Figure 1

FGF19
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH
RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP
FGLVTGLEAVRSPSFEK

FGF21
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA
S

M5
HPIPDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA
LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS
LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT
GLEAVRSPSFEK

M71
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHSLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA
S

M72
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYA
S

M73
HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALK
PGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLP
GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVVQDELQGVGG
EGCHMHPENCKTLLTDIDRTHTEKPVWDGITGE

M1
RPLAFSDASPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH
RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP
FGLVTGLEAVRSPSFEK

M2
RPLAFSDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKH
RLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDP
FGLVTGLEAVRSPSFEK

M69
RDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVA
LRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVS
LSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVT
GLEAVRSPSFEK

M3
RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEI
KAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHR
LPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPF
GLVTGLEAVRSPSFEK

M48
RDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS
AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL
EAVRSPSFEK

M49
RPLAFSDSSPLLQFGGQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKA
VALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLP
VSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGL
VTGLEAVRSPSFEK

M50
RHPIPDSSPLLQFGDQVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEILEDGYNVYRSEKHRLPV
SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV
TGLEAVRSPSFEK

M51
RHPIPDSSPLLQFGGNVRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV
SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV
TGLEAVRSPSFEK

M52
RDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS
AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL
EAVRSPSFEK

M53

MDSSPLLQWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRT
VAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPVSLSS
AKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGL
EAVRSPSFEK

M70

MRDSSPLVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDCAFEEEIRPDGYNVYRSEKHRLPV
SLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESDMFSSPLETDSMDPFGLV
TGLEAVRSPSFEK

Figure 2

FGF21 (amino acid position)		FGF19	Glucose Lowering	Lipid Elevation
1-181	FGF21	-	+	-
-	FGF19	1-194	+	+
1-16	M5	21-194	+	-
147-181	M41	1-147	+/-	+
1-16 & 147-181	M42	21-147	-	-
17-181	M44	1-20	+	+
1-146	M45	148-194	+	-
17-146	M46	1-20 & 148-194	+/-	-

Figure 3A

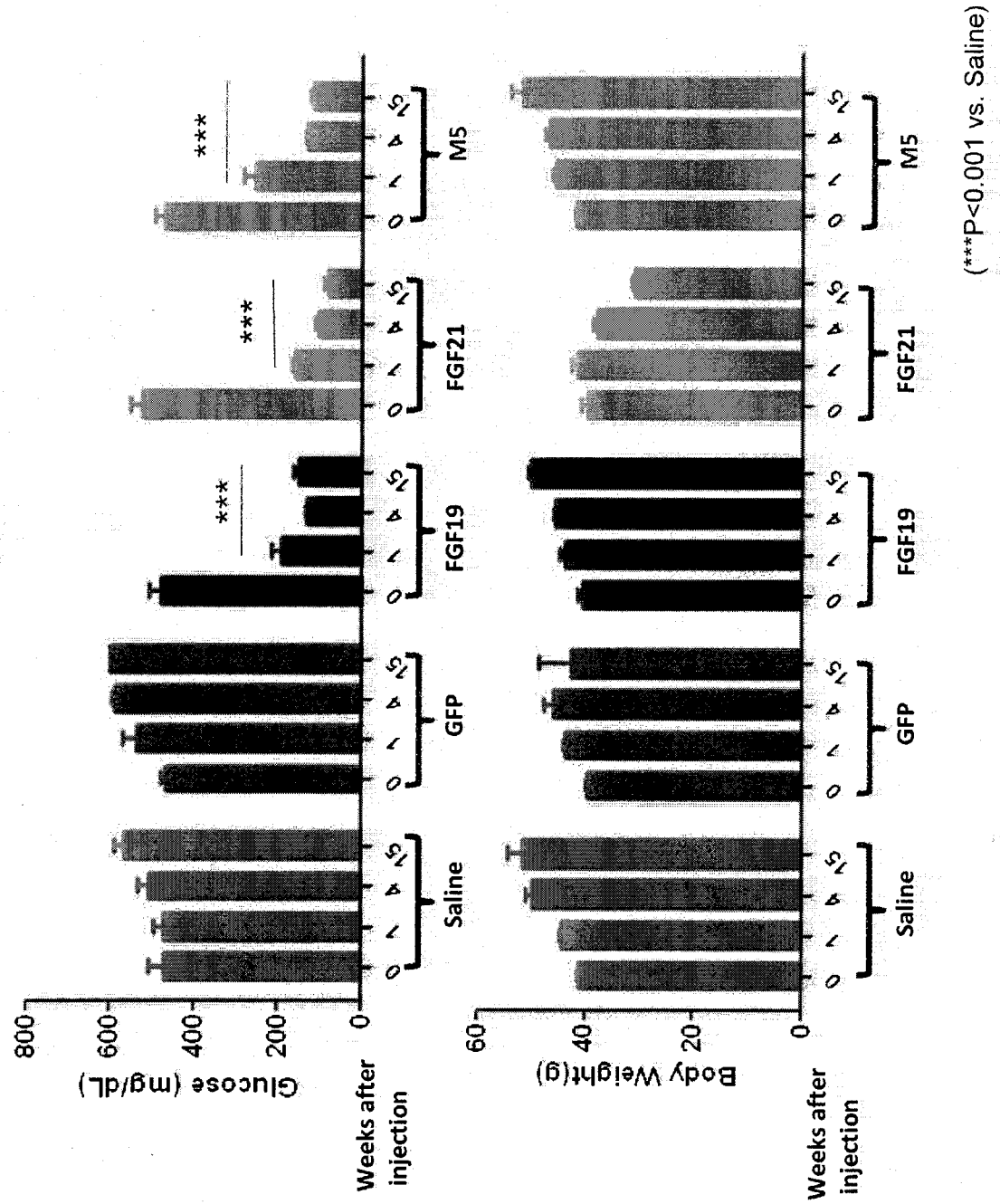

Glucose (mg/dL)
800
600
400
200
0
Weeks after injection
0
1
4
12
Saline
GFP
FGF19
FGF21
M5
***
***
***
Body Weight(g)
60
40
20
0
(***P<0.001 vs. Saline)

Figure 3B

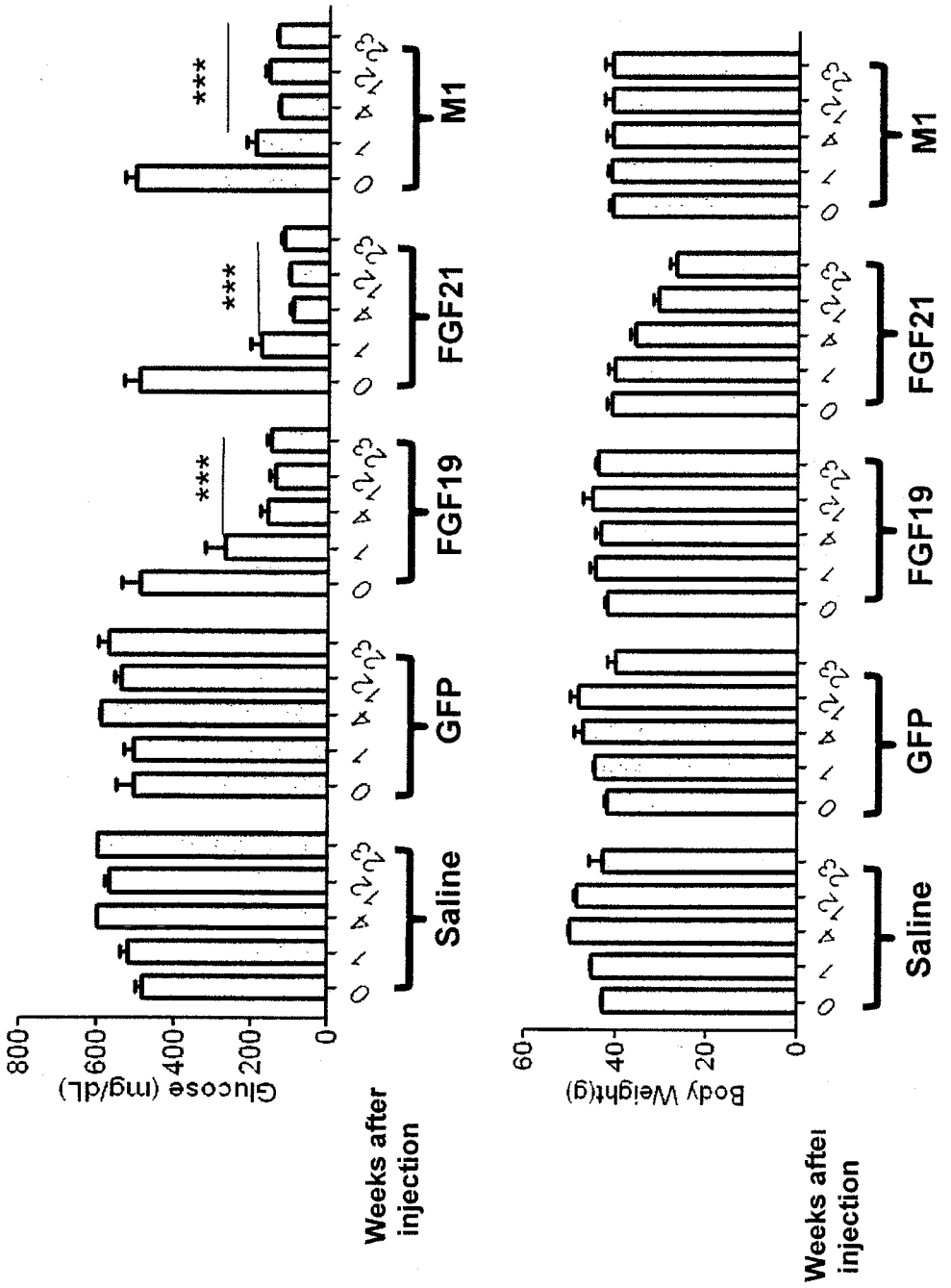

Glucose (mg/dL)
800
600
400
200
0
***
***
***
Saline
GFP
FGF19
FGF21
M1
Weeks after injection
Body Weight(g)
60
40
20
0
Saline
GFP
FGF19
FGF21
M1
Weeks after injection

Figure 3C

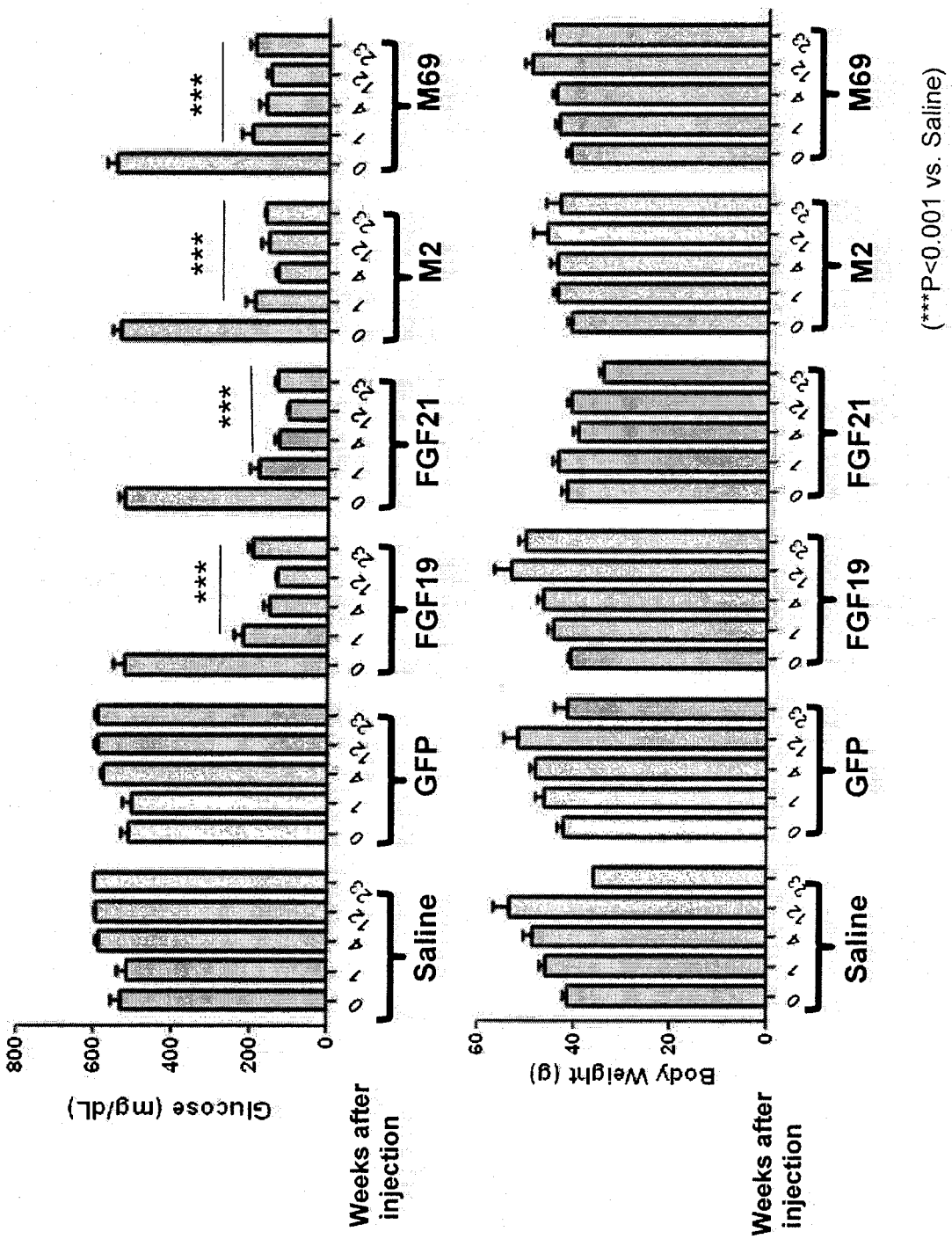

Glucose (mg/dL)
800
600
400
200
0
***
***
***
***
Saline
GFP
FGF19
FGF21
M2
M69
0 1 4 7 14 21
Weeks after injection
Body Weight (g)
60
40
20
0
(***P<0.001 vs. Saline)

Figure 3D

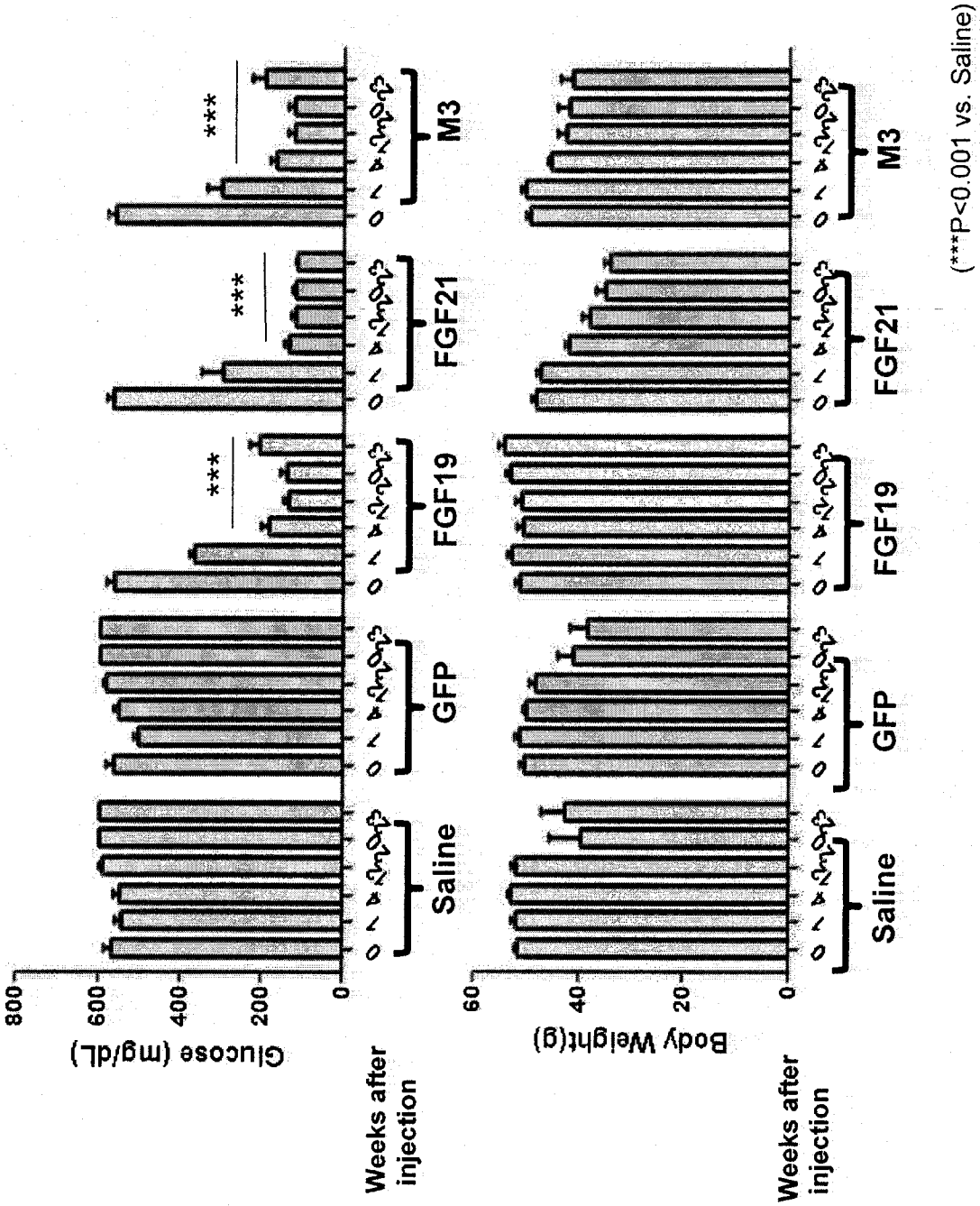

Glucose (mg/dL)
800
600
400
200
0
***
***
***
Saline
GFP
FGF19
FGF21
M3
0
1
2
4
7
Weeks after injection
Body Weight(g)
60
40
20
0
Saline
GFP
FGF19
FGF21
M3
0
1
2
4
7
Weeks after injection
(***P<0.001 vs. Saline)

Figure 3E

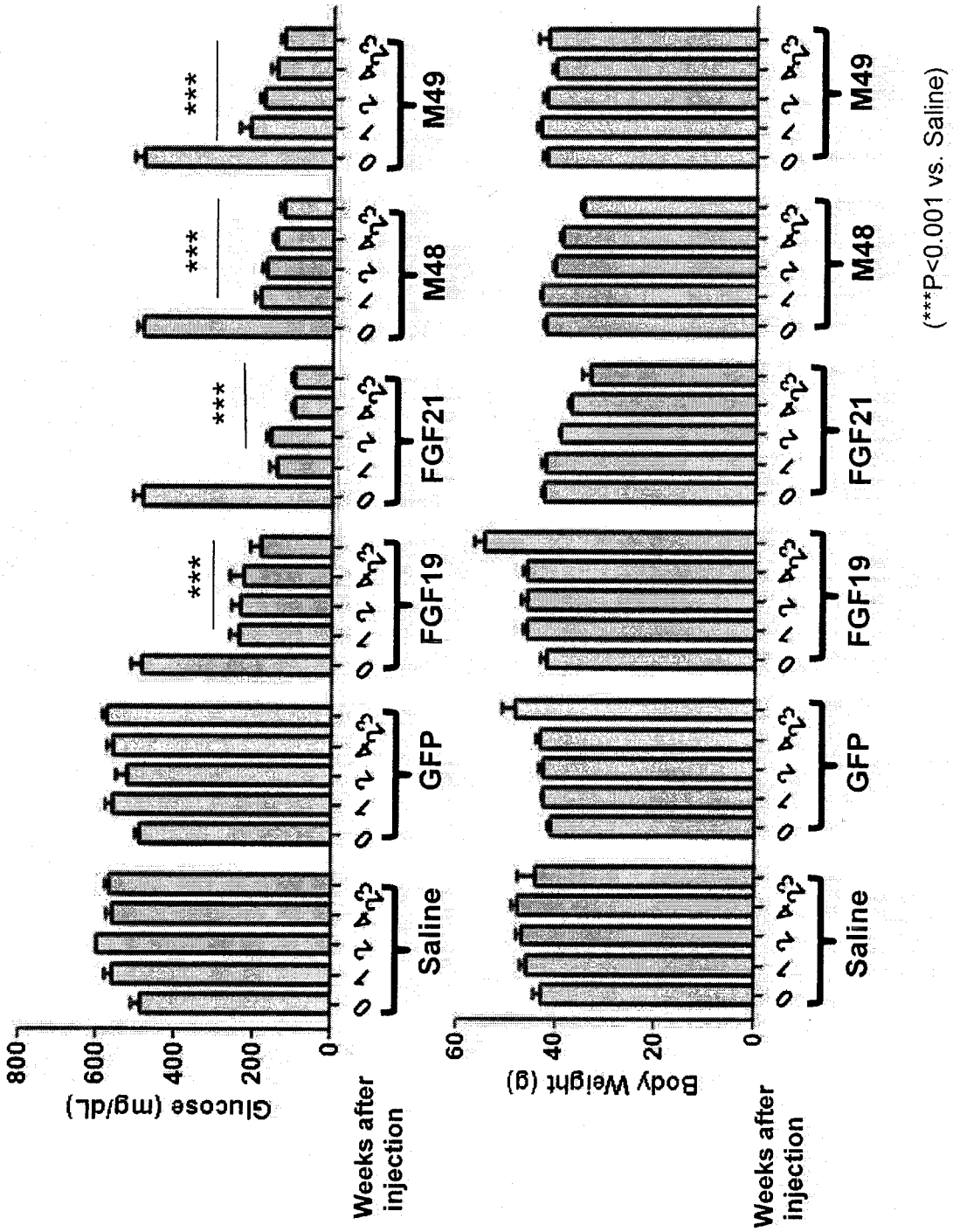

Glucose (mg/dL)
800
600
400
200
0
***
***
***
***
Saline
GFP
FGF19
FGF21
M48
M49
Weeks after injection
Body Weight (g)
60
40
20
0
Saline
GFP
FGF19
FGF21
M48
M49
Weeks after injection
(***P<0.001 vs. Saline)

Figure 3F

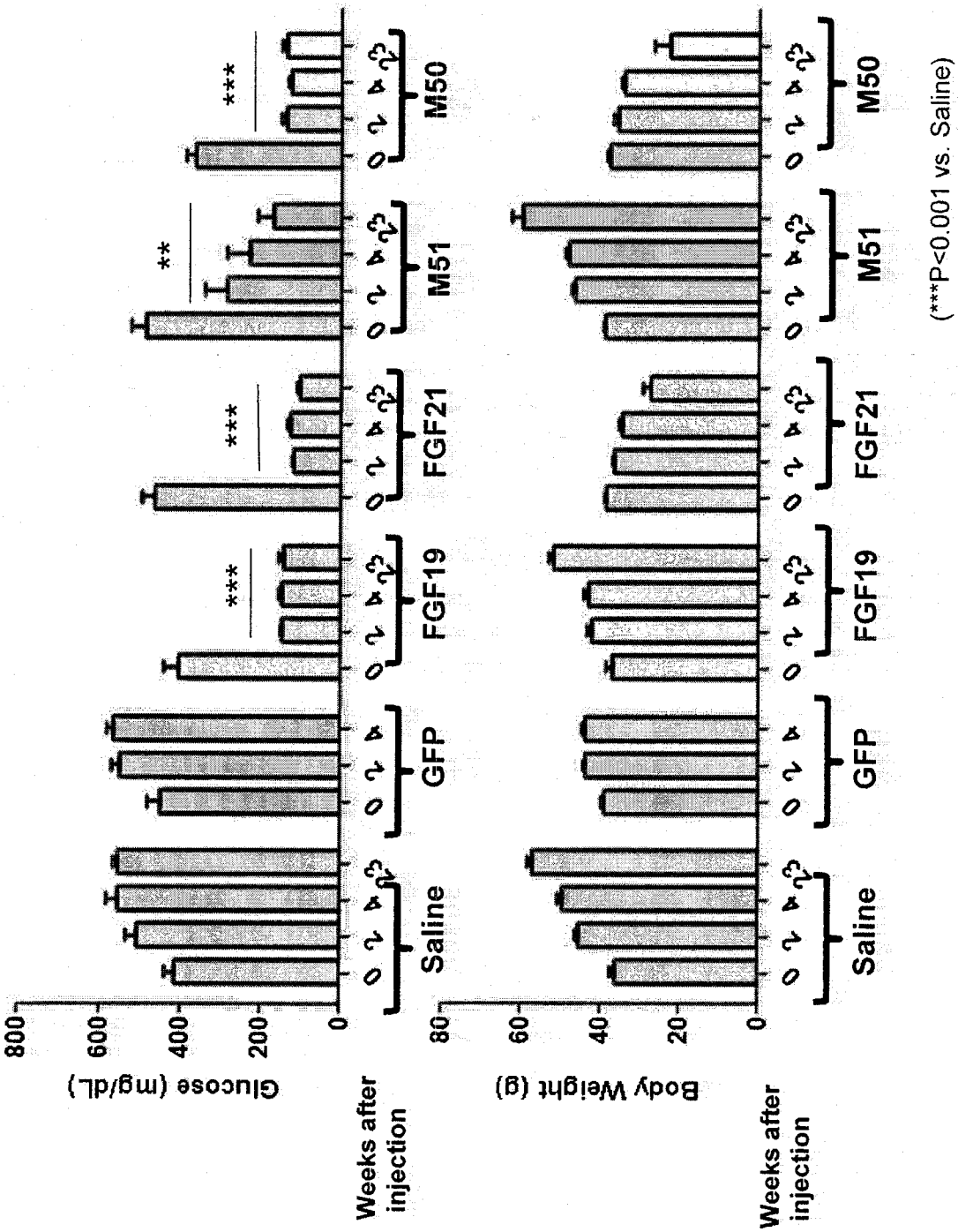

Glucose (mg/dL)
800
600
400
200
0
Weeks after injection
0
1
2
4
Saline
GFP
FGF19
FGF21
M51
M50
**
***
***
Body Weight (g)
80
60
40
20
0
(***P<0.001 vs. Saline)

Figure 3G

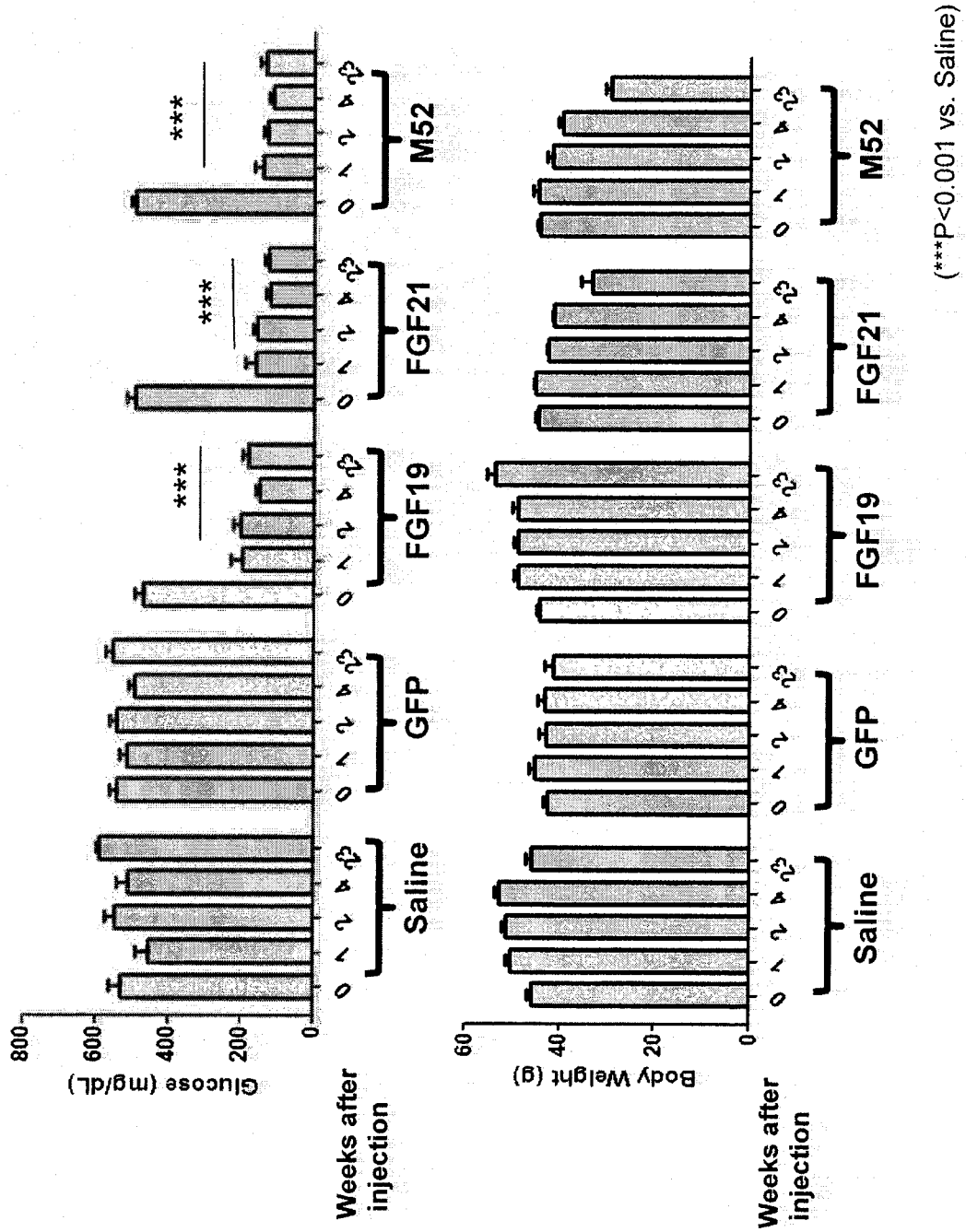

Glucose (mg/dL)
800
600
400
200
0
***
***
***
Saline
GFP
FGF19
FGF21
M52
0
1
2
4
Weeks after injection
Body Weight (g)
60
40
20
0
(***P<0.001 vs. Saline)

Figure 3H

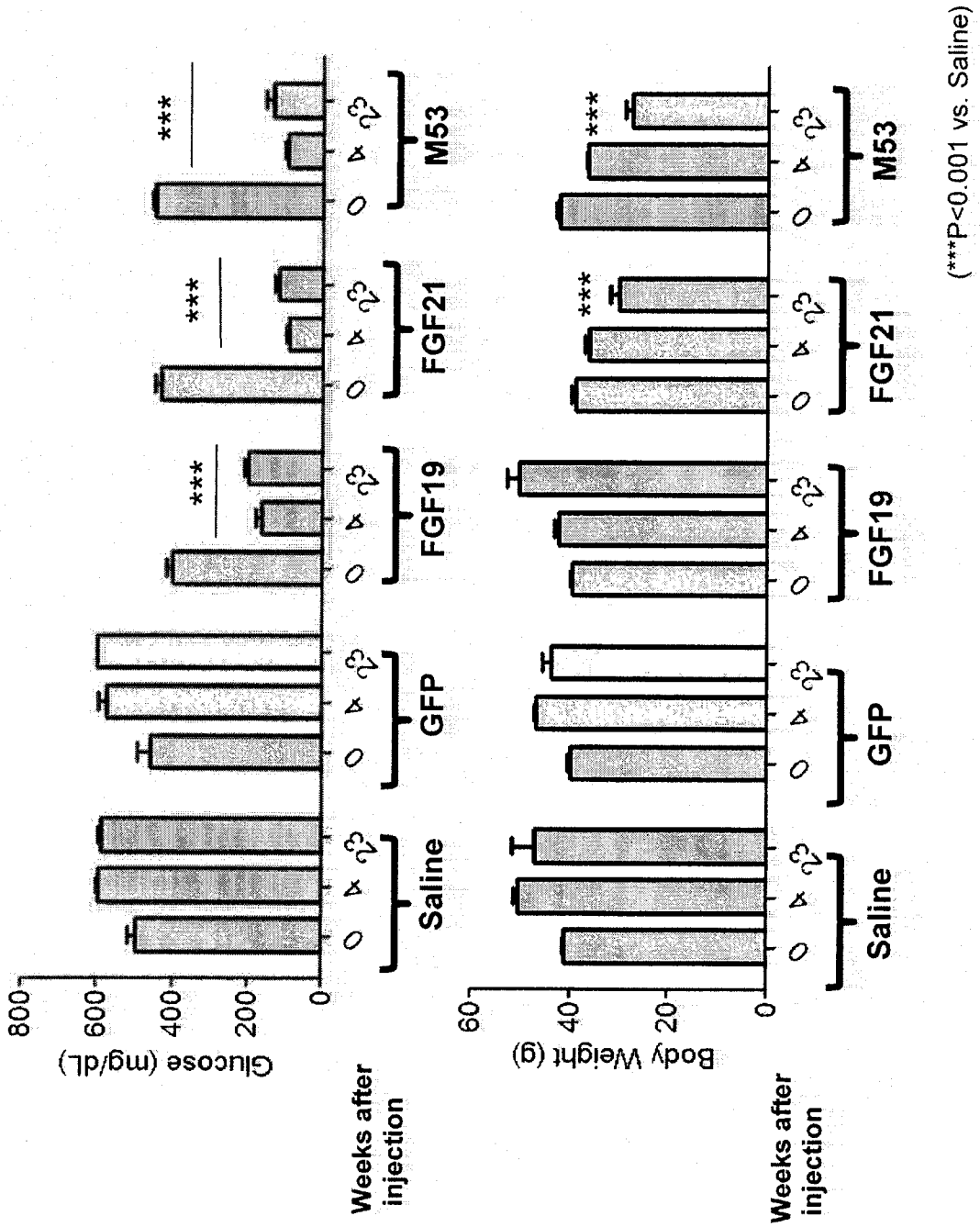
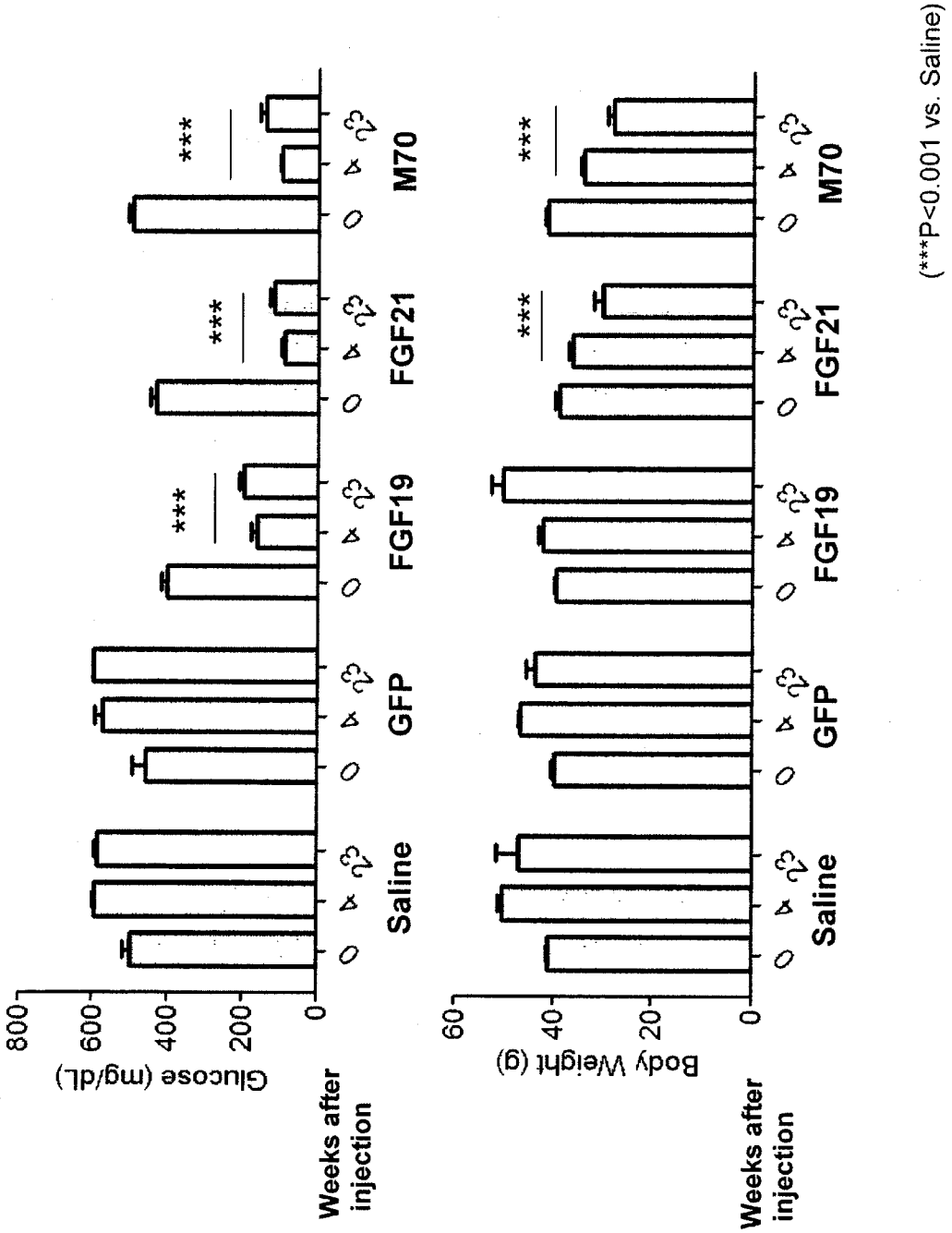

Glucose (mg/dL)
800
600
400
200
0
Body Weight (g)
60
40
20
0
Weeks after injection
0
4
Saline
GFP
FGF19
FGF21
M53
***
(***P<0.001 vs. Saline)

Figure 3I



(***P<0.001 vs. Saline)

Figure 4A

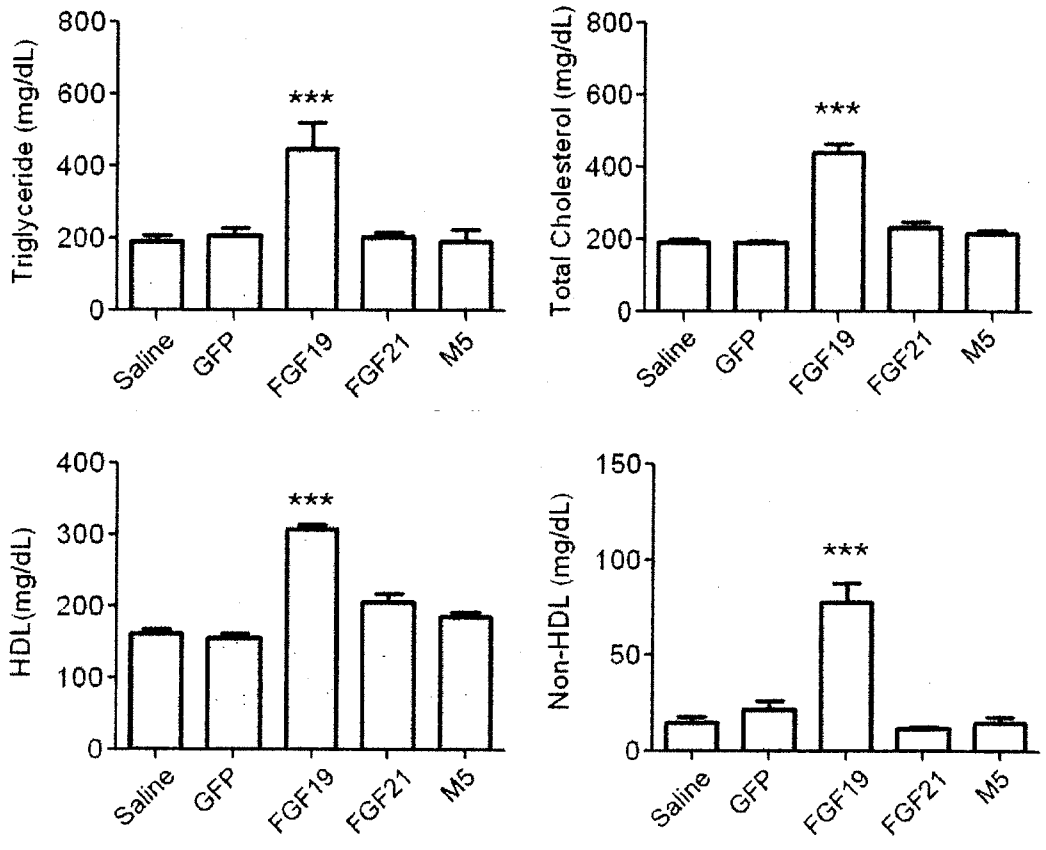

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M5
Total Cholesterol (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M5
HDL(mg/dL)
400
300
200
100
0
***
Saline
GFP
FGF19
FGF21
M5
Non-HDL (mg/dL)
150
100
50
0
***
Saline
GFP
FGF19
FGF21
M5

Figure 4B

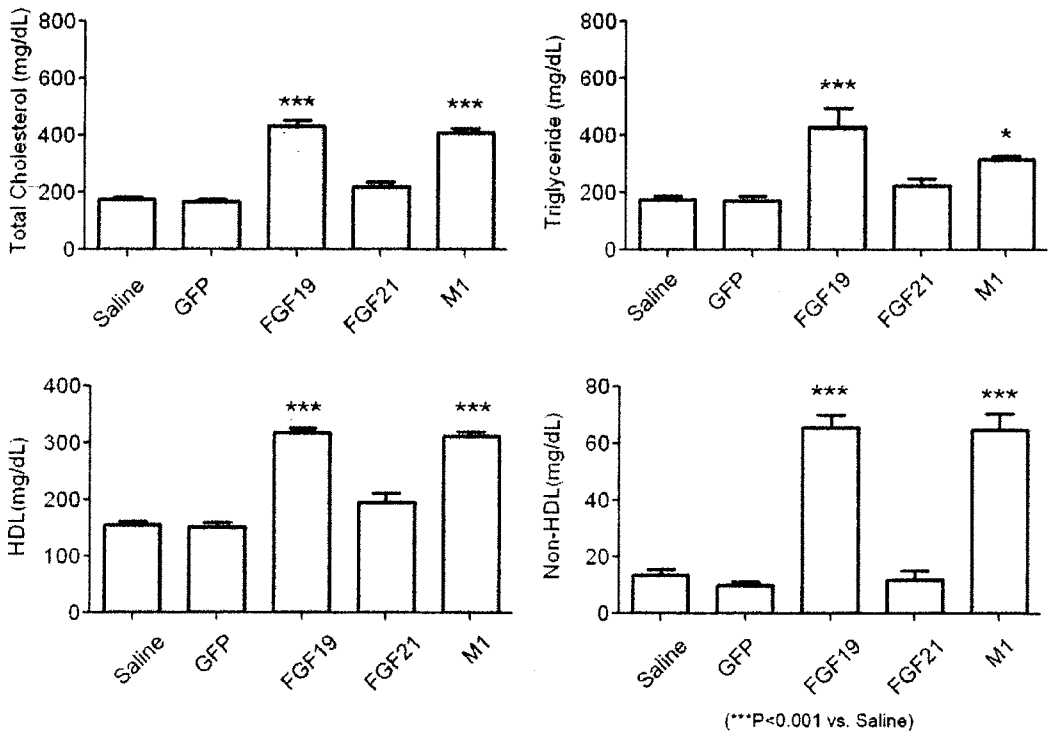

Total Cholesterol (mg/dL)
800
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M1
Triglyceride (mg/dL)
800
600
400
200
0
***
*
Saline
GFP
FGF19
FGF21
M1
HDL(mg/dL)
400
300
200
100
0
***
***
Saline
GFP
FGF19
FGF21
M1
Non-HDL(mg/dL)
80
60
40
20
0
***
***
Saline
GFP
FGF19
FGF21
M1
(***P<0.001 vs. Saline)

Figure 4C

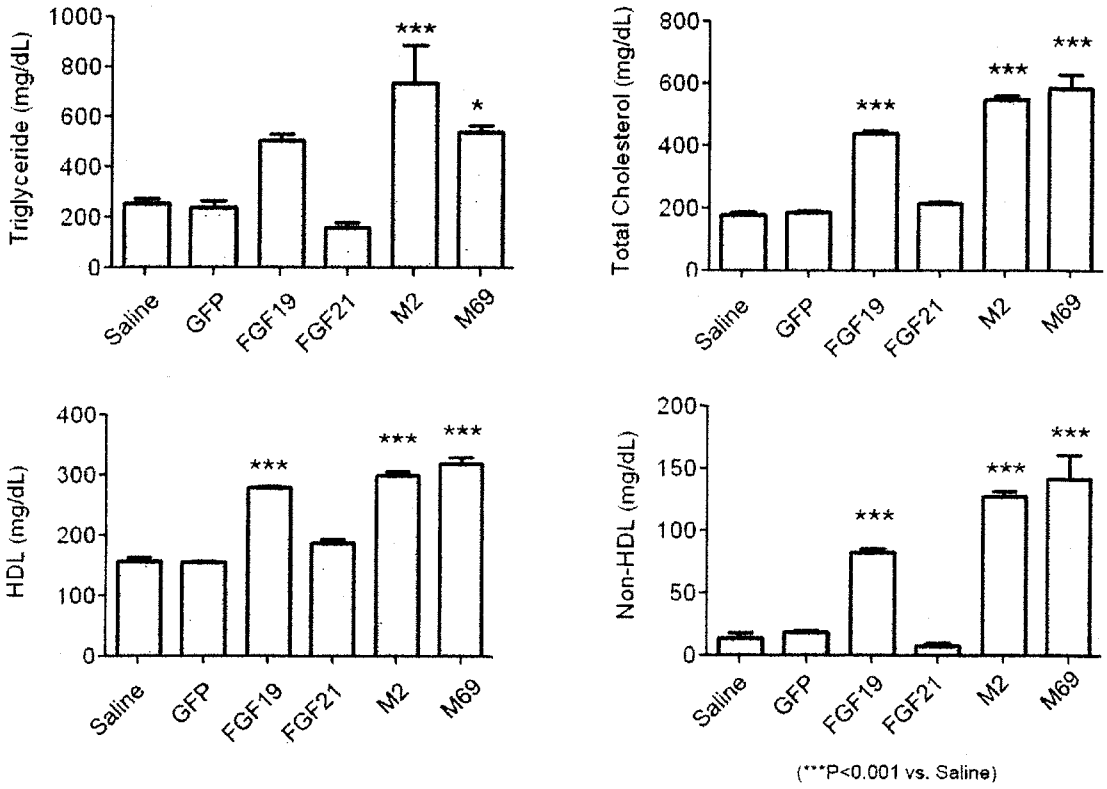

Triglyceride (mg/dL)
1000
800
600
400
200
0
***
*
Saline
GFP
FGF19
FGF21
M2
M69
Total Cholesterol (mg/dL)
800
600
400
200
0
***
***
***
HDL (mg/dL)
400
300
200
100
0
***
***
***
Non-HDL (mg/dL)
200
150
100
50
0
***
***
***
(***P<0.001 vs. Saline)

Figure 4D

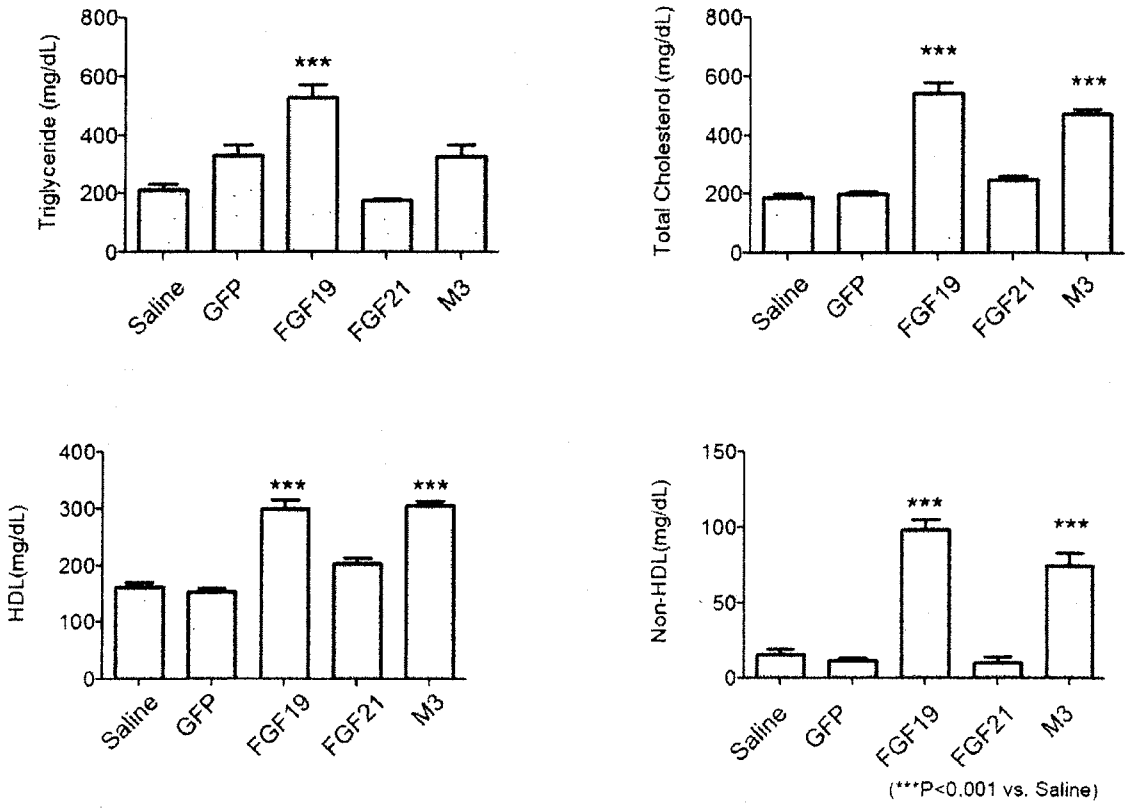

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M3
Total Cholesterol (mg/dL)
800
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M3
HDL(mg/dL)
400
300
200
100
0
***
***
Saline
GFP
FGF19
FGF21
M3
Non-HDL(mg/dL)
150
100
50
0
***
***
Saline
GFP
FGF19
FGF21
M3
(***P<0.001 vs. Saline)

Figure 4E

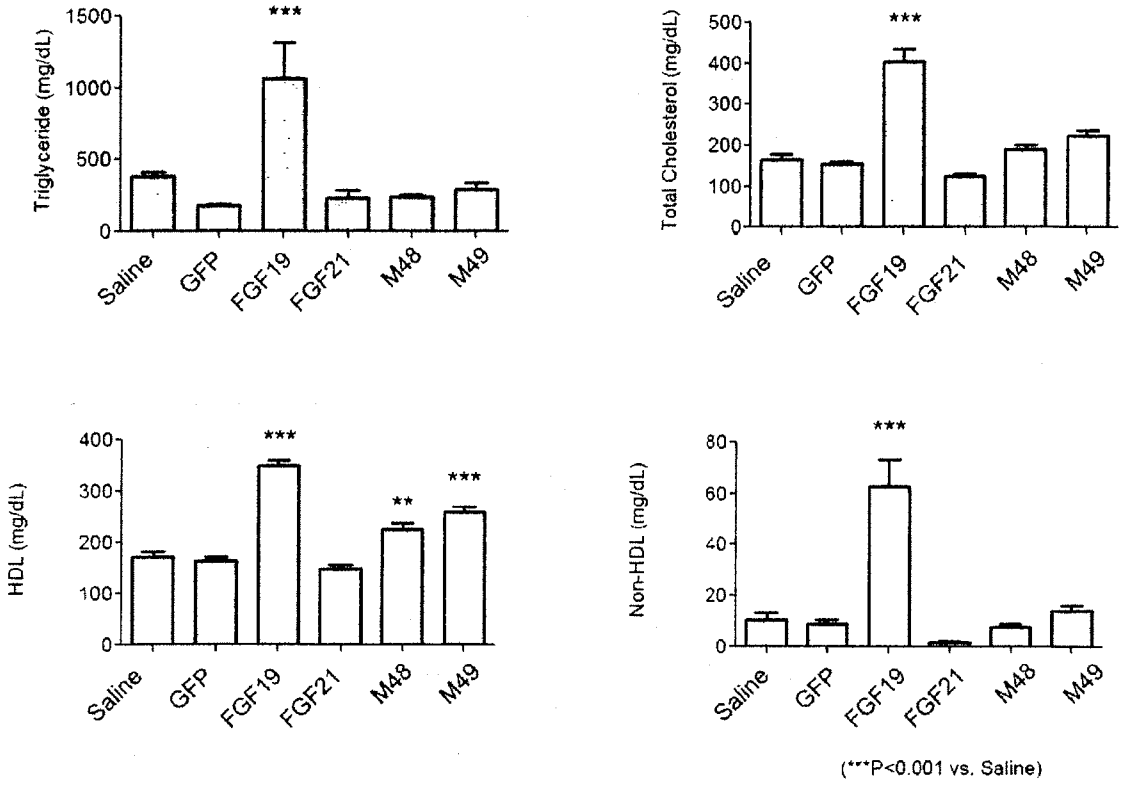

Triglyceride (mg/dL)
1500
1000
500
0
***
Saline
GFP
FGF19
FGF21
M48
M49
Total Cholesterol (mg/dL)
500
400
300
200
100
0
***
Saline
GFP
FGF19
FGF21
M48
M49
HDL (mg/dL)
400
300
200
100
0
***
**
***
Saline
GFP
FGF19
FGF21
M48
M49
Non-HDL (mg/dL)
80
60
40
20
0
***
Saline
GFP
FGF19
FGF21
M48
M49
(***P<0.001 vs. Saline)

Figure 4F

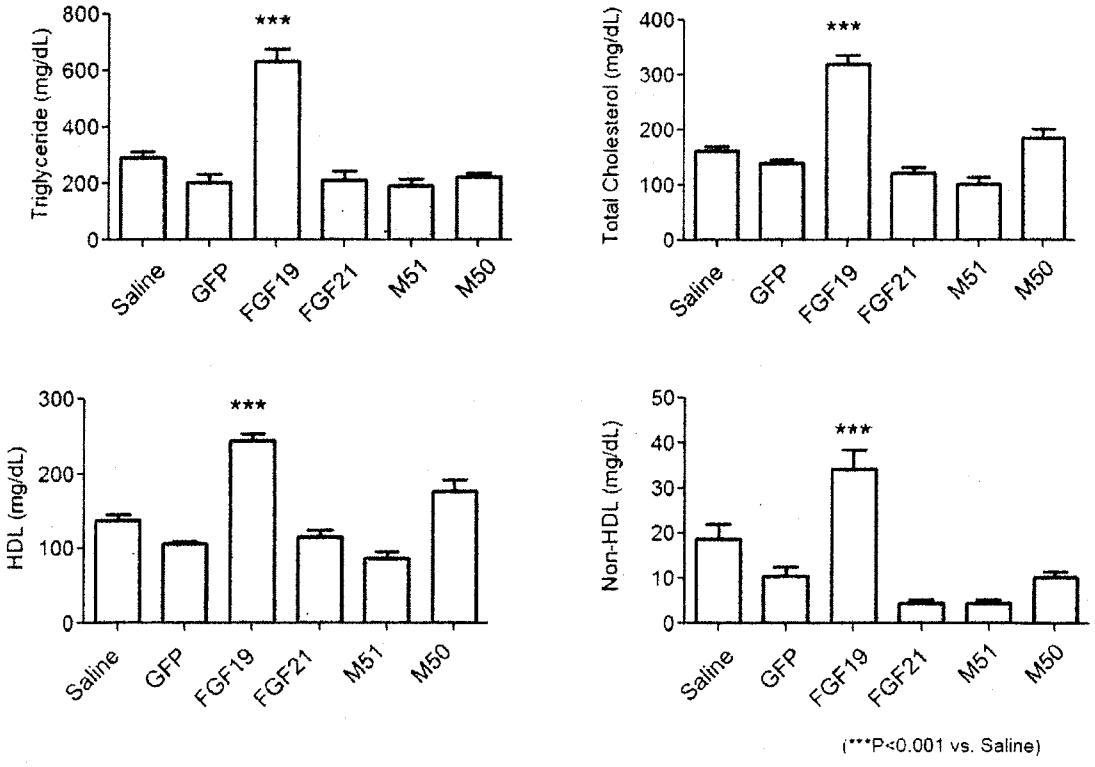

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M51
M50
Total Cholesterol (mg/dL)
400
300
200
100
0
***
Saline
GFP
FGF19
FGF21
M51
M50
HDL (mg/dL)
300
200
100
0
***
Saline
GFP
FGF19
FGF21
M51
M50
Non-HDL (mg/dL)
50
40
30
20
10
0
***
Saline
GFP
FGF19
FGF21
M51
M50
(***P<0.001 vs. Saline)

Figure 4G

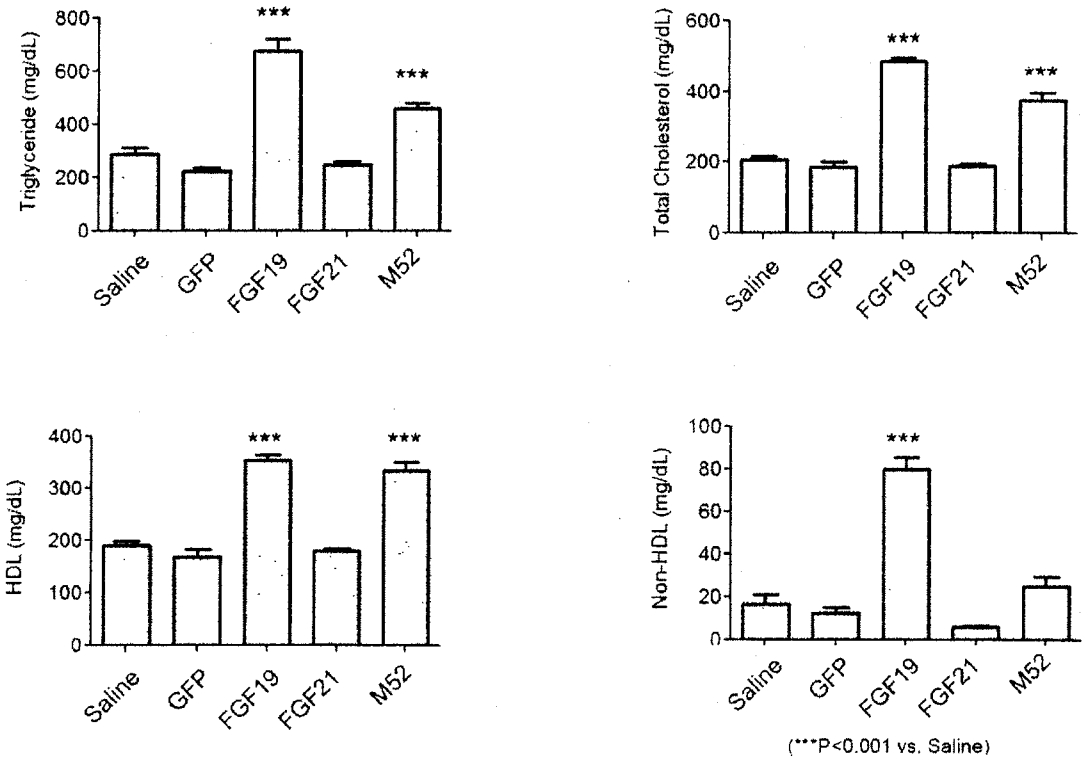

Triglycende (mg/dL)
800
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M52
Total Cholesterol (mg/dL)
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M52
HDL (mg/dL)
400
300
200
100
0
***
***
Saline
GFP
FGF19
FGF21
M52
Non-HDL (mg/dL)
100
80
60
40
20
0
***
Saline
GFP
FGF19
FGF21
M52
(***P<0.001 vs. Saline)

Figure 4H

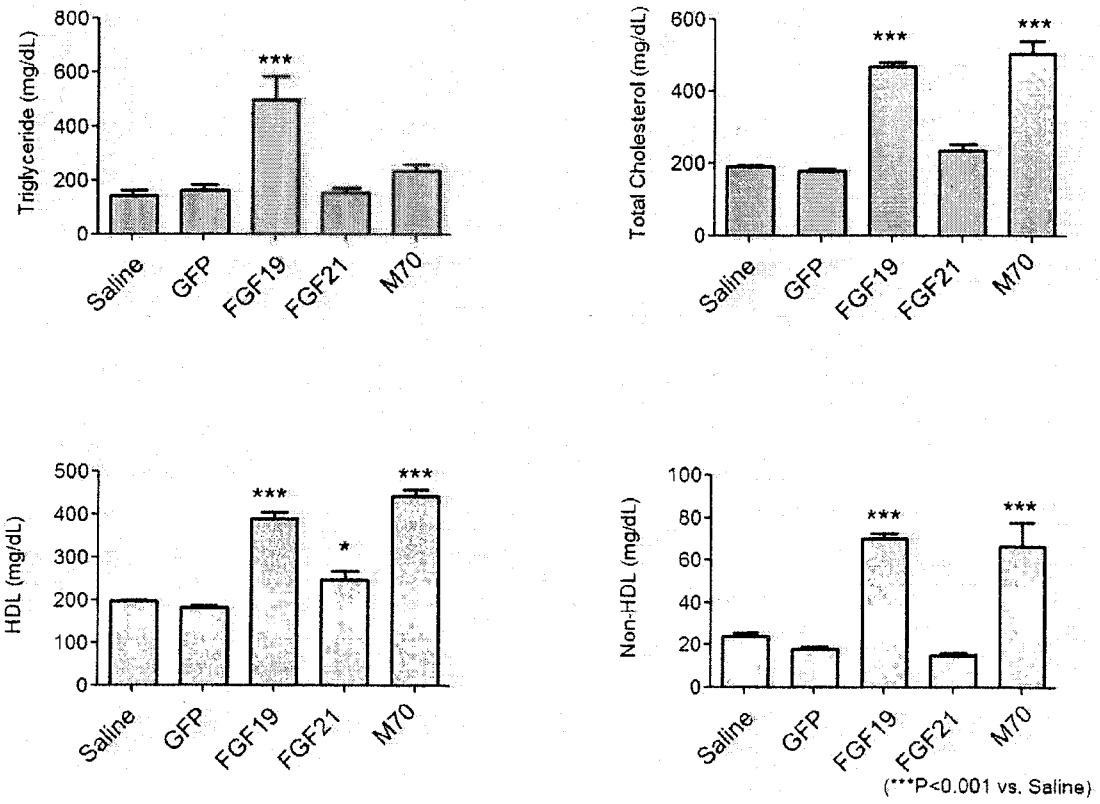
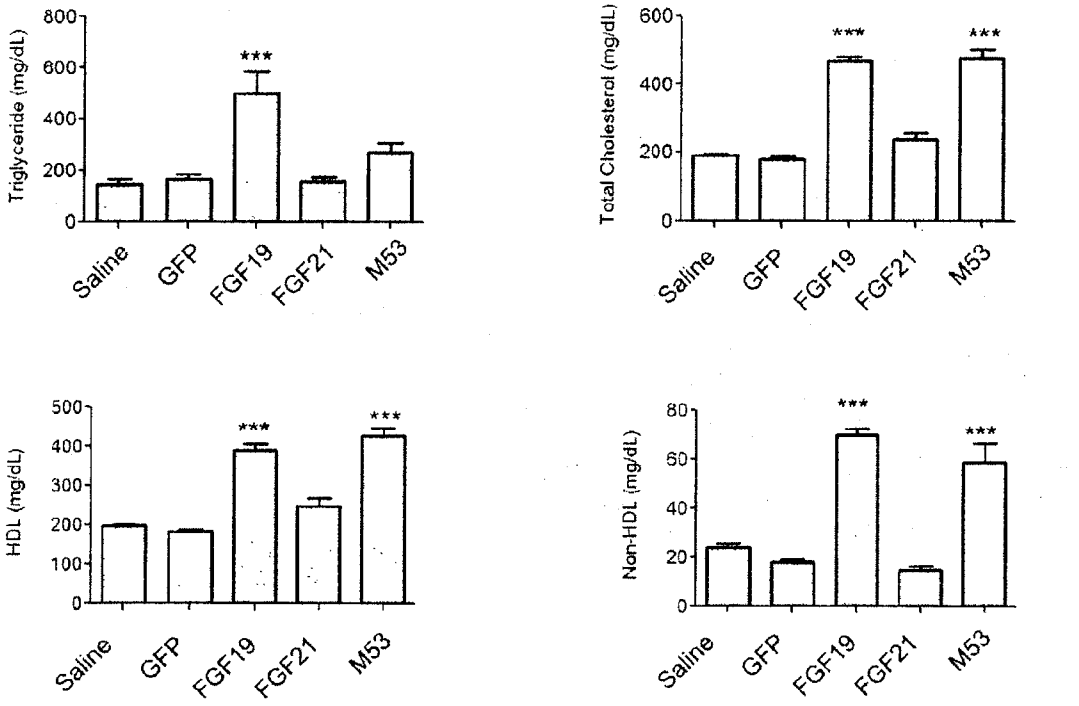
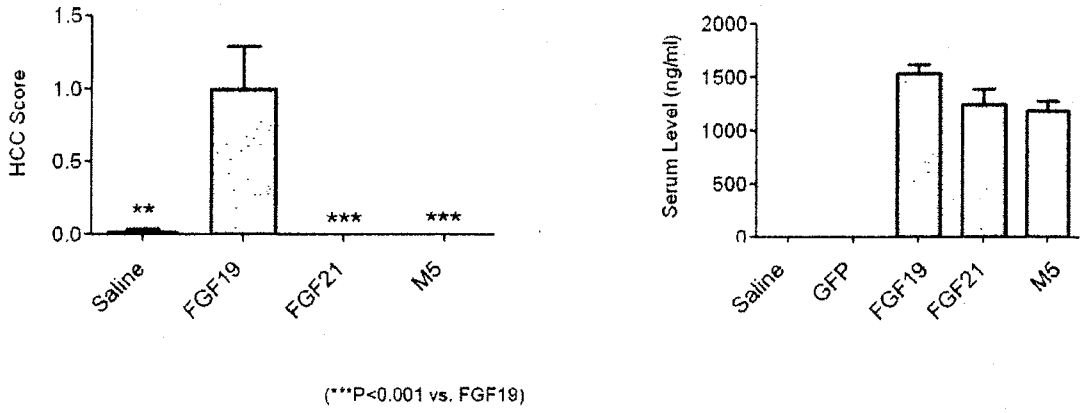

Triglyceride (mg/dL)
800
600
400
200
0
***
Saline
GFP
FGF19
FGF21
M70
Total Cholesterol (mg/dL)
600
400
200
0
***
***
Saline
GFP
FGF19
FGF21
M70
HDL (mg/dL)
500
400
300
200
100
0
***
*
***
Saline
GFP
FGF19
FGF21
M70
Non-HDL (mg/dL)
100
80
60
40
20
0
***
***
Saline
GFP
FGF19
FGF21
M70
(***P<0.001 vs. Saline)

Figure 4I



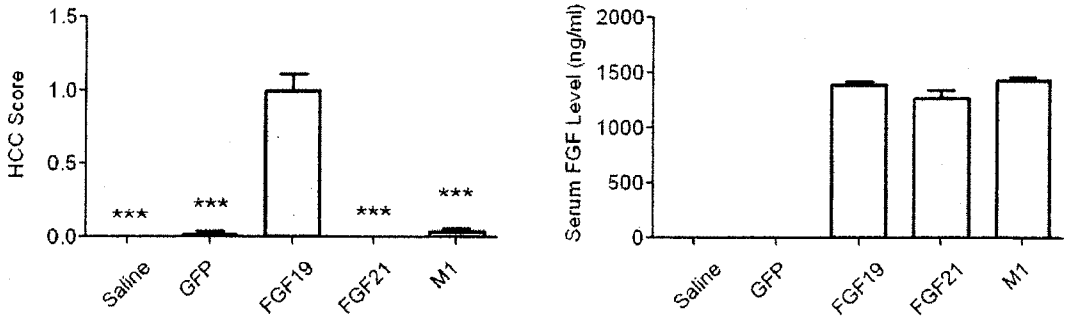
(***P<0.001 vs. Saline)

Figure 5A



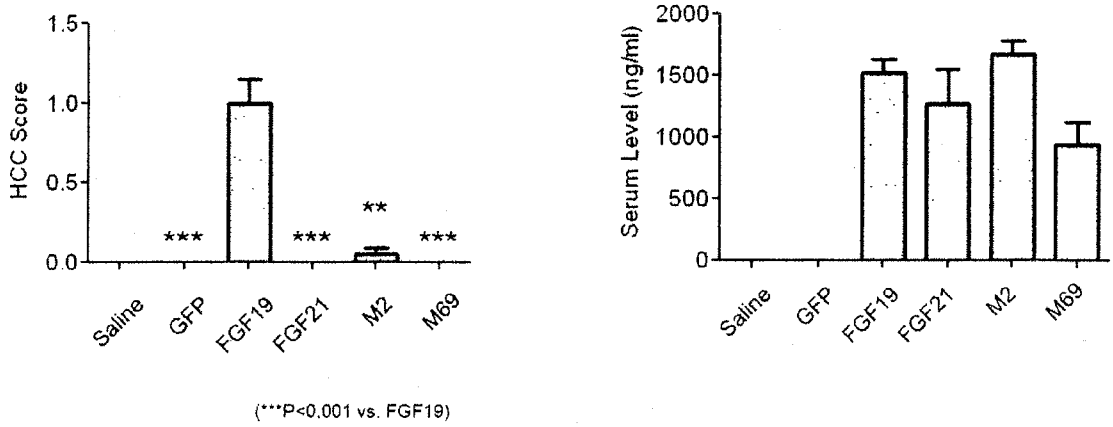
(***P<0.001 vs. FGF19)

Figure 5B



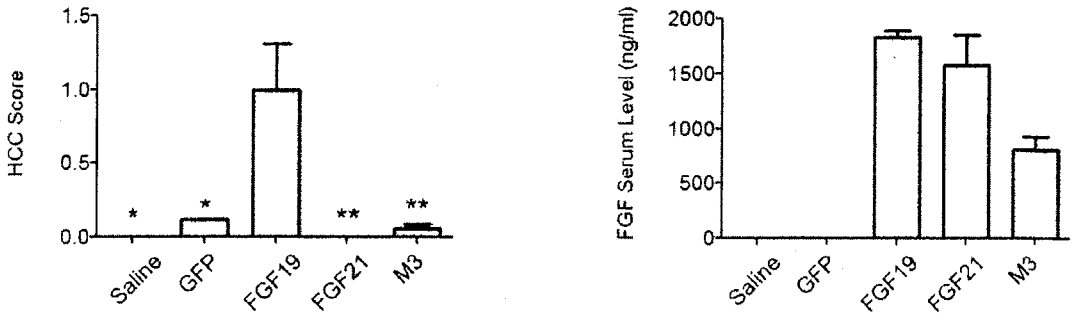
(***P<0.001 vs. FGF19)

Figure 5C



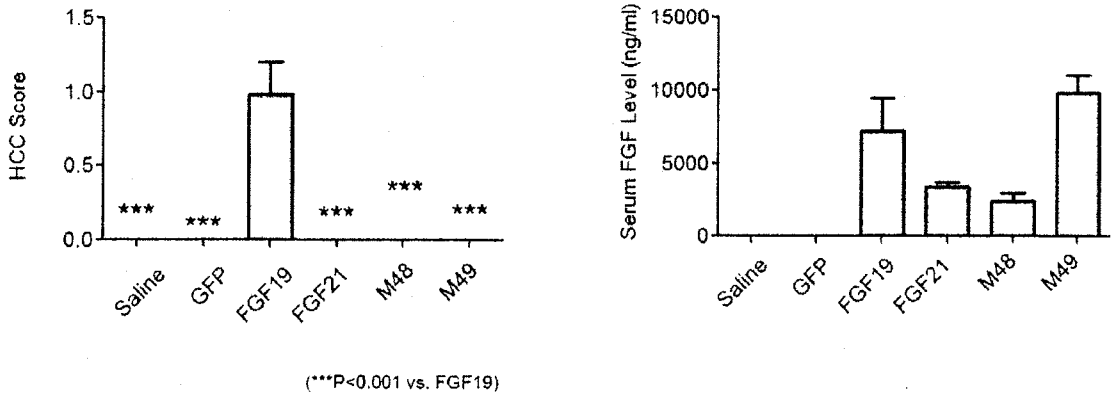
(***P<0.001 vs. FGF19)

Figure 5D



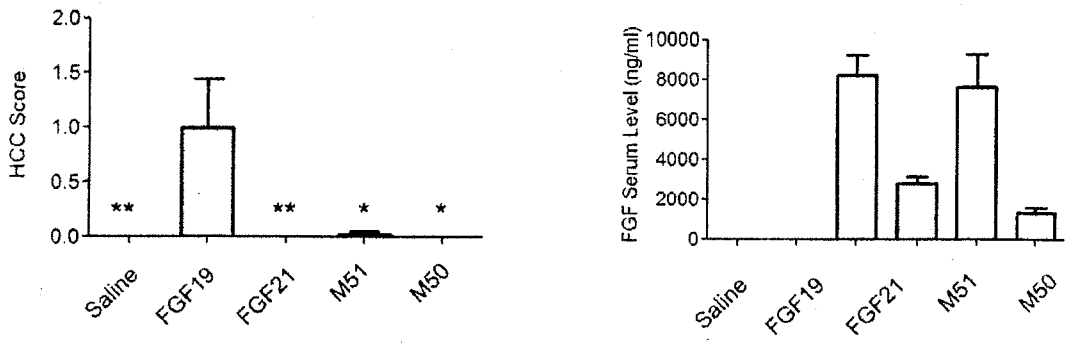
(***P<0.001 vs. FGF19)

Figure 5E



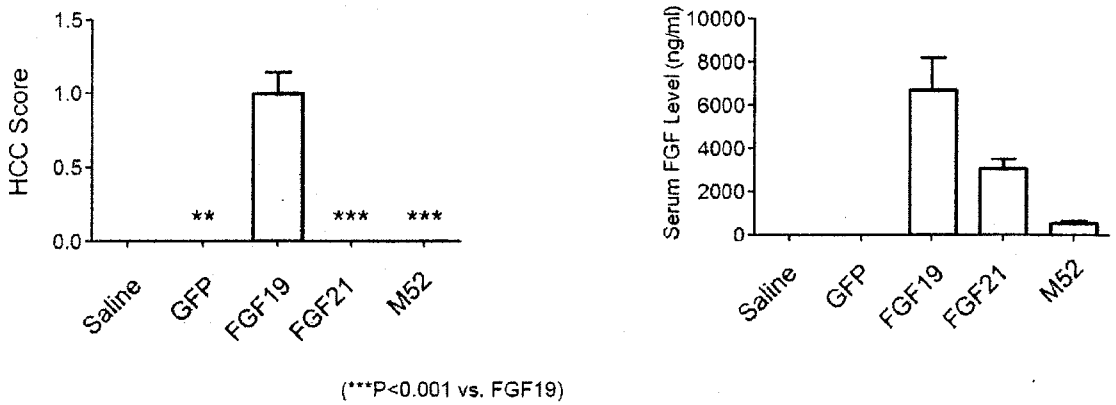
(***P<0.001 vs. FGF19)

Figure 5F



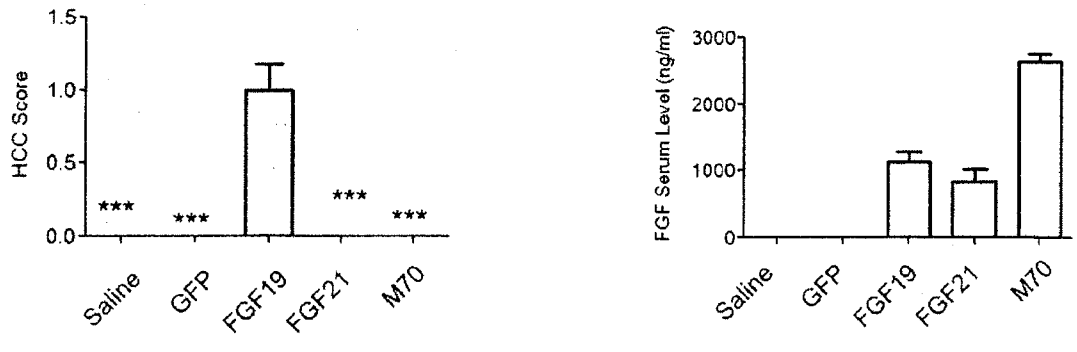
(**P<0.01, *P<0.05 vs. FGF19)

Figure 5G



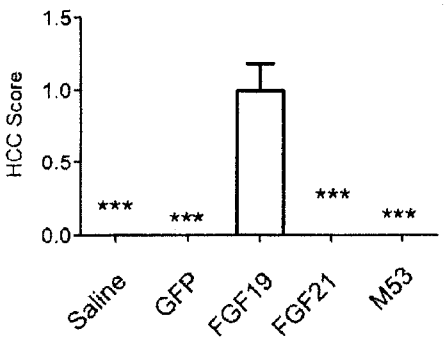
(***P<0.001 vs. FGF19)

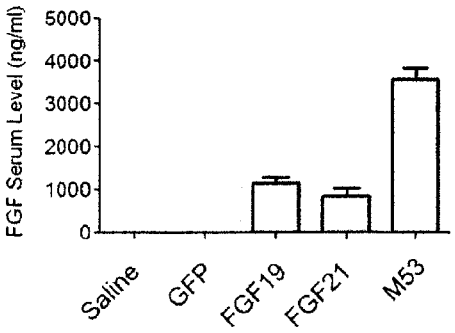
Figure 5H



(***P<0.001 vs. FGF19)

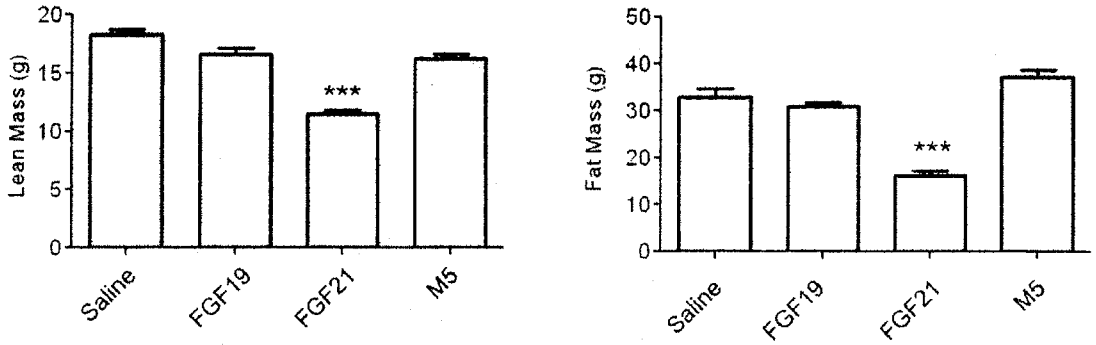
Figure 5I





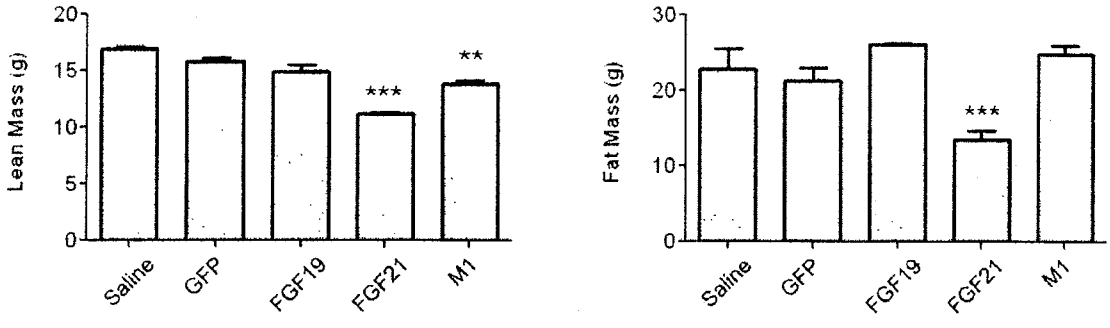
(***P<0.001 vs. FGF19)

Figure 6A



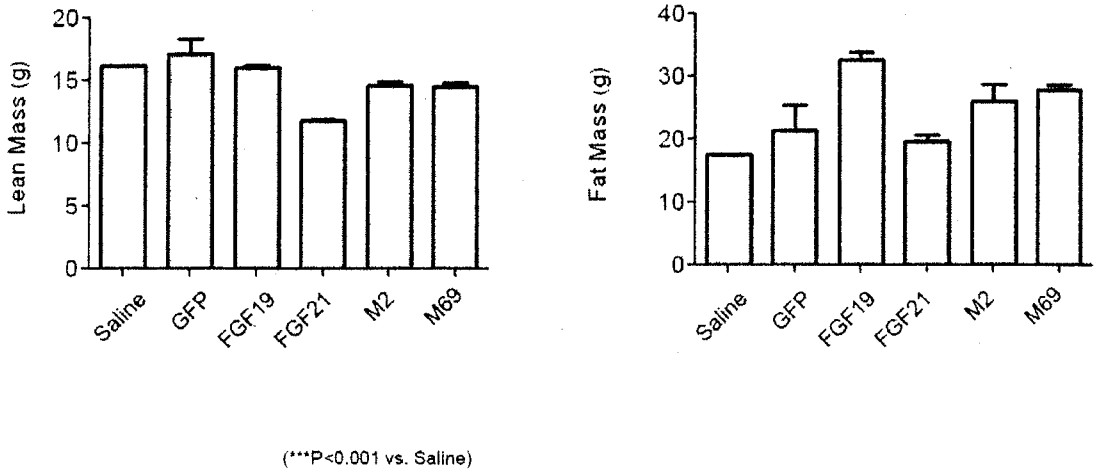
(***P<0.001 vs. Saline)

Figure 6B



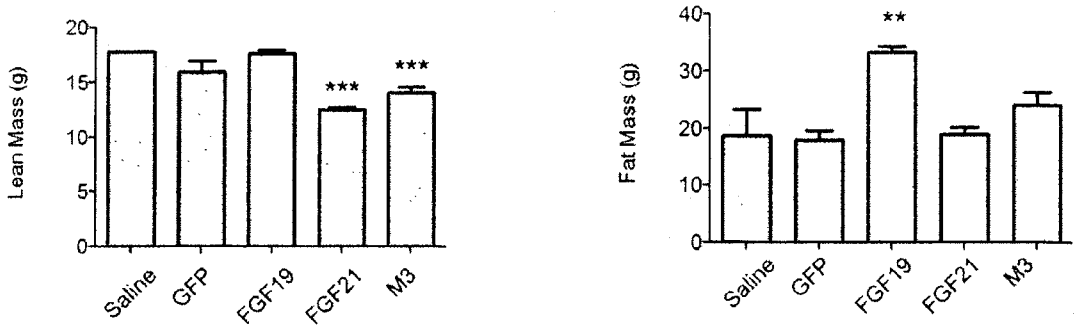
(***P<0.001 vs. Saline)

Figure 6C



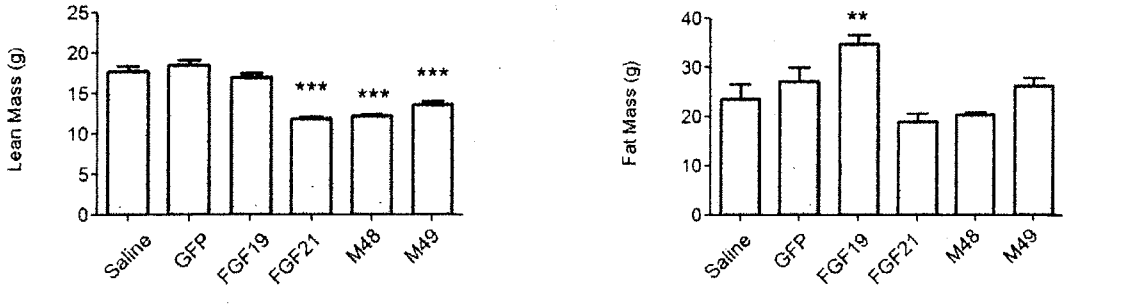
(***P<0.001 vs. Saline)

Figure 6D



(***P<0.001 vs. Saline)

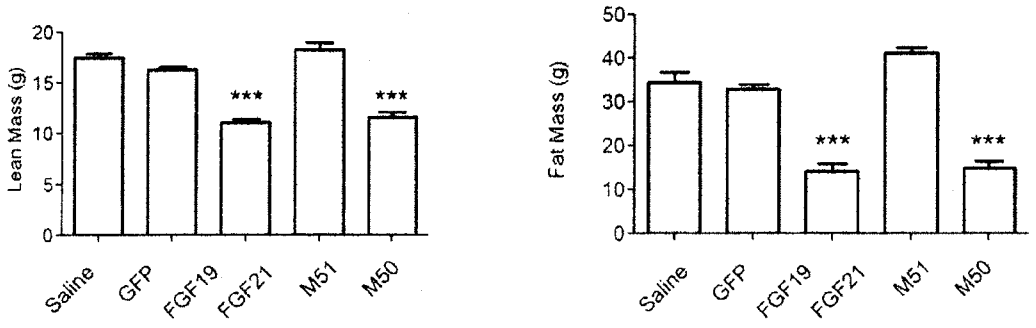
Figure 6E



(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

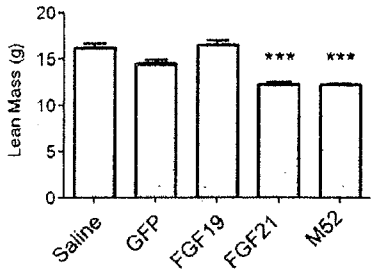
Figure 6F

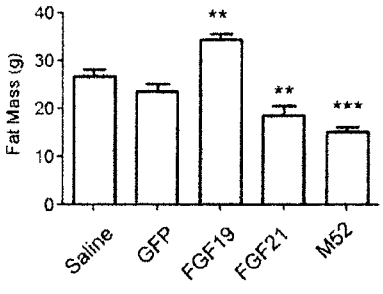


(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

Figure 6G

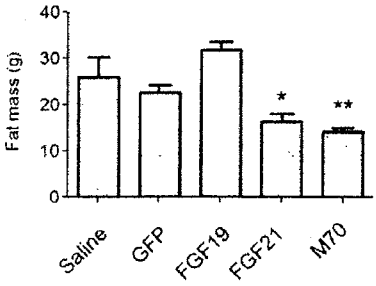


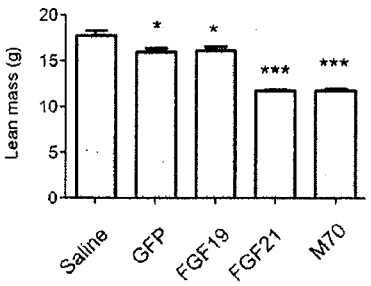


(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

Figure 6H

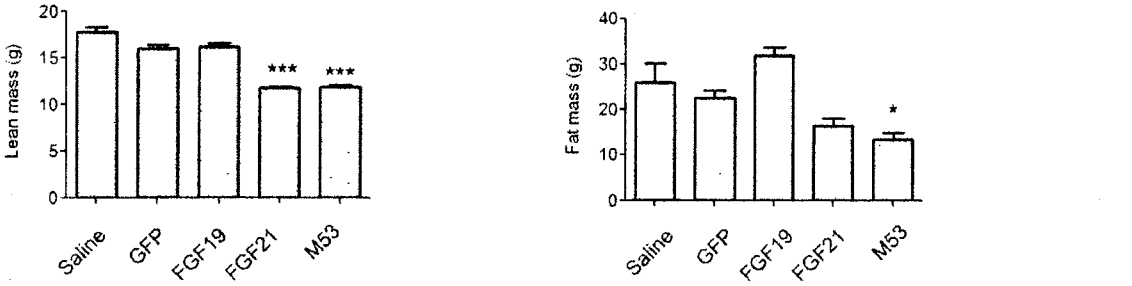




(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

Figure 6I



(***P<0.001 vs. Saline)

(*db/db* mice, 6 months after AAV injection)

Figure 7A

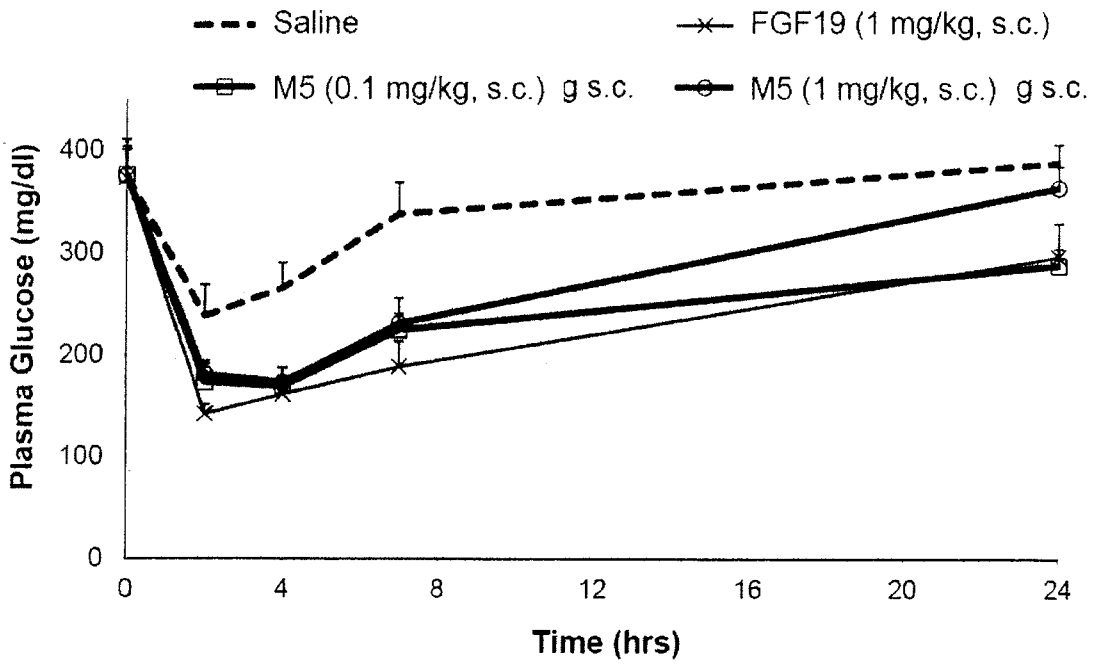


Figure 7B

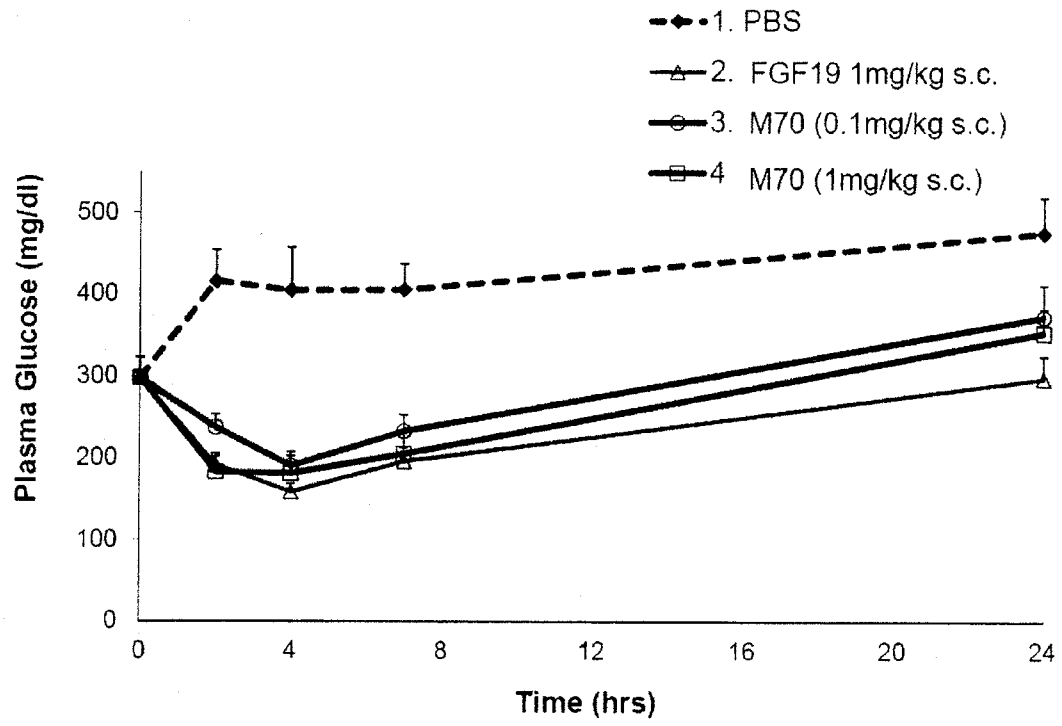
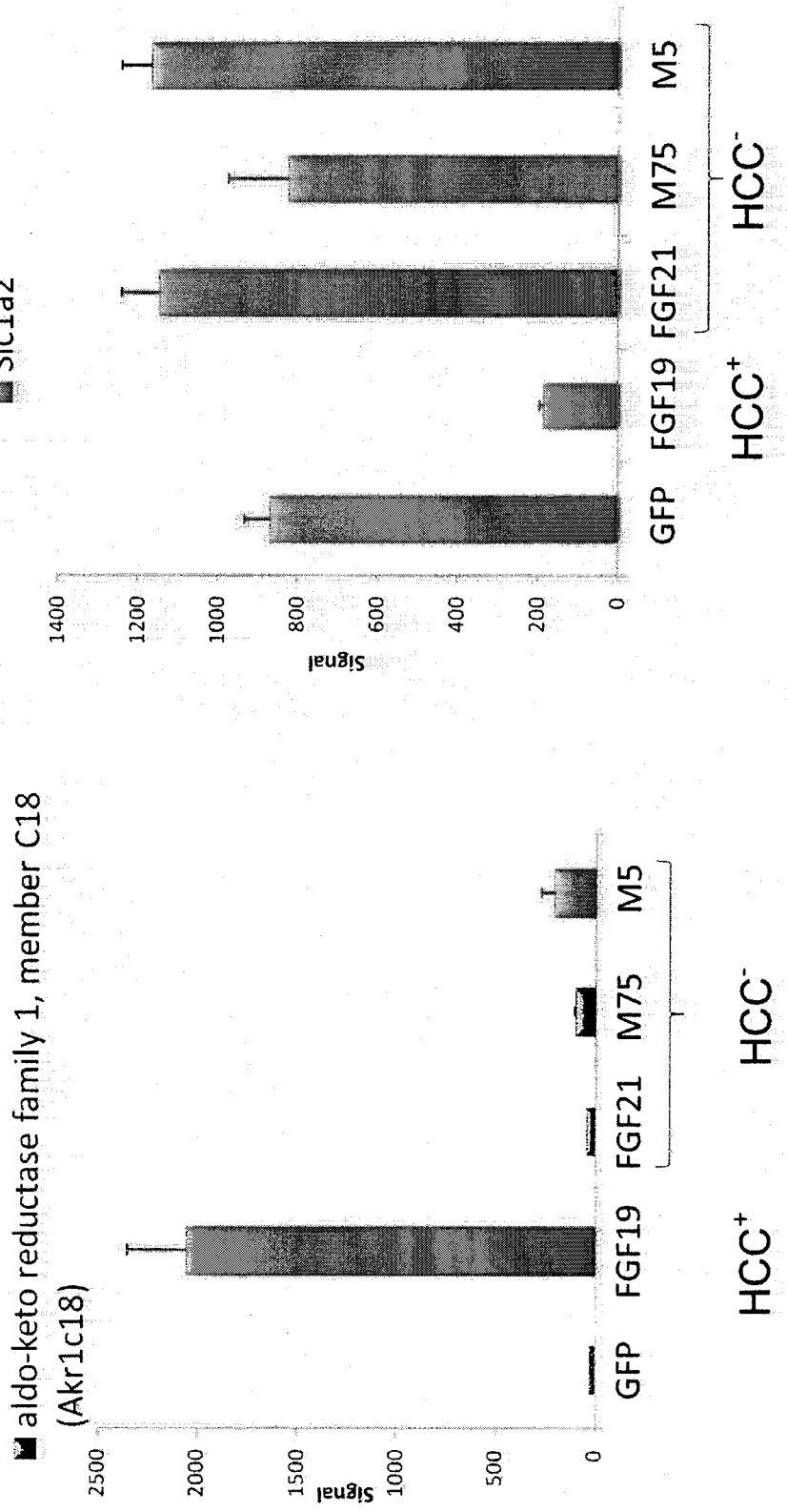


Figure 8


Slc1a2
Signal
1400
1200
1000
800
600
400
200
0
GFP
FGF19
FGF21
M75
M5
HCC+
HCC-
aldo-keto reductase family 1, member C18 (Akr1c18)
Signal
2500
2000
1500
1000
500
0
GFP
FGF19
FGF21
M75
M5
HCC+
HCC-