FGF19 (SEQ ID NO:42):

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVV
DCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLL
QYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFL
PLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLE
AVRSPSFEKDYKDDDDK

FIG.1

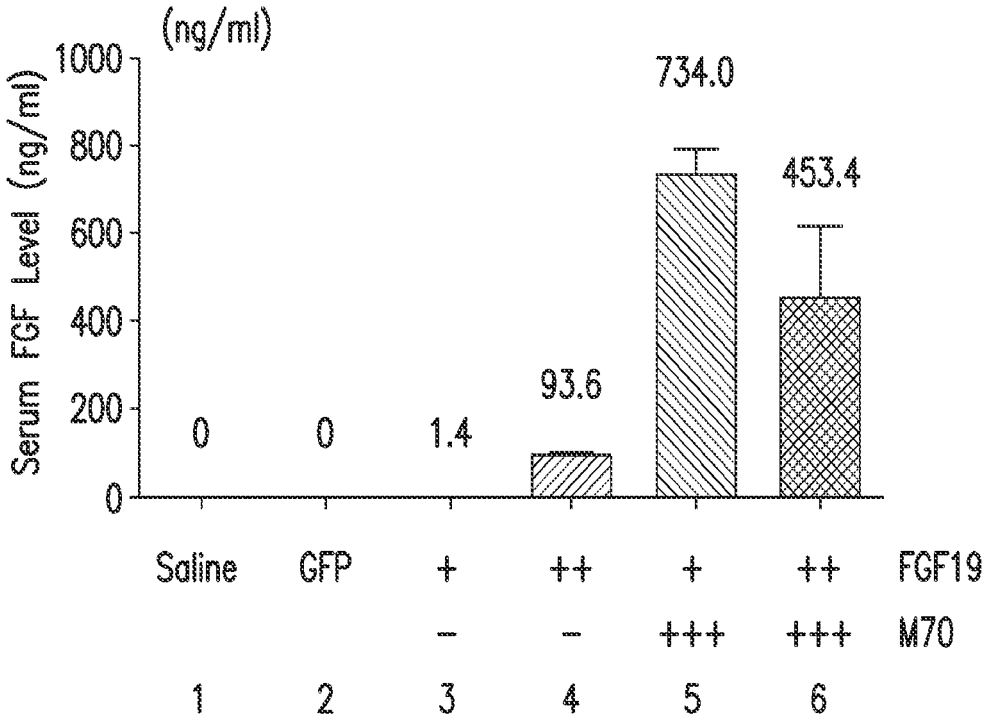

(ng/ml)
Serum FGF Level (ng/ml)
1000
800
600
400
200
0
0
0
1.4
93.6
734.0
453.4
Saline
GFP
+
++
+
++
FGF19
–
–
+++
+++
M70
1
2
3
4
5
6

FIG.2

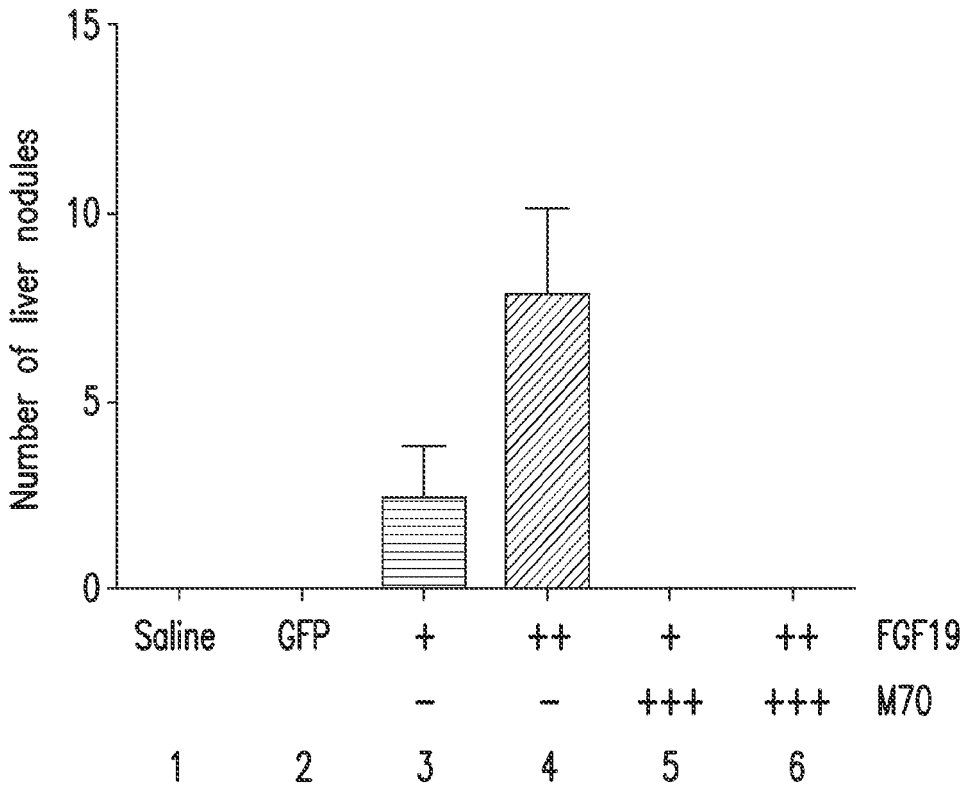


FIG.3

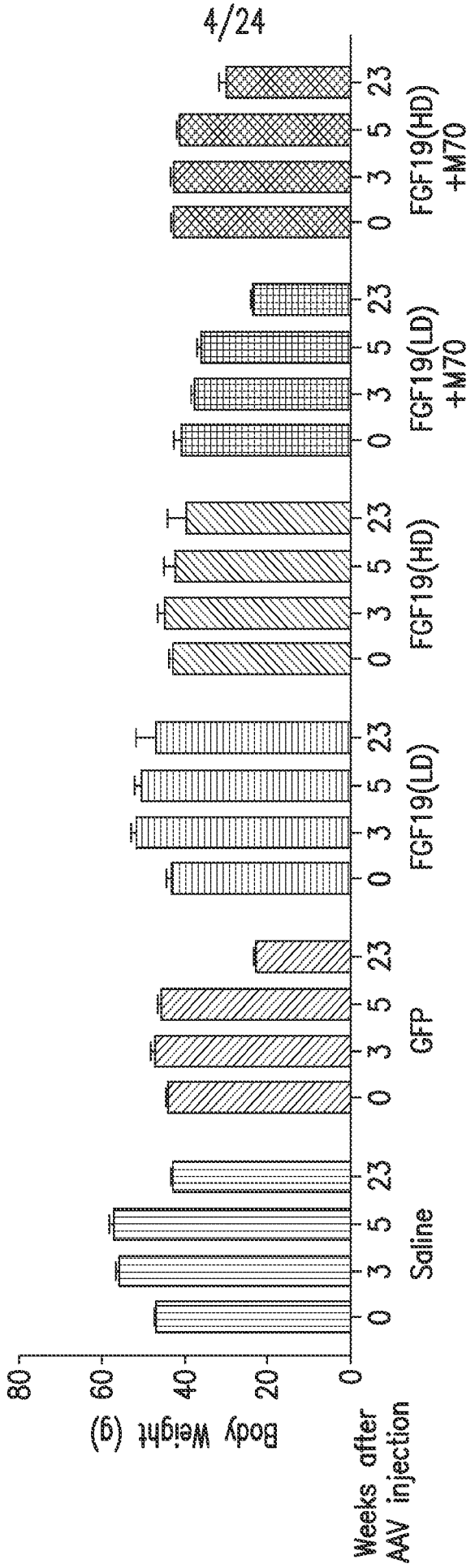

Body Weight (g)
0
20
40
60
80
Weeks after AAV injection
0 3 5 23
Saline
GFP
FGF19(LD)
FGF19(HD)
FGF19(LD) +M70
FGF19(HD) +M70

FIG.4

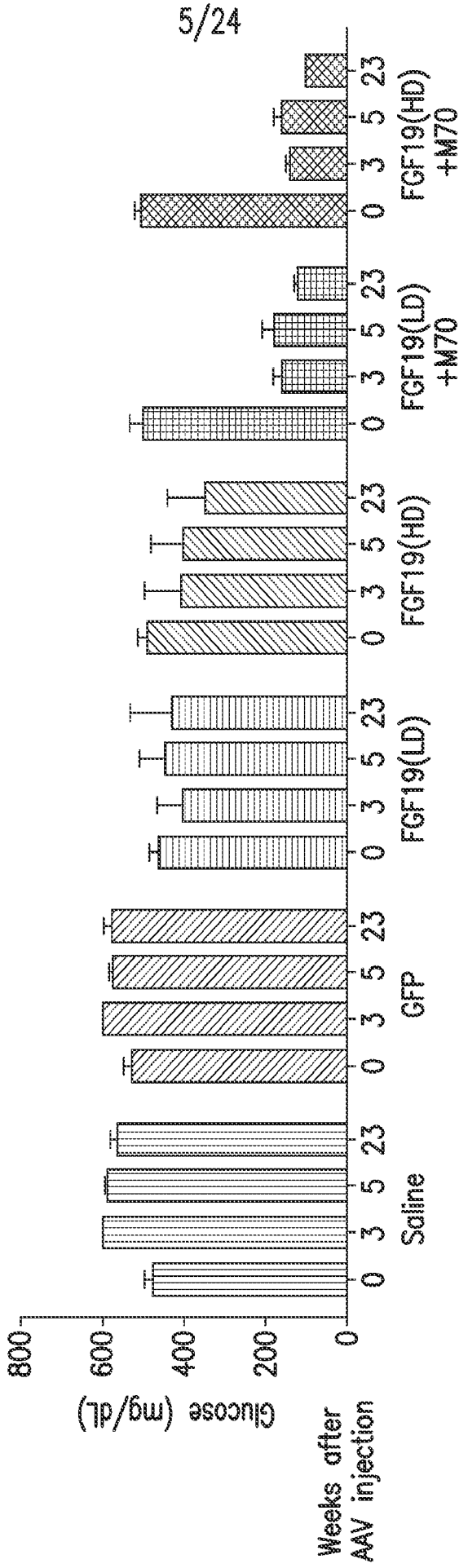

Glucose (mg/dL)
800
600
400
200
0
Weeks after AAV injection
0 3 5 23
Saline
0 3 5 23
GFP
0 3 5 23
FGF19(LD)
0 3 5 23
FGF19(HD)
0 3 5 23
FGF19(LD) +M70
0 3 5 23
FGF19(HD) +M70

FIG. 5

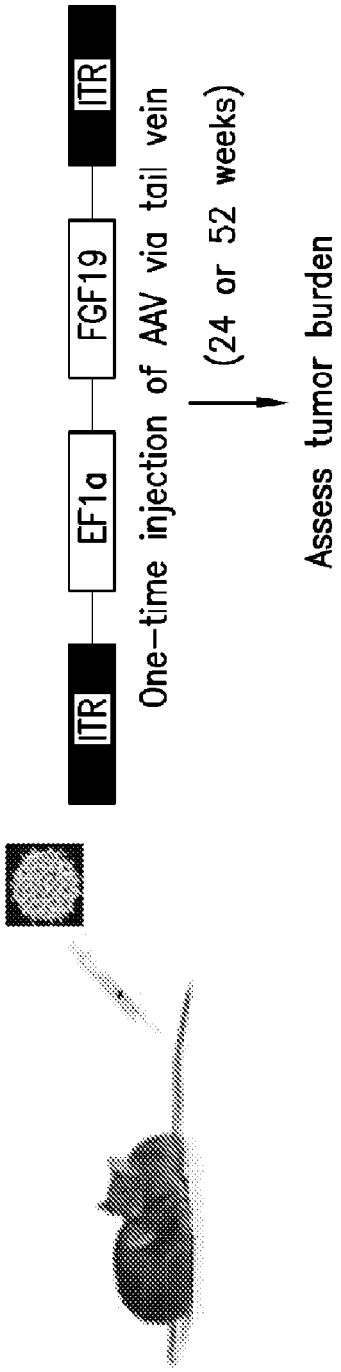

ITR
EF1a
FGF19
ITR
One-time injection of AAV via tail vein
(24 or 52 weeks)
Assess tumor burden

FIG.6A

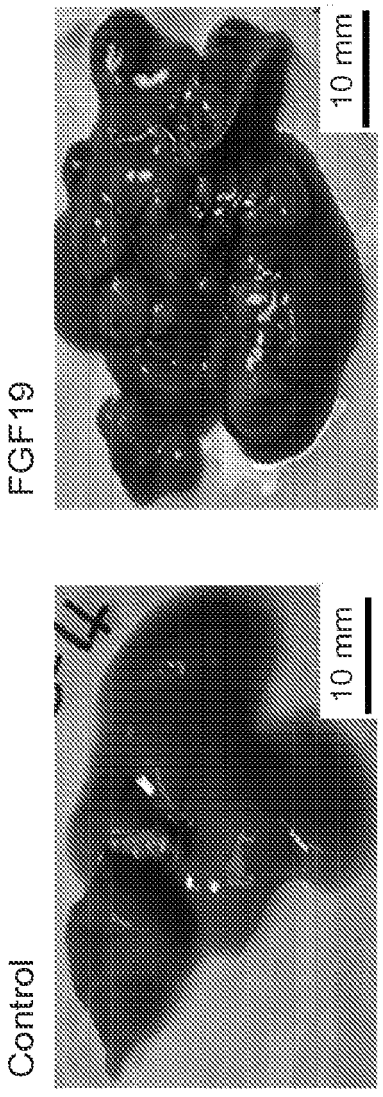

FGF19
Control
10 mm
10 mm

FIG.6B

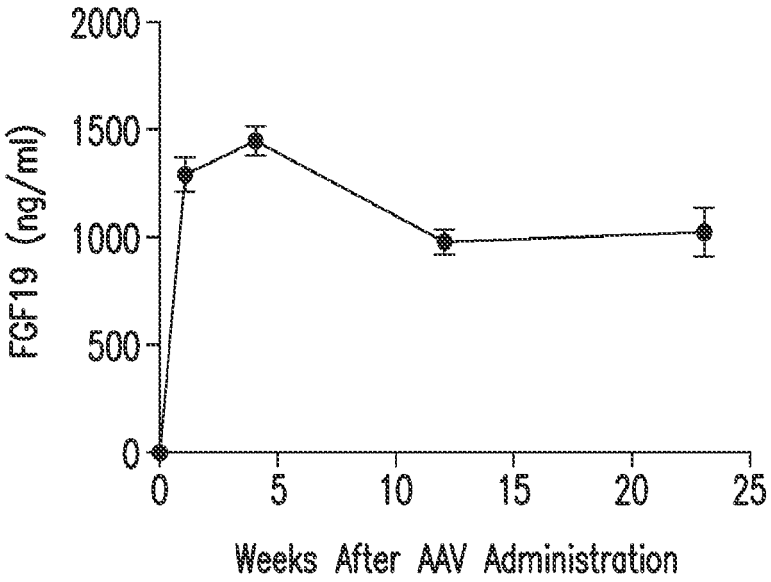

2000
1500
1000
500
0
FGF19 (ng/ml)
0
5
10
15
20
25
Weeks After AAV Administration

FIG.6C

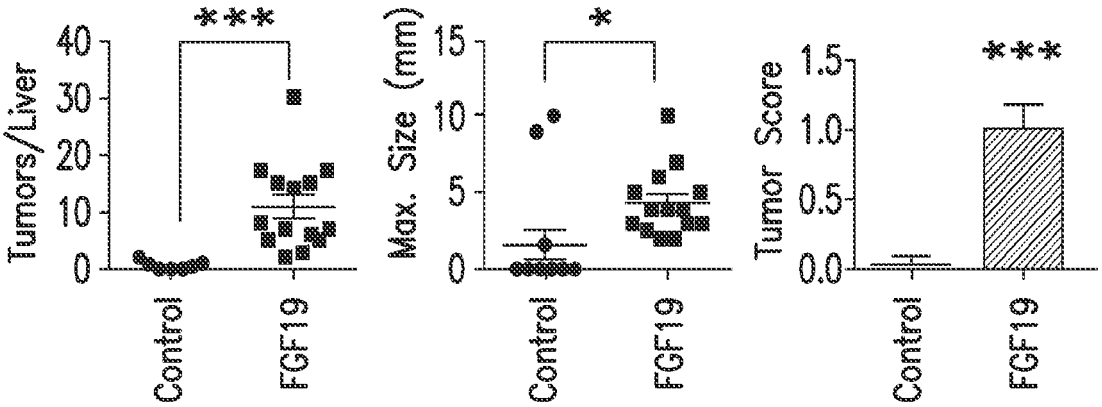

***
Tumors/Liver
40
30
20
10
0
Control
FGF19
*
Max. Size (mm)
15
10
5
0
Control
FGF19
***
Tumor Score
1.5
1.0
0.5
0.0
Control
FGF19

FIG.6D

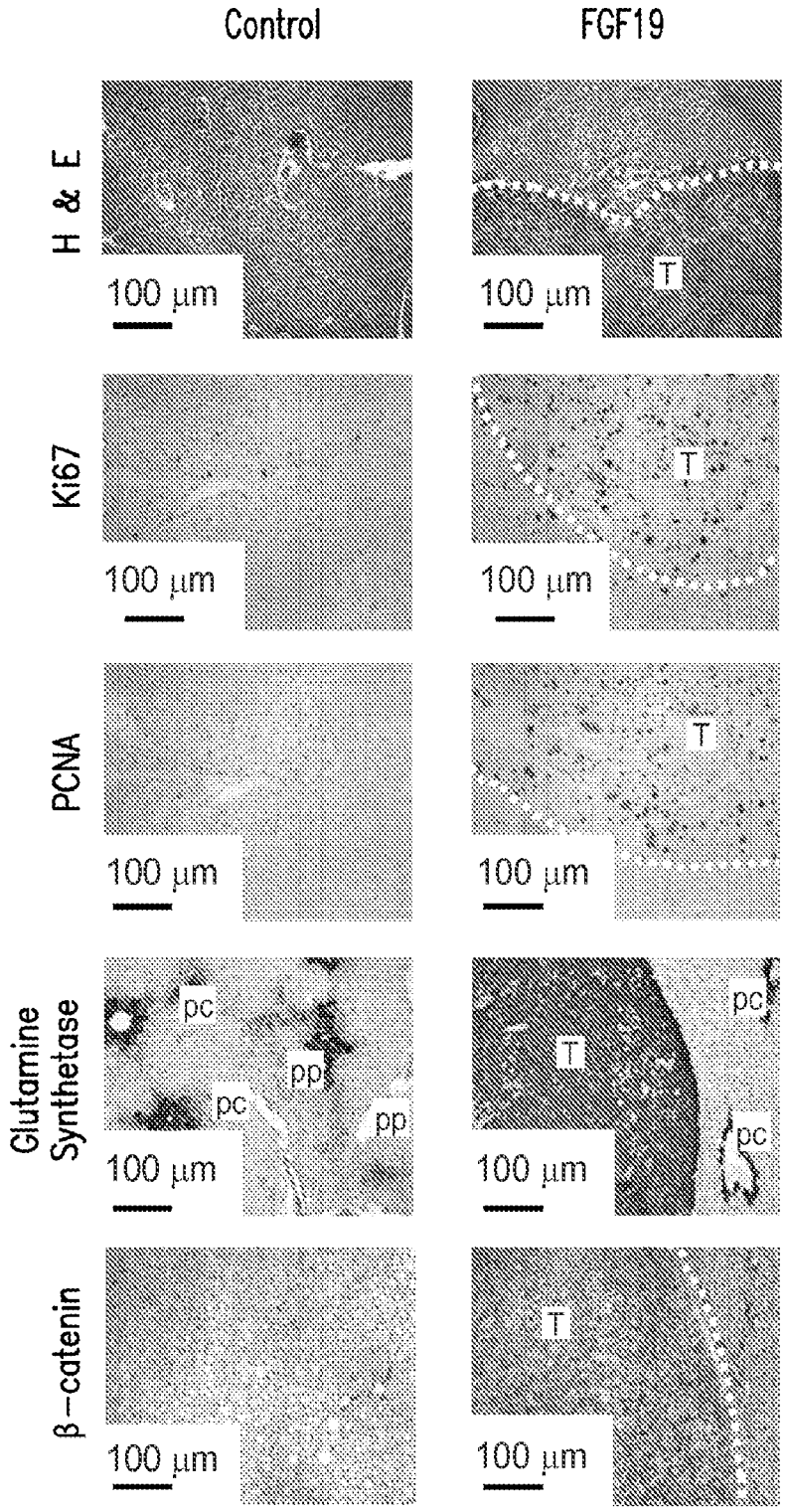

Control
FGF19
H & E
Ki67
PCNA
Glutamine Synthetase
β-catenin
100 μm
T
pc
pp

FIG.6E

FGF19 RPLAFSDAGPHVHYGWGDPI-

M70 MR------DSSPLVHYGWGDPI-

FIG.7A

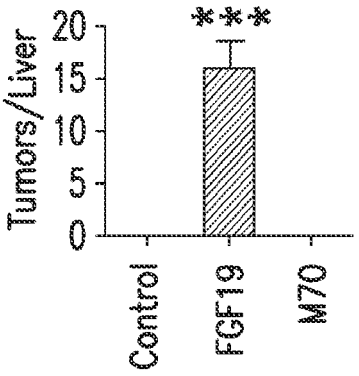


FIG.7B

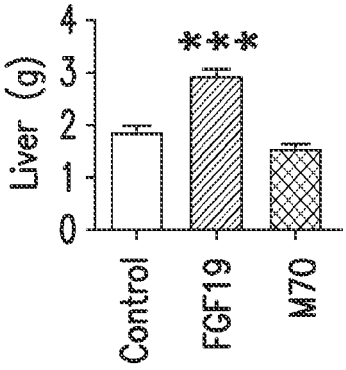


FIG.7C

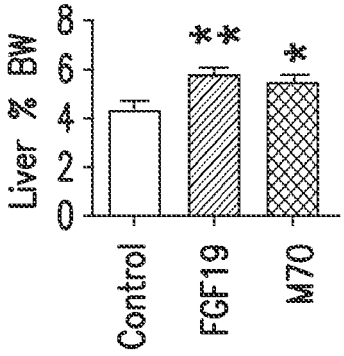


FIG.7D

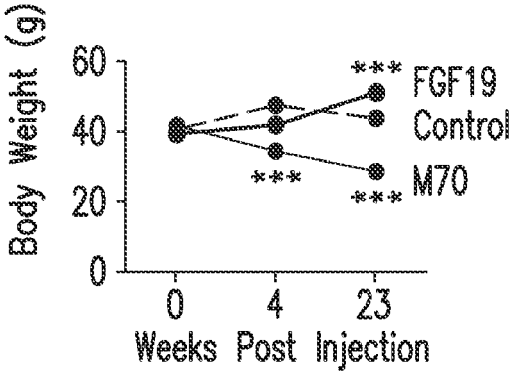


FIG.7E

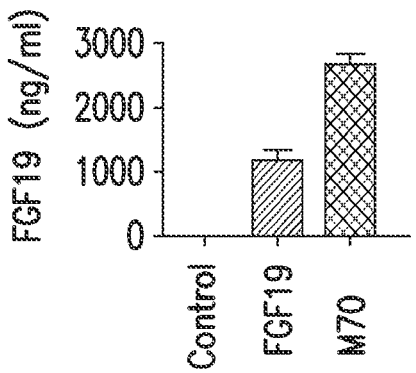


FIG.7F

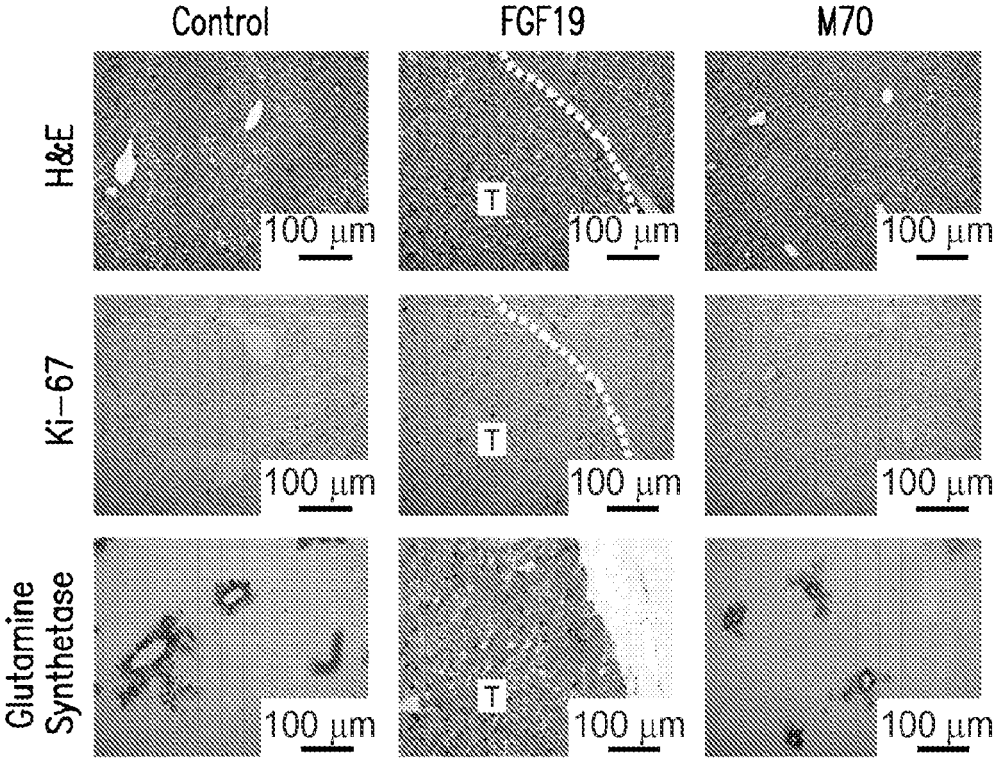

Control
FGF19
M70
H&E
Ki−67
Glutamine Synthetase
T
100 μm

FIG.7G

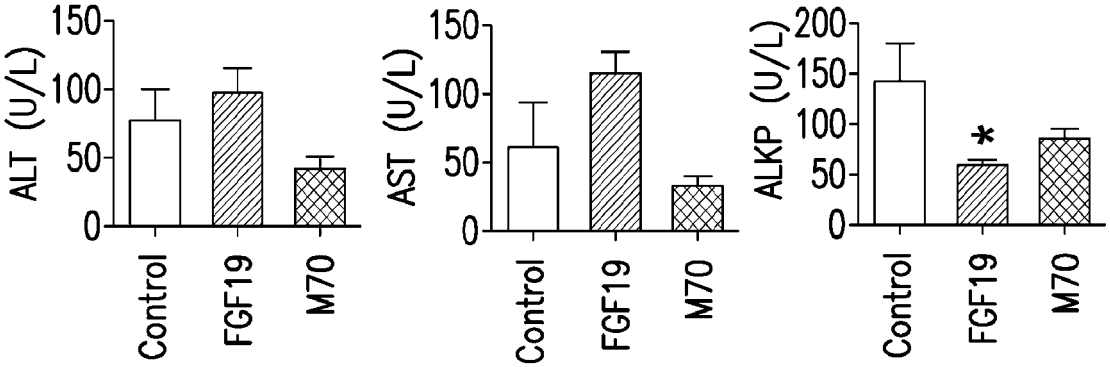

ALT (U/L)
AST (U/L)
ALKP (U/L)
150
100
50
0
200
*
Control
FGF19
M70

FIG.7H

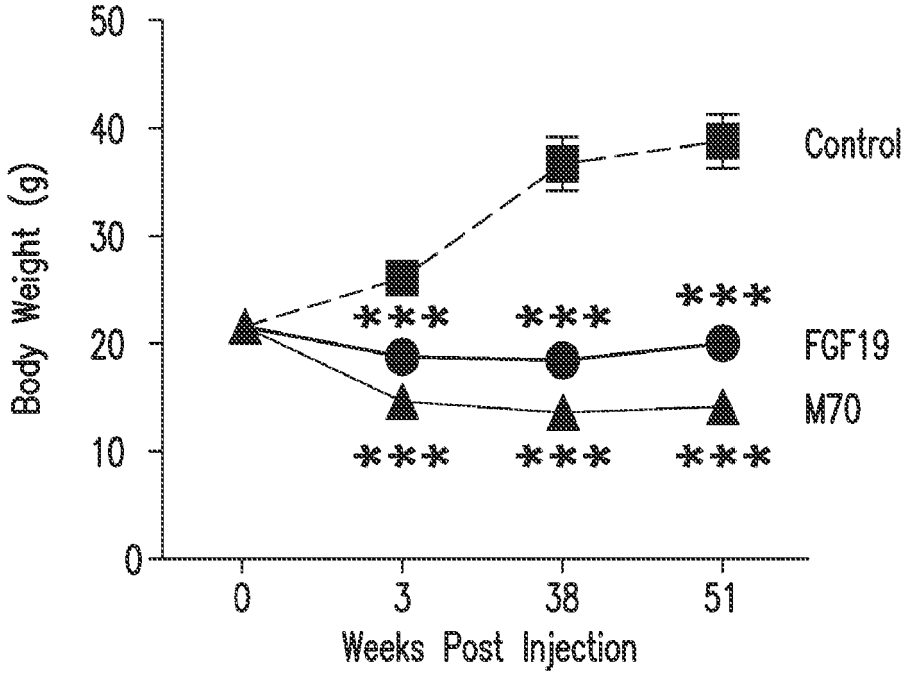


FIG.8A

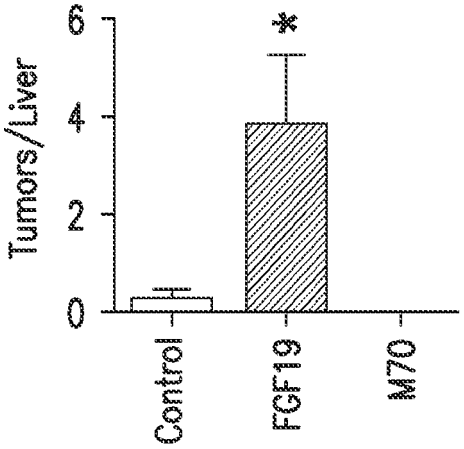


FIG.8B

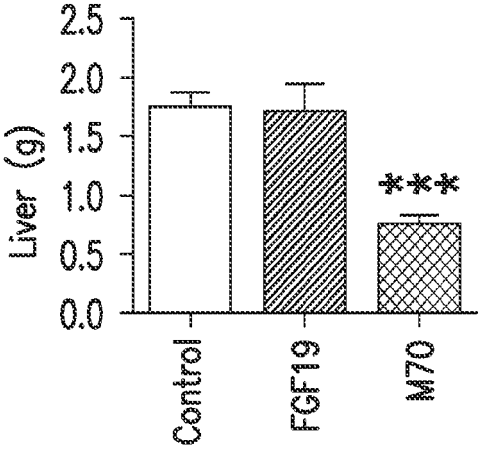


FIG.8C

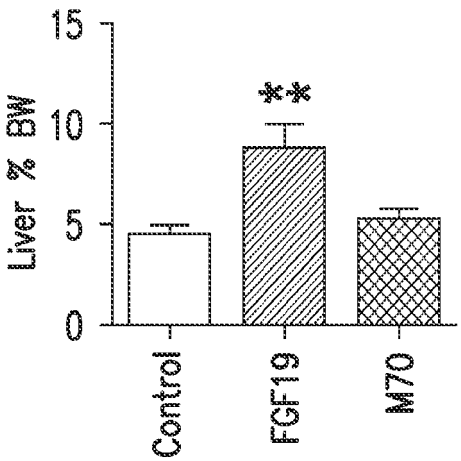


FIG.8D

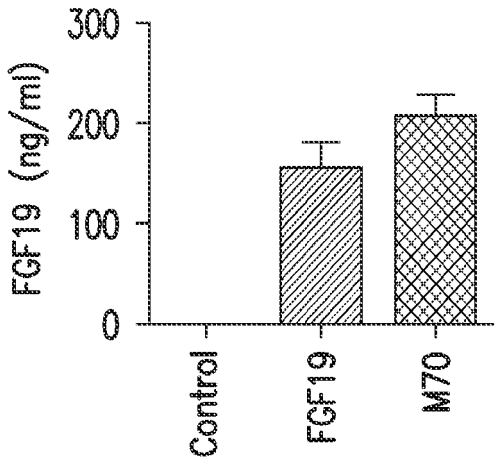


FIG.8E

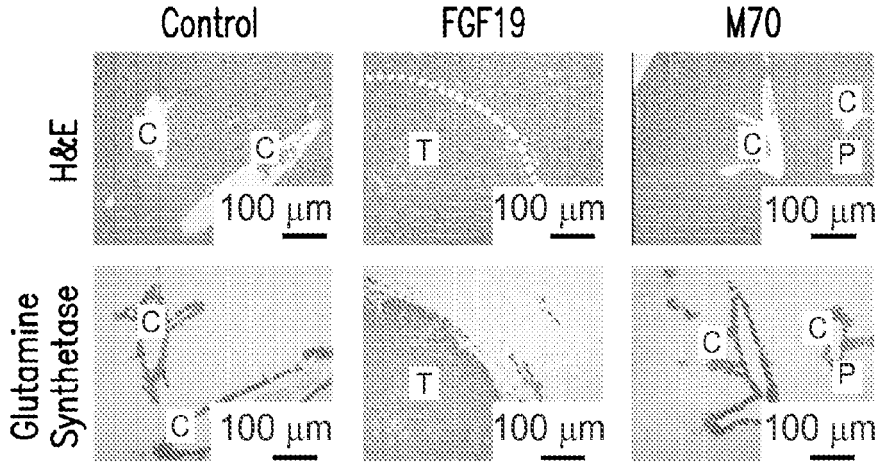

Control
FGF19
M70
H&E
Glutamine Synthetase
C
T
P
100 μm

FIG.8F

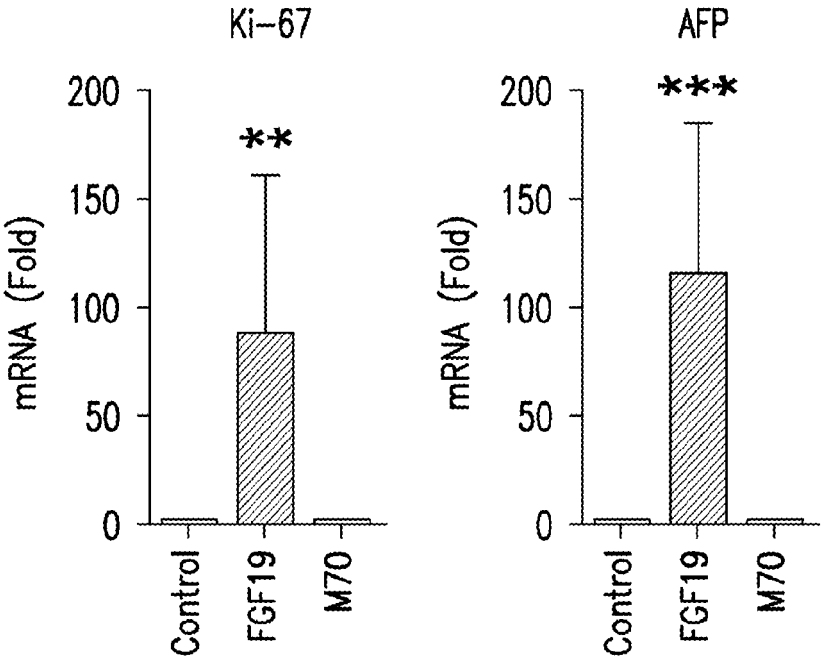

Ki-67
AFP
mRNA (Fold)
200
150
100
50
0
**
***
Control
FGF19
M70

FIG.8G

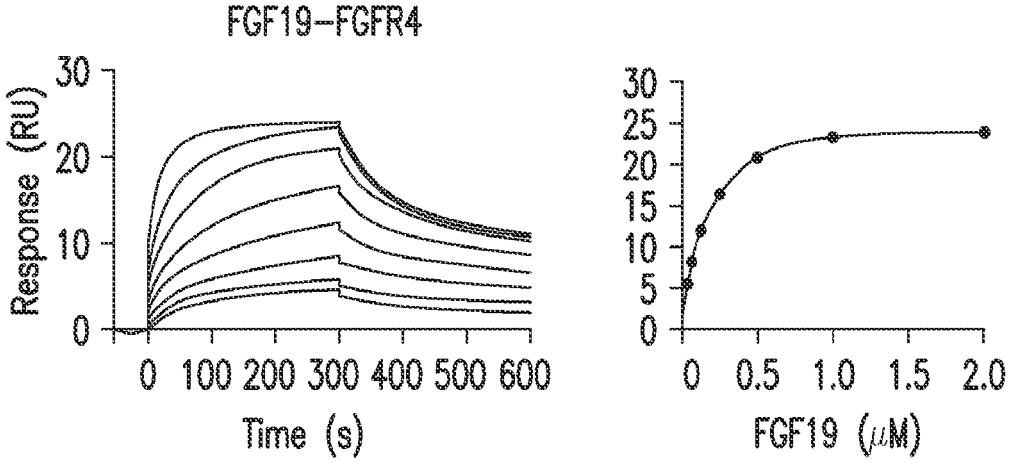

FGF19–FGFR4
Response (RU)
30
20
10
0
0 100 200 300 400 500 600
Time (s)
30
25
20
15
10
5
0
0 0.5 1.0 1.5 2.0
FGF19 (μM)

FIG.9A

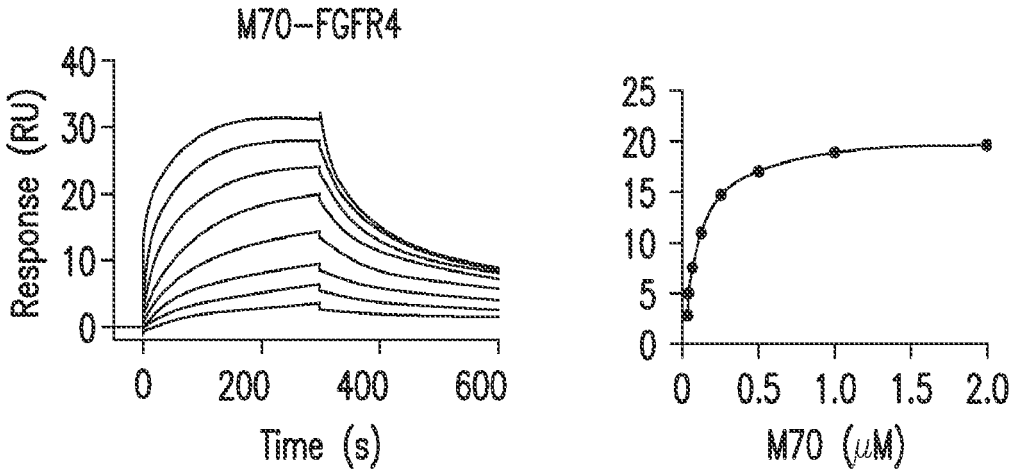

M70–FGFR4
Response (RU)
40
30
20
10
0
0 200 400 600
Time (s)
25
20
15
10
5
0
0 0.5 1.0 1.5 2.0
M70 (μM)

FIG.9B

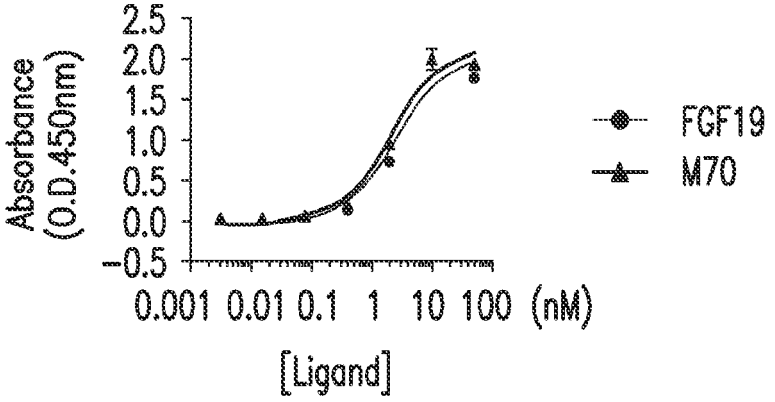


FIG.9C

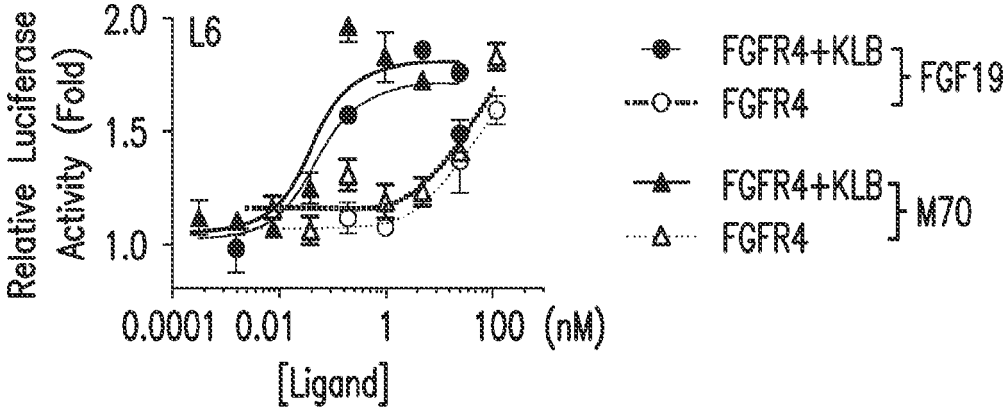


FIG.9D

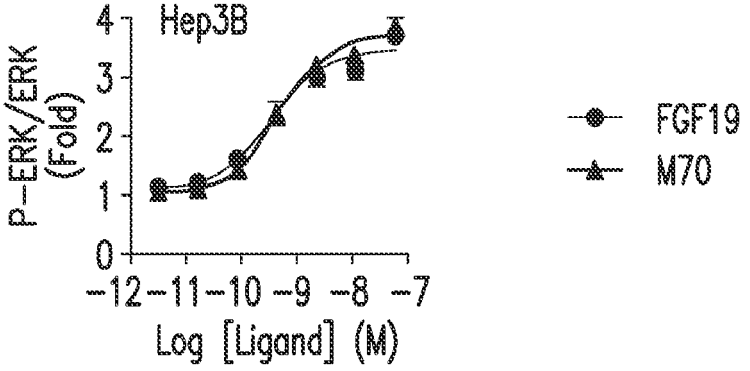


FIG.9E

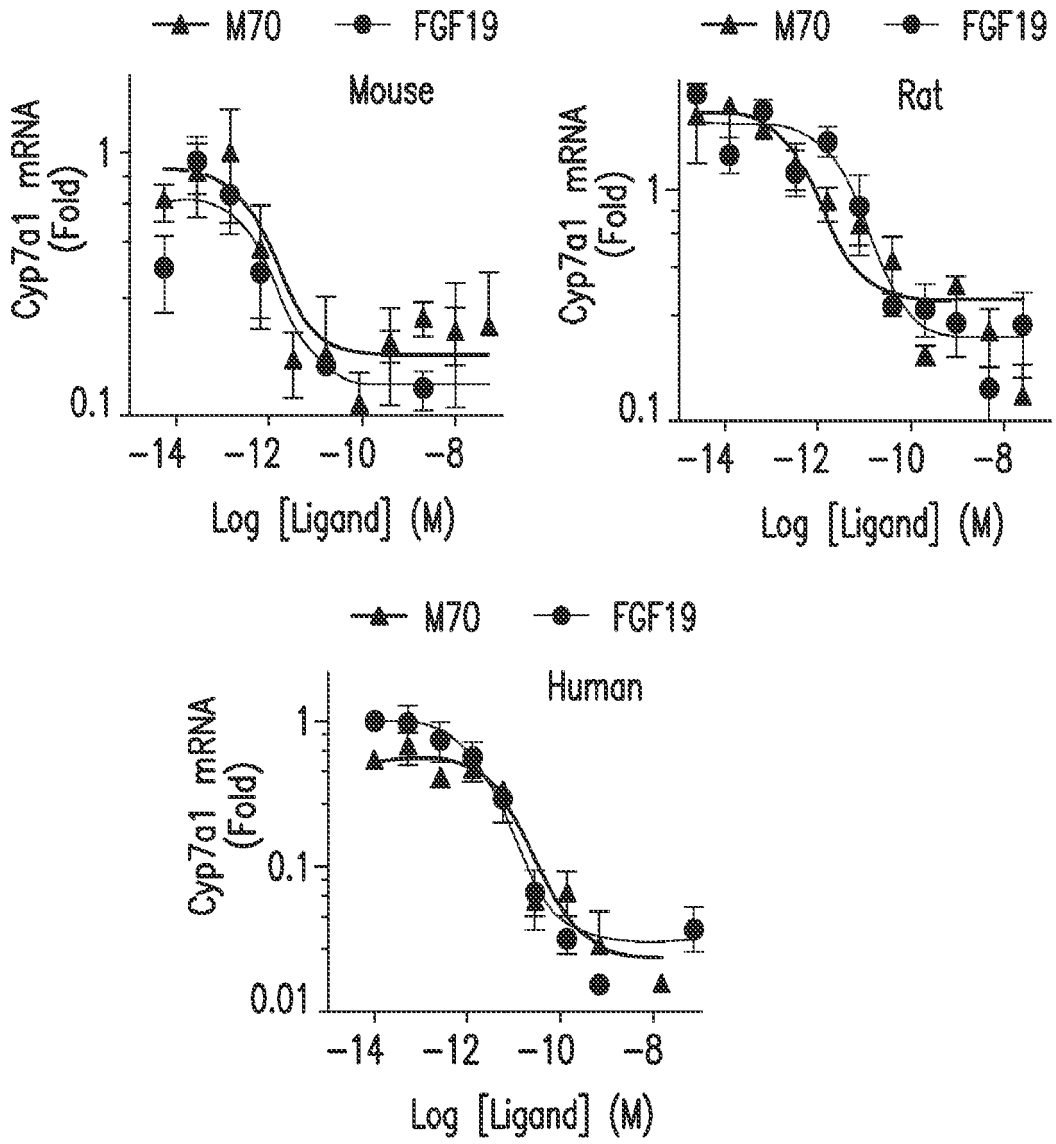

M70
FGF19
Mouse
Cyp7a1 mRNA (Fold)
1
0.1
-14
-12
-10
-8
Log [Ligand] (M)
M70
FGF19
Rat
Cyp7a1 mRNA (Fold)
1
0.1
-14
-12
-10
-8
Log [Ligand] (M)
M70
FGF19
Human
Cyp7a1 mRNA (Fold)
1
0.1
0.01
-14
-12
-10
-8
Log [Ligand] (M)

FIG.9F

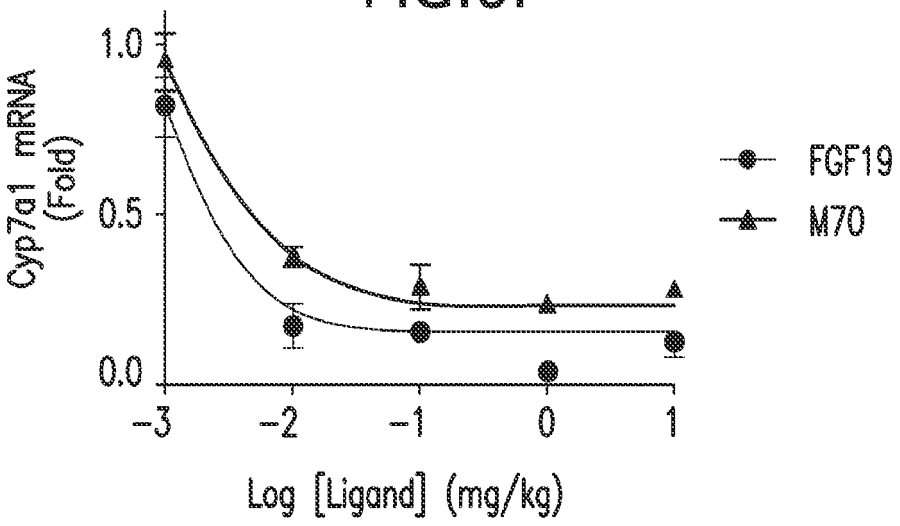

Cyp7a1 mRNA (Fold)
1.0
0.5
0.0
-3
-2
-1
0
1
Log [Ligand] (mg/kg)
FGF19
M70

FIG.9G

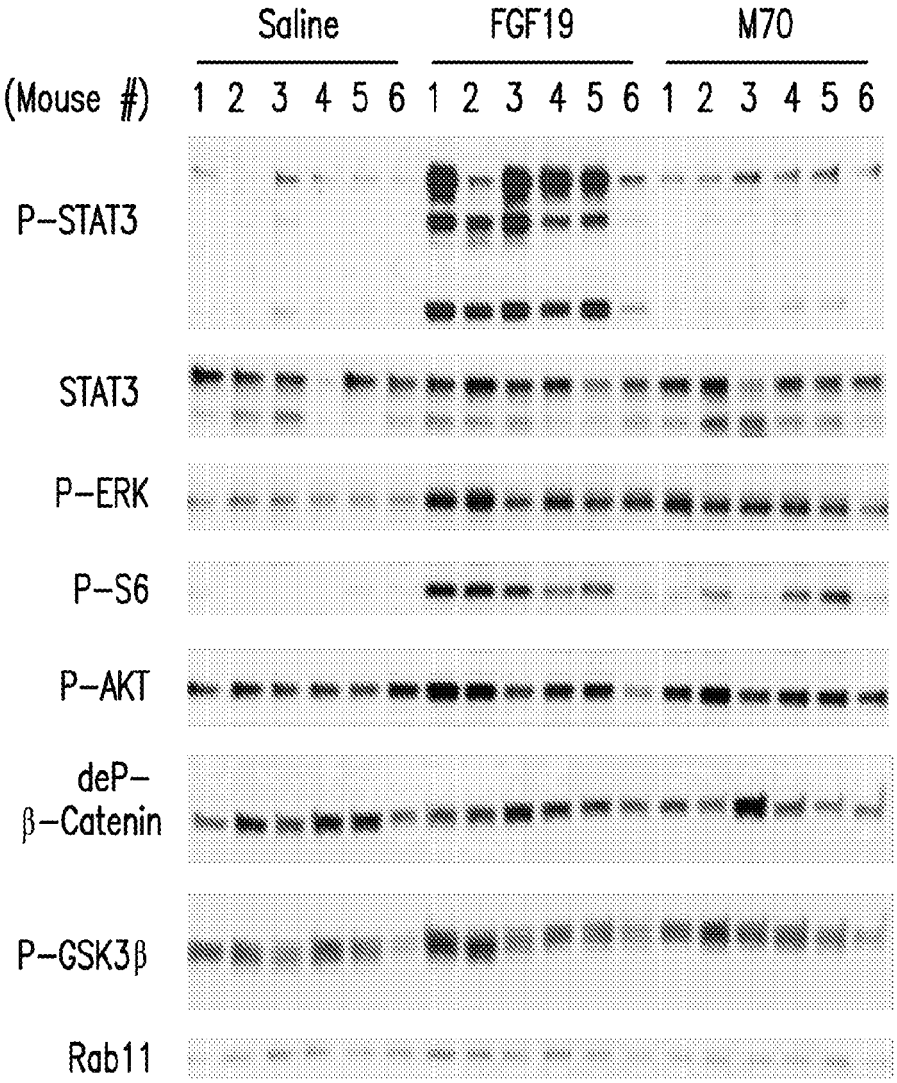

Saline
FGF19
M70
(Mouse #)
1 2 3 4 5 6 1 2 3 4 5 6 1 2 3 4 5 6
P-STAT3
STAT3
P-ERK
P-S6
P-AKT
deP-
β-Catenin
P-GSK3β
Rab11

FIG.10A

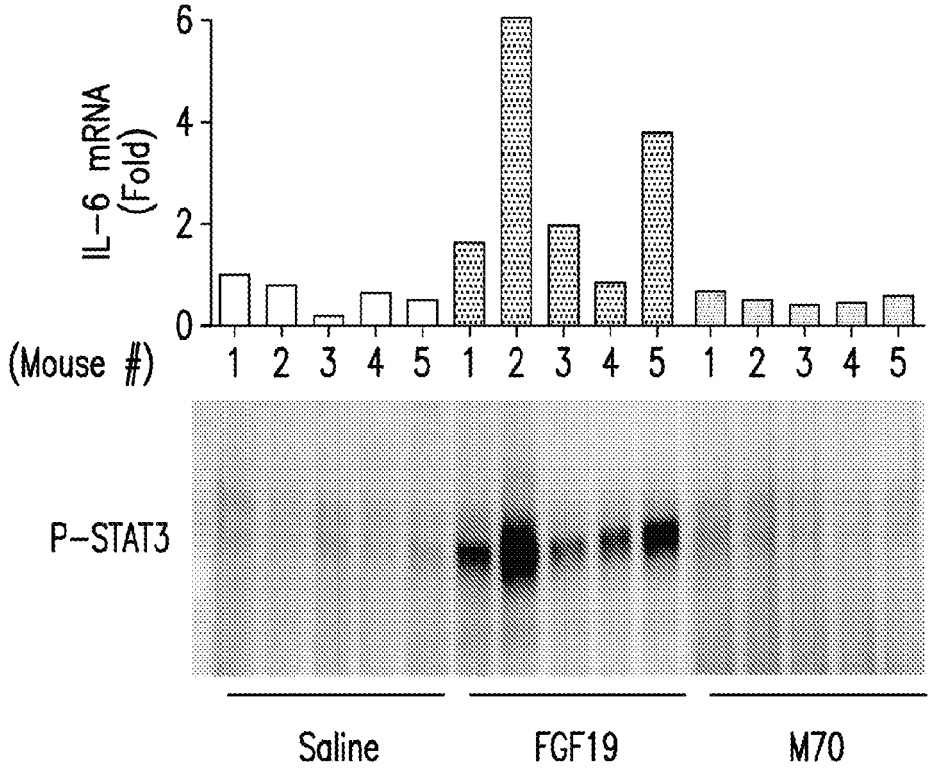


FIG.10B

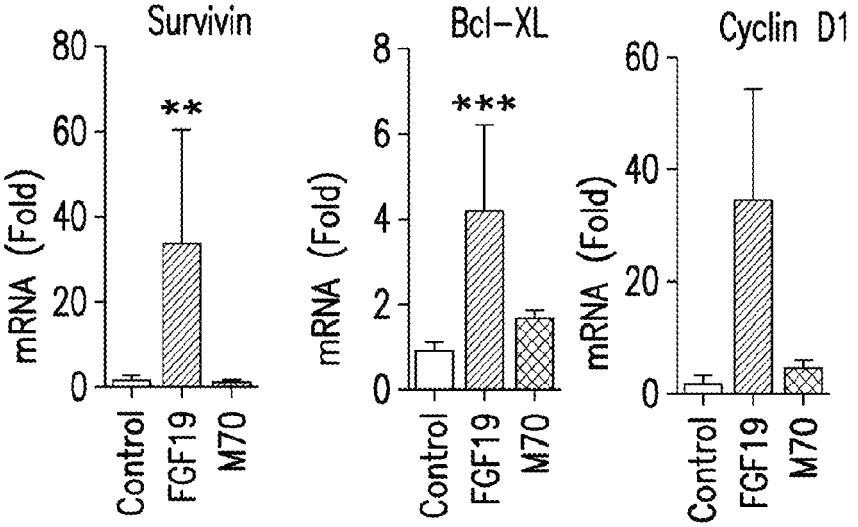


FIG.10C

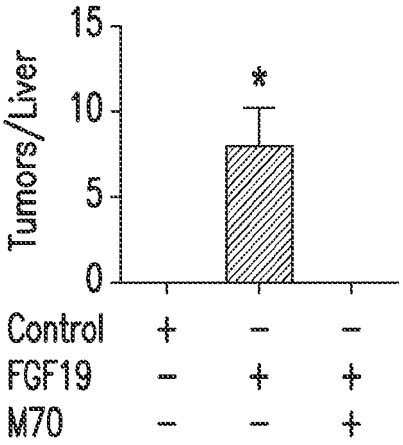


FIG.11A

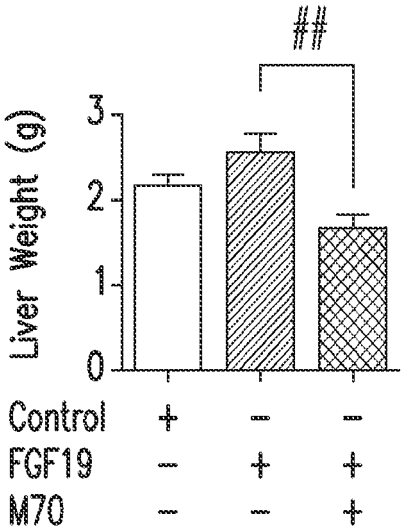


FIG.11B

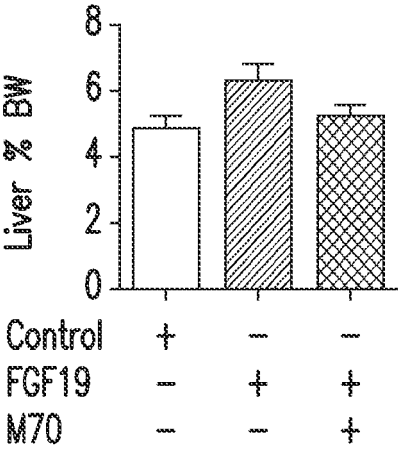


FIG.11C

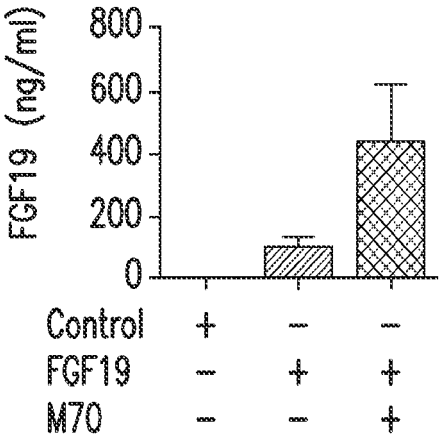


FIG.11D

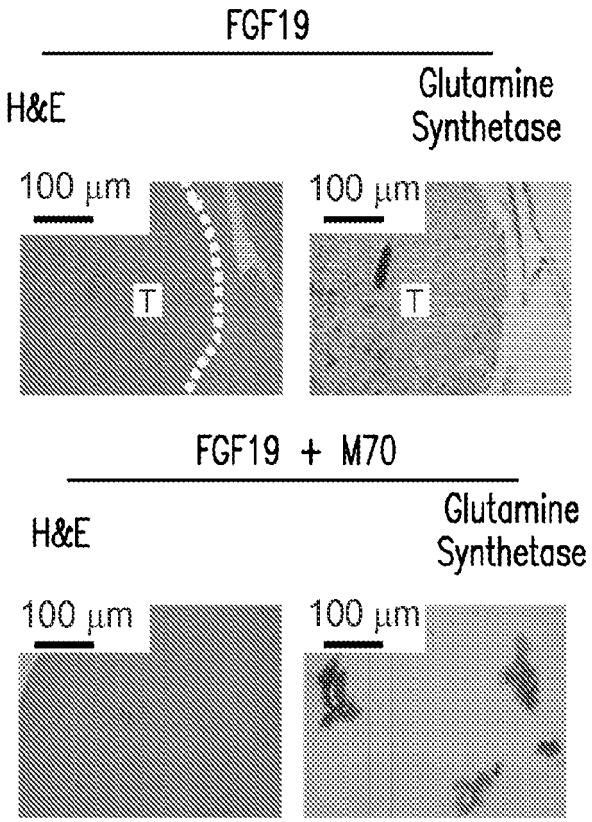


FIG.11E

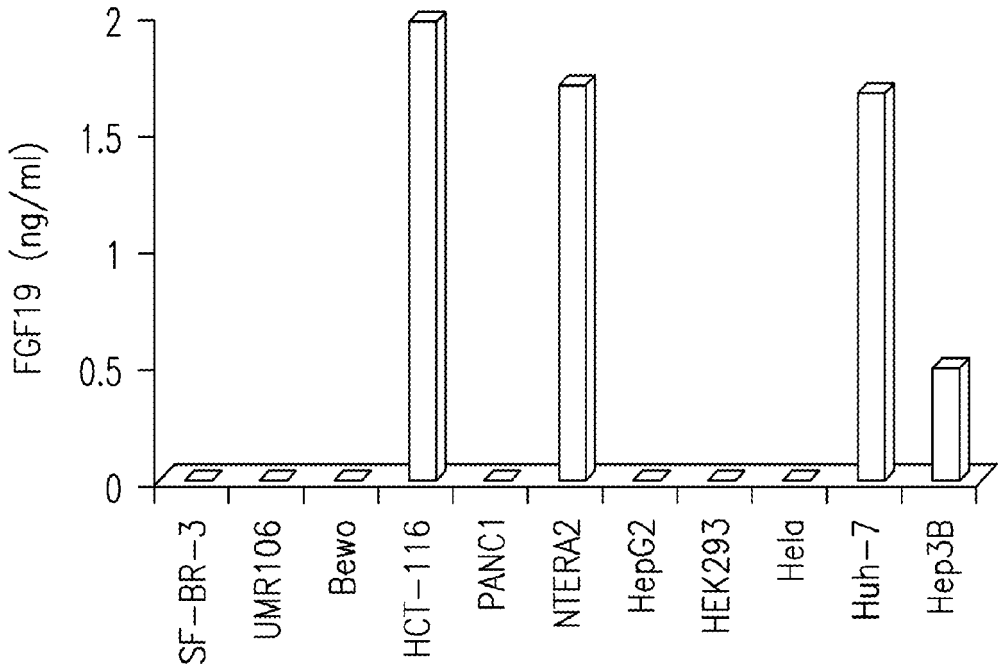


FIG.11F

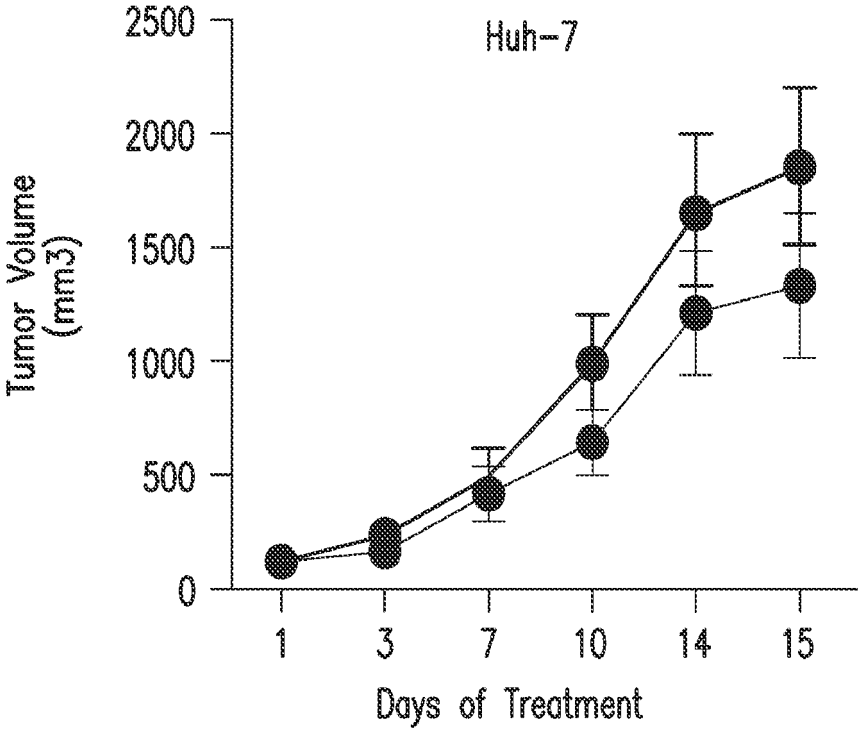


FIG.11G

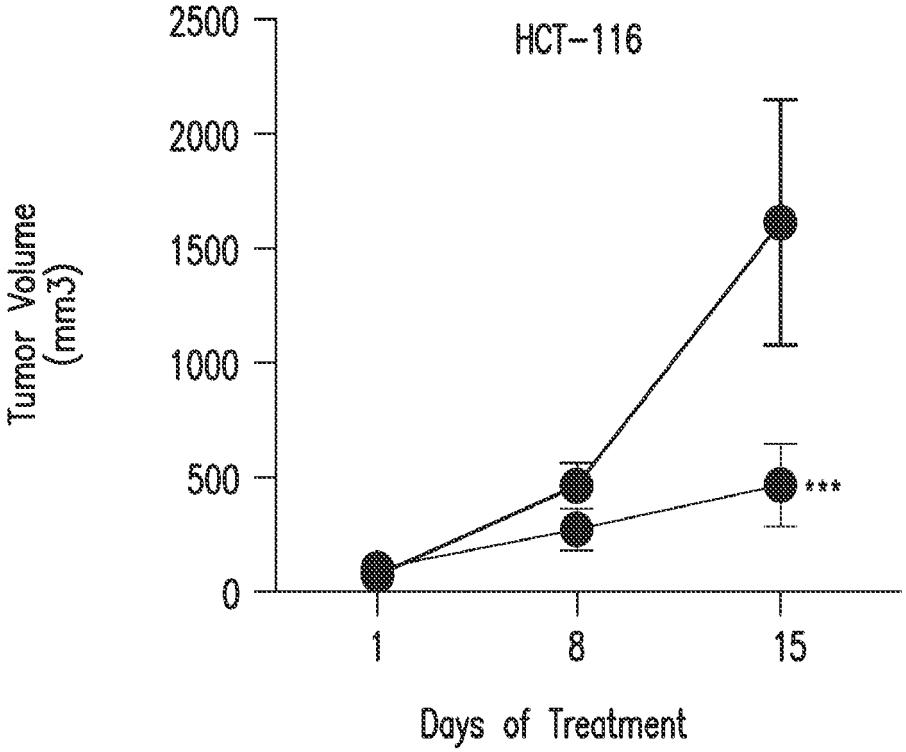


FIG.11H

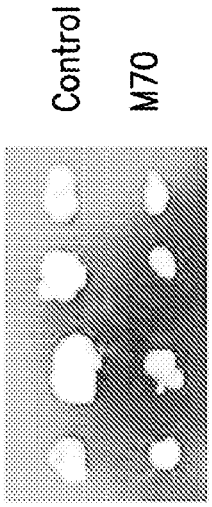


FIG.11I

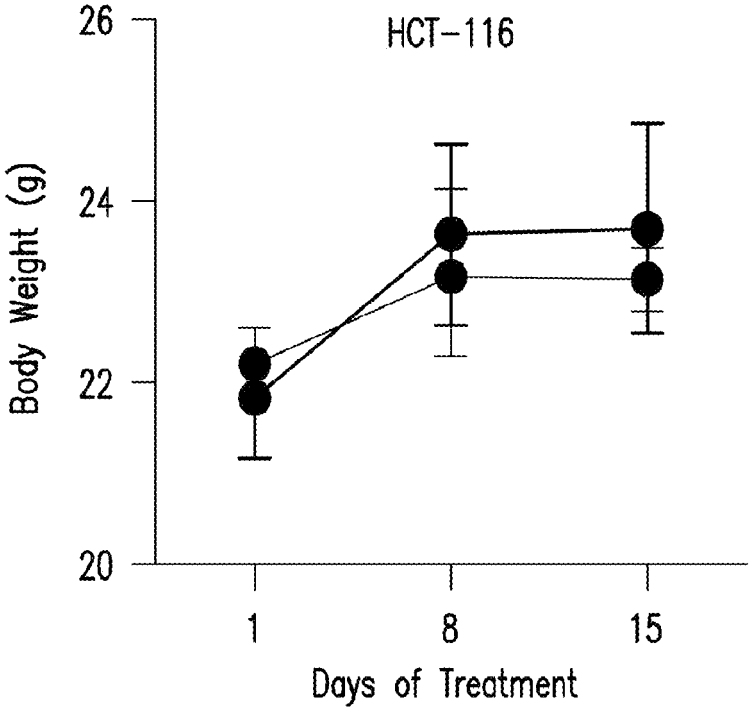


FIG.11J

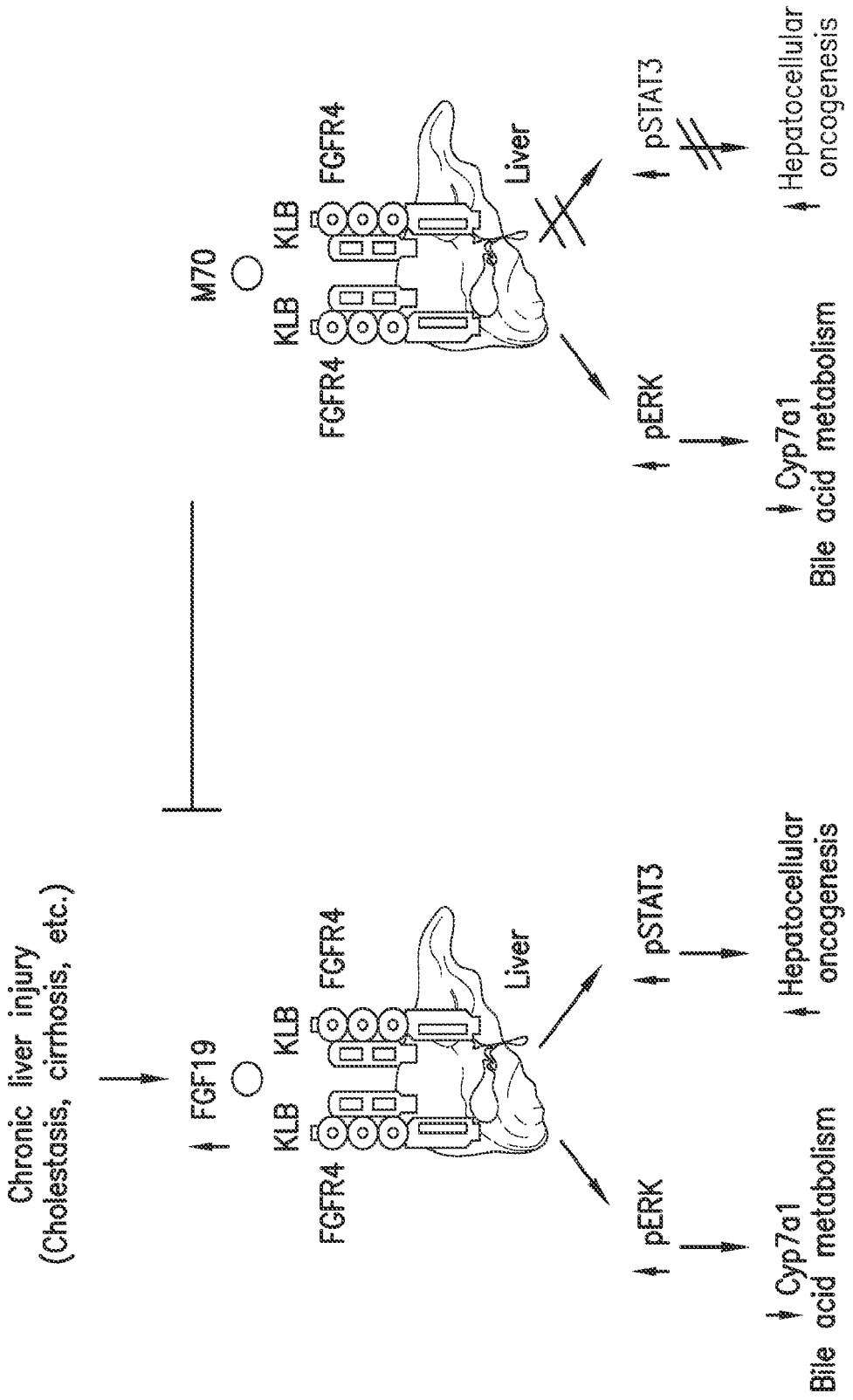


FIG. 12A

FIG. 12B

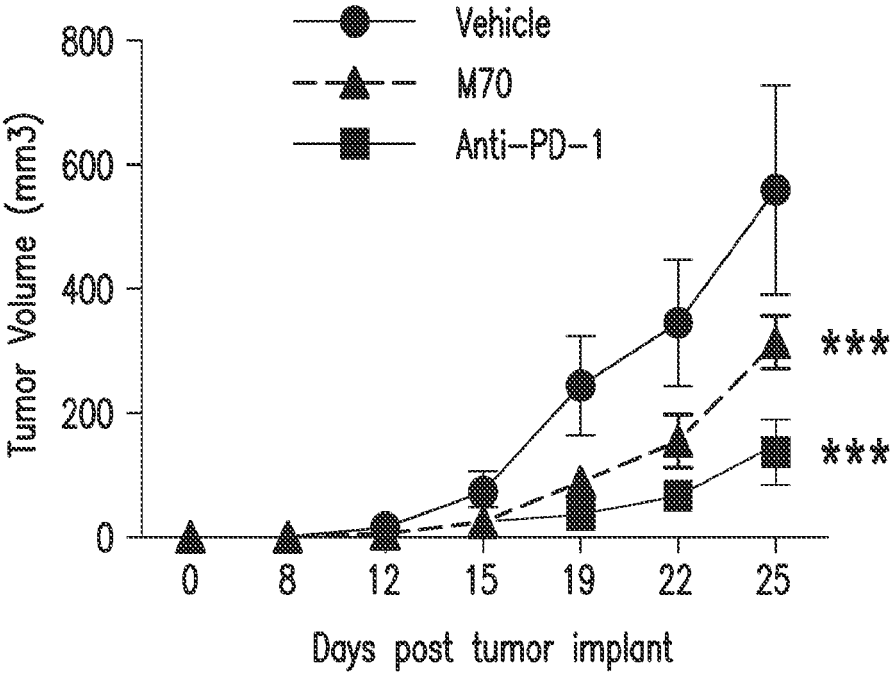


FIG.13A

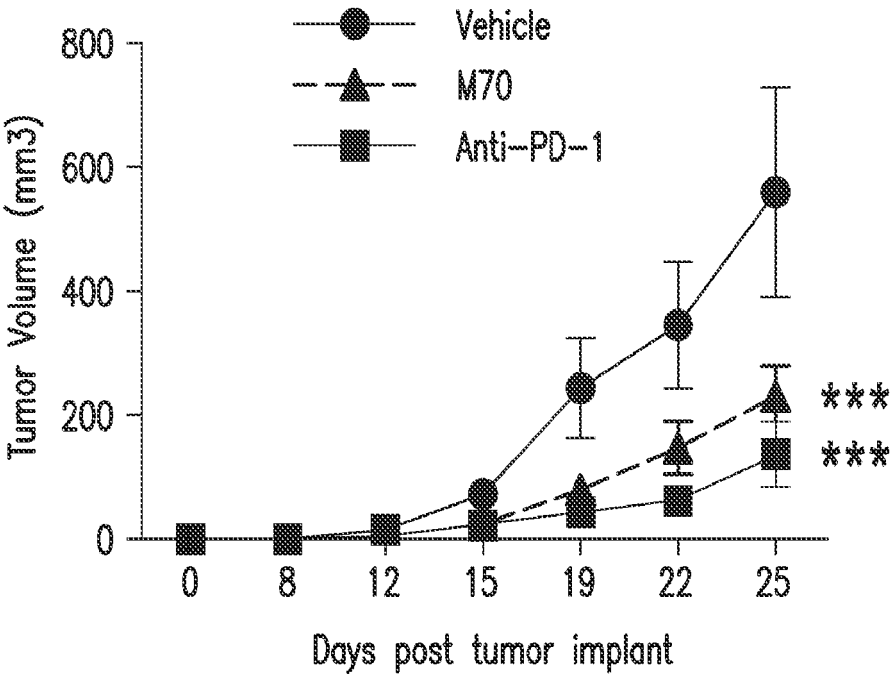


FIG.13B

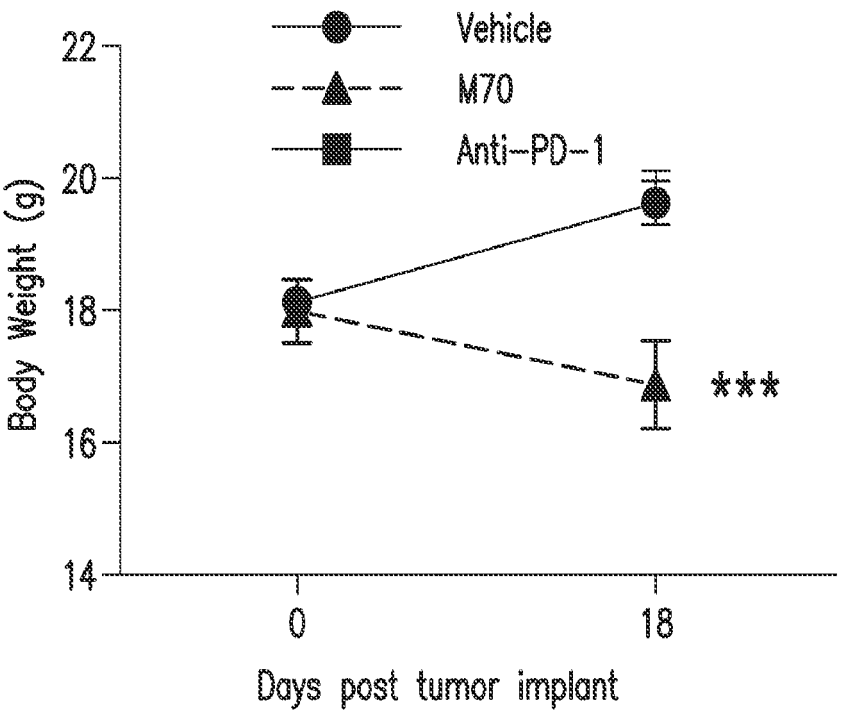


FIG.14A

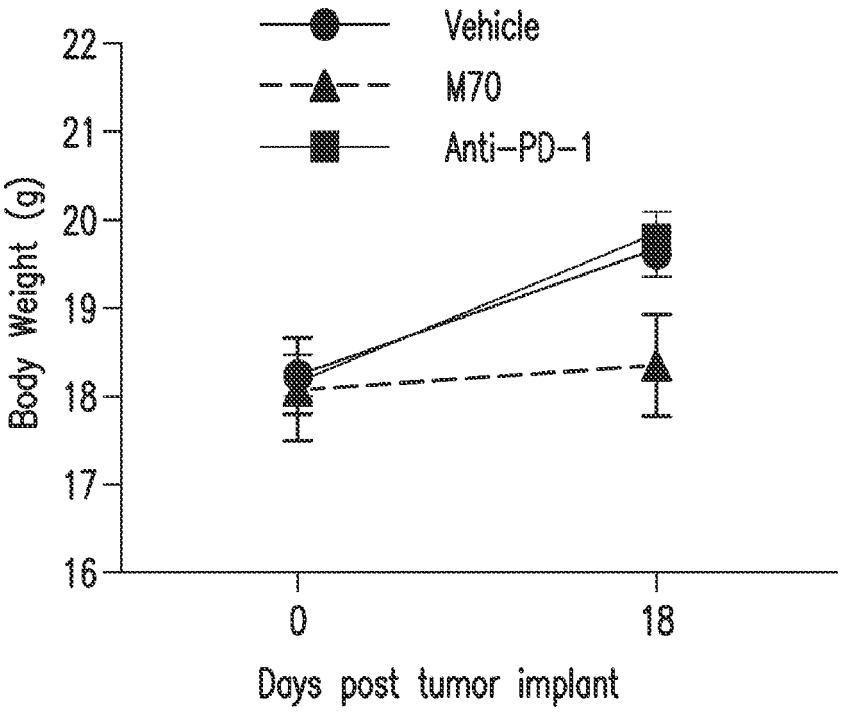


FIG.14B