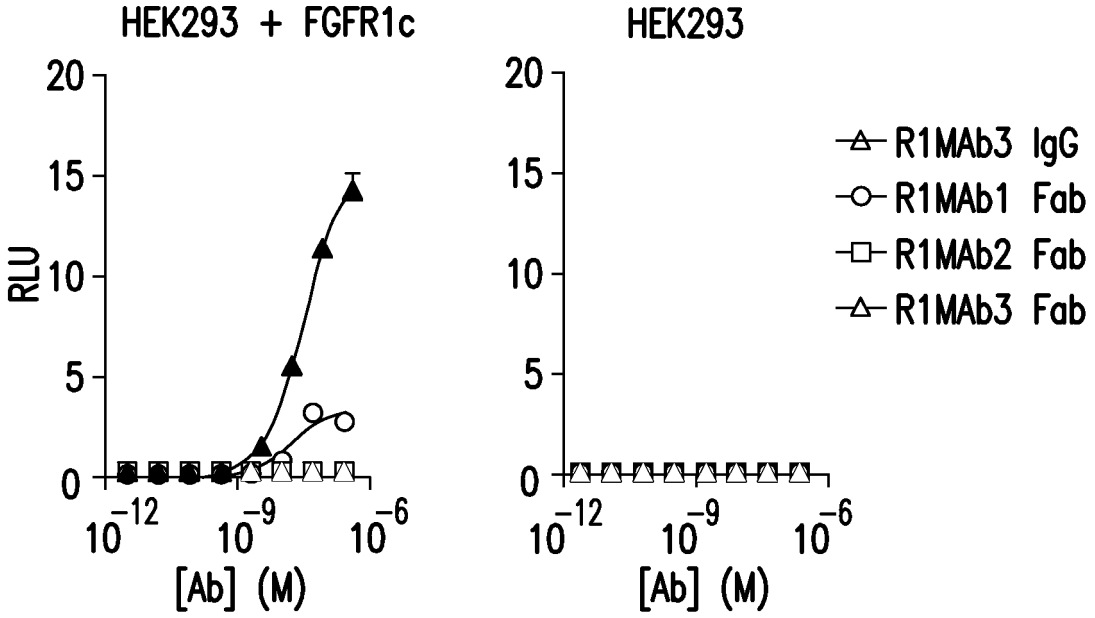


FIG. 1A

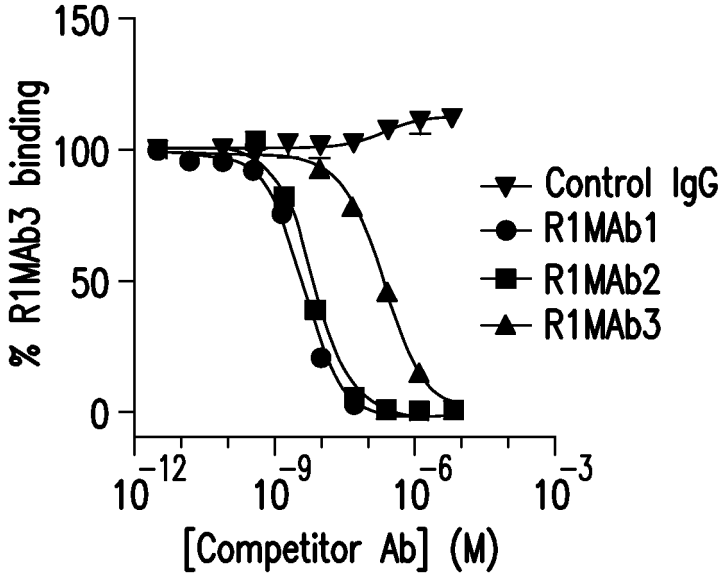


FIG. 1B

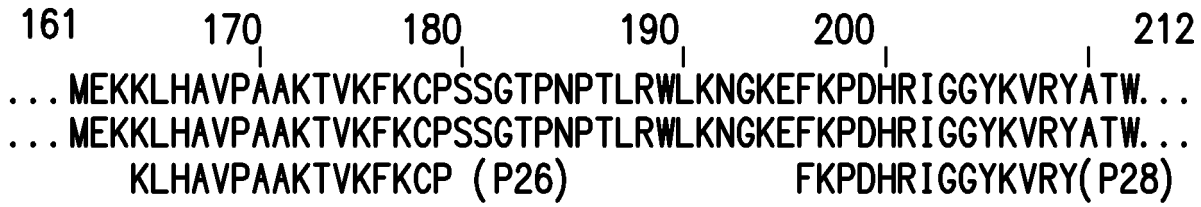


FIG. 1C

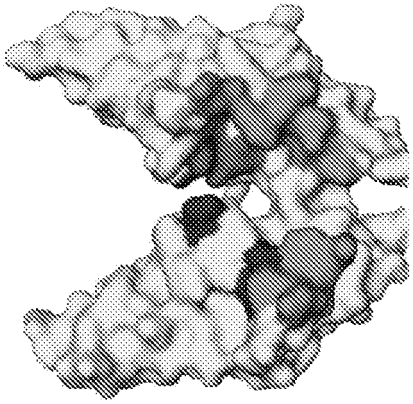


FIG. 1F

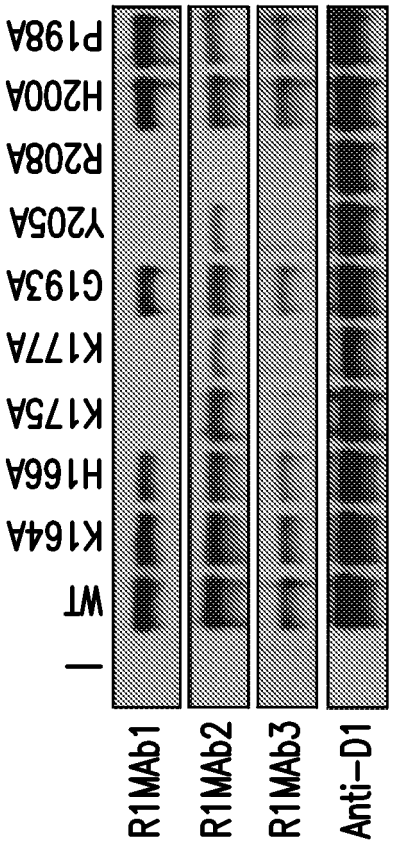


FIG. 1D

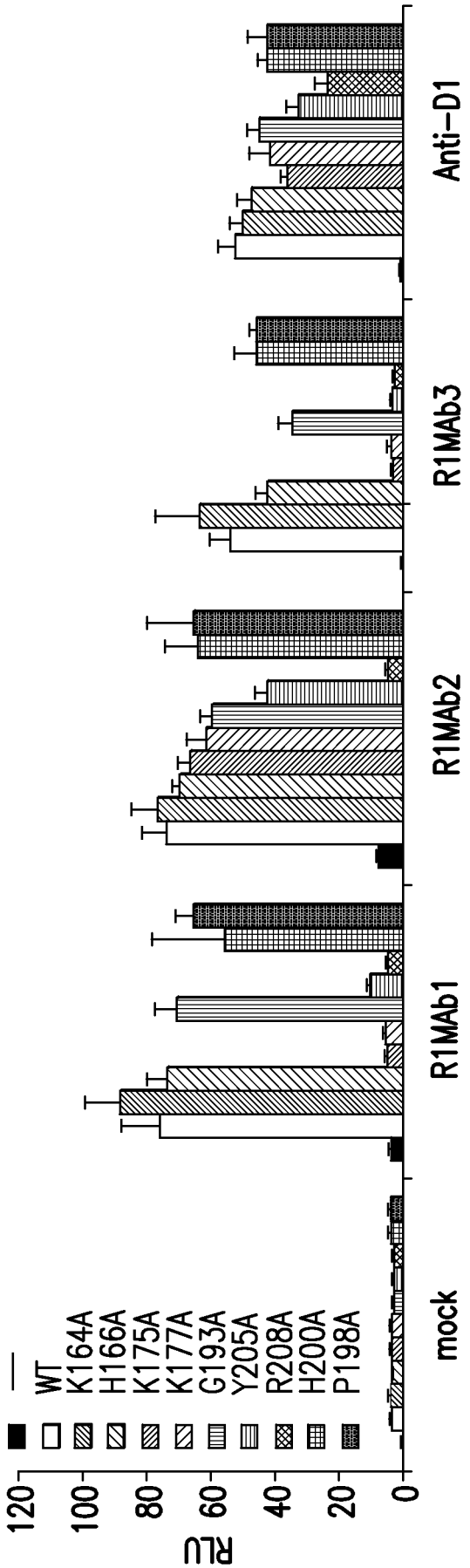


FIG. 1E

		k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)
R1MAb1	FGFR1b	1.9×10^{6}	2.2×10^{-3}	11.3×10^{-10}
	FGFR1c	4.6×10^{6}	3.6×10^{-3}	7.8×10^{-10}
R1MAb2	FGFR1b	4.5×10^{5}	3.7×10^{-4}	8.2×10^{-10}
	FGFR1c	7.3×10^{5}	5.1×10^{-4}	7.1×10^{-10}

FIG. 2A

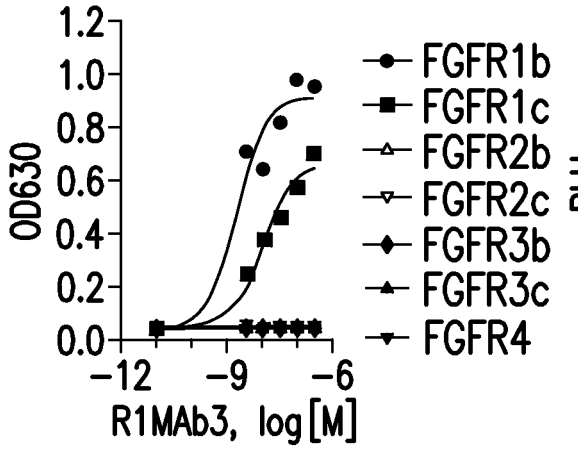


FIG. 2B

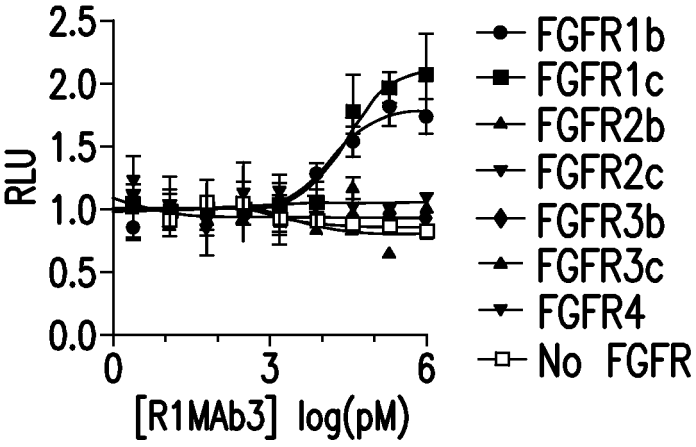


FIG. 2C

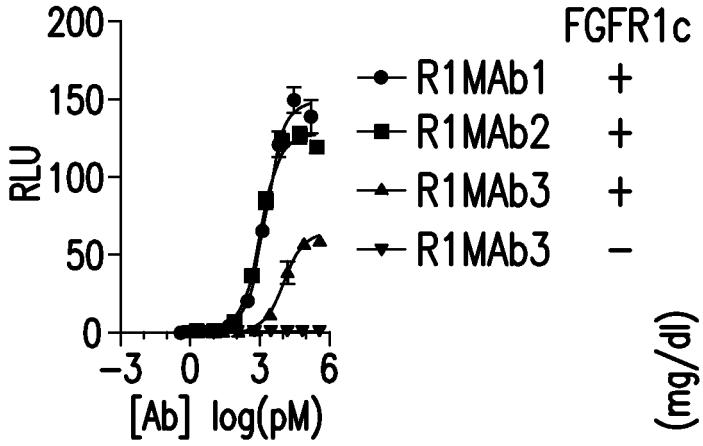


FIG. 2D

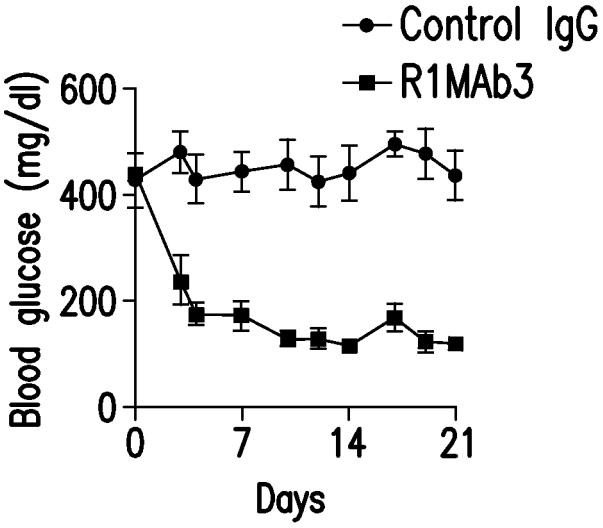


FIG. 2E

CDR sequences according to Kabat definition are underlined

Light chain variable region

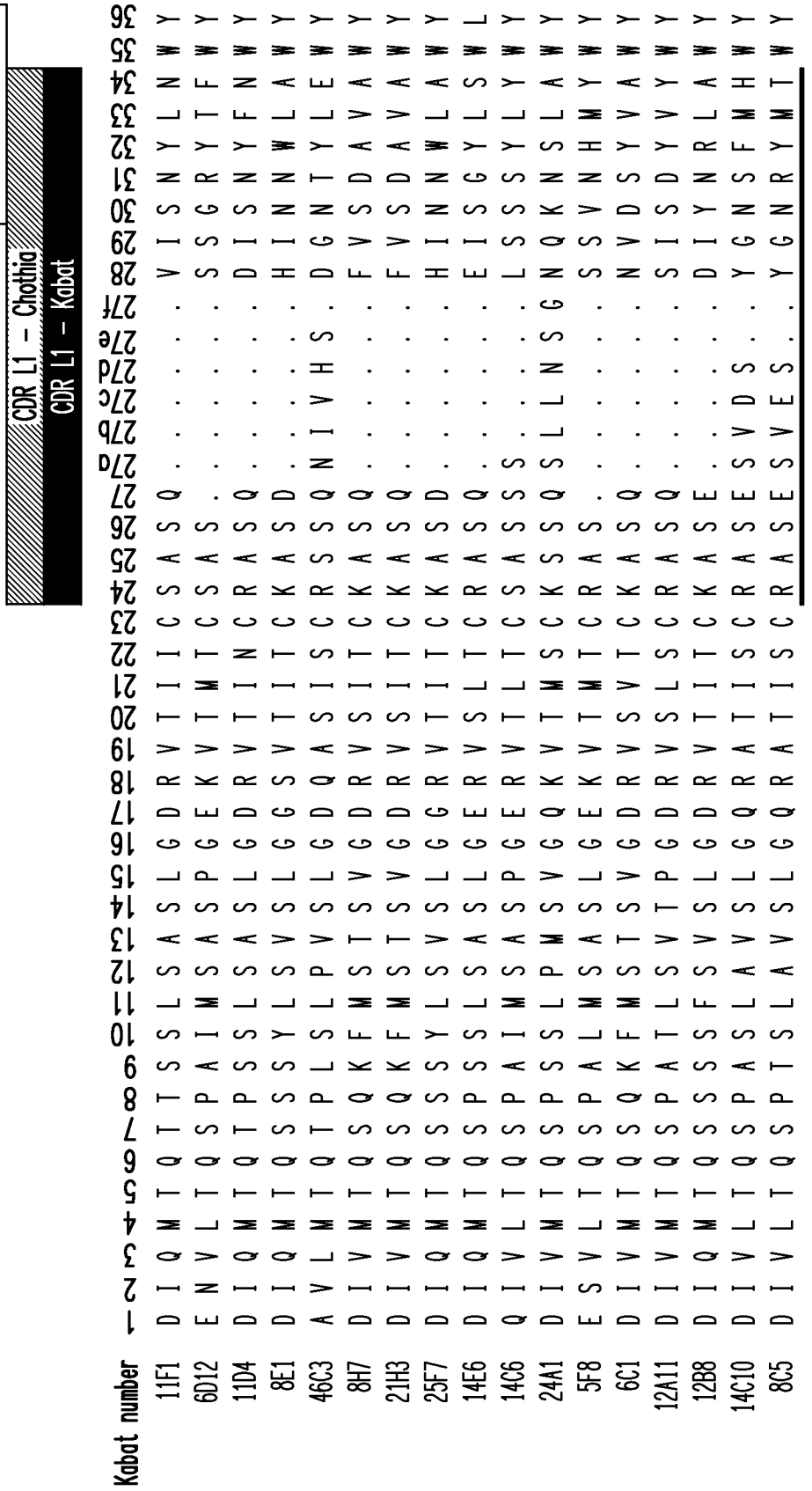


FIG. 3A

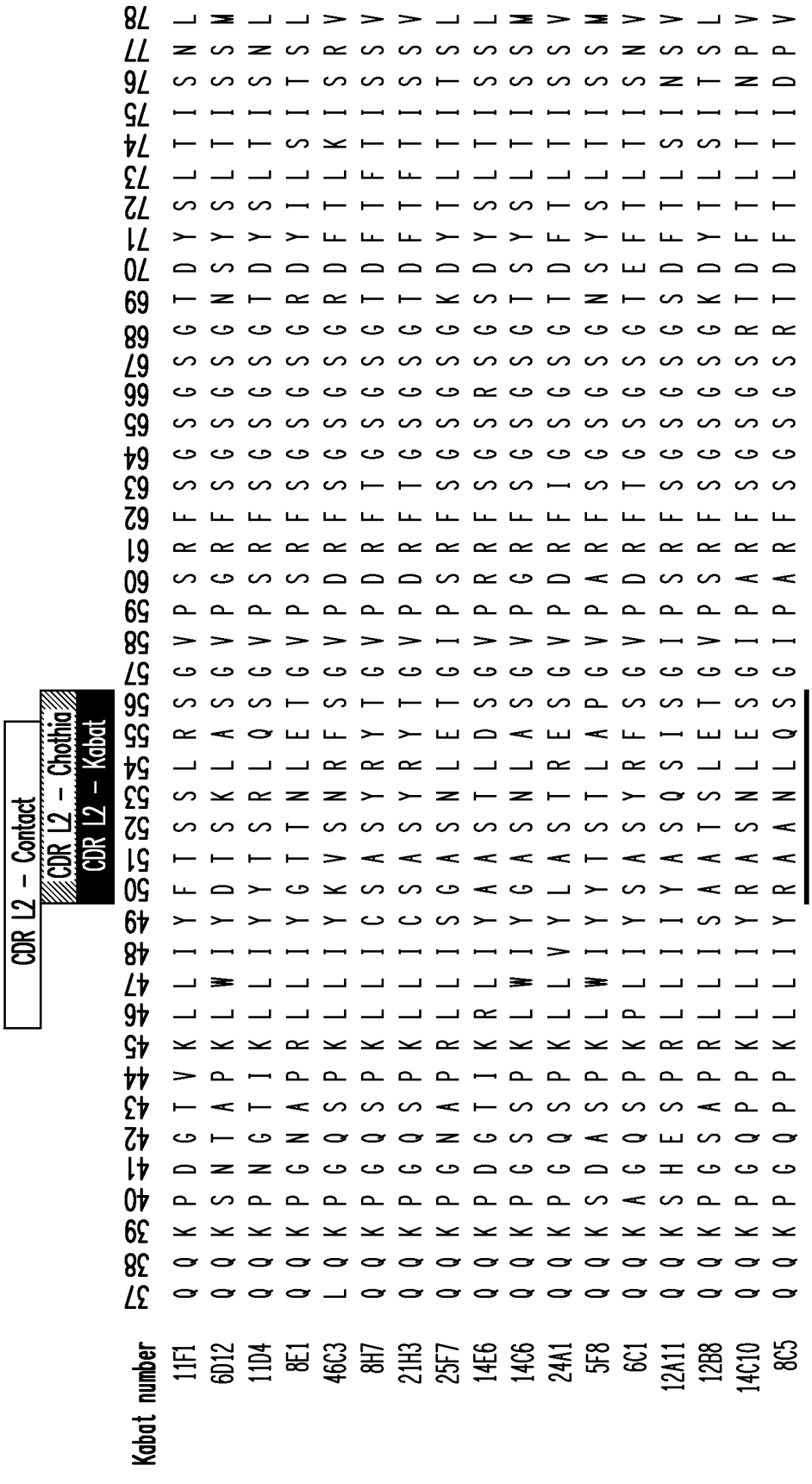


FIG. 3A continued

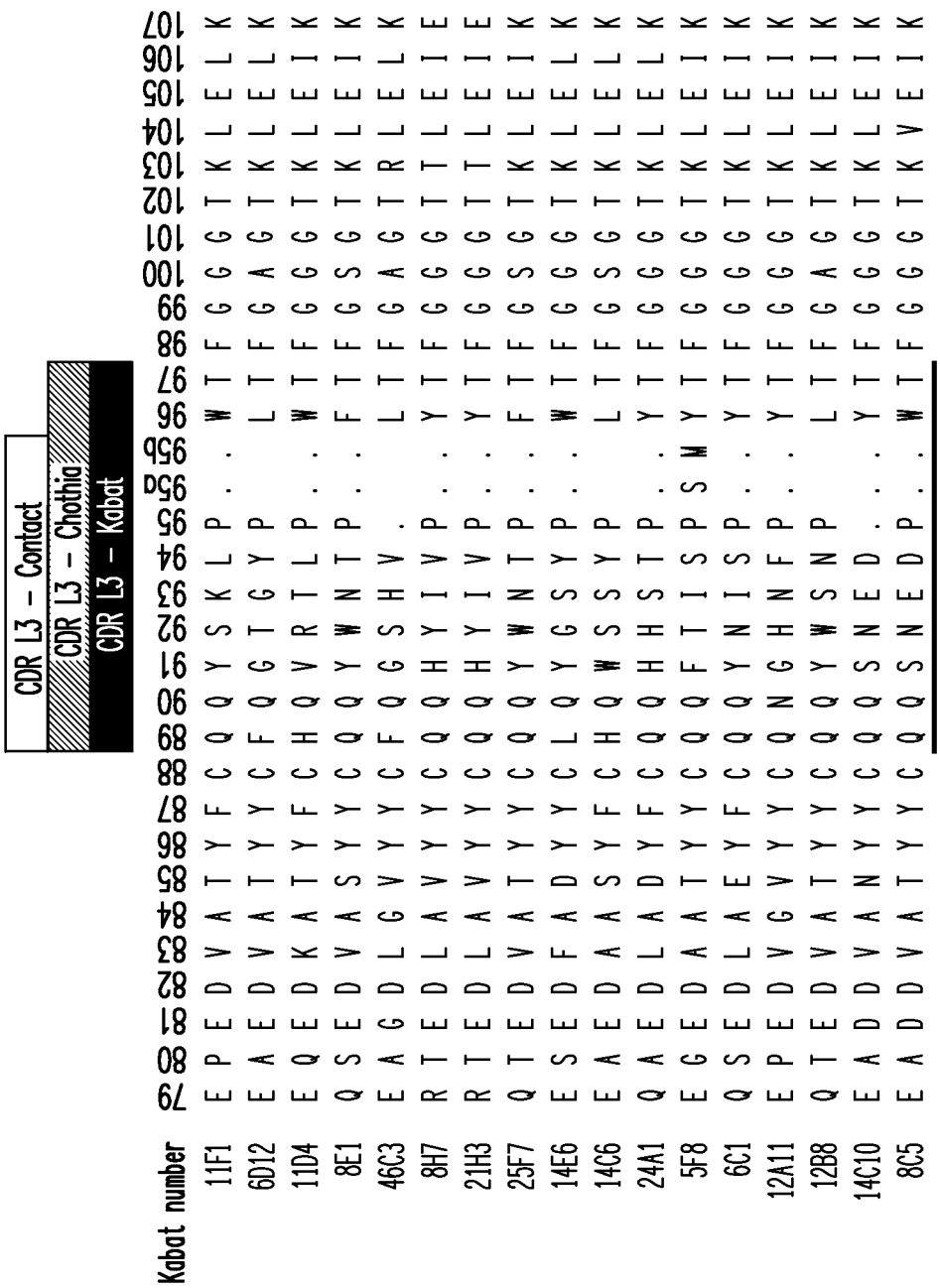


FIG. 3A continued

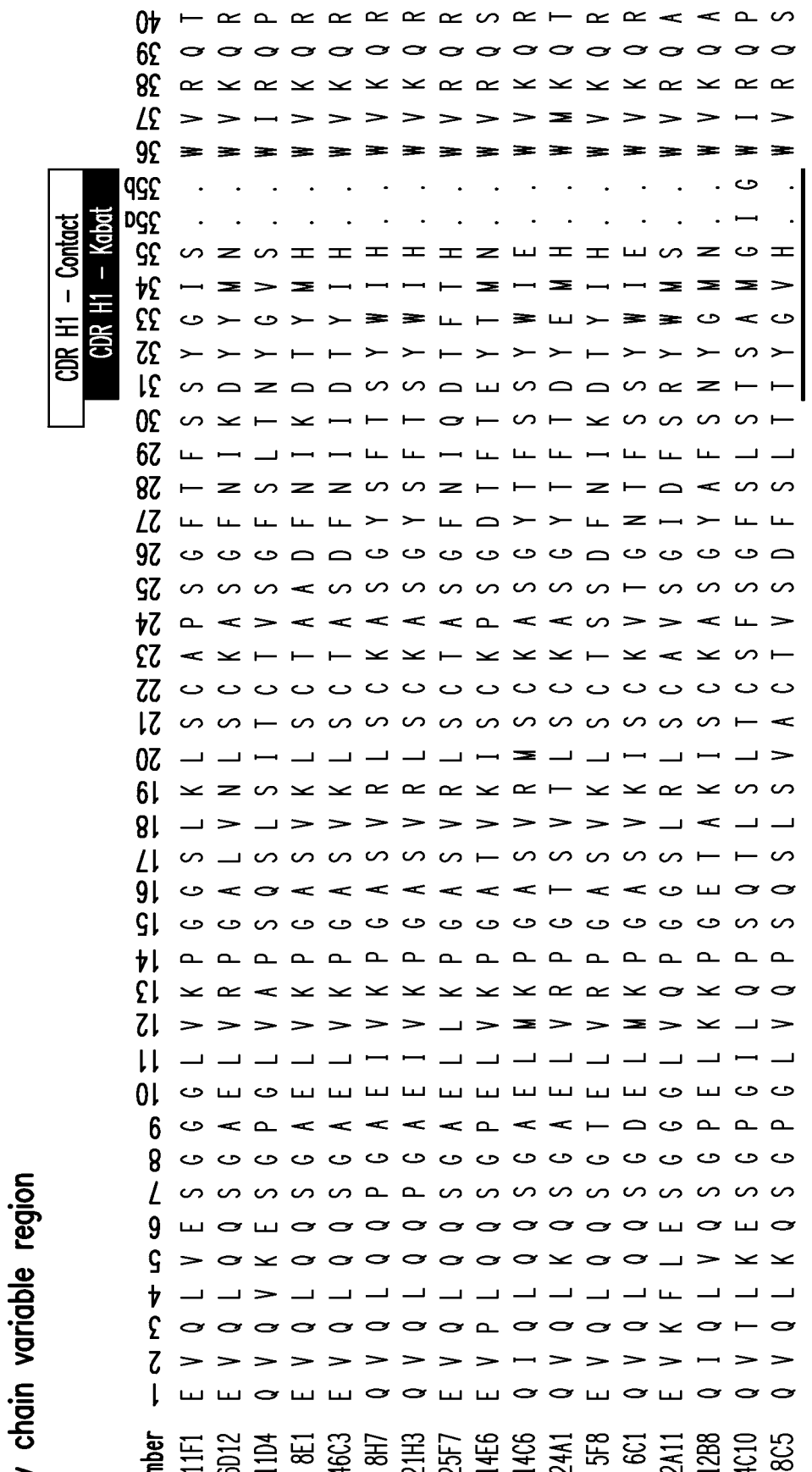

Heavy chain variable region
CDR H1 – Contact
CDR H1 – Kabat
Kabat number
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 35a 35b 36 37 38 39 40
11F1 E V Q L V E S G G G L V K P G G S L K L S C A P S G F T F S S Y G I S . . W V R Q T
6D12 E V Q L Q Q S G A E L V R P G A L V N L S C K A S G F N I K D Y Y M N . . W V K Q R
11D4 Q V Q V K E S G P G L V A P S Q S L S I T C T V S G F S L T N Y G V S . . W I R Q P
8E1 E V Q L Q Q S G A E L V K P G A S V K L S C T A A D F N I K D T Y M H . . W V K Q R
46C3 E V Q L Q Q S G A E L V K P G A S V K L S C T A S D F N I I D T Y I H . . W V K Q R
8H7 Q V Q L Q Q P G A E I V K P G A S V R L S C K A S G Y S F T S Y W I H . . W V K Q R
21H3 Q V Q L Q Q P G A E I V K P G A S V R L S C K A S G Y S F T S Y W I H . . W V K Q R
25F7 E V Q L Q Q S G A E L L K P G A S V R L S C T A S G F N I Q D T F I H . . W V R Q R
14E6 E V P L Q Q S G P E L V K P G A T V K I S C K P S G D T F T E Y T M N . . W V R Q S
14C6 Q I Q L Q Q S G A E L M K P G A S V R M S C K A S G Y T F S S Y W I E . . W V K Q R
24A1 Q V Q L K Q S G A E L V R P G T S V T L S C K A S G Y T F T D Y E M H . . W M K Q T
5F8 E V Q L Q Q S G T E L V R P G A S V K L S C T S S D F N I K D T Y I H . . W V K Q R
6C1 Q V Q L Q Q S G D E L M K P G A S V K I S C K V T G N T F S S Y W I E . . W V K Q R
12A11 E V K F L E S G G G L V Q P G G S L R L S C A V S G I D F S R Y W M S . . W V R Q A
12B8 Q I Q L V Q S G P E L K K P G E T A K I S C K A S G Y A F S N Y G M N . . W V K Q A
14C10 Q V T L K E S G P G I L Q P S Q T L S L T C S F S G F S L S T S A M G I G W I R Q P
8C5 Q V Q L K Q S G P G L V Q P S Q S L S V A C T V S D F S L T T Y G V H . . W V R Q S

FIG. 3B

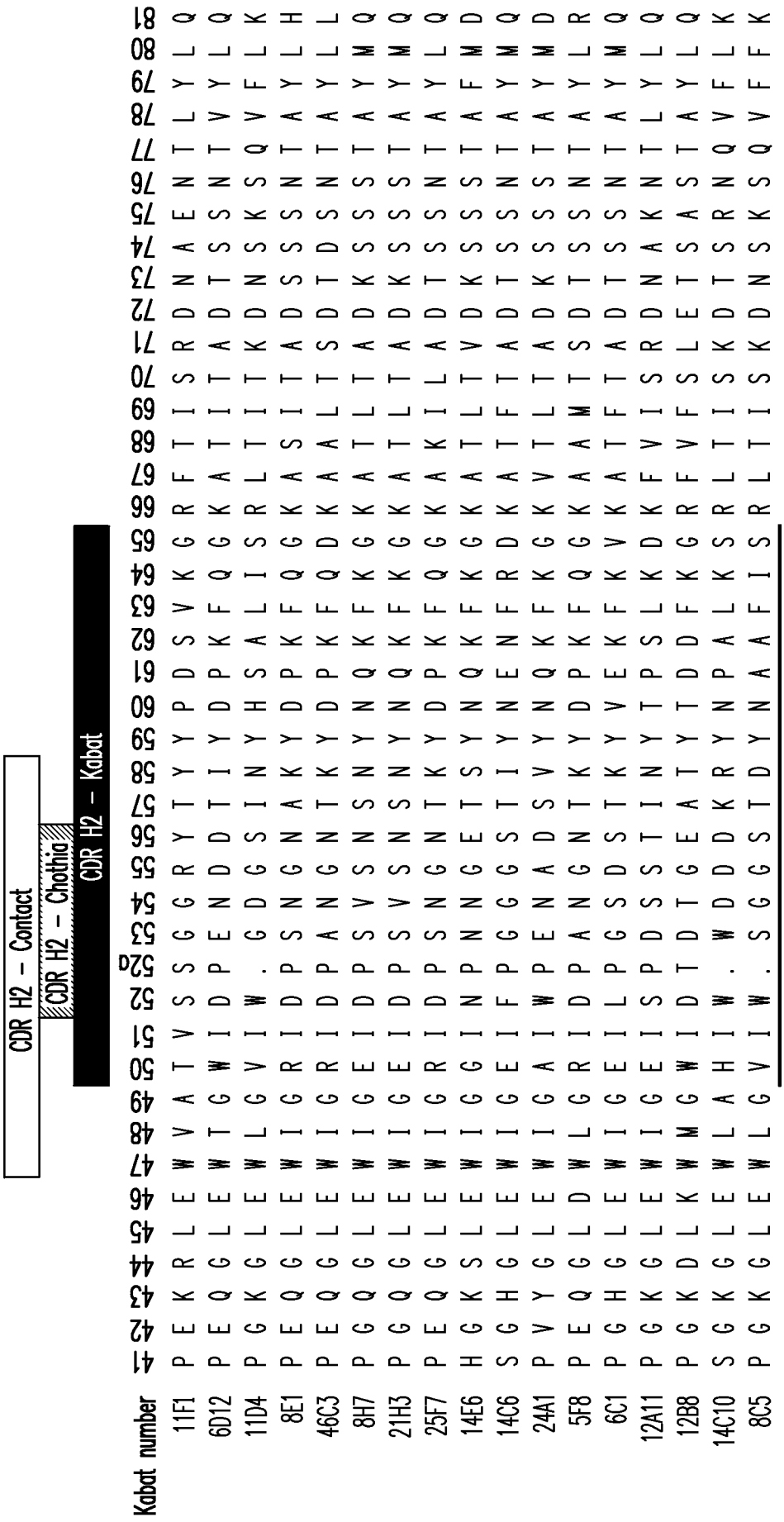


FIG. 3B continued

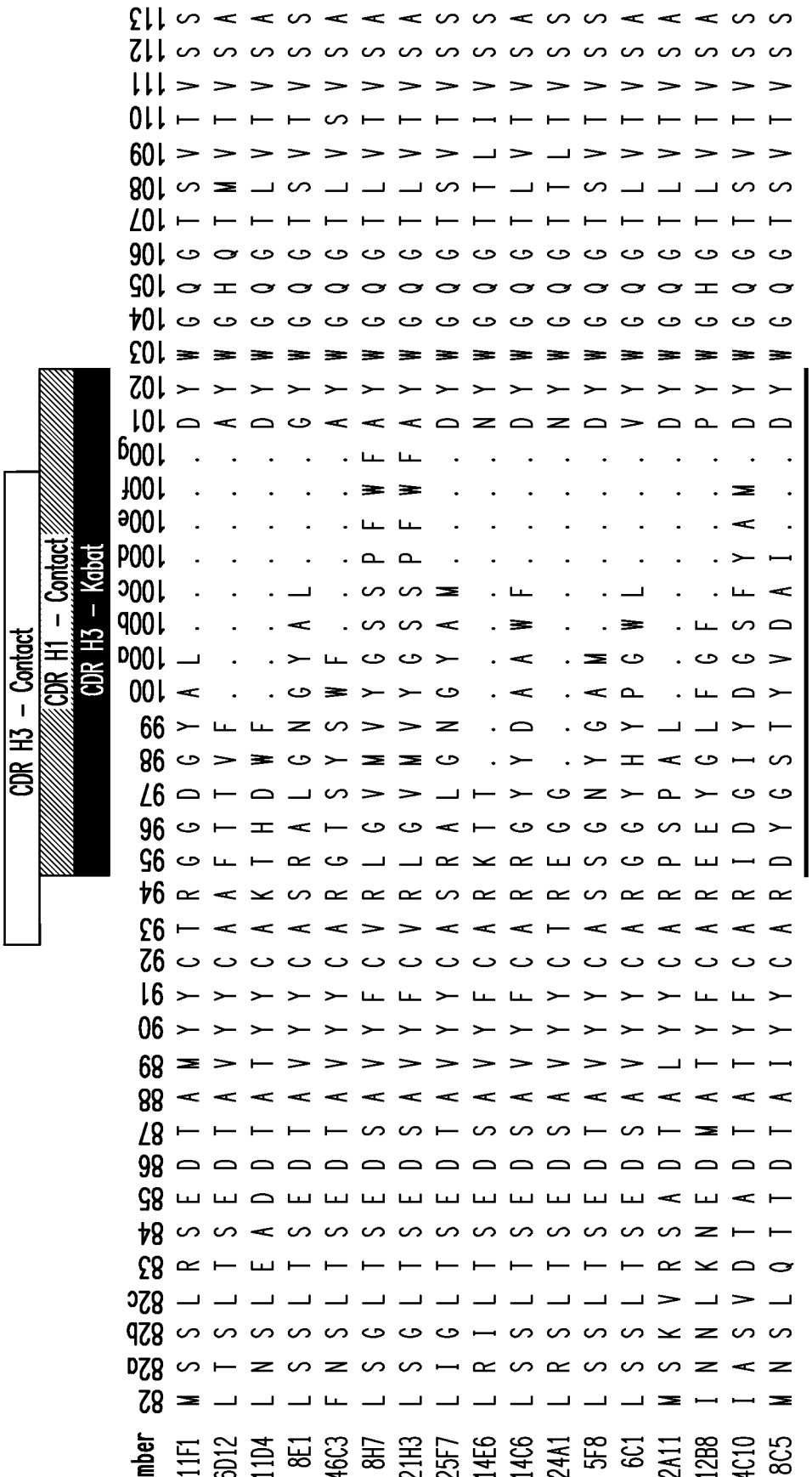


FIG. 3B continued

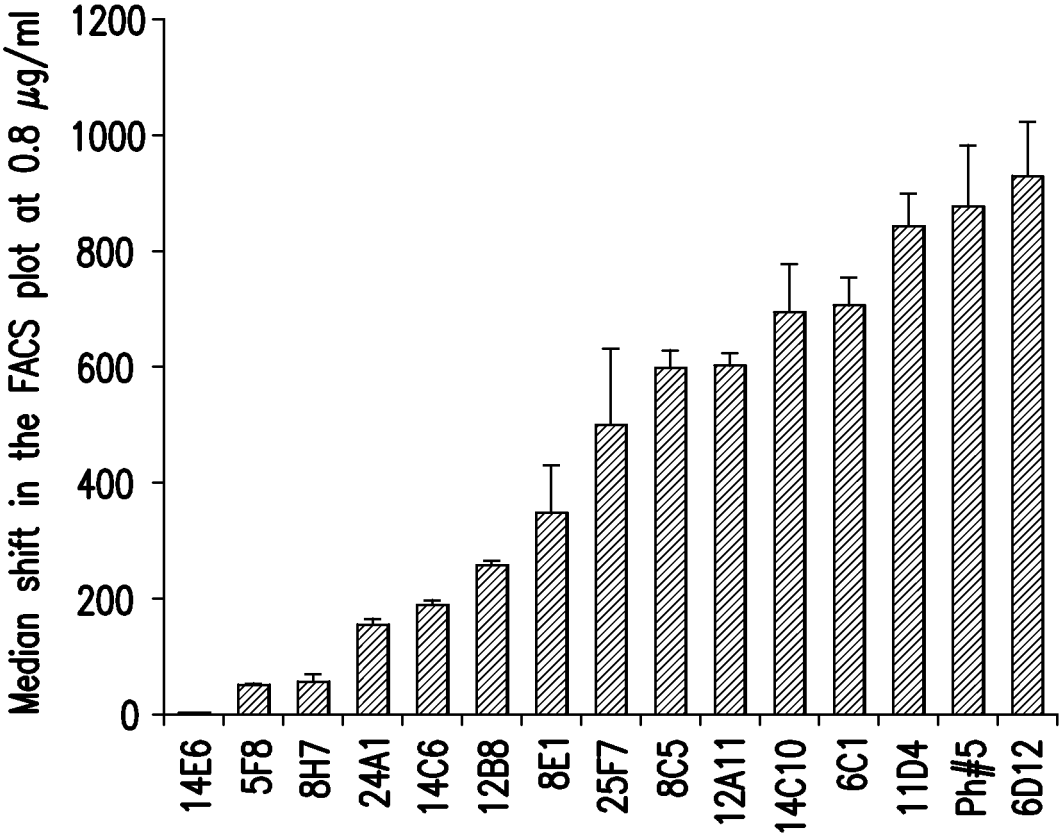

Median shift in the FACS plot at 0.8 μg/ml
1200
1000
800
600
400
200
0
14E6
5F8
8H7
24A1
14C6
12B8
8E1
25F7
8C5
12A11
14C10
6C1
11D4
Ph#5
6D12

FIG. 4

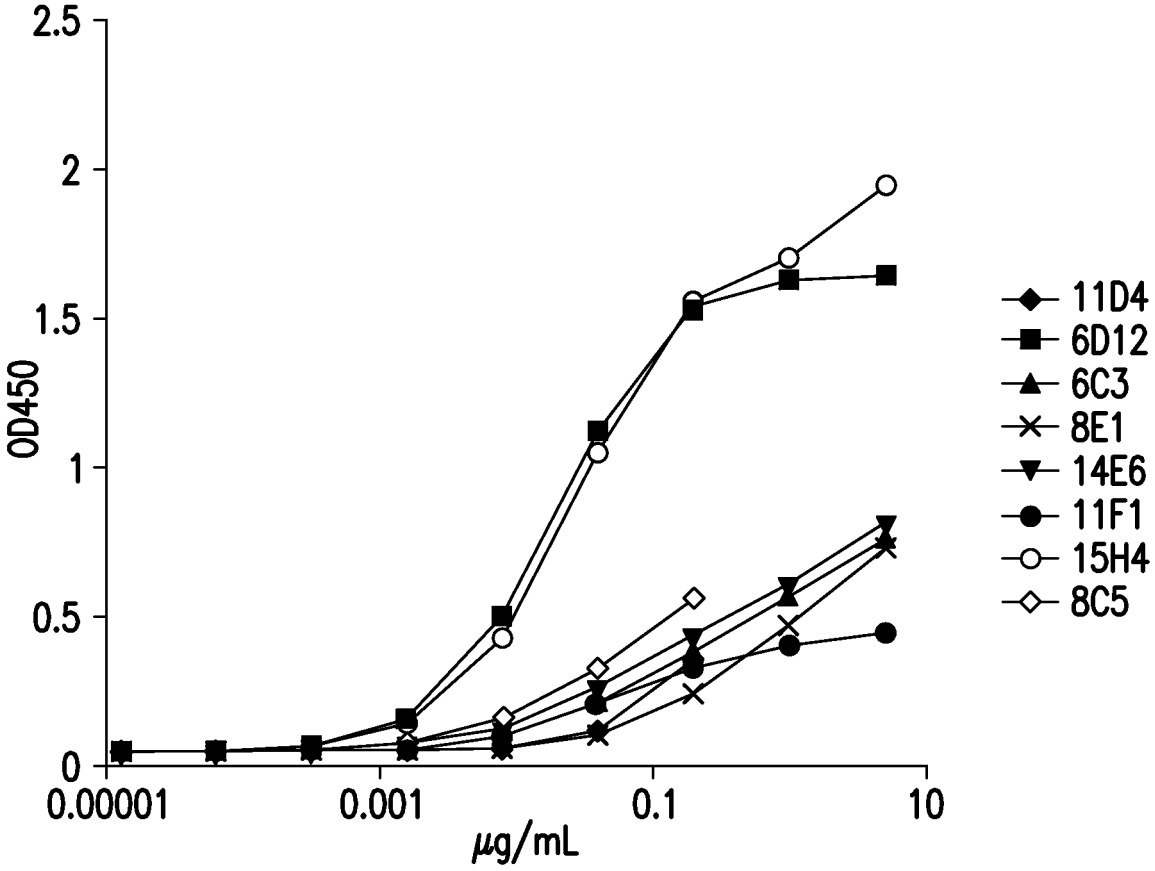

OD450
2.5
2
1.5
1
0.5
0
0.00001
0.001
0.1
10
μg/mL
11D4
6D12
6C3
8E1
14E6
11F1
15H4
8C5

FIG. 5

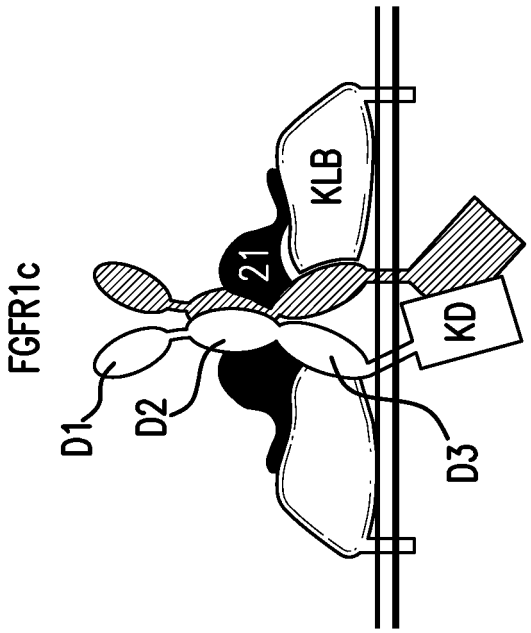

FGFR1c
D1
D2
21
KLB
KD
D3

FIG. 6B

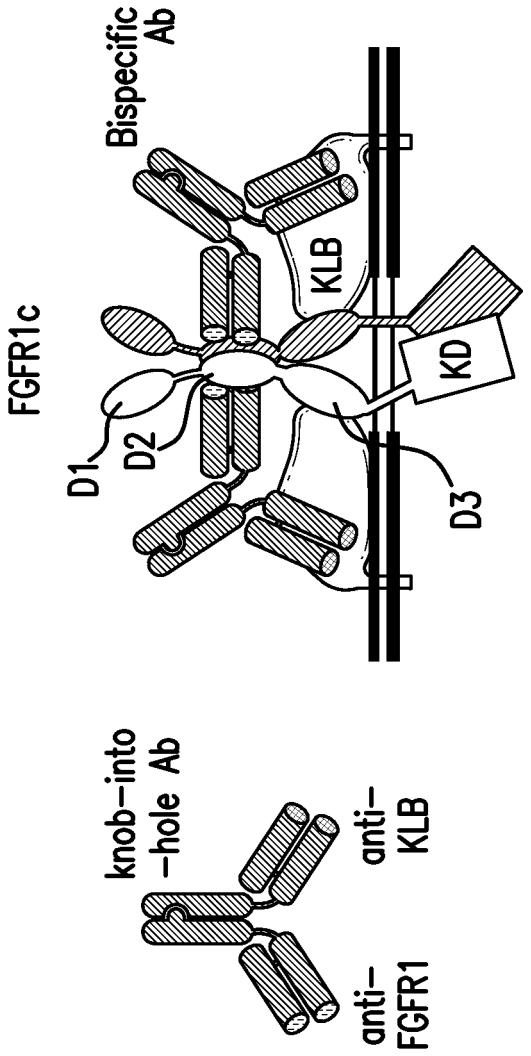

Bispecific Ab
FGFR1c
D1
D2
KLB
KD
D3
knob–into –hole Ab
anti– KLB
anti– FGFR1

FIG. 6A

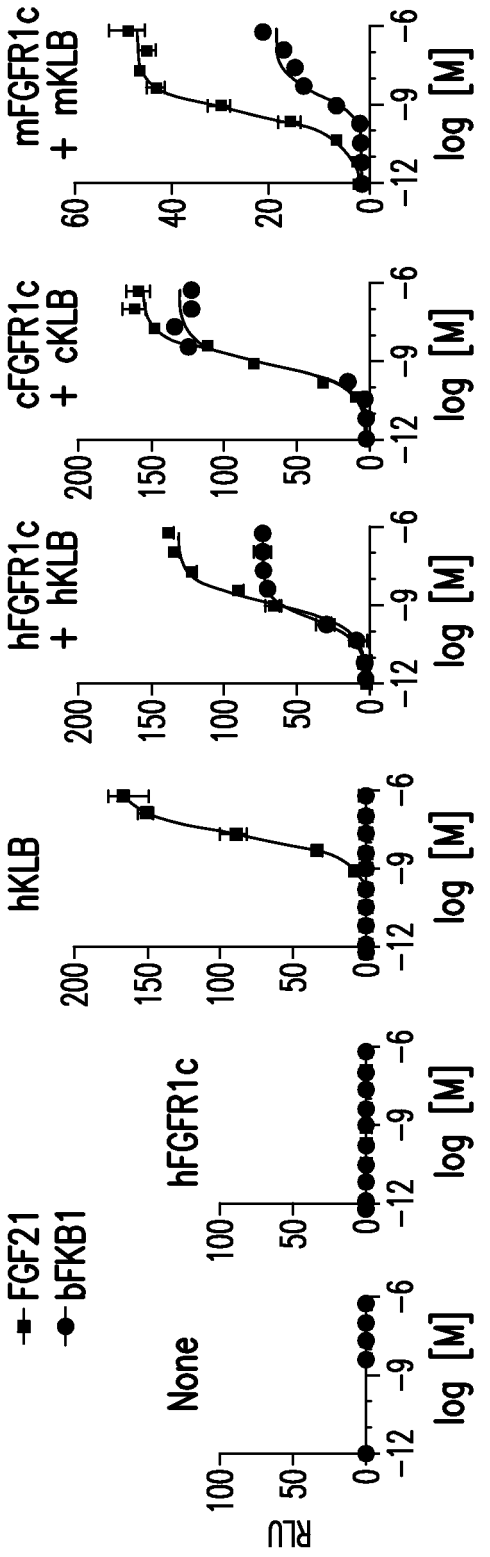

FGF21
bFKB1
None
hFGFR1c
hKLB
hFGFR1c + hKLB
cFGFR1c + cKLB
mFGFR1c + mKLB
RLU
log [M]

FIG. 6C

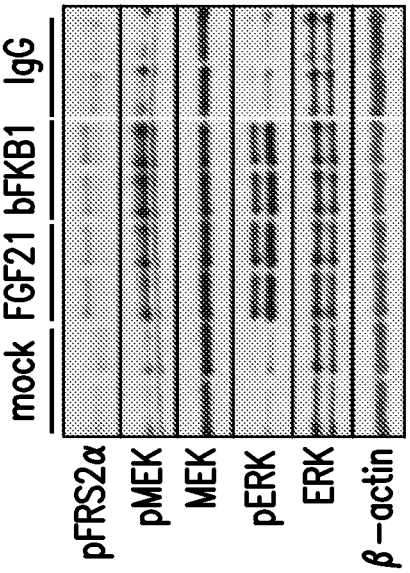

mock FGF21 bFKB1 IgG
pFRS2α
pMEK
MEK
pERK
ERK
β−actin

FIG. 6D

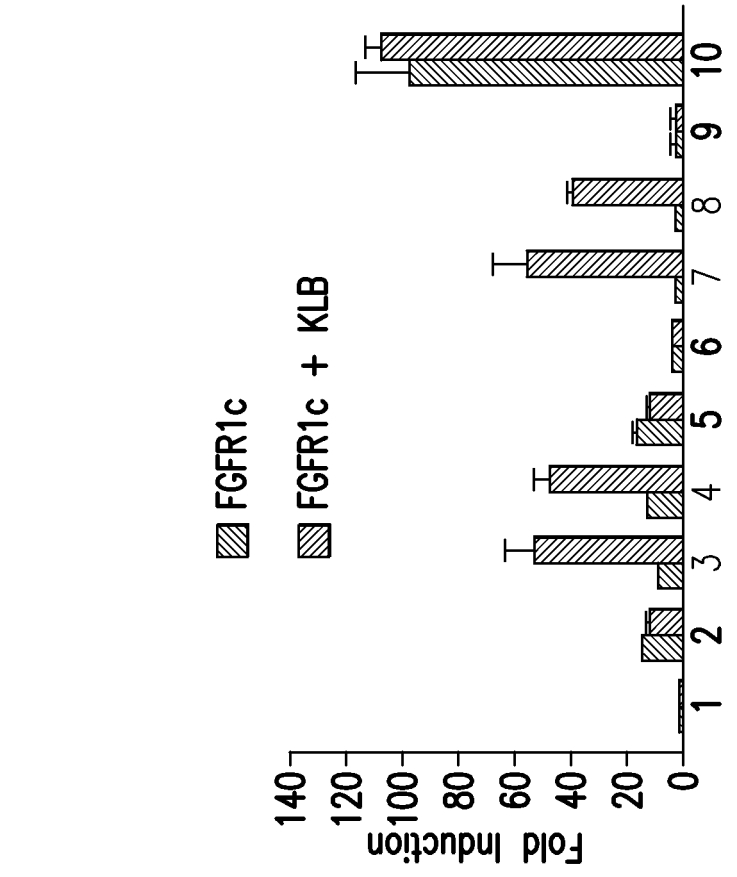

FGFR1c
FGFR1c + KLB
Fold Induction
0
20
40
60
80
100
120
140
1 2 3 4 5 6 7 8 9 10
1. Mock transfection
2. R1MAb1/trastumab
3. R1MAb1/KLBmAb1
4. R1MAb1/KLBmAb3
5. R1MAb1/KLBmAb7
6. R1MAb2/trastumab
7. R1MAb2/KLBmAb1
8. R1MAb2/KLBmAb3
9. R1MAb2/KLBmAb7
10. Purified R1MAb1 (133 nM)

FIG. 7A

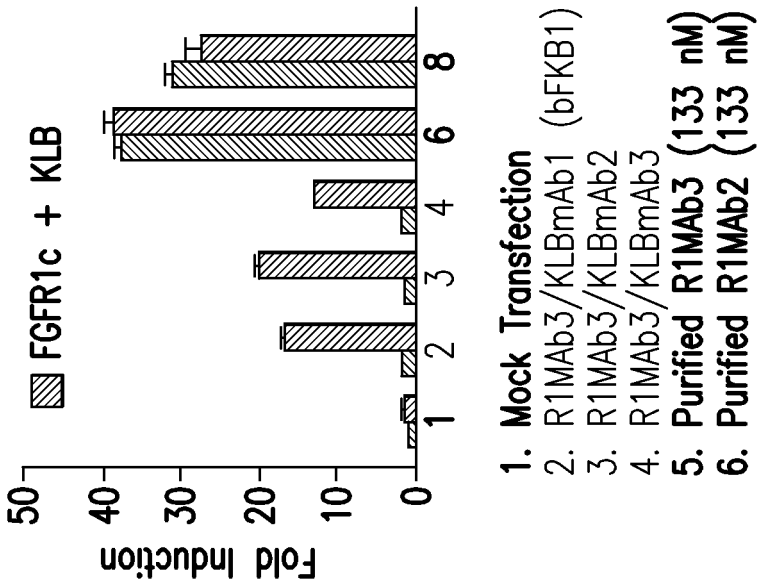

FGFR1c
FGFR1c + KLB
Fold Induction
0
10
20
30
40
50
1 2 3 4 6 8
1. Mock Transfection
2. R1MAb3/KLBmAb1 (bFKB1)
3. R1MAb3/KLBmAb2
4. R1MAb3/KLBmAb3
5. Purified R1MAb3 (133 nM)
6. Purified R1MAb2 (133 nM)

FIG. 7B

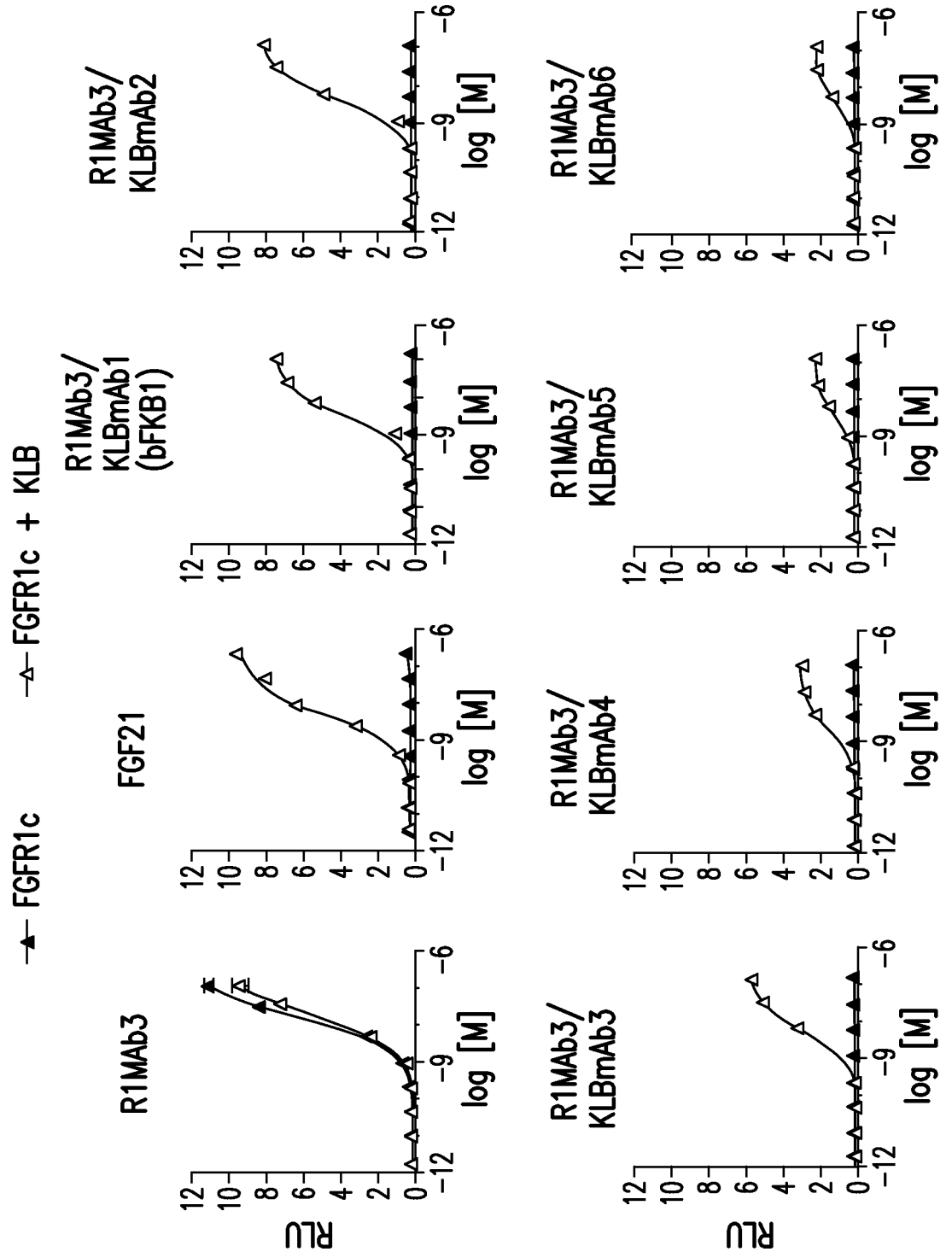

FGFR1c
FGFR1c + KLB
R1MAb3
FGF21
R1MAb3/ KLBmAb1 (bFKB1)
R1MAb3/ KLBmAb2
R1MAb3/ KLBmAb3
R1MAb3/ KLBmAb4
R1MAb3/ KLBmAb5
R1MAb3/ KLBmAb6
RLU
log [M]

FIG. 7C

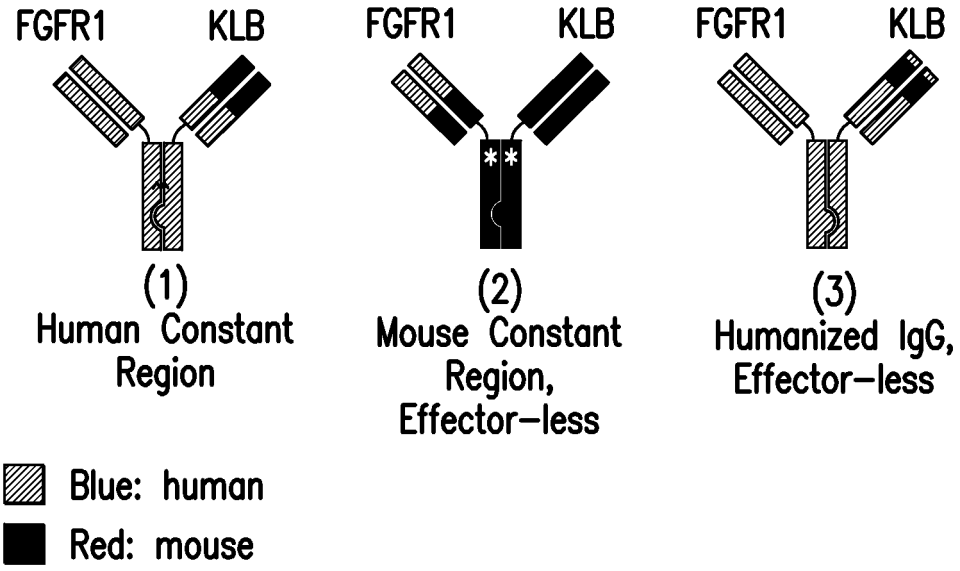

FGFR1
KLB
FGFR1
KLB
FGFR1
KLB
(1)
Human Constant Region
(2)
Mouse Constant Region, Effector-less
(3)
Humanized IgG, Effector-less
Blue: human
Red: mouse

FIG. 8A

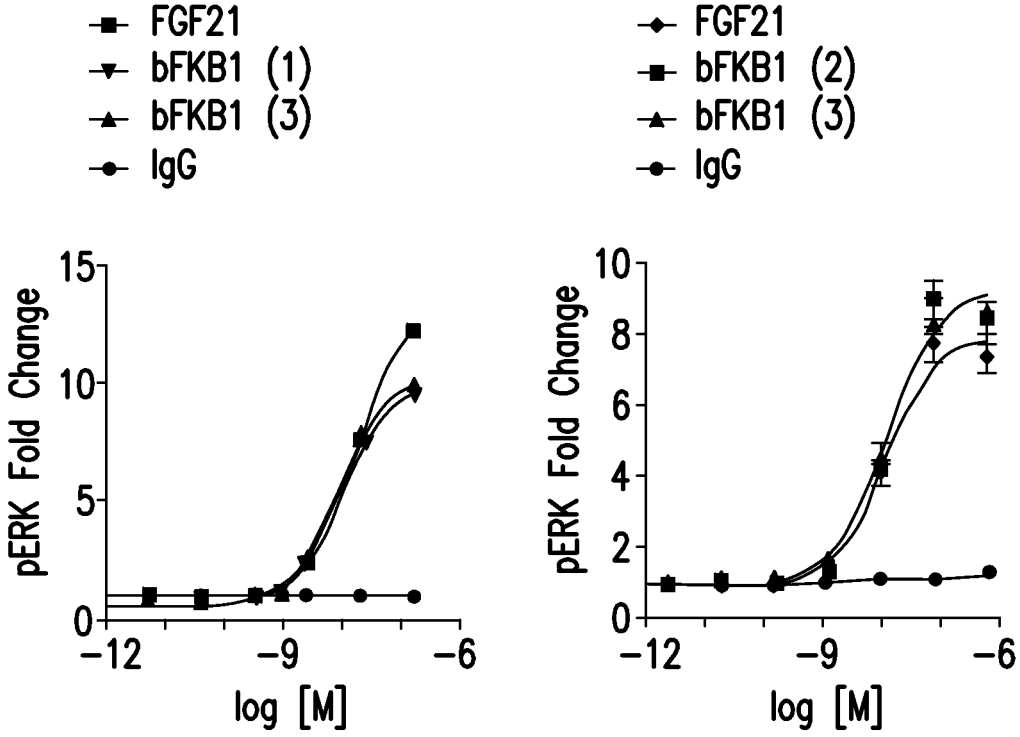

FGF21
bFKB1 (1)
bFKB1 (3)
IgG
pERK Fold Change
15
10
5
0
-12
-9
-6
log [M]
FGF21
bFKB1 (2)
bFKB1 (3)
IgG
pERK Fold Change
10
8
6
4
2
0
-12
-9
-6
log [M]

FIG. 8B

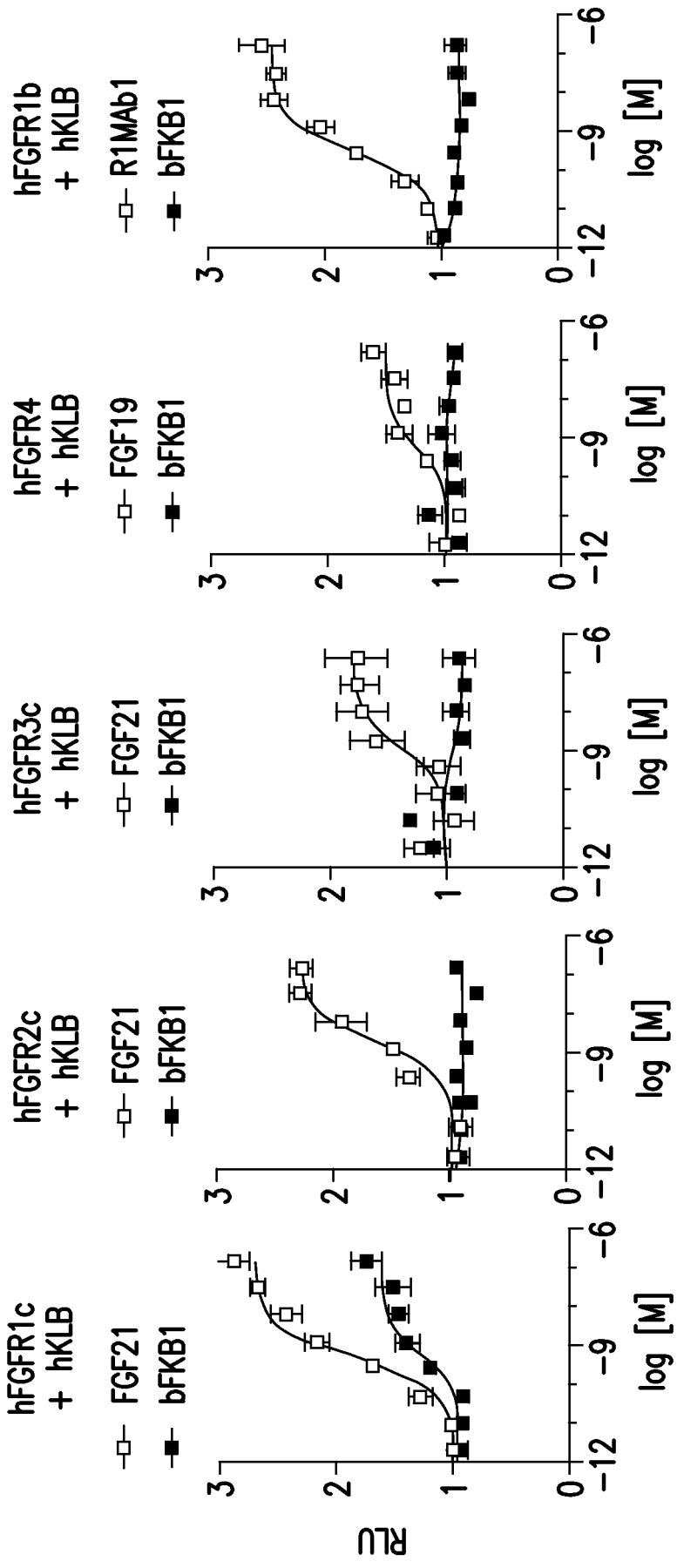

hFGFR1c
+ hKLB
FGF21
bFKB1
hFGFR2c
+ hKLB
FGF21
bFKB1
hFGFR3c
+ hKLB
FGF21
bFKB1
hFGFR4
+ hKLB
FGF19
bFKB1
hFGFR1b
+ hKLB
R1MAb1
bFKB1
RLU
log [M]

FIG. 9A

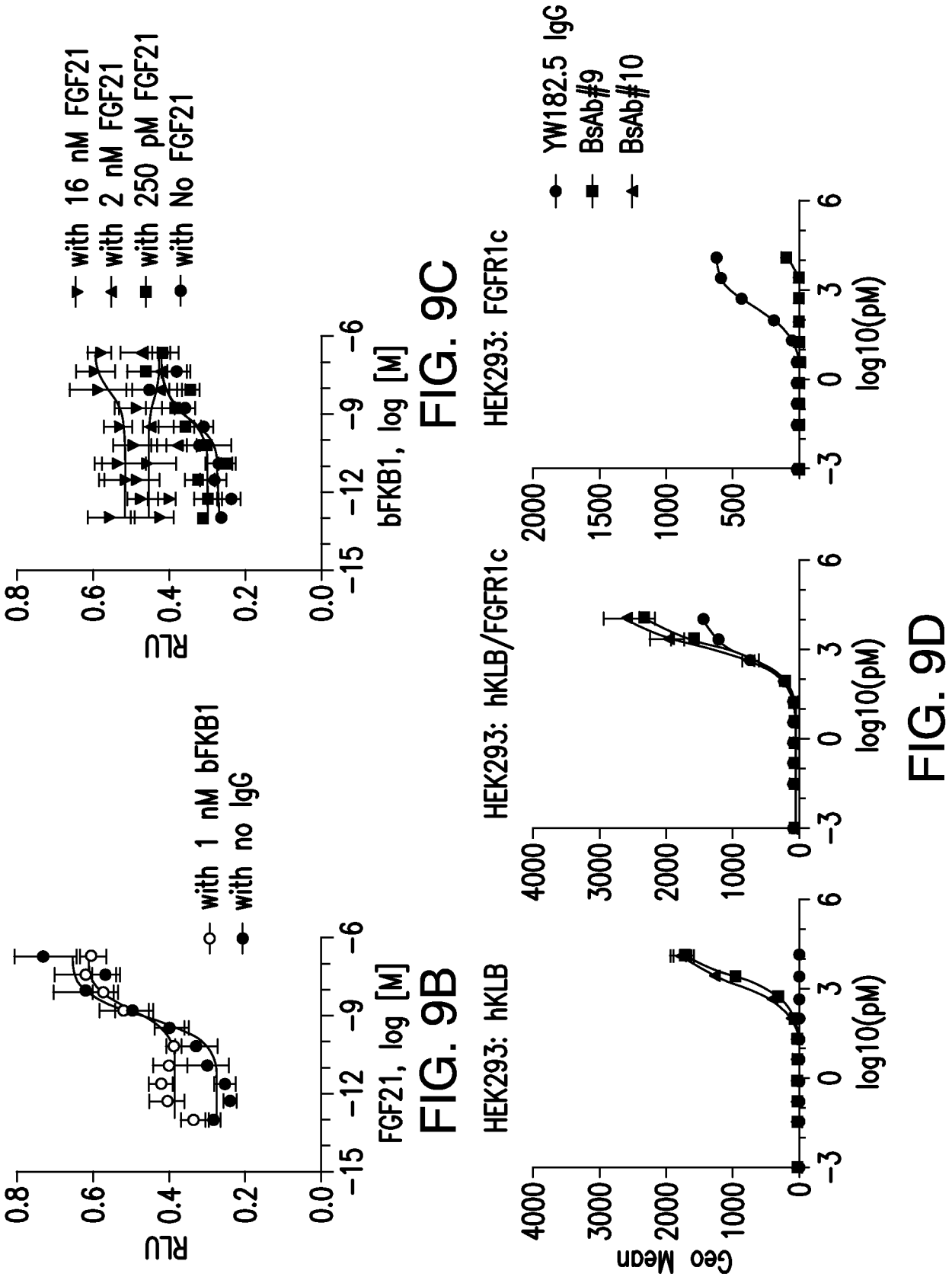


FIG. 9B

FIG. 9C

FIG. 9D

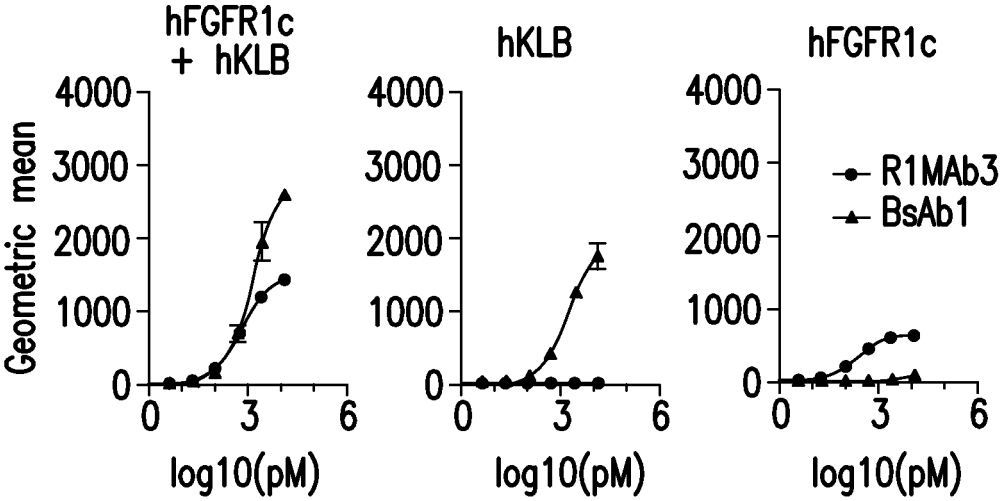


FIG. 10A

FGFR1 KLB	Human Human	Human (none)	(none) Human	(none) Mouse
BsAb1	2.3 nM	>300nM	6.6nM	15.5 nM
FGF21	5.3 nM	n.d.	n.d.	n.d.

FIG. 10B

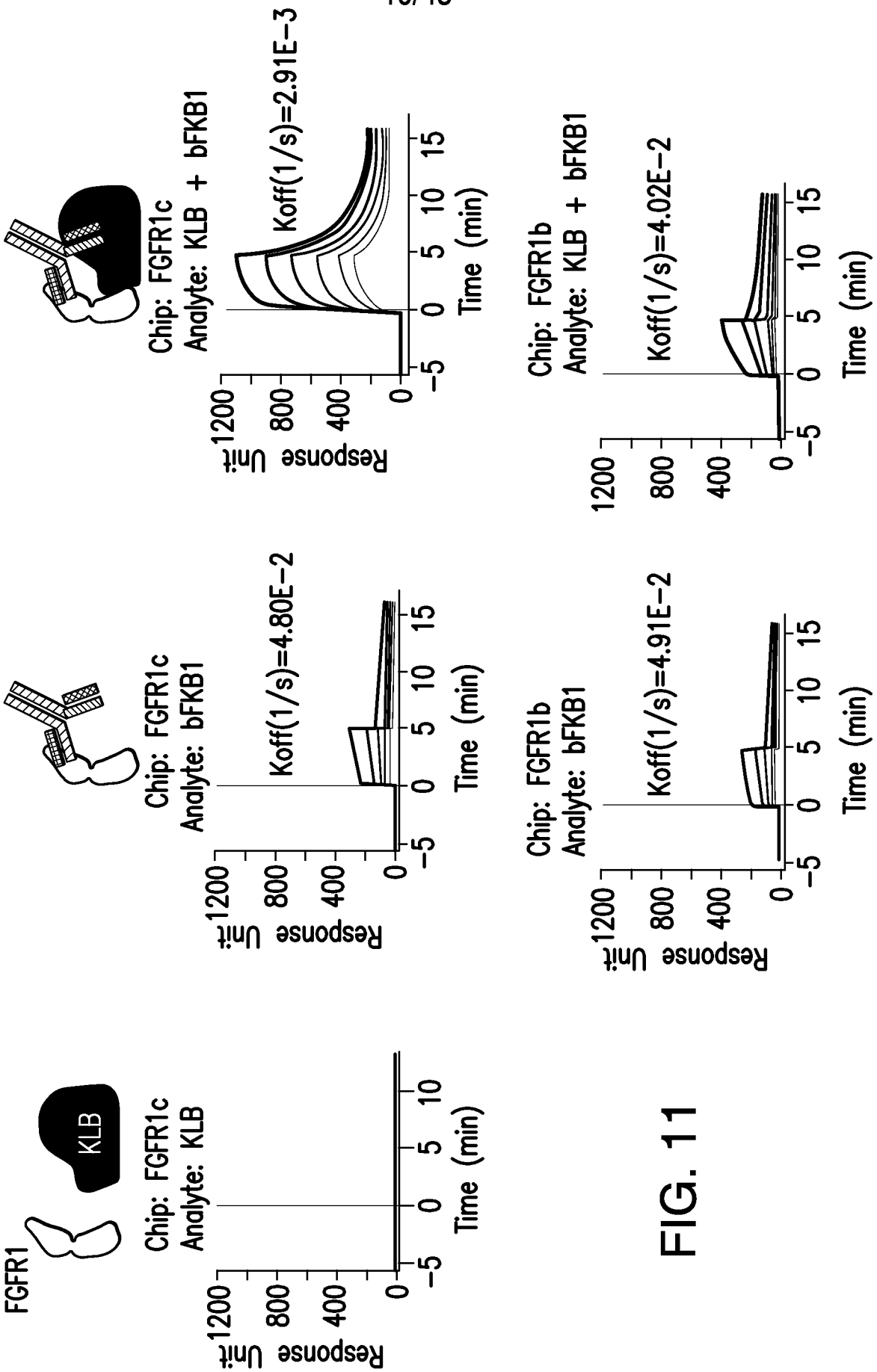

FGFR1
KLB
Chip: FGFR1c
Analyte: KLB
Response Unit
Time (min)
Chip: FGFR1c
Analyte: bFKB1
Koff(1/s)=4.80E−2
Chip: FGFR1c
Analyte: KLB + bFKB1
Koff(1/s)=2.91E−3
Chip: FGFR1b
Analyte: bFKB1
Koff(1/s)=4.91E−2
Chip: FGFR1b
Analyte: KLB + bFKB1
Koff(1/s)=4.02E−2

FIG. 11

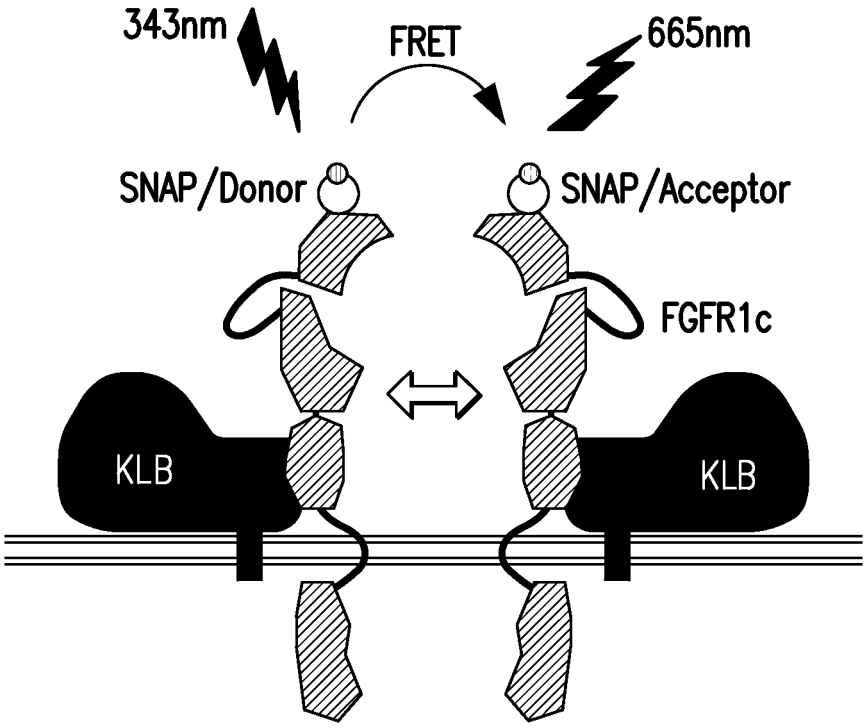


FIG. 12A

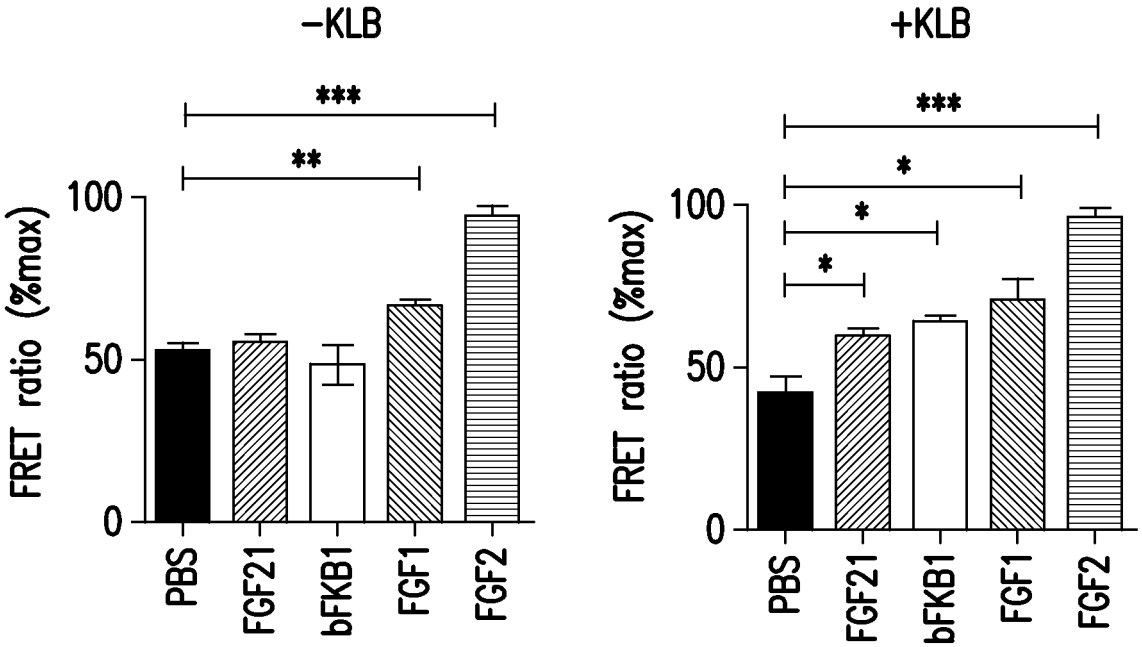


FIG. 12B

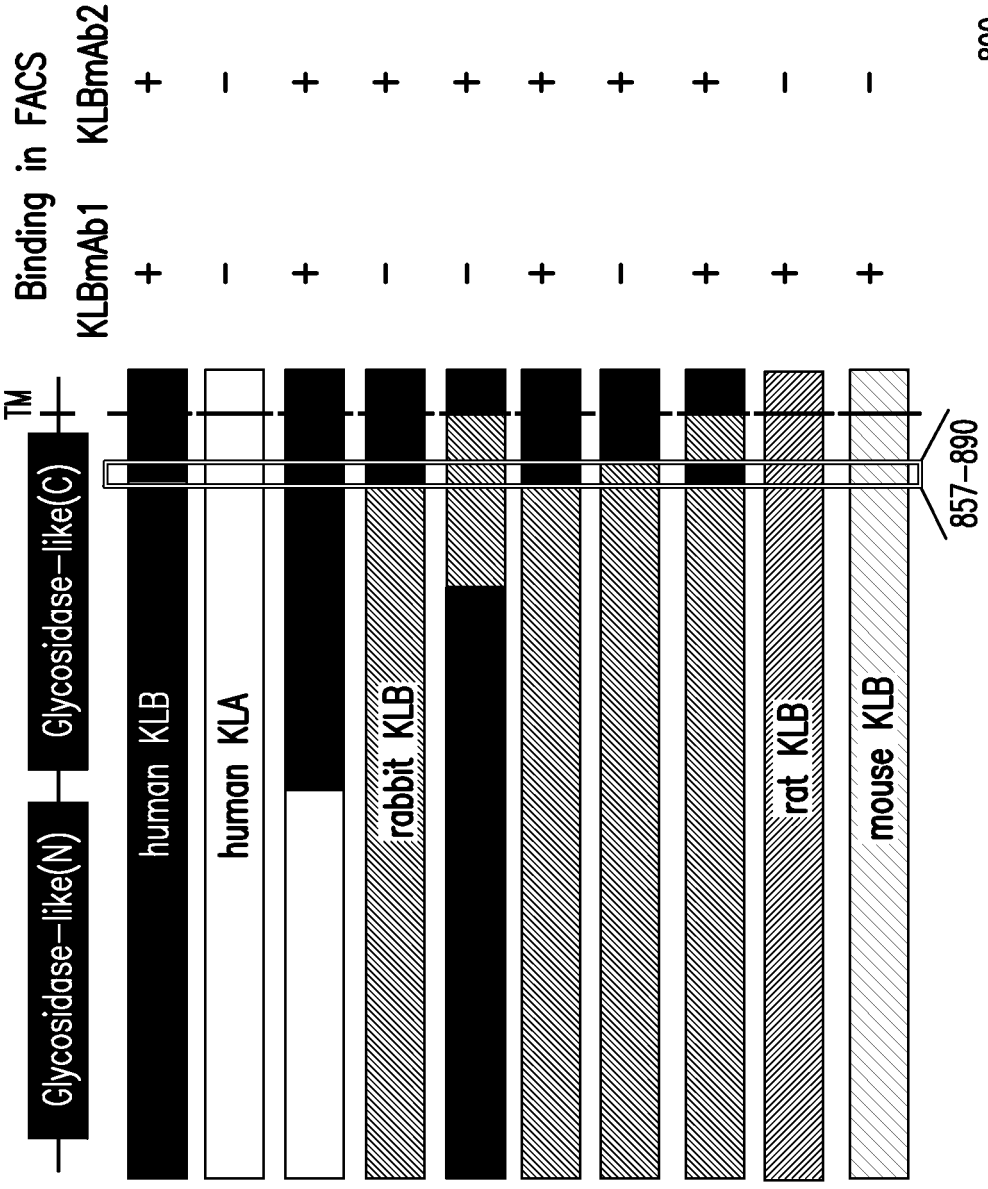


FIG. 13A

FIG. 13B

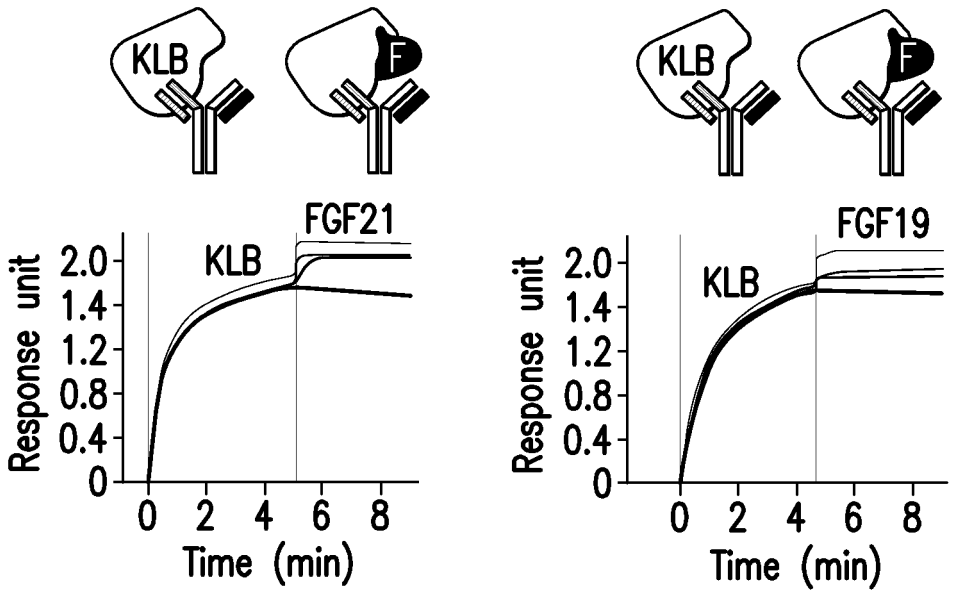


FIG. 14A

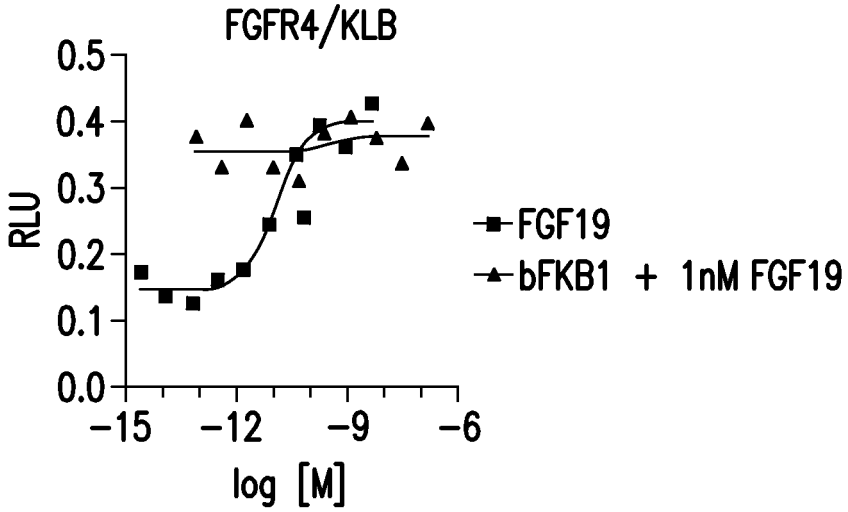


FIG. 14B

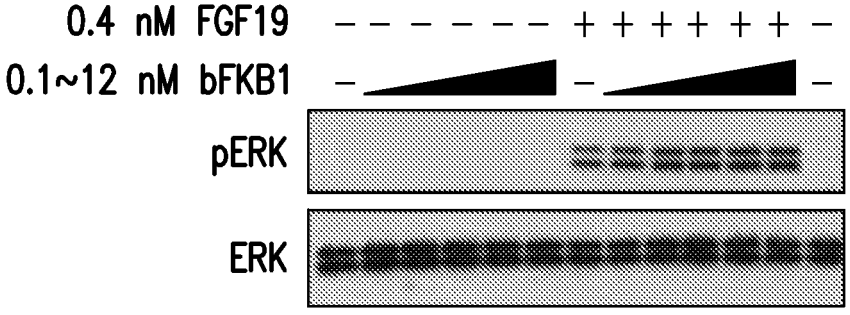


FIG. 14C

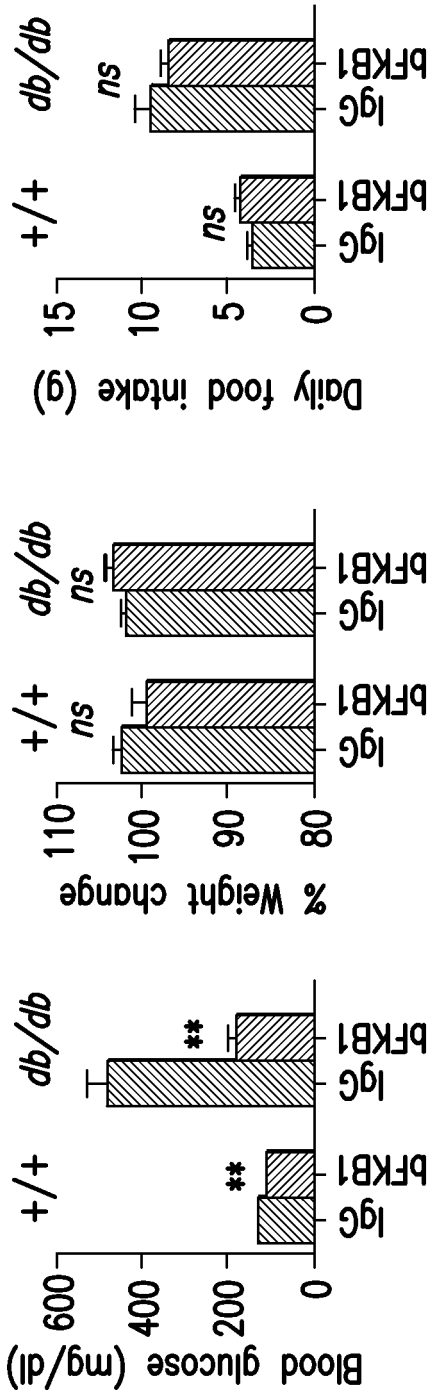


FIG. 15A

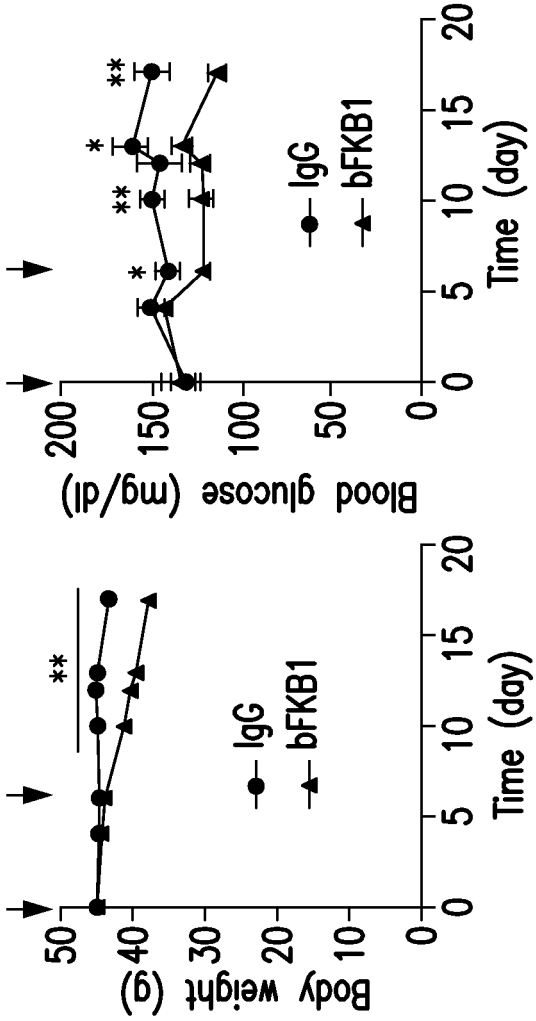


FIG. 15B

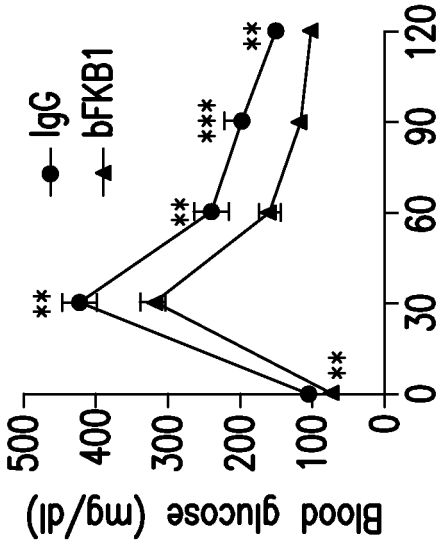


FIG. 15C

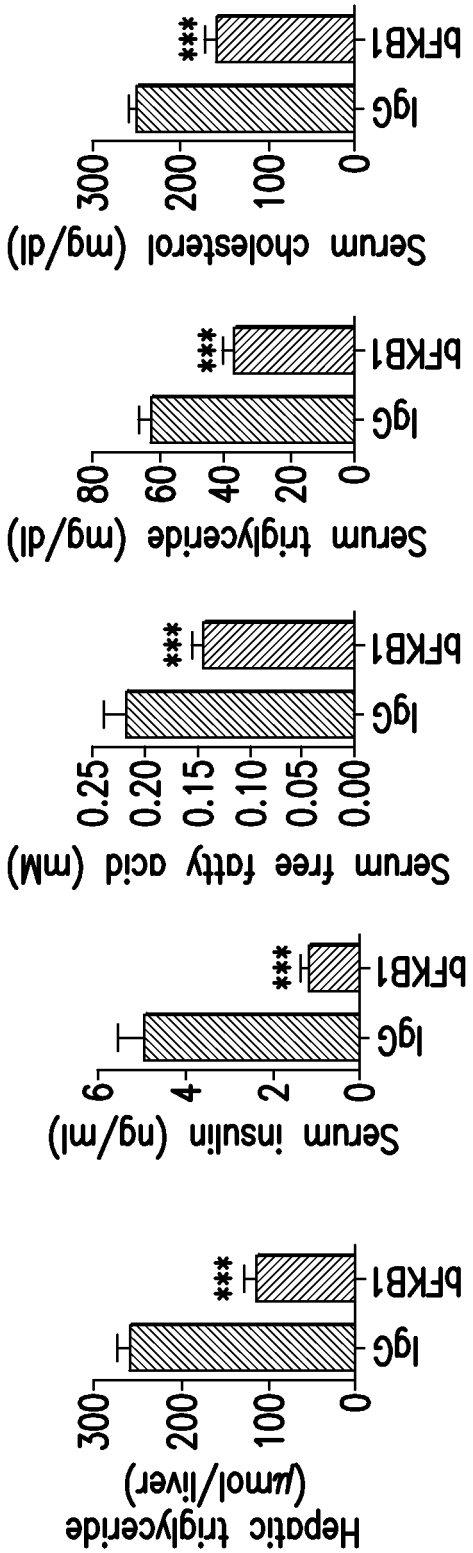


FIG. 15D

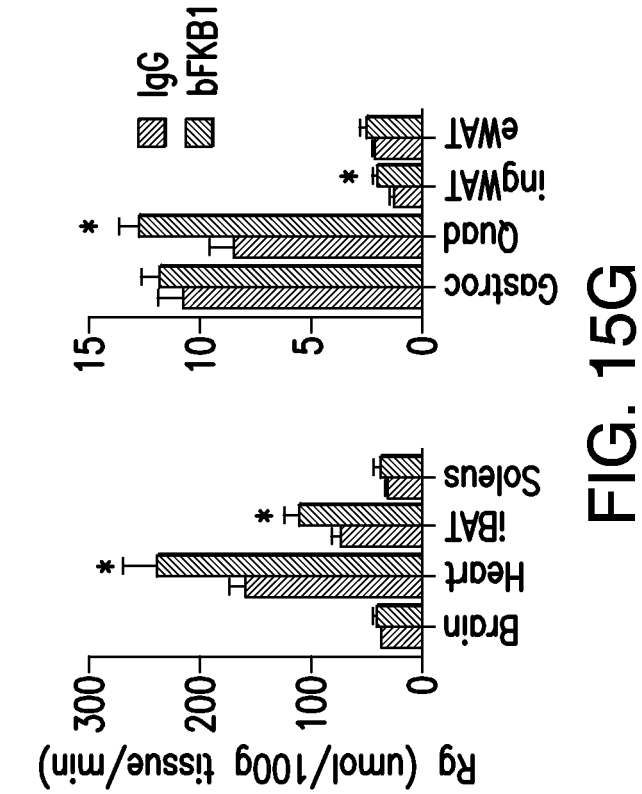


FIG. 15G

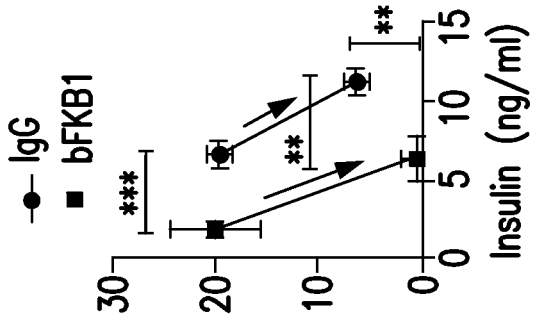


FIG. 15F

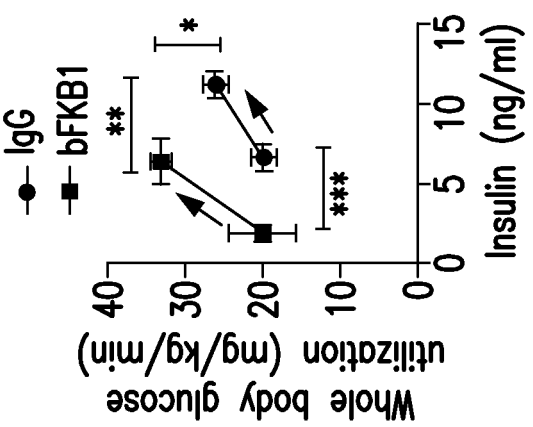


FIG. 15E

wt: F S G D G K A I W D K K Q Y V S P . . .
ko: F S E T G K Q Y G I K N S T *

FIG. 16A

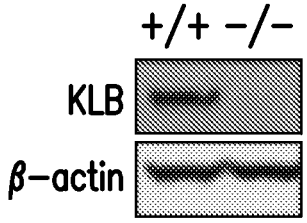


FIG. 16B

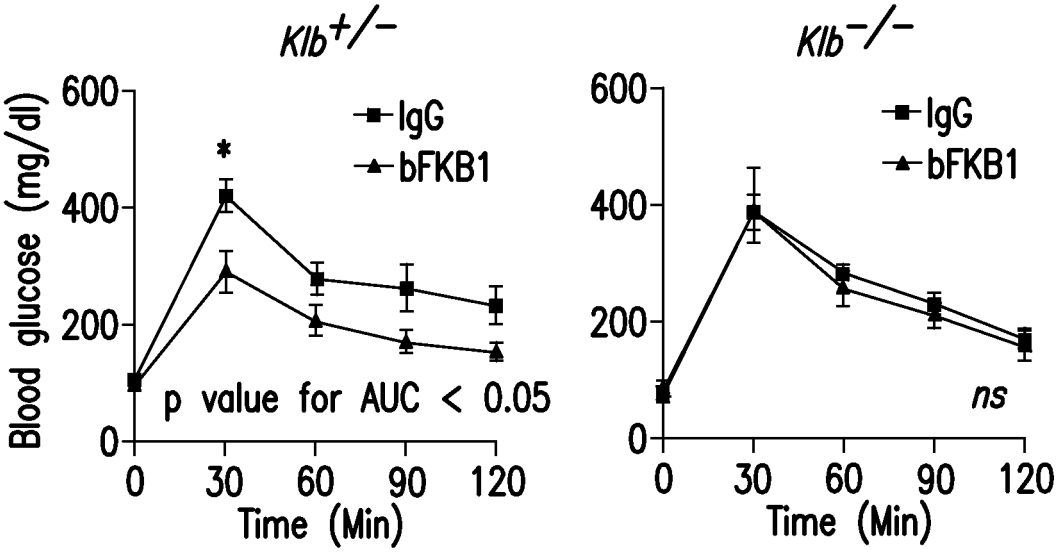


FIG. 16C

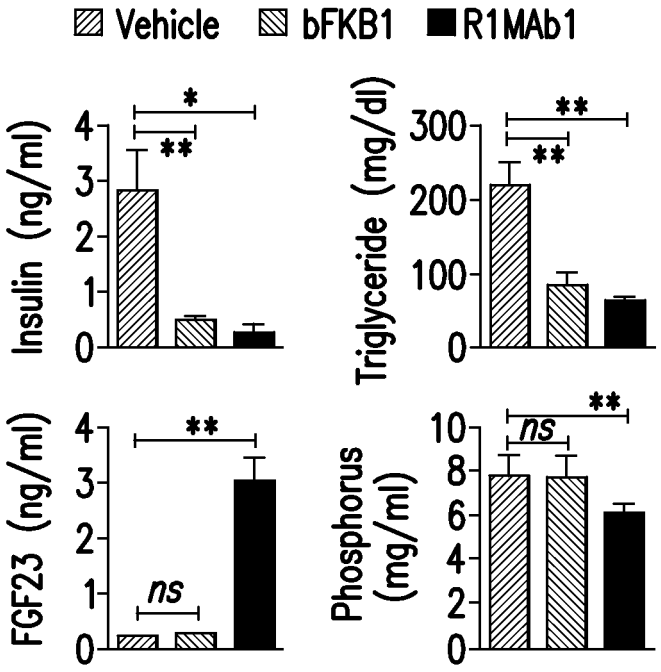


FIG. 16D

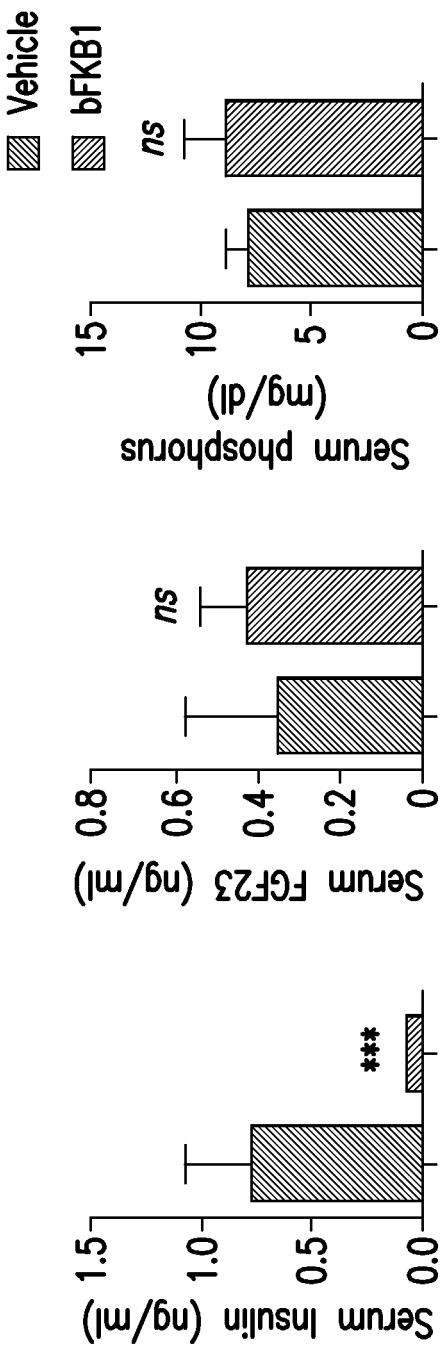

Vehicle
bFKB1
ns
Serum phosphorus (mg/dl)
15
10
5
0
ns
Serum FGF23 (ng/ml)
0.8
0.6
0.4
0.2
0
***
Serum Insulin (ng/ml)
1.5
1.0
0.5
0.0

FIG. 17

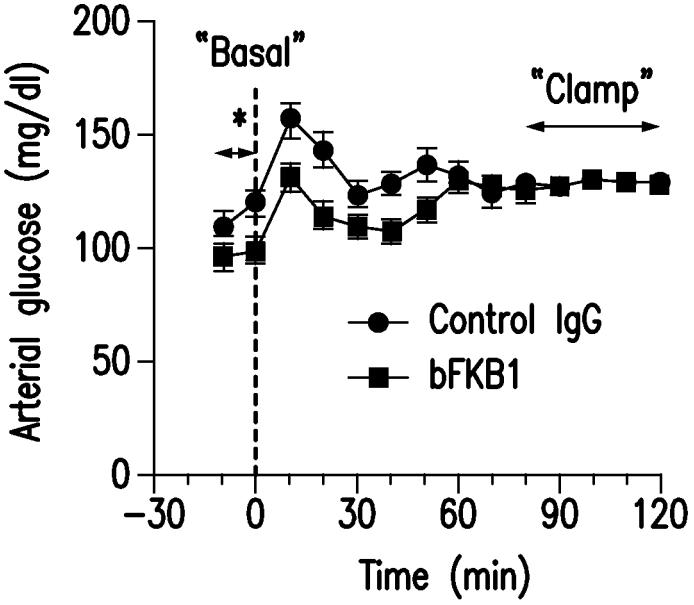


FIG. 18A

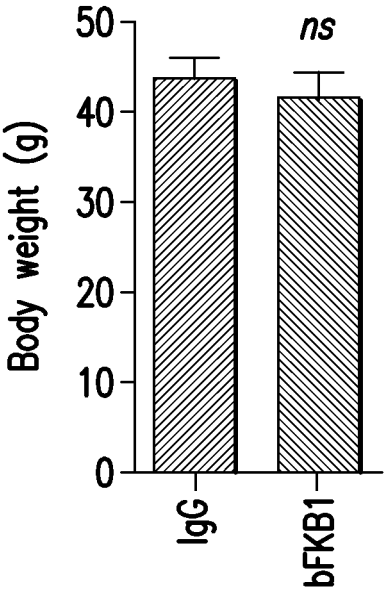


FIG. 18B

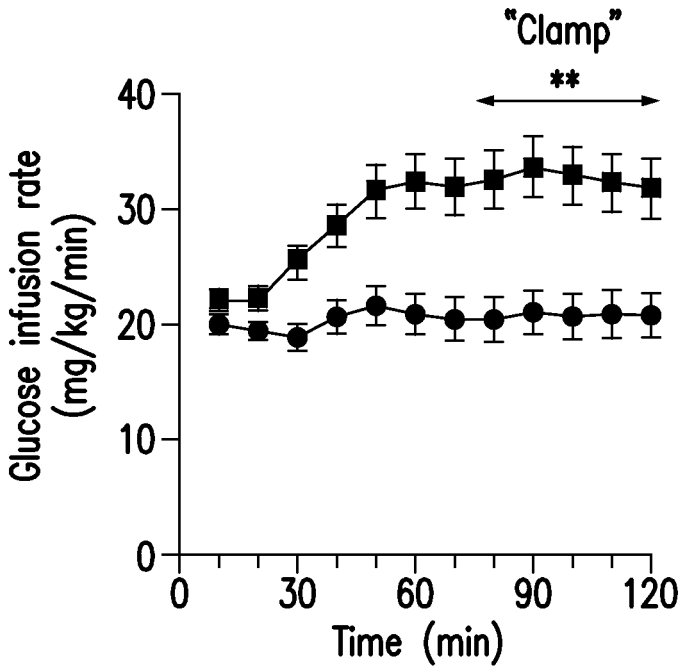


FIG. 18C

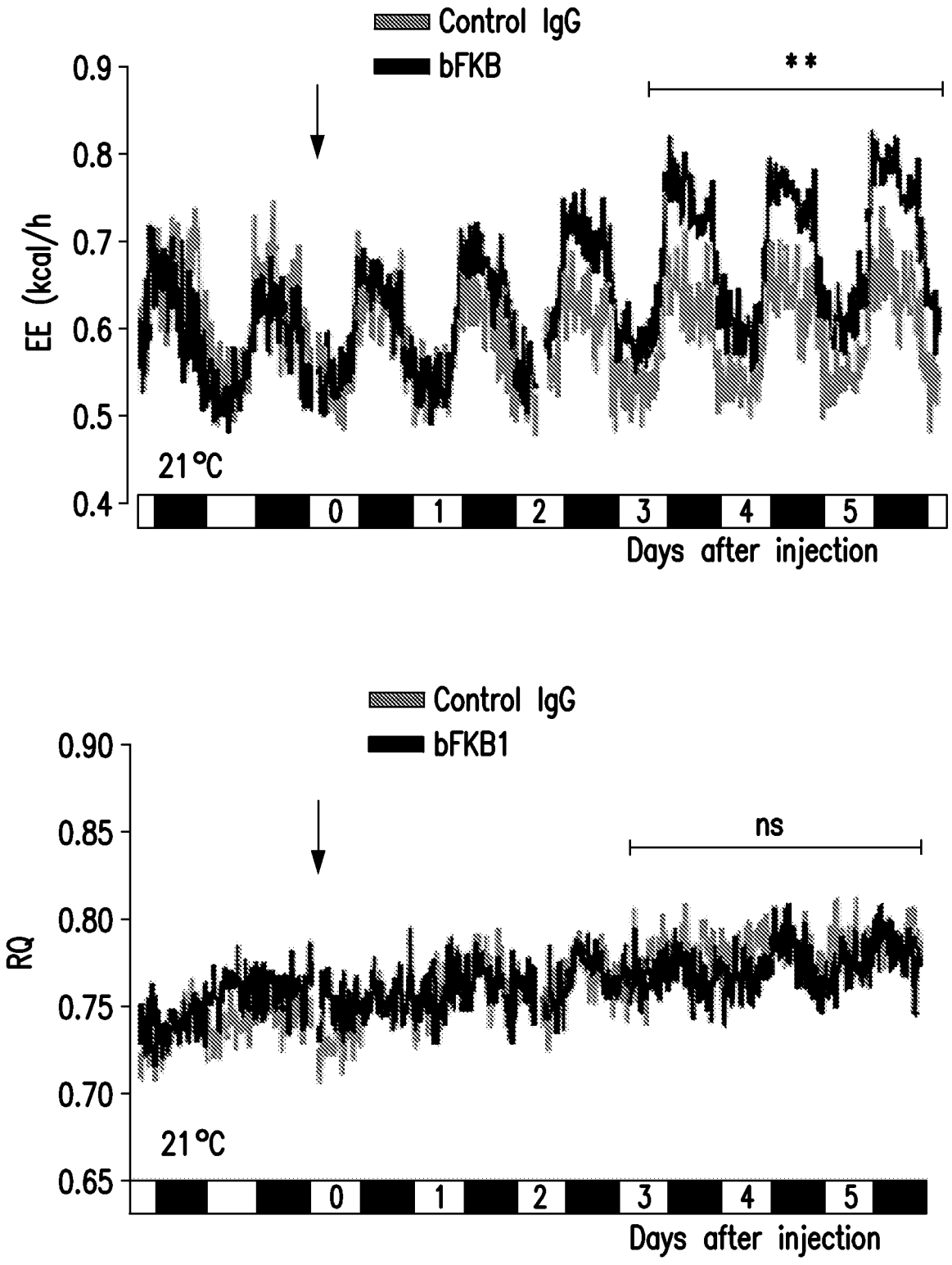

Control IgG
bFKB
**
0.9
0.8
0.7
0.6
0.5
0.4
EE (kcal/h
21°C
0
1
2
3
4
5
Days after injection
Control IgG
bFKB1
ns
0.90
0.85
0.80
0.75
0.70
0.65
RQ
21°C
0
1
2
3
4
5
Days after injection

FIG. 19A

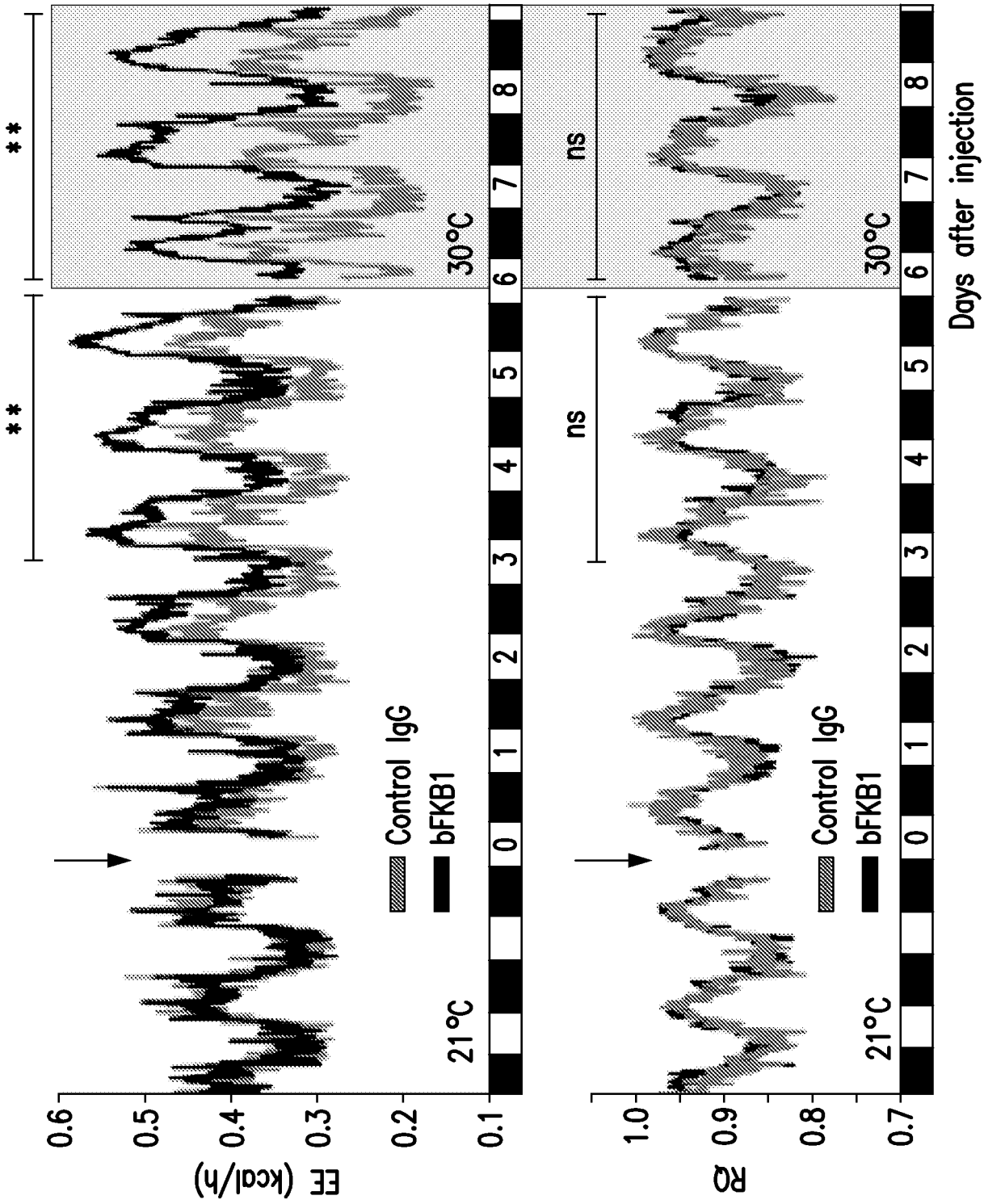
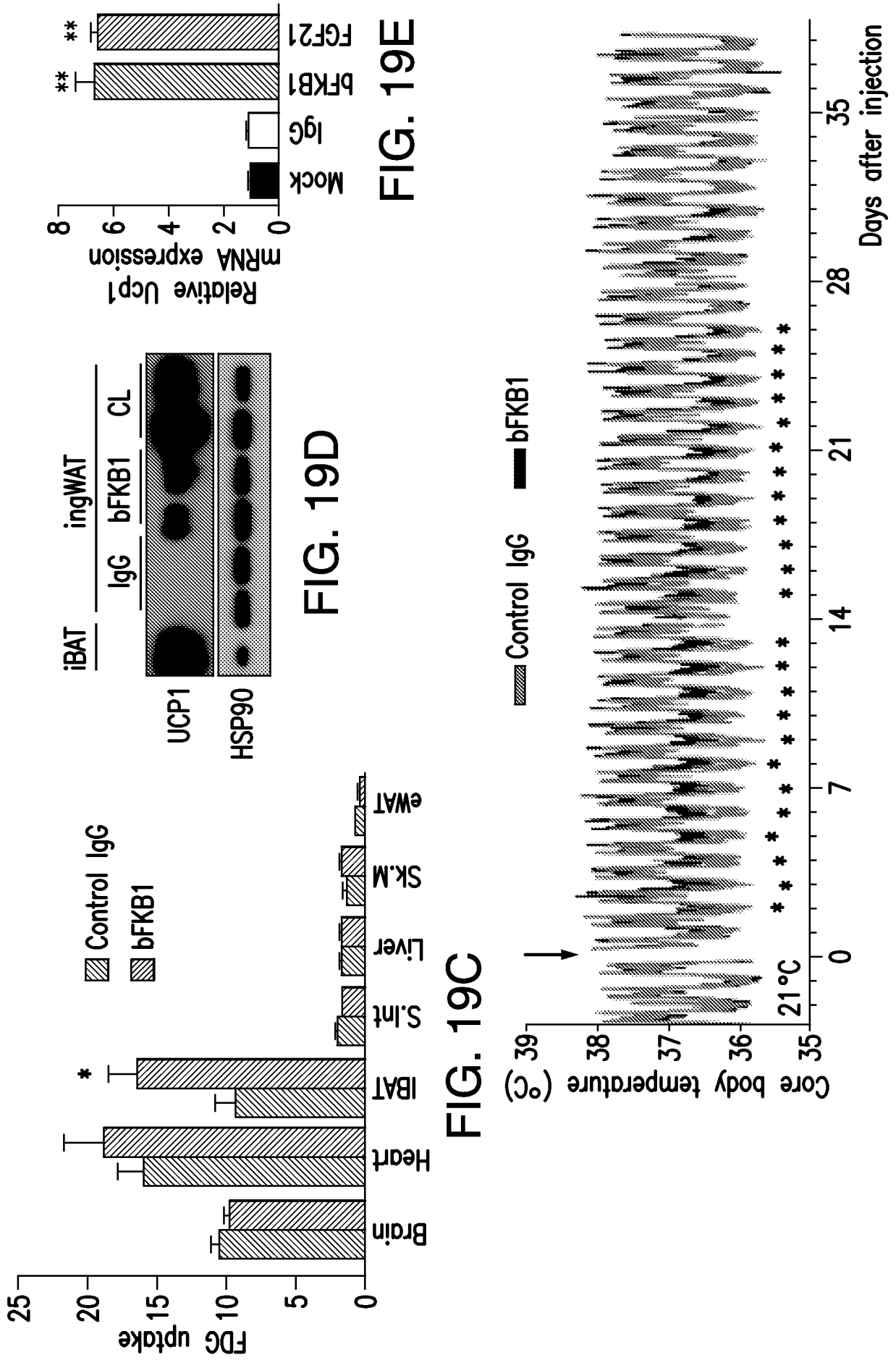

EE (kcal/h)
0.6
0.5
0.4
0.3
0.2
0.1
**
**
Control IgG
bFKB1
21°C
30°C
0
1
2
3
4
5
6
7
8
RQ
1.0
0.9
0.8
0.7
ns
ns
Days after injection

FIG. 19B


Core body temperature (°C)
39
38
37
36
35
21°C
0
7
14
21
28
35
Days after injection
Control IgG
bFKB1
FIG. 19C
FDG uptake
25
20
15
10
5
0
Brain
Heart
IBAT
S.Int
Liver
Sk.M
eWAT
Control IgG
bFKB1
FIG. 19D
iBAT
ingWAT
IgG
bFKB1
CL
UCP1
HSP90
Relative Ucp1 mRNA expression
8
6
4
2
0
Mock
IgG
bFKB1
FGF21
FIG. 19E

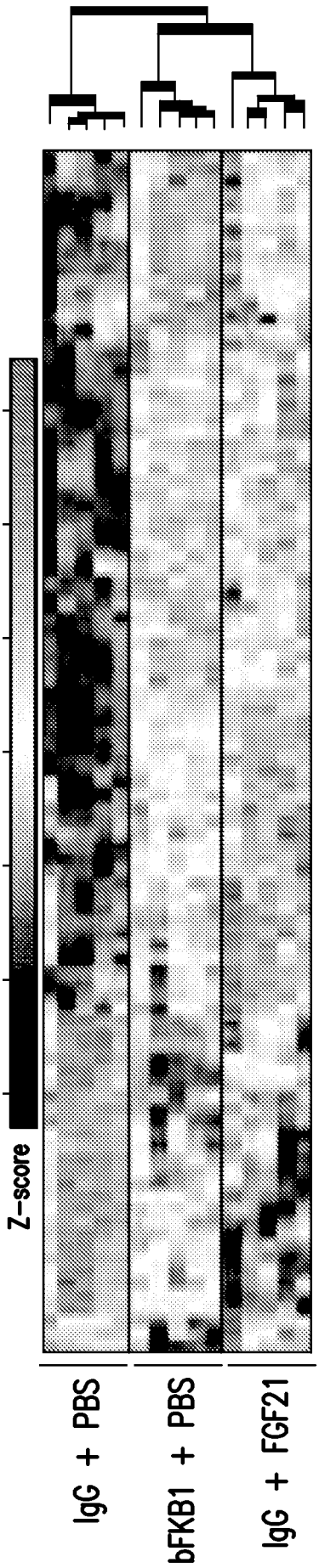


FIG. 19G

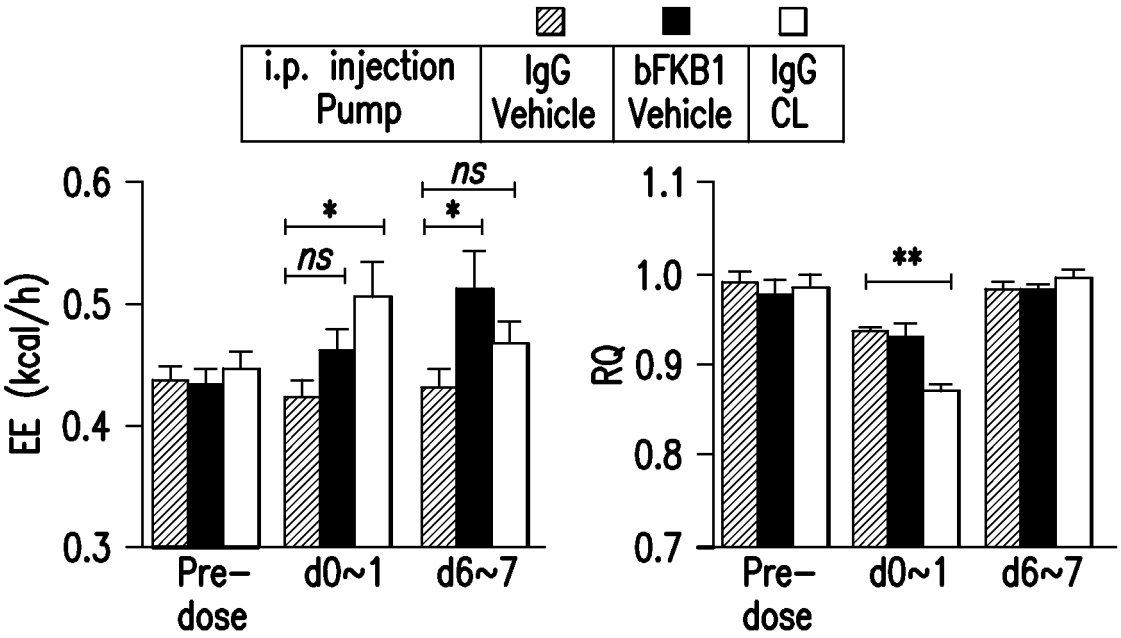

i.p. injection Pump
IgG Vehicle
bFKB1 Vehicle
IgG CL
EE (kcal/h)
0.6
0.5
0.4
0.3
ns
*
ns
*
Pre-dose
d0~1
d6~7
RQ
1.1
1.0
0.9
0.8
0.7
**
Pre-dose
d0~1
d6~7

FIG. 19H

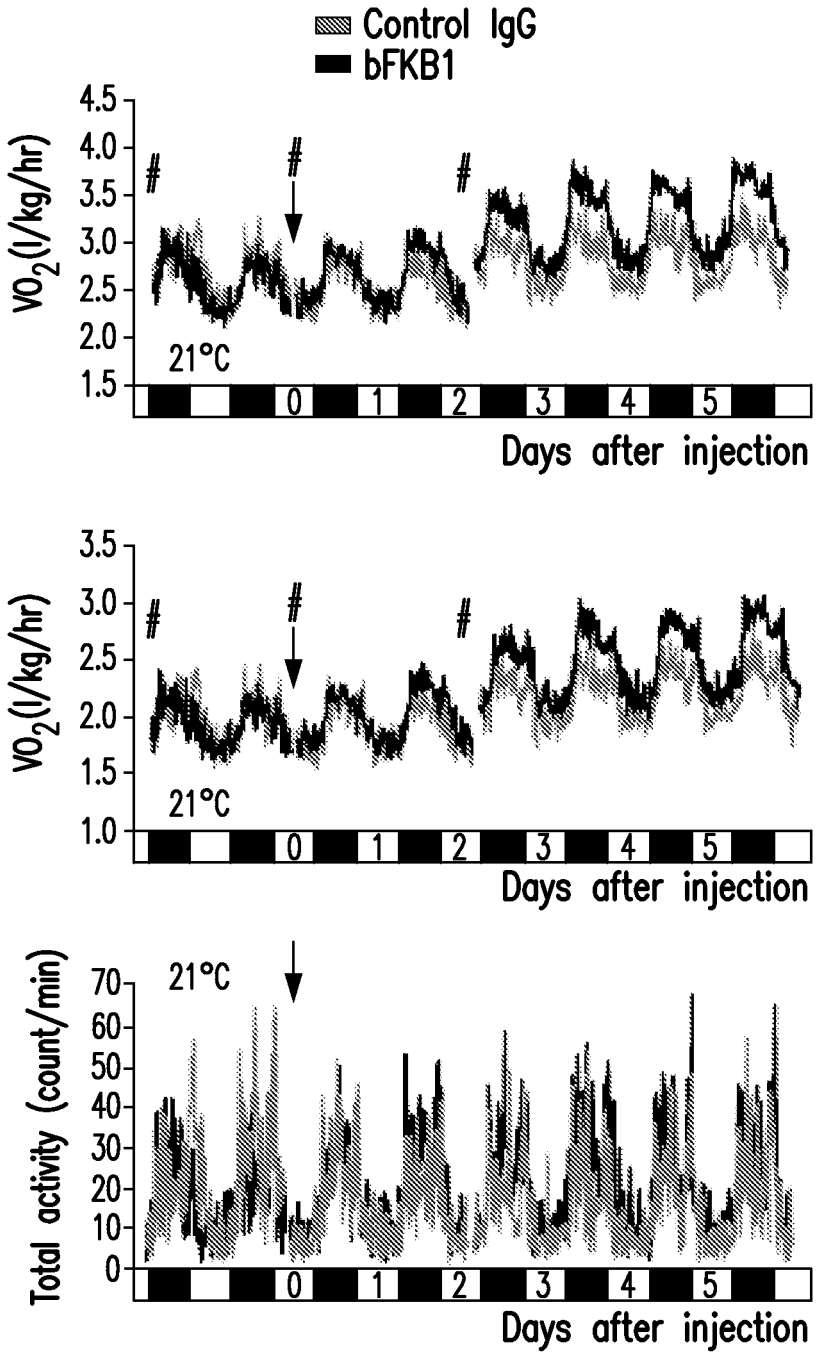

Control IgG
bFKB1
VO_2(l/kg/hr)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
#
#
#
21°C
0
1
2
3
4
5
Days after injection
VO_2(l/kg/hr)
3.5
3.0
2.5
2.0
1.5
1.0
#
#
#
21°C
0
1
2
3
4
5
Days after injection
Total activity (count/min)
70
60
50
40
30
20
10
0
21°C
0
1
2
3
4
5
Days after injection

FIG. 20A

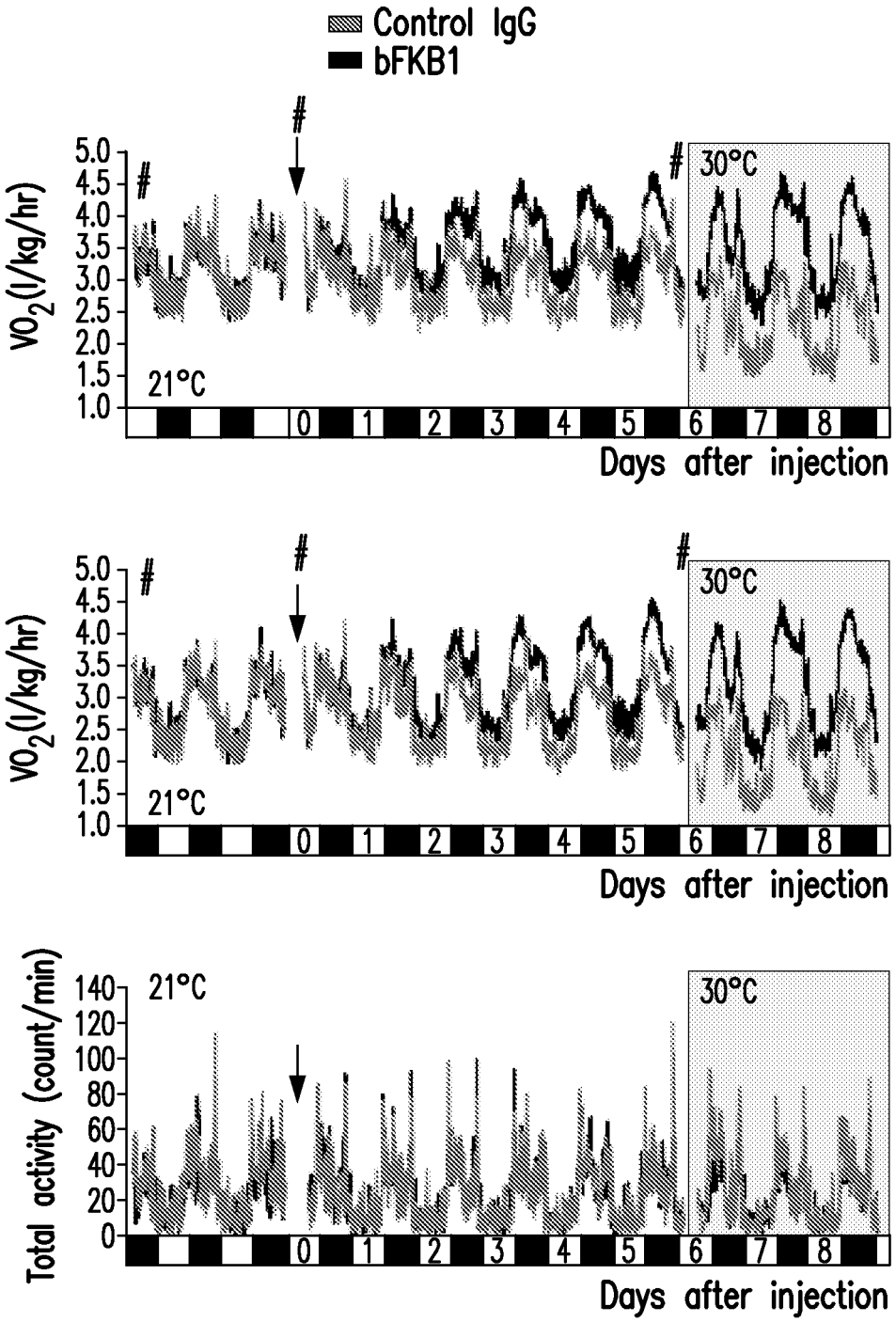

Control IgG
bFKB1
VO_2(l/kg/hr)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
#
21°C
30°C
0 1 2 3 4 5 6 7 8
Days after injection
VO_2(l/kg/hr)
Days after injection
Total activity (count/min)
140
120
100
80
60
40
20
0
Days after injection

FIG. 20B

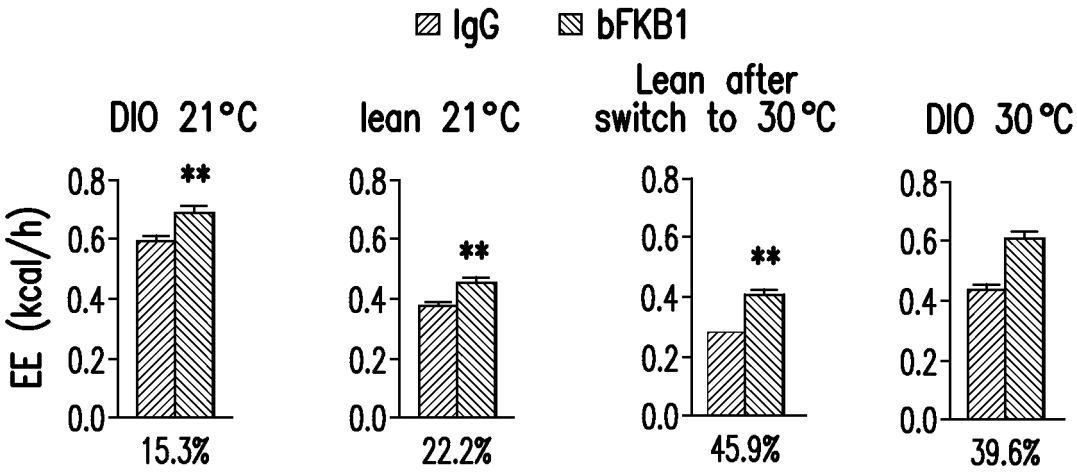


FIG. 21A

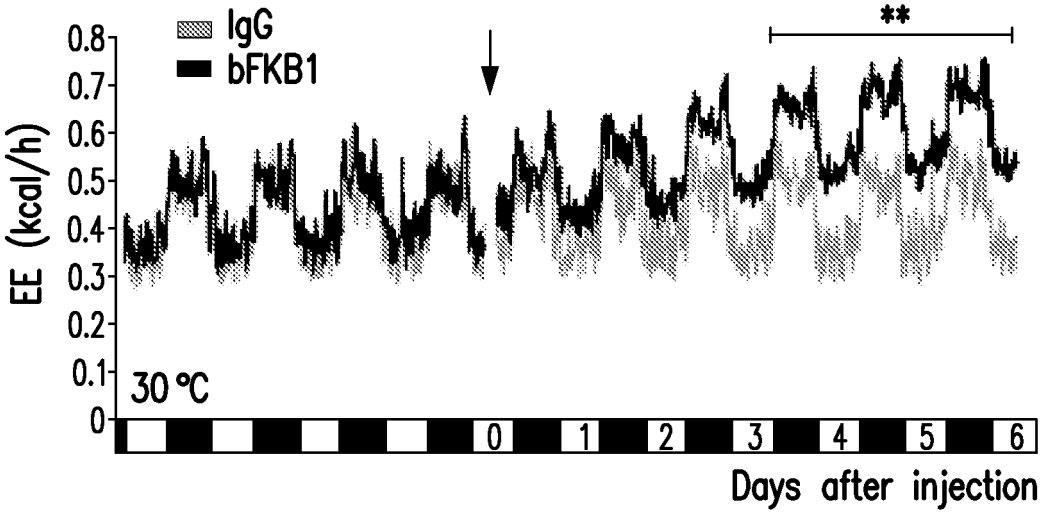


FIG. 21B

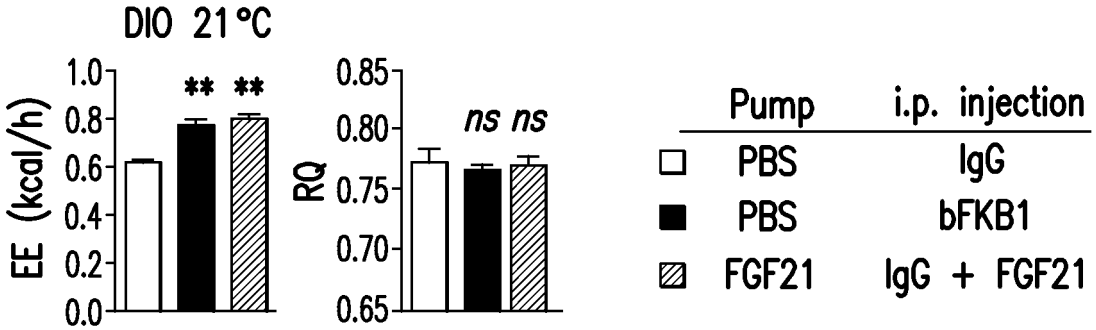


FIG. 21C

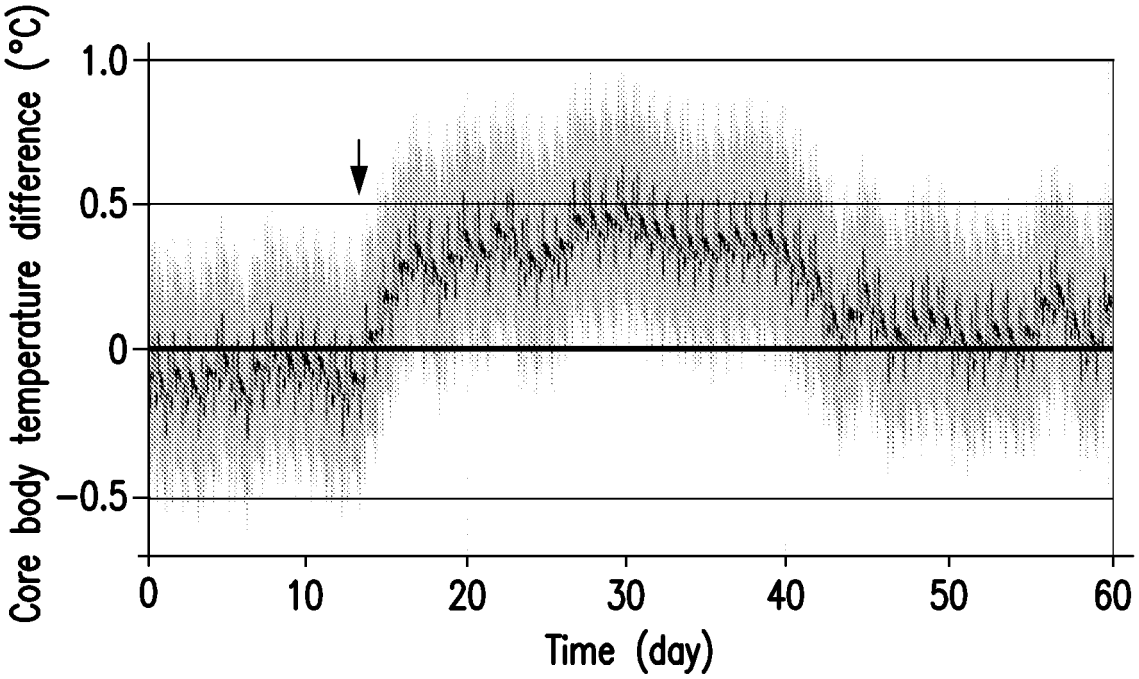

Core body temperature difference (°C)
1.0
0.5
0
−0.5
0
10
20
30
40
50
60
Time (day)

FIG. 22

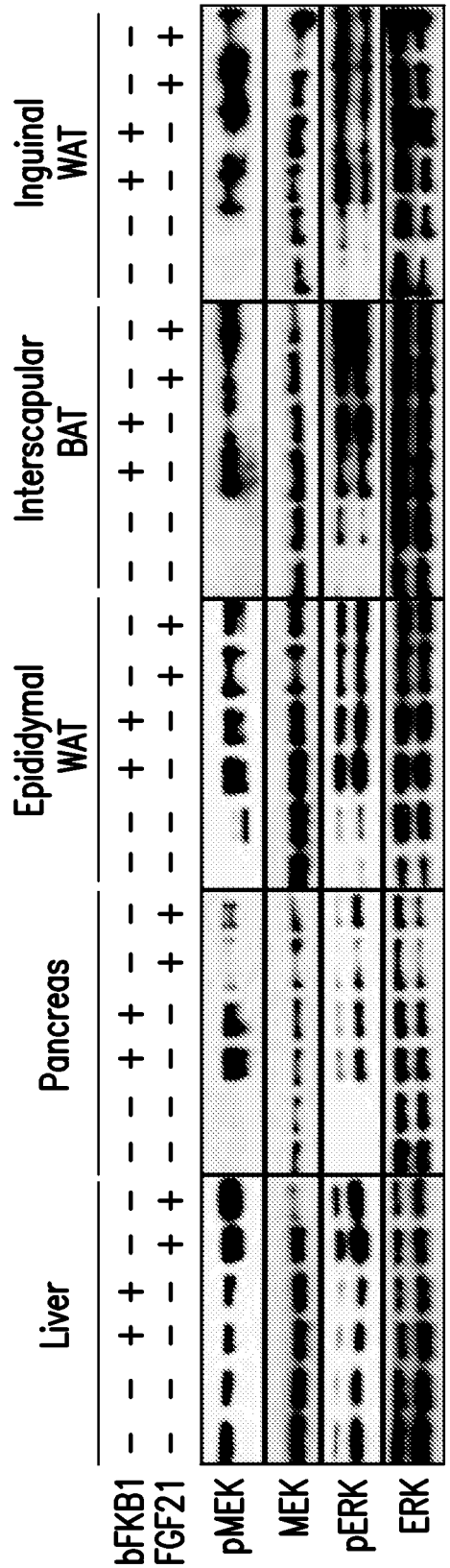

Liver
Pancreas
Epididymal WAT
Interscapular BAT
Inguinal WAT
bFKB1
FGF21
pMEK
MEK
pERK
ERK

FIG. 23

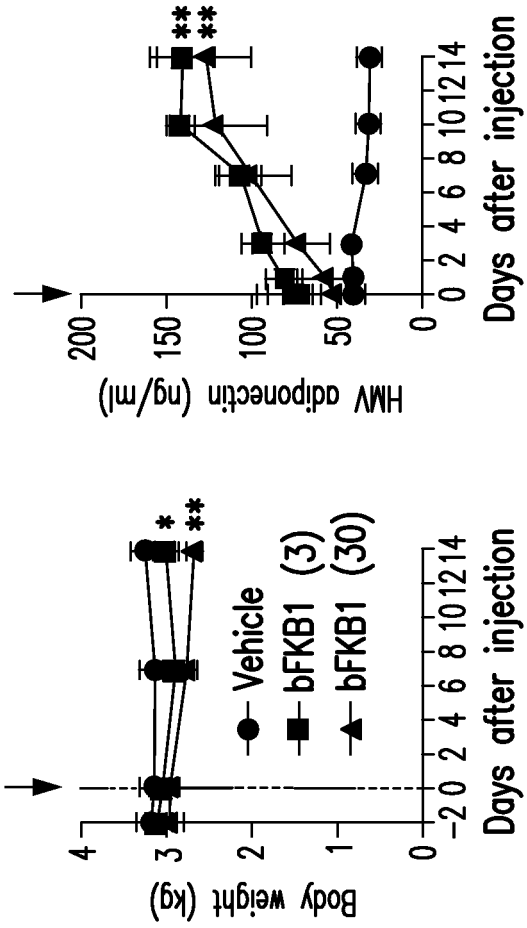


FIG. 24A

FIG. 24B

FIG. 24C

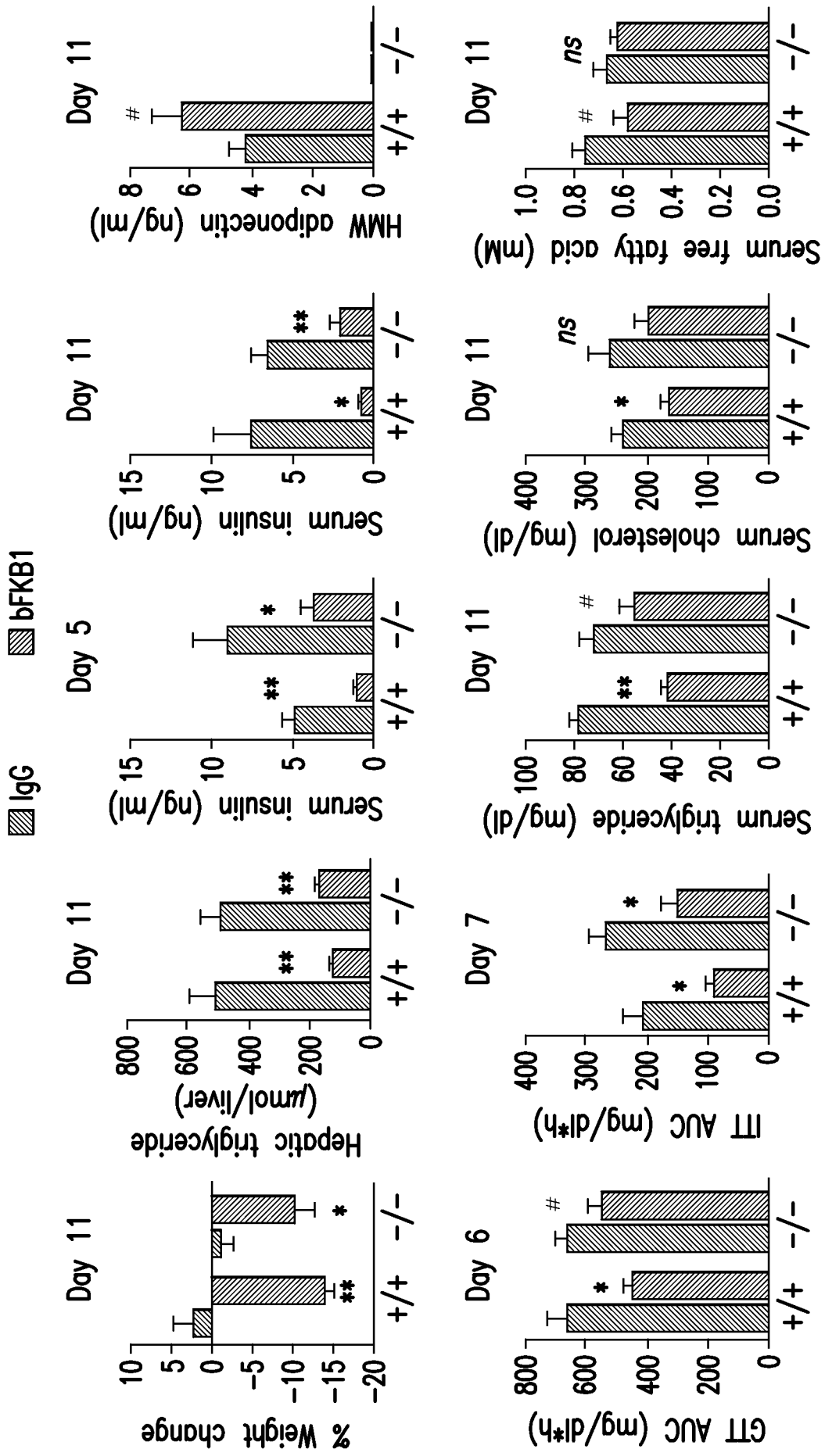

IgG
bFKB1
% Weight change
Day 11
Hepatic triglyceride (μmol/liver)
Day 11
Serum insulin (ng/ml)
Day 5
Serum insulin (ng/ml)
Day 11
HMW adiponectin (ng/ml)
Day 11
GTT AUC (mg/dl*h)
Day 6
ITT AUC (mg/dl*h)
Day 7
Serum triglyceride (mg/dl)
Day 11
Serum cholesterol (mg/dl)
Day 11
Serum free fatty acid (mM)
Day 11
+/+
-/-
ns

FIG. 24D

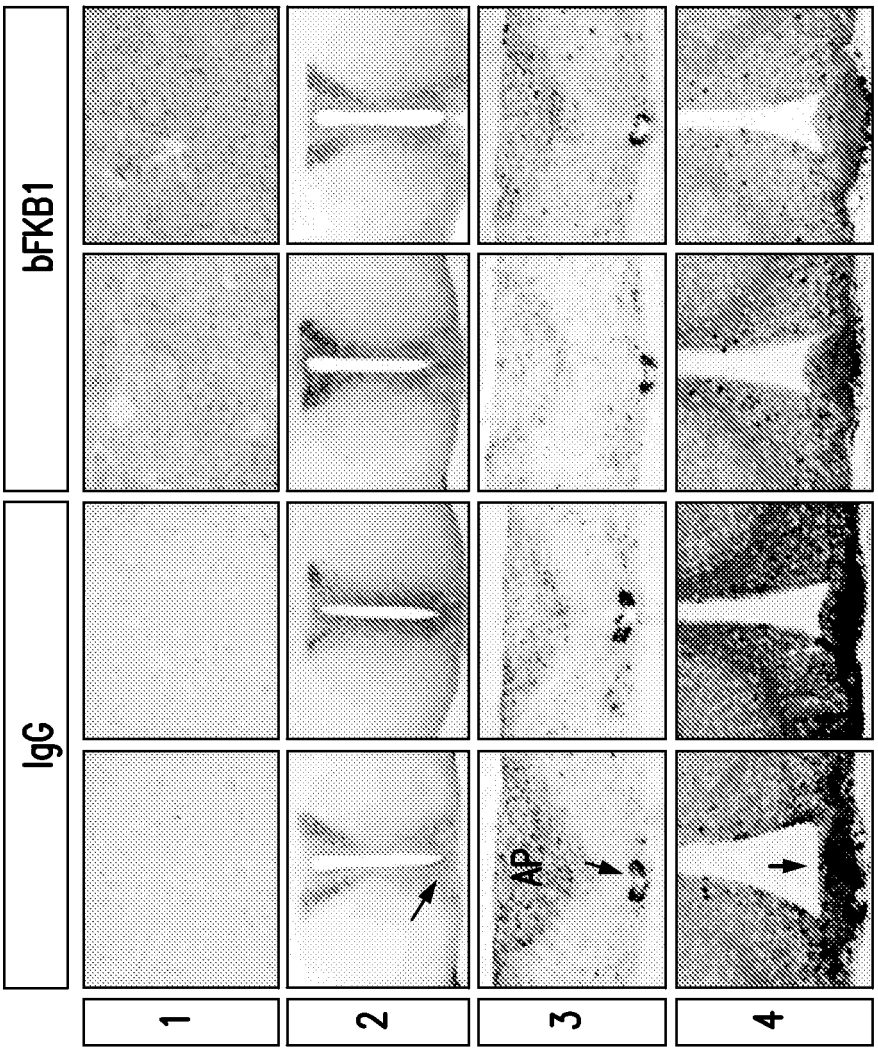


FIG. 26

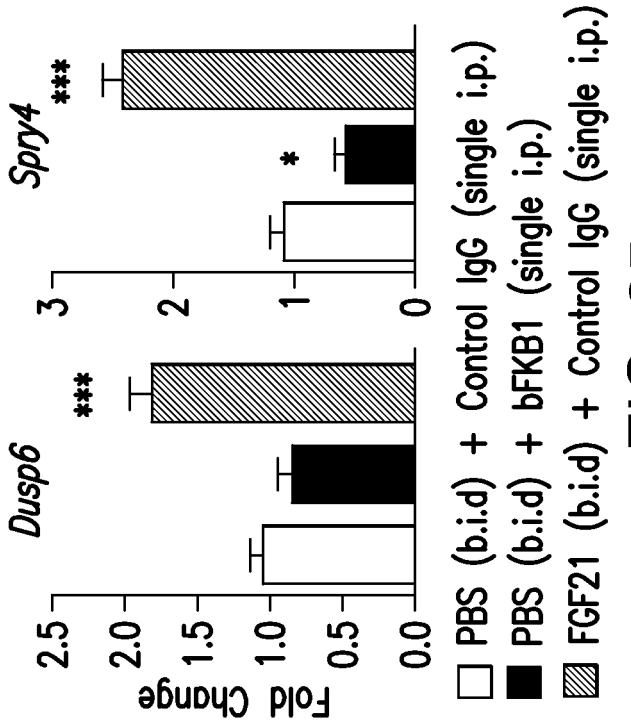


FIG. 25

FIG. 27

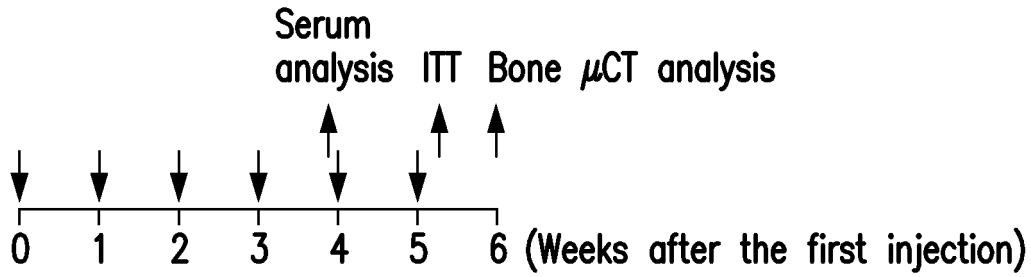


FIG. 28A

	Control IgG	bFKB1 (1 mpk)	bFKB1 (3 mpk)	Lean control
Body weight change (%)	112.8 ± 1.1	116.6 ± 1.1	102.3 ± 4.7 *	
ITT AUC (h*mg/kg)	226 ± 18	153 ± 15 *	156 ± 23 *	
Serum analysis				
Insulin (ng/ml)	3.87 ± 0.42	2.00 ± 0.54 *	1.37 ± 0.65 *	0.59 ± 0.60 ***
FGF21 (pg/ml)	824 ± 67	754 ± 65	696 ± 62 #	690 ± 60 *
Leptin (pg/ml)	46.5 ± 2.3	45.6 ± 2.1	32.9 ± 1.9 *	3.20 ± 1.8 ***
HMW Adiponectin (ng/ml)	2802 ± 202	4174 ± 199	5667 ± 299 *	2745 ± 321 *
Total cholesterol (mg/dl)	240.6 ± 9.3	200.7 ± 9.4 **	177.4 ± 9.7 ***	74.6 ± 9.6 ***
Triglyceride (mg/dl)	41.3 ± 2.7	44.8 ± 2.8	31.9 ± 2.9 $	57.69 ± 2.8 **
FFA (mM)	1.01 ± 0.04	1.04 ± 0.04	0.81 ± 0.04 **	0.77 ± 0.03 **
Trabecular bone μCT analysis				
BV/TV	0.107 ± 0.006	0.114 ± 0.006	0.117 ± 0.010	0.136 ± 0.004 *
Bone Density (mg HA/ccm)	1028 ± 3	1026 ± 6	1033 ± 3	975 ± 6 ***
Bone Volume (mm^3)	0.286 ± 0.026	0.327 ± 0.025	0.330 ± 0.033	0.390 ± 0.017 *
Total Volume (mm^3)	2.65 ± 0.09	2.86 ± 0.07	2.80 ± 0.10	2.87 ± 0.09
Tb.N (mm^{-1})	4.11 ± 0.04	4.08 ± 0.09	4.22 ± 0.13	4.73 ± 0.07 ***
Tb.Th (mm)	0.0517 ± 0.0009	0.0526 ± 0.0008	0.0528 ± 0.0014	0.0477 ± 0.0002 *
Tb.Sp (mm)	0.234 ± 0.003	0.235 ± 0.006	0.228 ± 0.008	0.202 ± 0.003 ***
Bone surface area (mm^2)	13.6 ± 1.0	15.5 ± 1.0	15.3 ± 1.2	19.5 ± 0.9 **
BS/BV(mm^{-1})	52.6 ± 1.7	51.3 ± 1.1	51.2 ± 2.1	53.5 ± 0.4
Cortical bone μCT analysis				
BV/TV	0.404 ± 0.005	0.391 ± 0.005	0.391 ± 0.006	0.393 ± 0.007
Bone Density (mg HA/cm^3)	1236 ± 2	1239 ± 3	1240 ± 22	1243 ± 2 *
Bone Volume (mm^3)	2.55 ± 0.06	2.57 ± 0.06	2.46 ± 0.07	2.56 ± 0.09
Total Volume (mm^3)	6.33 ± 0.17	6.6 ± 0.23	6.33 ± 0.26	6.52 ± 0.26
Bone Thickness (mm)	0.119 ± 0.001	0.116 ± 0.001	0.115 ± 0.001 $	0.115 ± 0.002
Marrow Volume (mm^3)	3.79 ± 0.12	4.05 ± 0.17	3.88 ± 0.22	3.98 ± 0.18

FIG. 28B

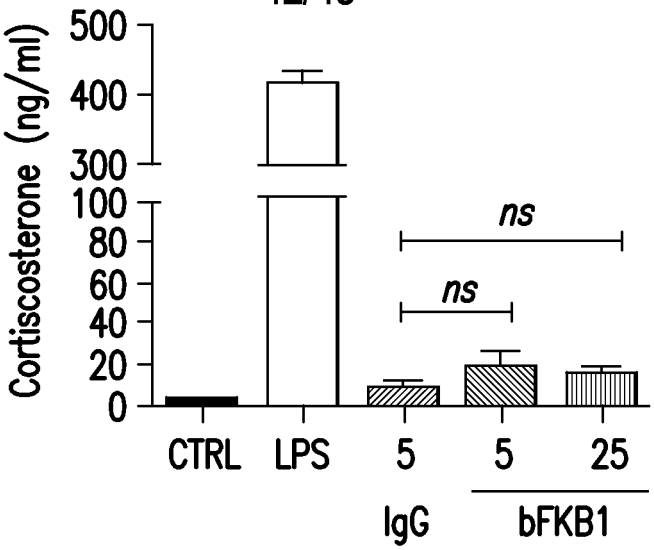

Cortiscosterone (ng/ml)
500
400
300
100
80
60
40
20
0
ns
ns
CTRL
LPS
5
5
25
IgG
bFKB1

FIG. 29

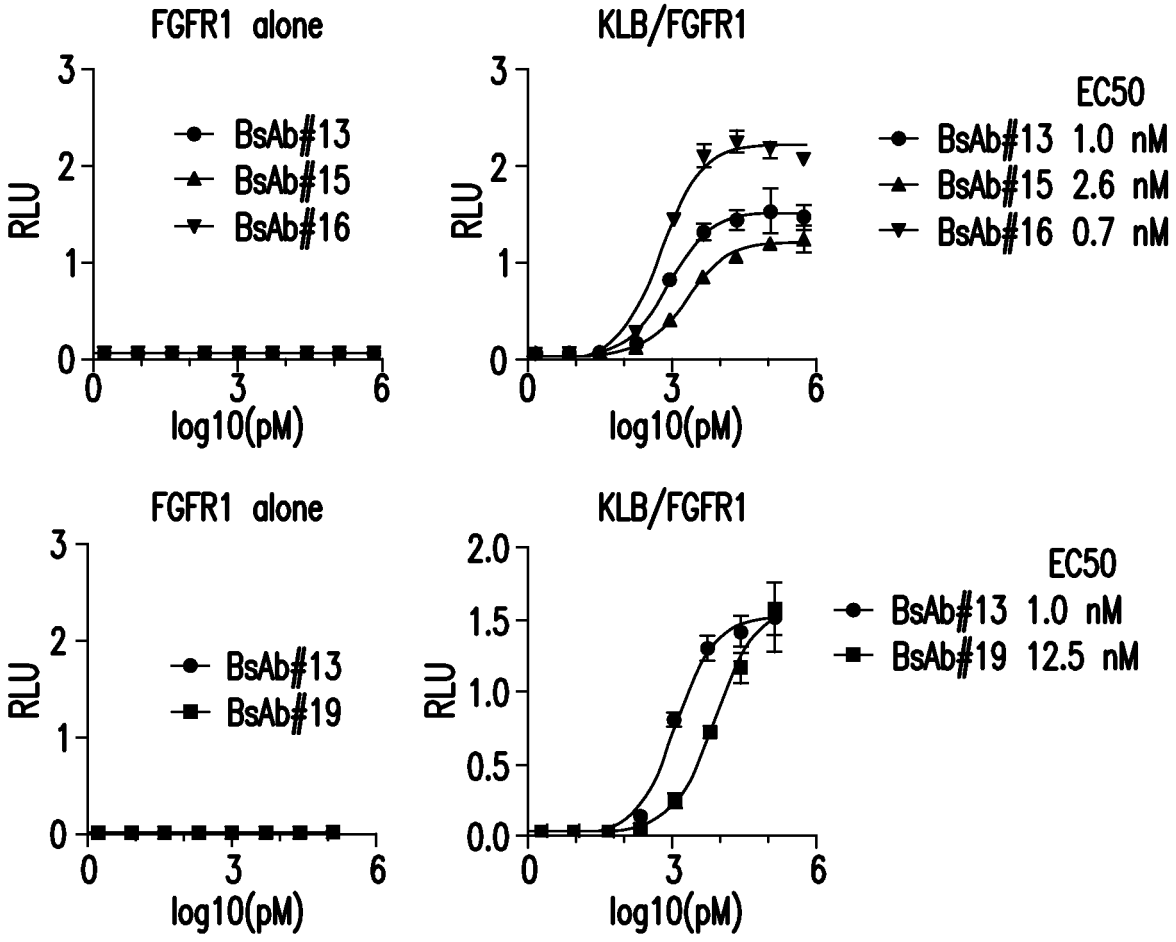

FGFR1 alone
KLB/FGFR1
RLU
log10(pM)
BsAb#13
BsAb#15
BsAb#16
EC50
BsAb#13 1.0 nM
BsAb#15 2.6 nM
BsAb#16 0.7 nM
FGFR1 alone
KLB/FGFR1
RLU
log10(pM)
BsAb#13
BsAb#19
EC50
BsAb#13 1.0 nM
BsAb#19 12.5 nM

FIG. 30

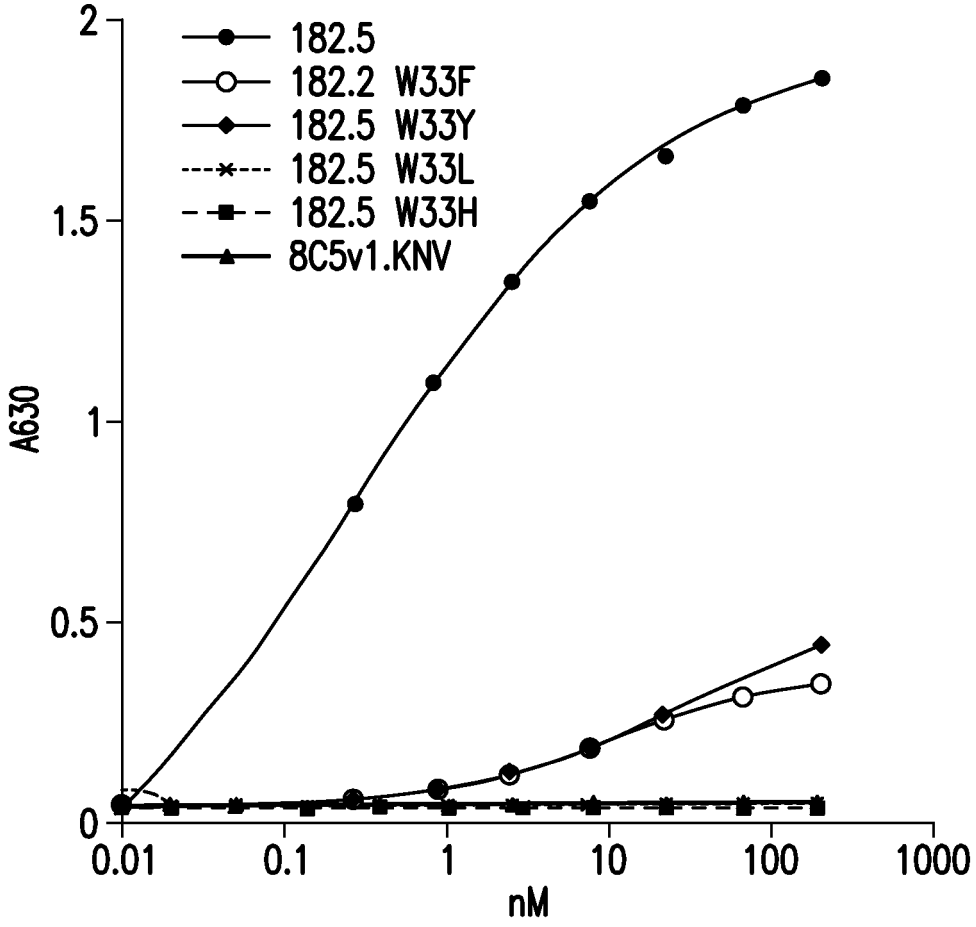

182.5
182.2 W33F
182.5 W33Y
182.5 W33L
182.5 W33H
8C5v1.KNV
A630
2
1.5
1
0.5
0
0.01
0.1
1
10
100
1000
nM

FIG. 31