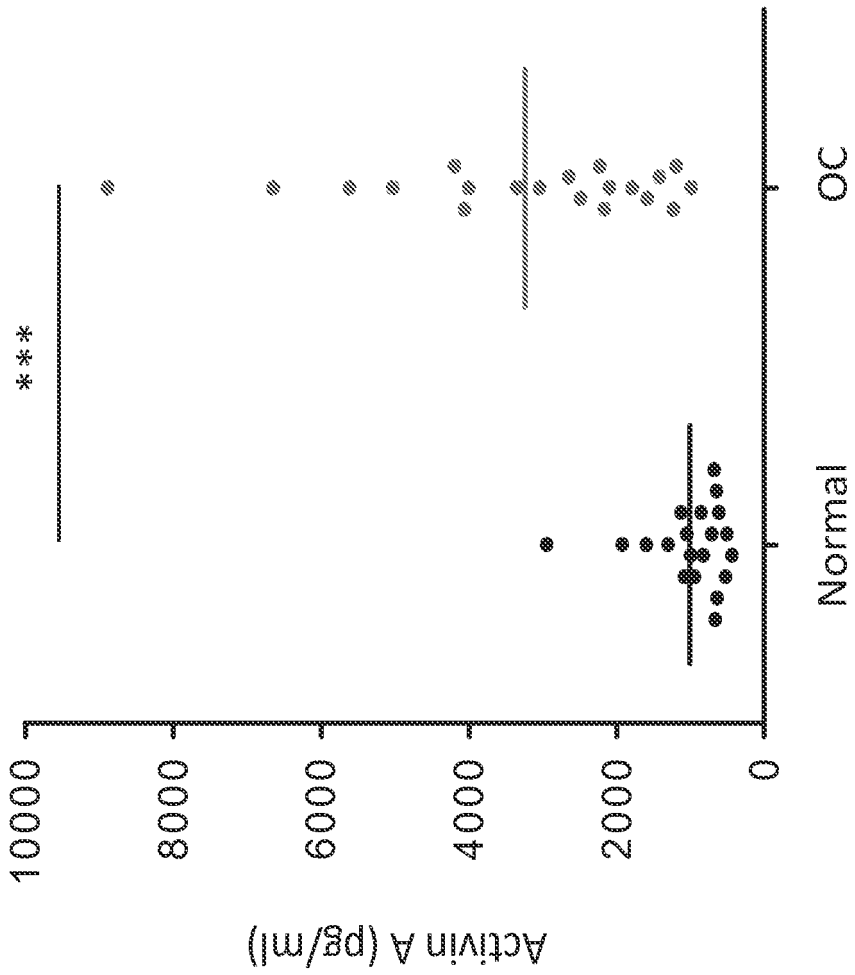


FIG. 1

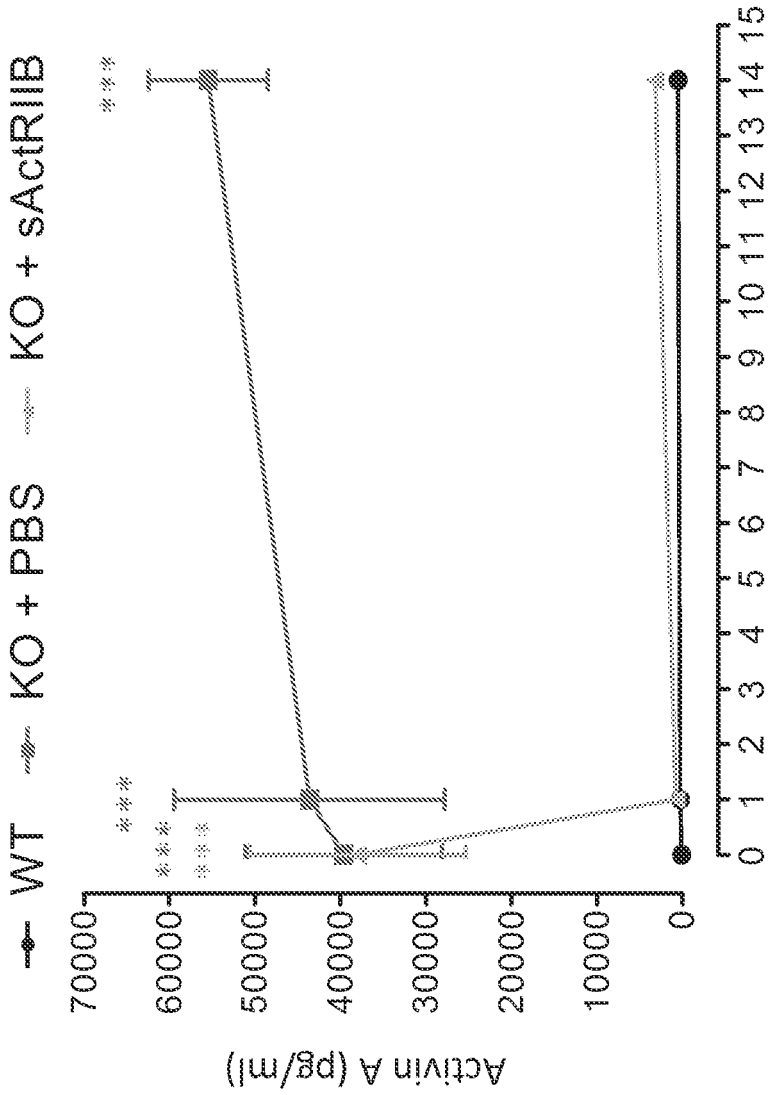

WT
KO + PBS
KO + sActRIIB
Activin A (pg/ml)
70000
60000
50000
40000
30000
20000
10000
0
***
***
***
***
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Treatment (Day)

FIG. 2A

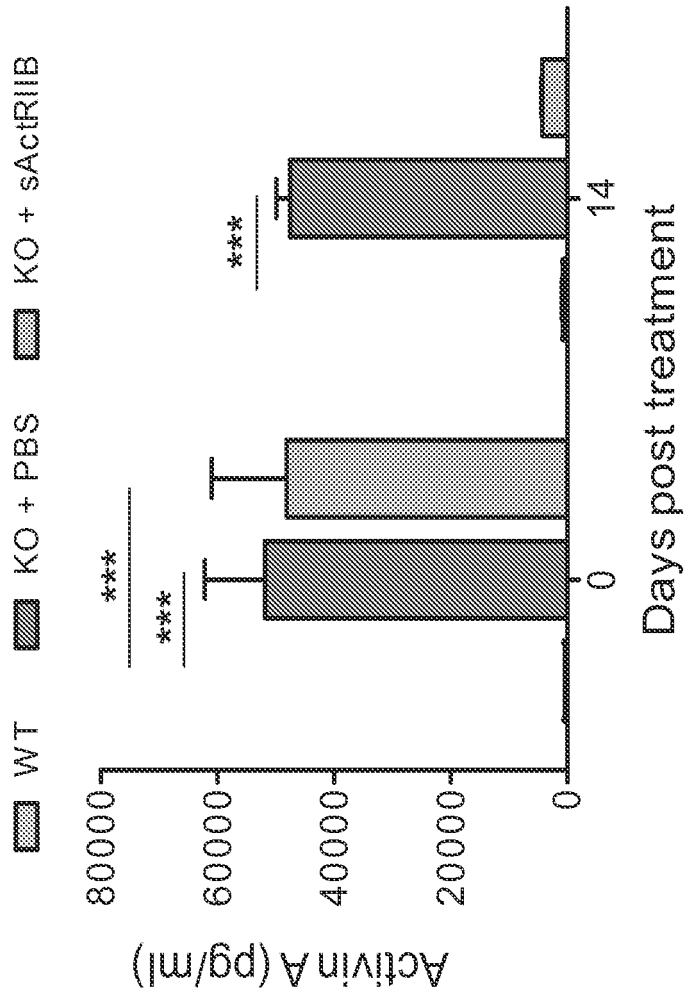

WT
KO + PBS
KO + sActRIIB
***
***
***
80000
60000
40000
20000
0
Activin A (pg/ml)
0
14
Days post treatment

FIG. 2B

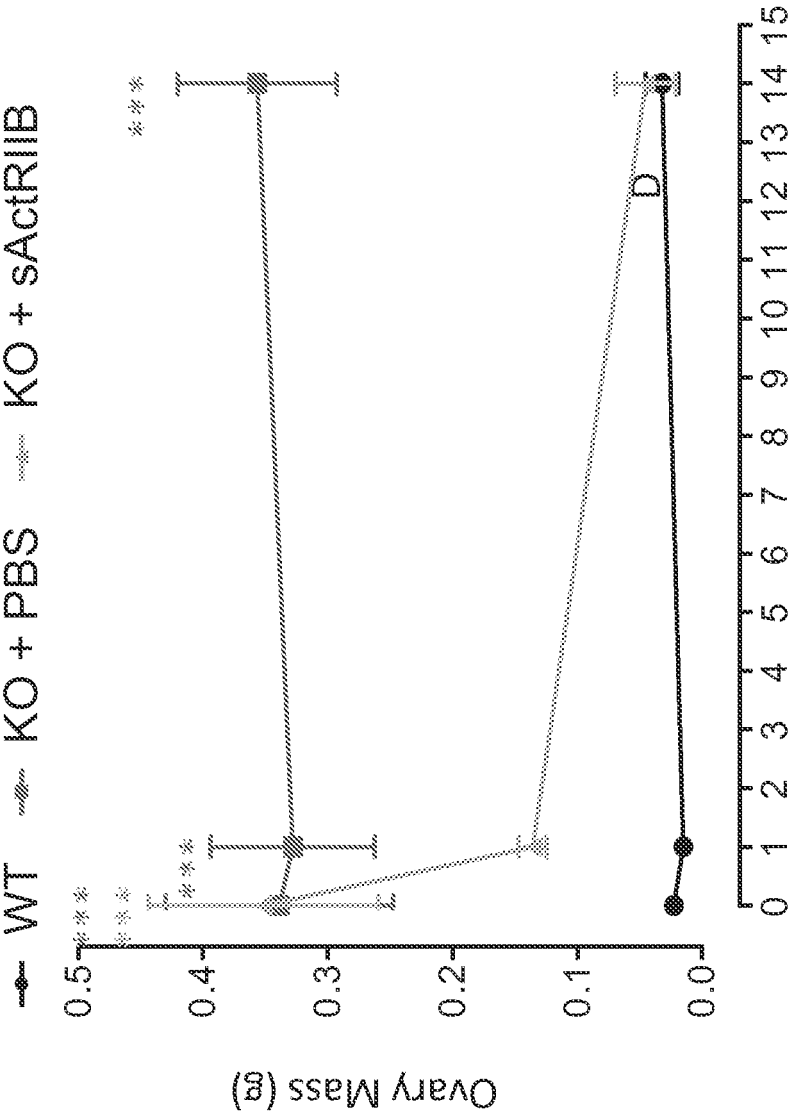

WT
KO + PBS
KO + sActRIIB
Ovary Mass (g)
0.5
0.4
0.3
0.2
0.1
0.0
***
***
***
***
D
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Treatment (Day)

FIG. 3A

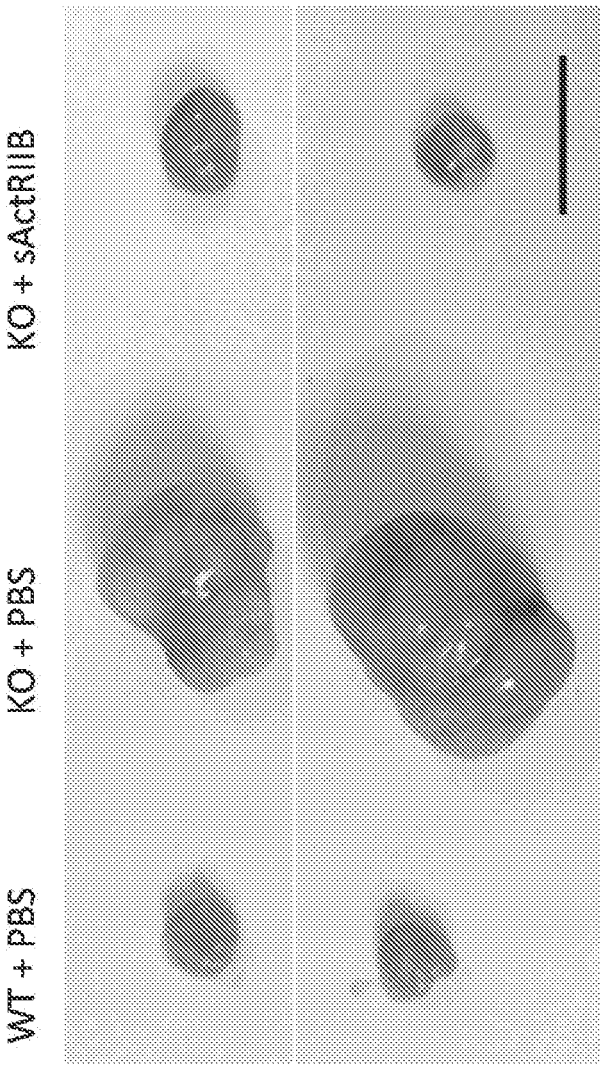


FIG. 3B

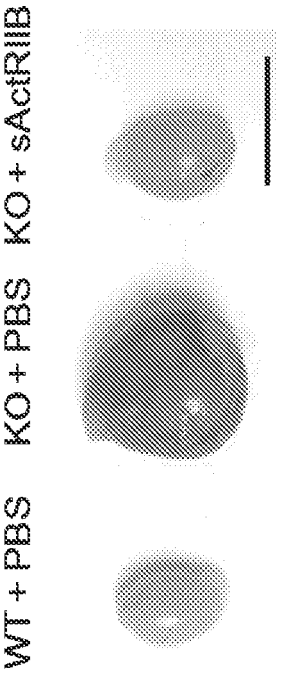

WT + PBS
KO + PBS
KO + sActRIIB

FIG. 4B

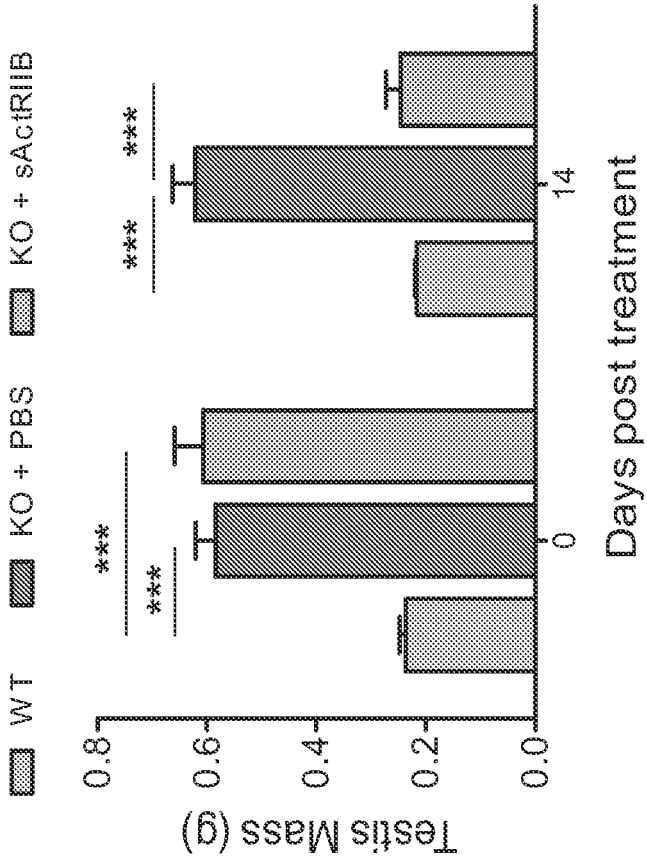

WT
KO + PBS
KO + sActRIIB
Testis Mass (g)
0.0
0.2
0.4
0.6
0.8
***
***
***
***
0
14
Days post treatment

FIG. 4A

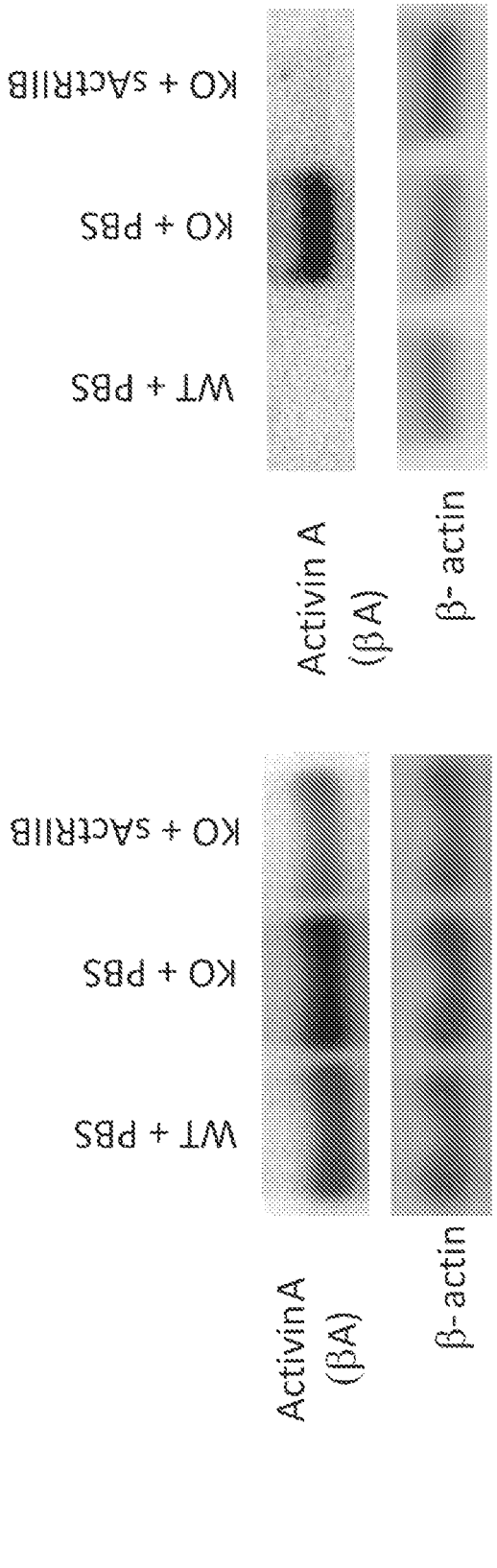

WT + PBS
KO + PBS
KO + sActRIIB
ActivinA (βA)
β-actin

FIG. 5A

WT + PBS
KO + PBS
KO + sActRIIB
p-Smad2
Smad2
α-Tubulin

FIG. 5B

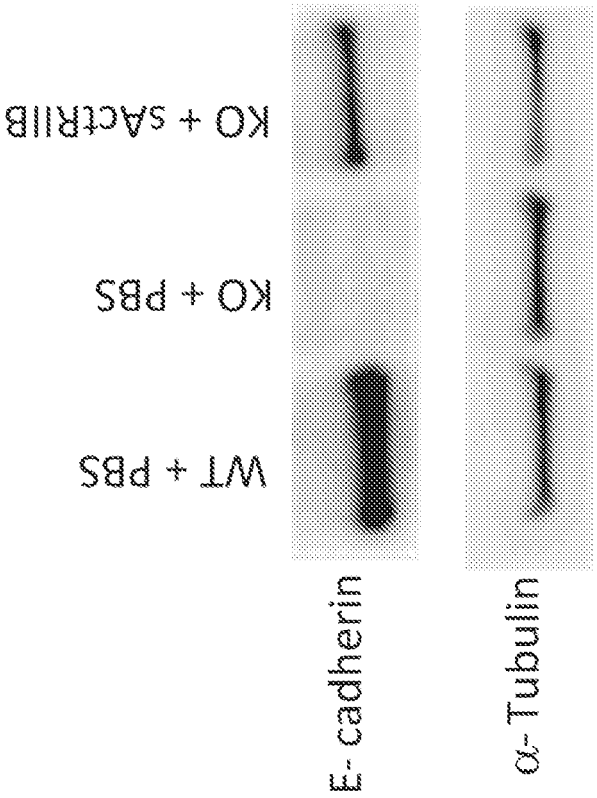

WT + PBS
KO + PBS
KO + sActRIIB
E- cadherin
α- Tubulin

FIG. 6A


WT + PBS
KO + PBS
KO + sActRIIB

FIG. 6B

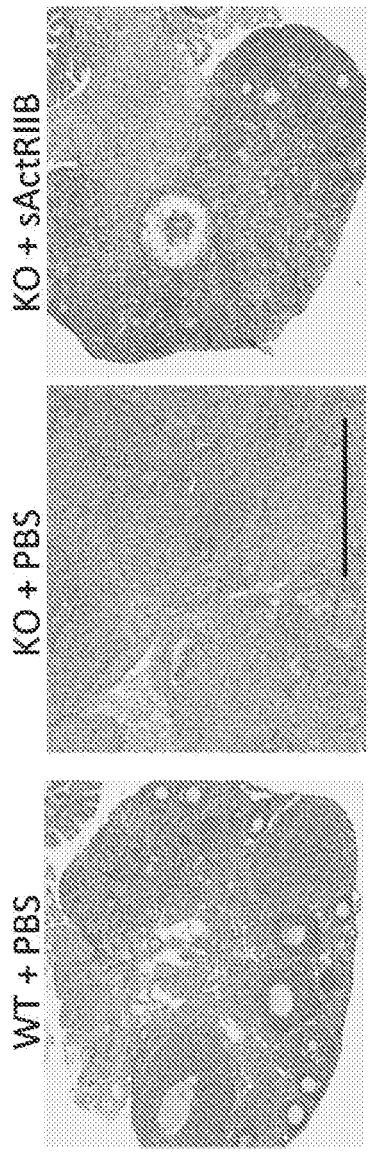

WT + PBS
KO + PBS
KO + sActRIIB

FIG. 7A

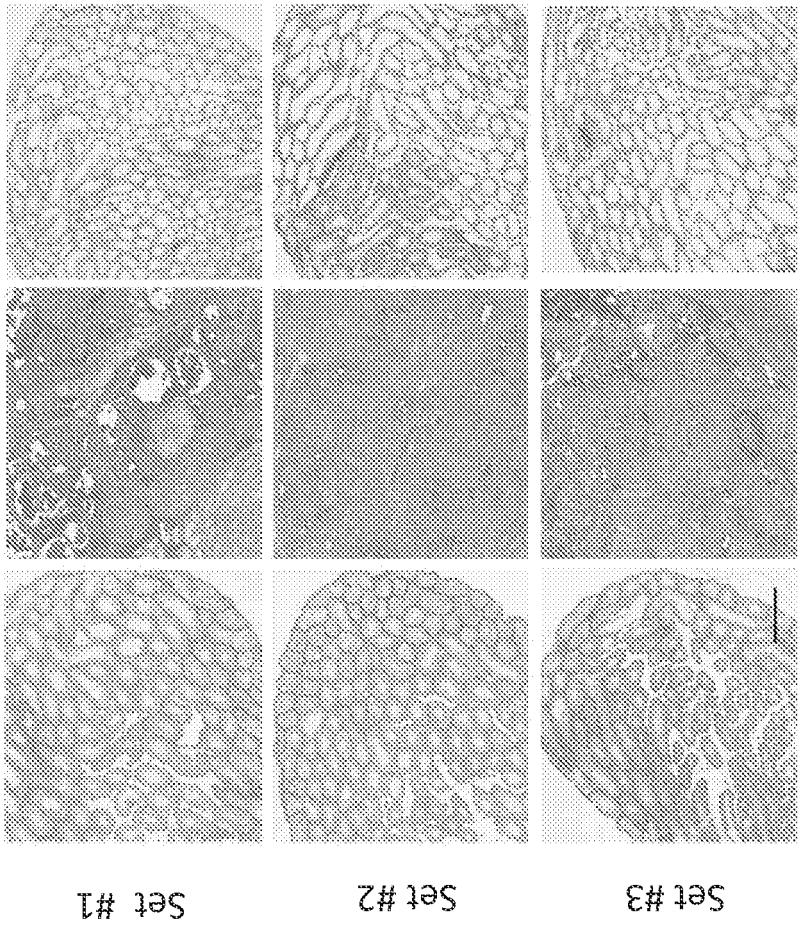

WT
Control
KO
+ PBS
KO
+ sActRIIB
Set #1
Set #2
Set #3

FIG. 7B

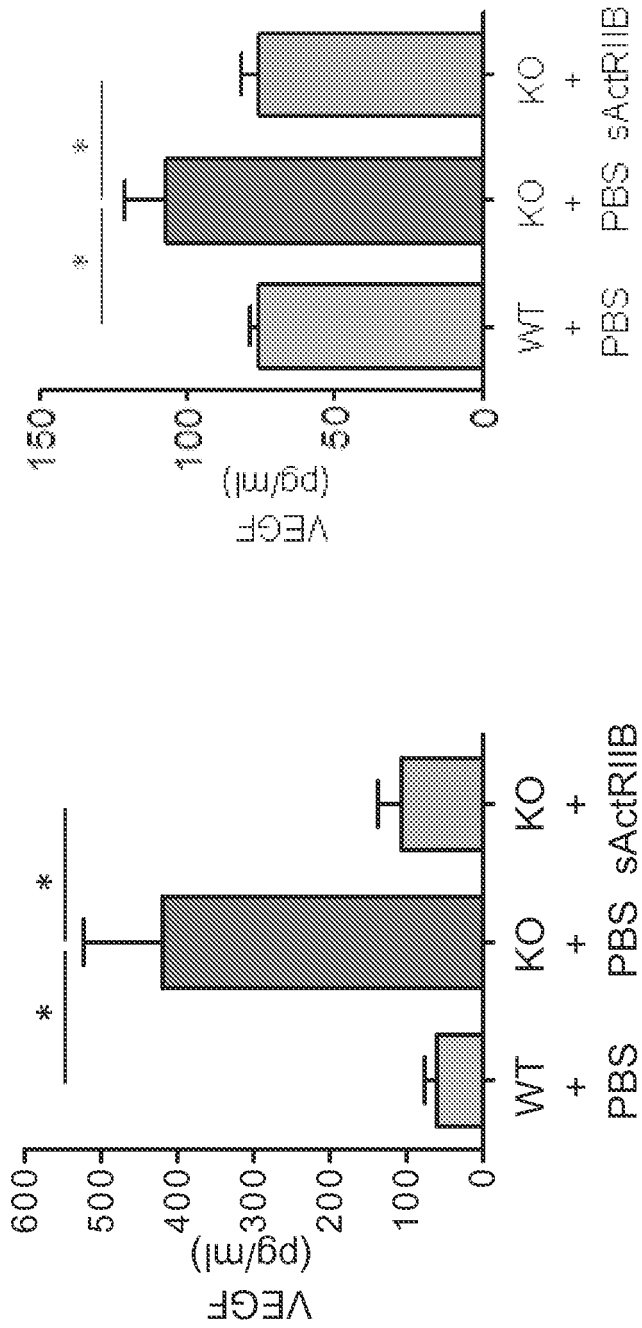
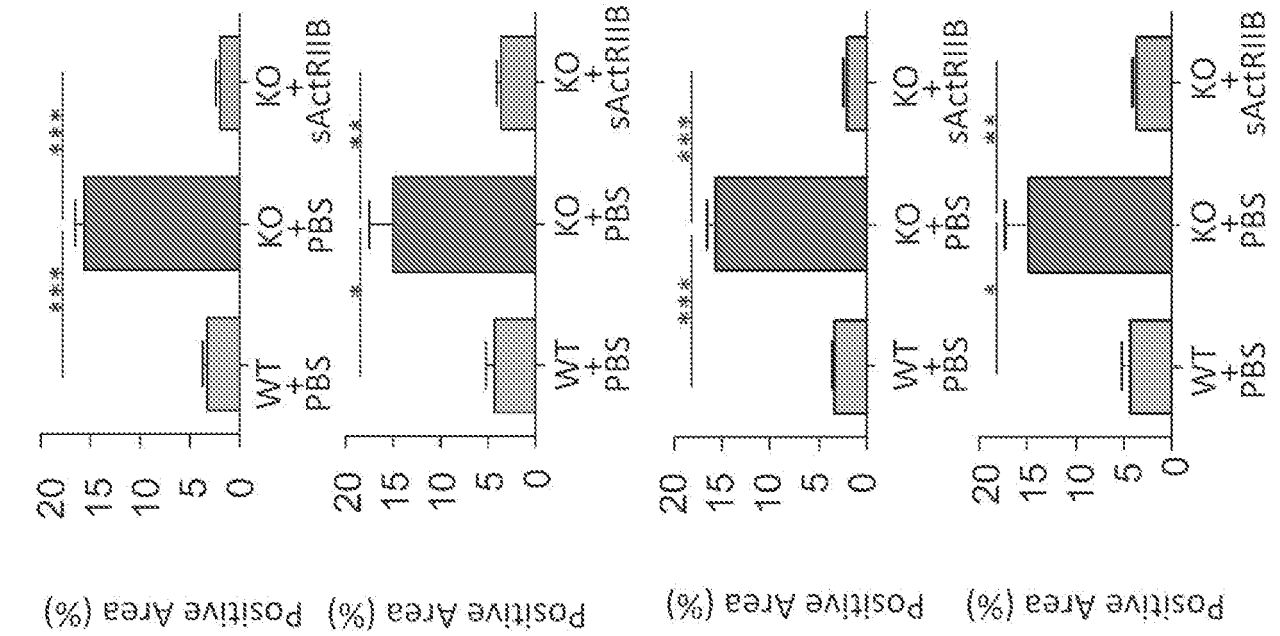

VEGF
(pg/ml)
600
500
400
300
200
100
0
*
*
WT
KO
KO
PBS
PBS
sActRIIB
+
+
+
VEGF
(pg/ml)
150
100
50
0
*
*
WT
KO
KO
PBS
PBS
sActRIIB
+
+
+

FIG. 8A


Positive Area (%)
20
15
10
5
0
***
***
WT + PBS
KO + PBS
KO + sActRIIB
Positive Area (%)
*
**
Positive Area (%)
***
***
Positive Area (%)
*
**

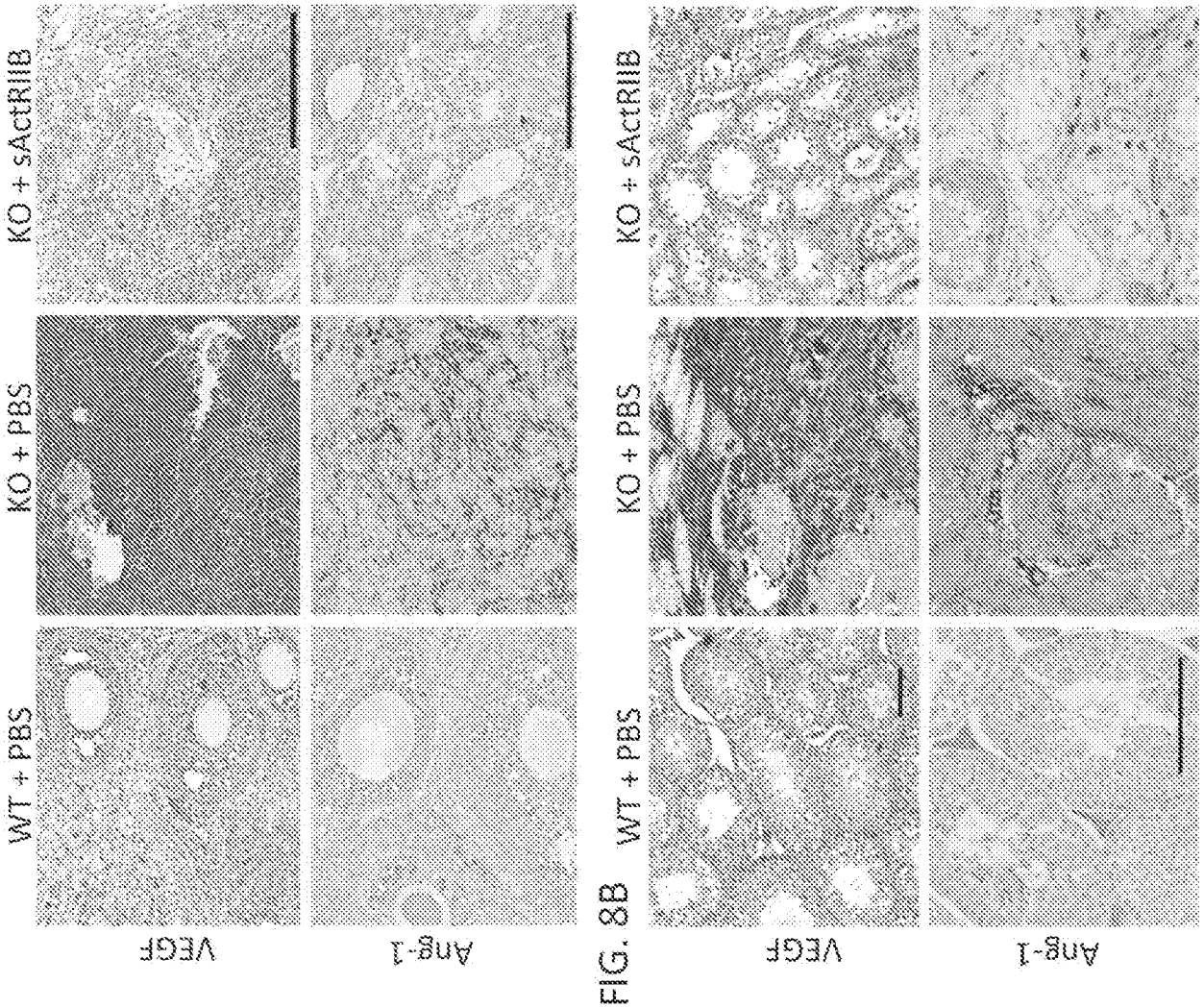

WT + PBS
KO + PBS
KO + sActRIIB
VEGF
Ang-1
VEGF
Ang-1

FIG. 8B

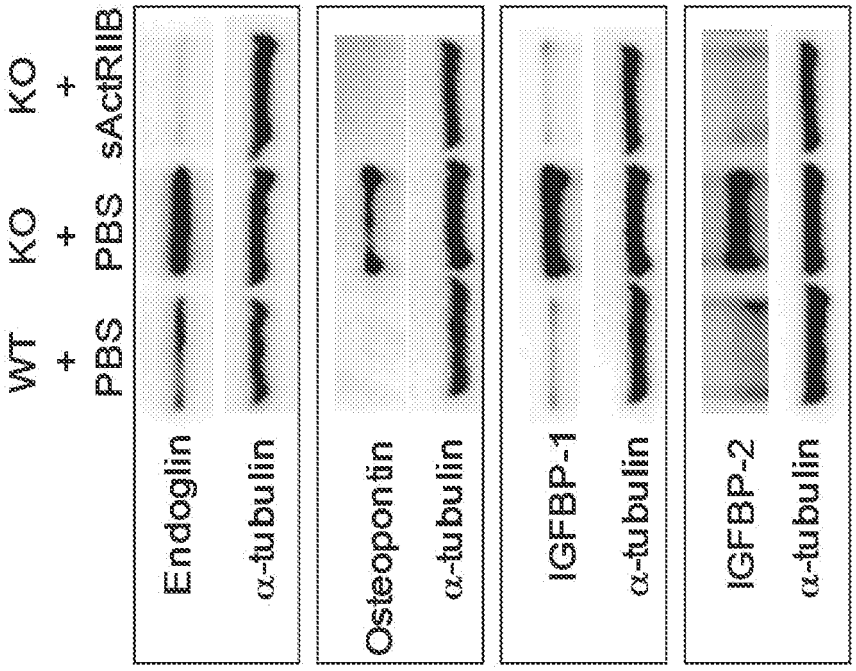
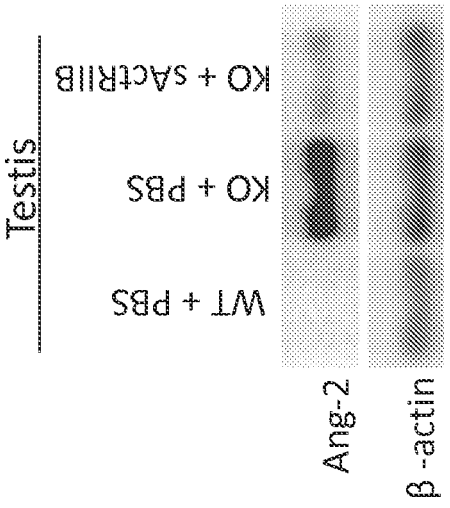

WT + PBS
KO + PBS
KO + sActRIIB
Endoglin
α-tubulin
Osteopontin
α-tubulin
IGFBP-1
α-tubulin
IGFBP-2
α-tubulin

FIG. 8D


Testis
WT + PBS
KO + PBS
KO + sActRIIB
Ang-2
β-actin

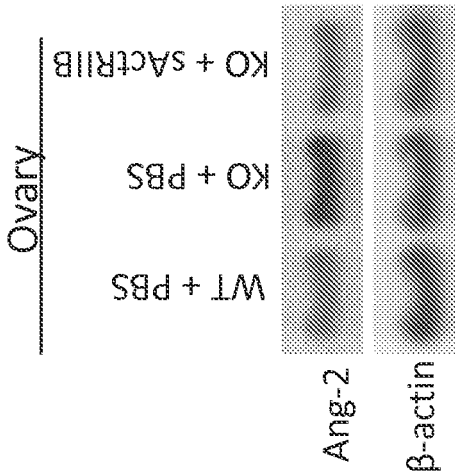

Ovary
WT + PBS
KO + PBS
KO + sActRIIB
Ang-2
β-actin

FIG. 8C

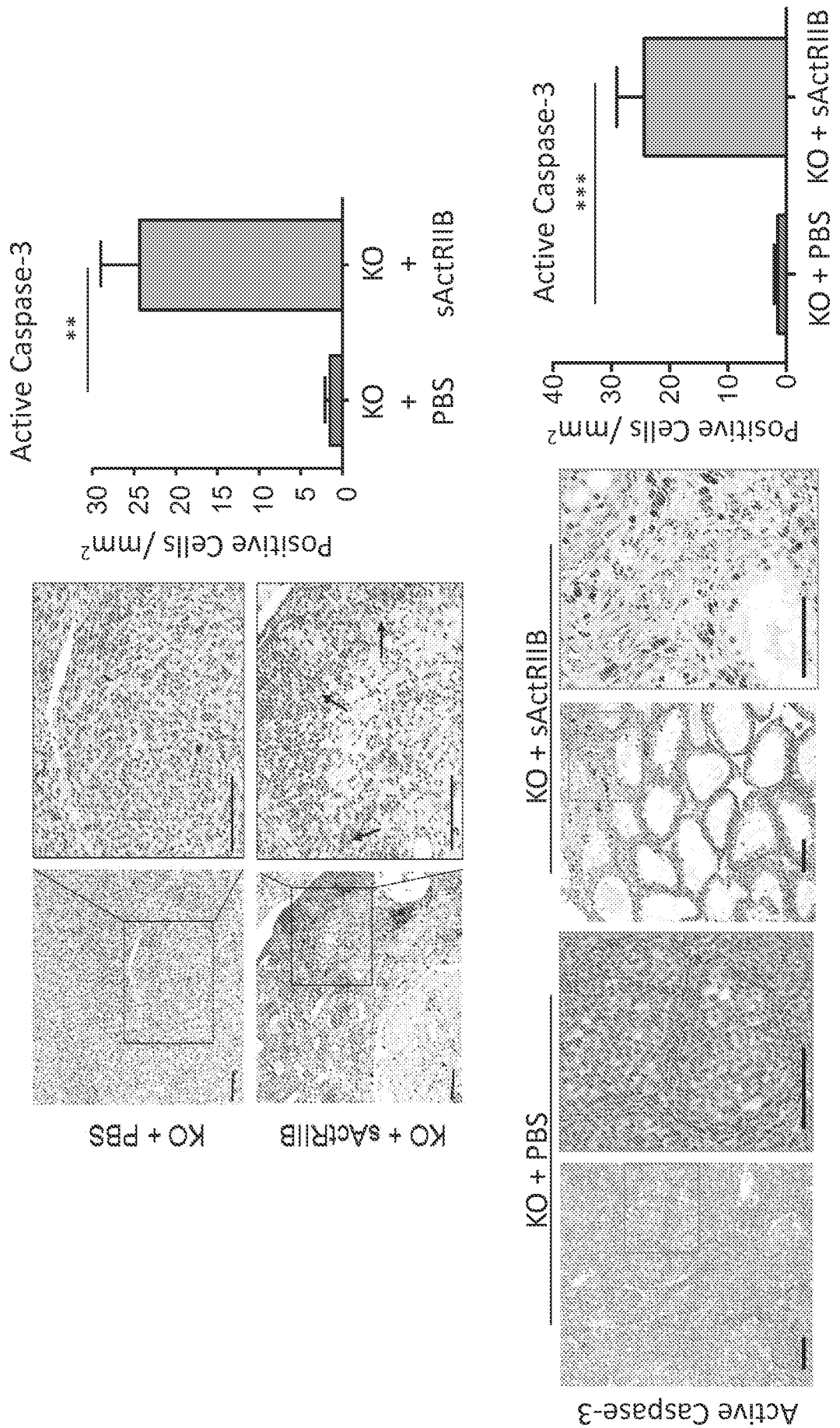

Active Caspase-3
**
Positive Cells /mm2
30
25
20
15
10
5
0
KO + PBS
KO + sActRIIB
KO + PBS
KO + sActRIIB
Active Caspase-3
***
Positive Cells /mm2
40
30
20
10
0
KO + PBS
KO + sActRIIB
Active Caspase-3

FIG. 9

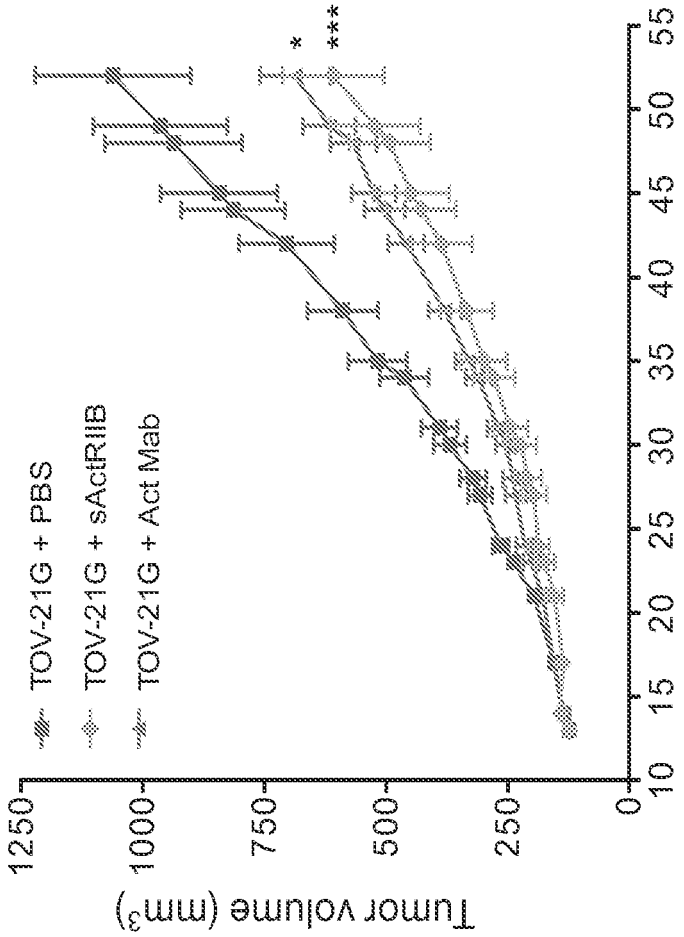


FIG. 10B

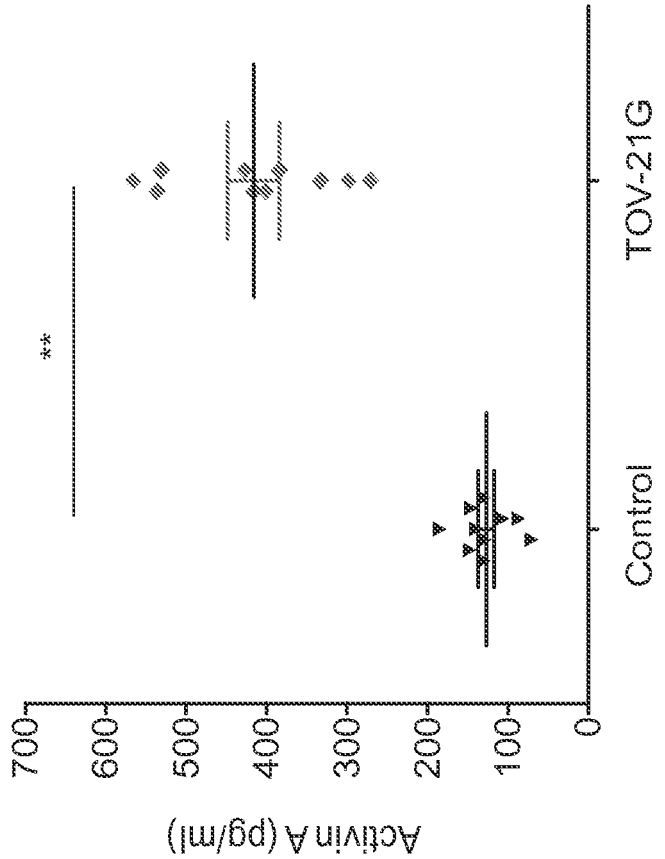


FIG. 10A

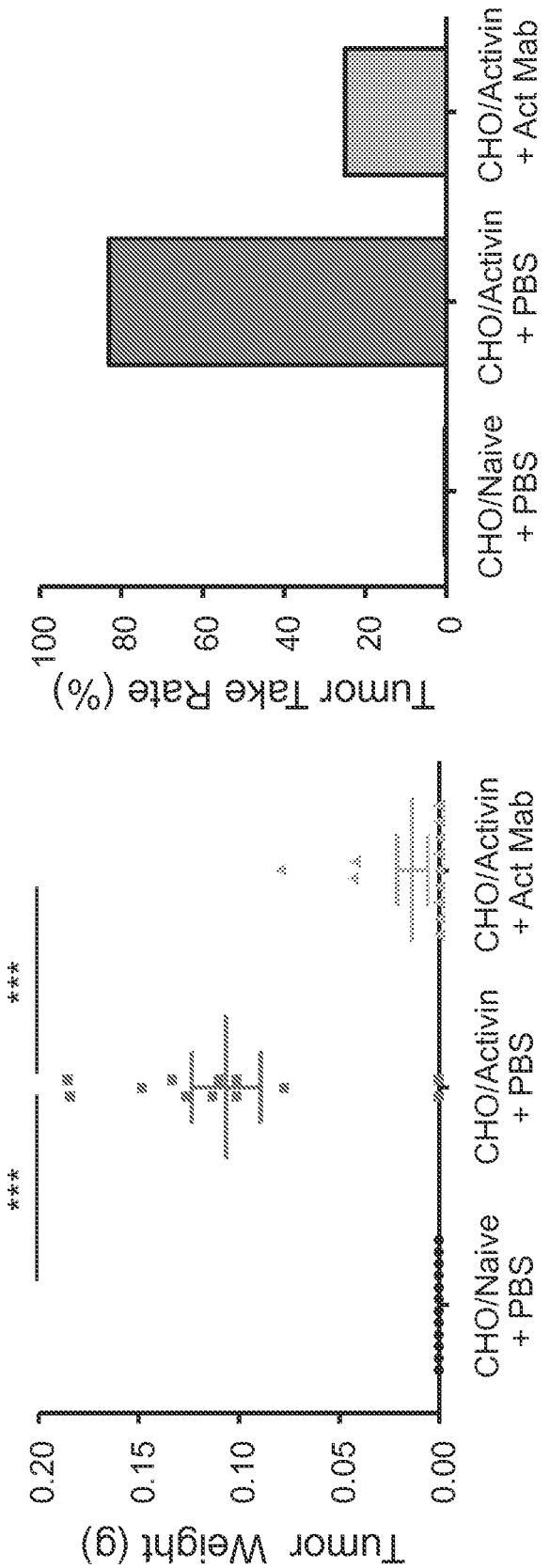
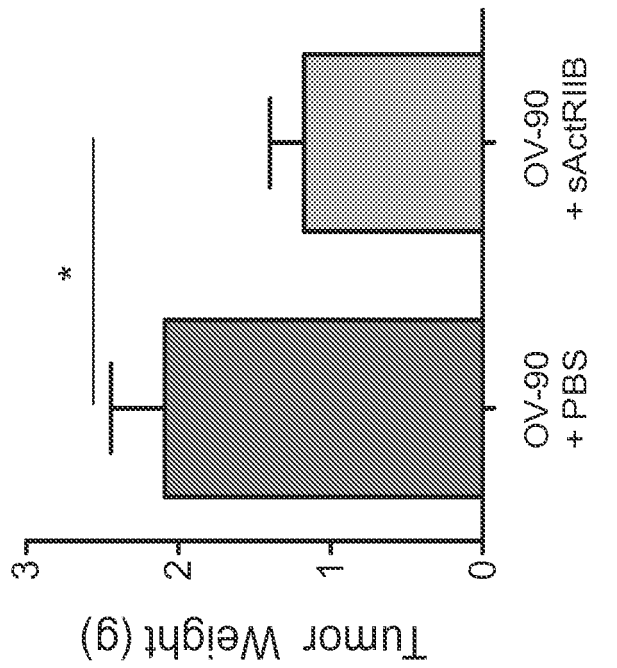

Tumor Weight (g)
0.20
0.15
0.10
0.05
0.00
***
***
CHO/Naive + PBS
CHO/Activin + PBS
CHO/Activin + Act Mab
Tumor Take Rate (%)
100
80
60
40
20
0
CHO/Naive + PBS
CHO/Activin + PBS
CHO/Activin + Act Mab

FIG. 11


Tumor Weight (g)
3
2
1
0
*
OV-90 + PBS
OV-90 + sActRIIB

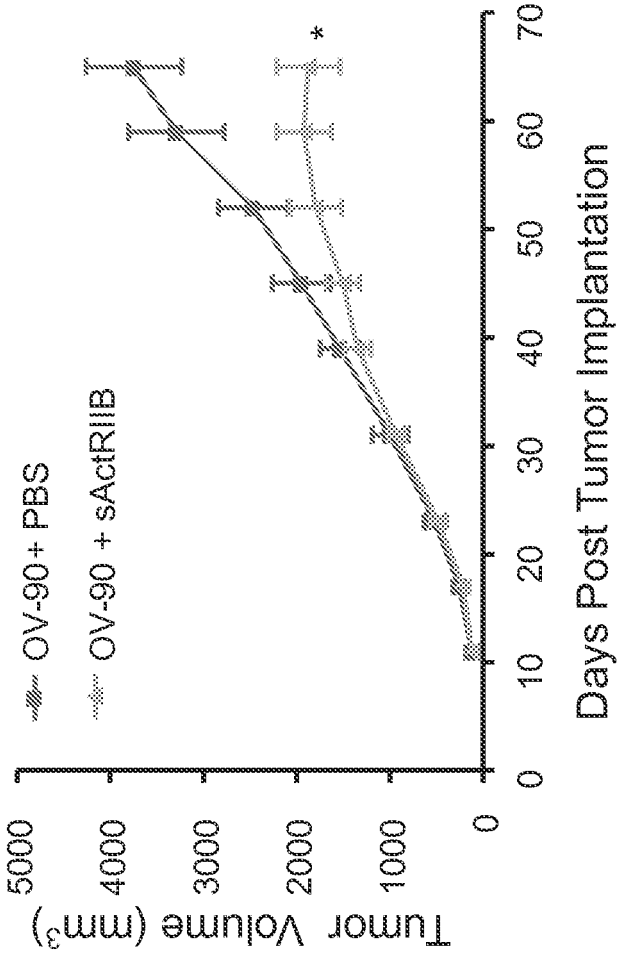

Tumor Volume (mm³)
5000
4000
3000
2000
1000
0
0
10
20
30
40
50
60
70
Days Post Tumor Implantation
OV-90 + PBS
OV-90 + sActRIIB
*

FIG. 12

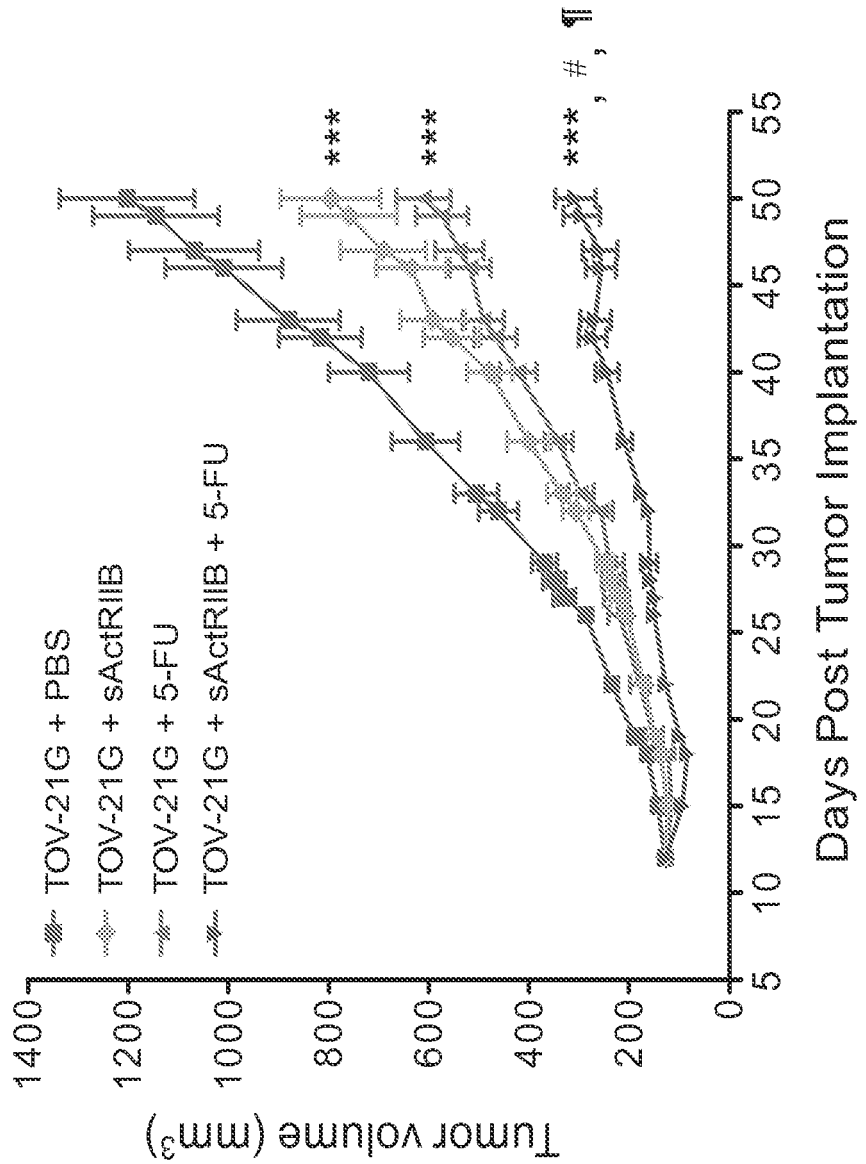

TOV-21G + PBS
TOV-21G + sActRIIB
TOV-21G + 5-FU
TOV-21G + sActRIIB + 5-FU
Tumor volume (mm3)
Days Post Tumor Implantation
0
200
400
600
800
1000
1200
1400
5
10
15
20
25
30
35
40
45
50
55
***
***
***
#
,

FIG. 13

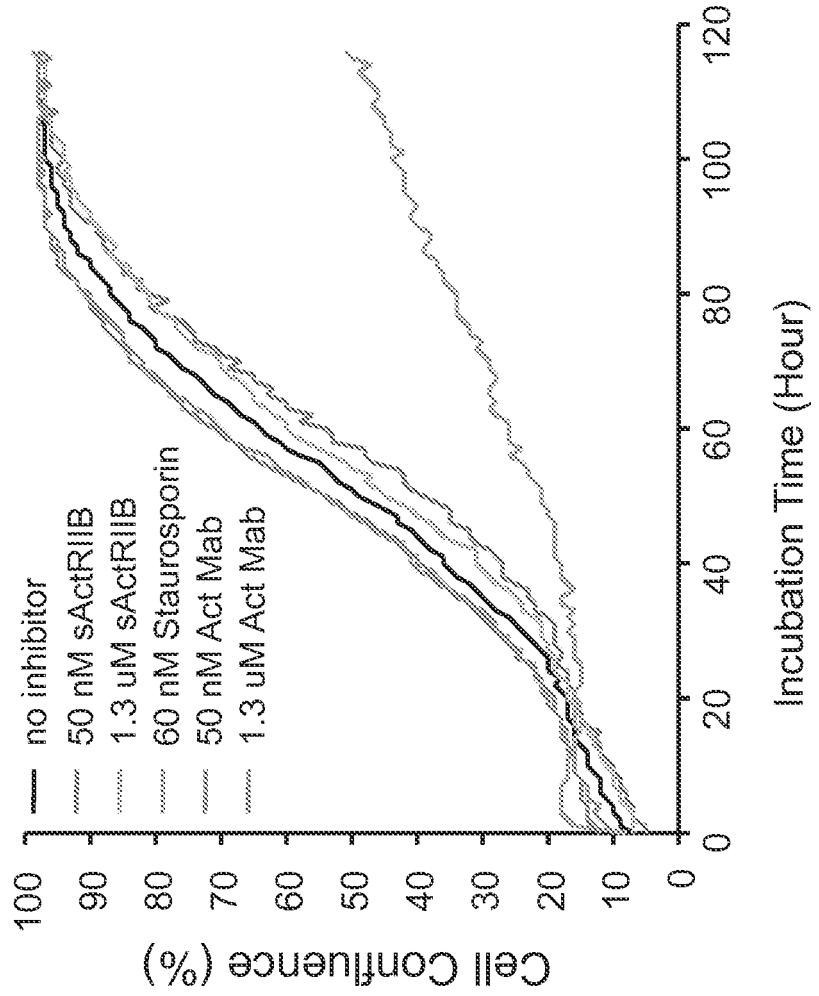

Cell Confluence (%)
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Incubation Time (Hour)
no inhibitor
50 nM sActRIIB
1.3 uM sActRIIB
60 nM Staurosporin
50 nM Act Mab
1.3 uM Act Mab

FIG. 14

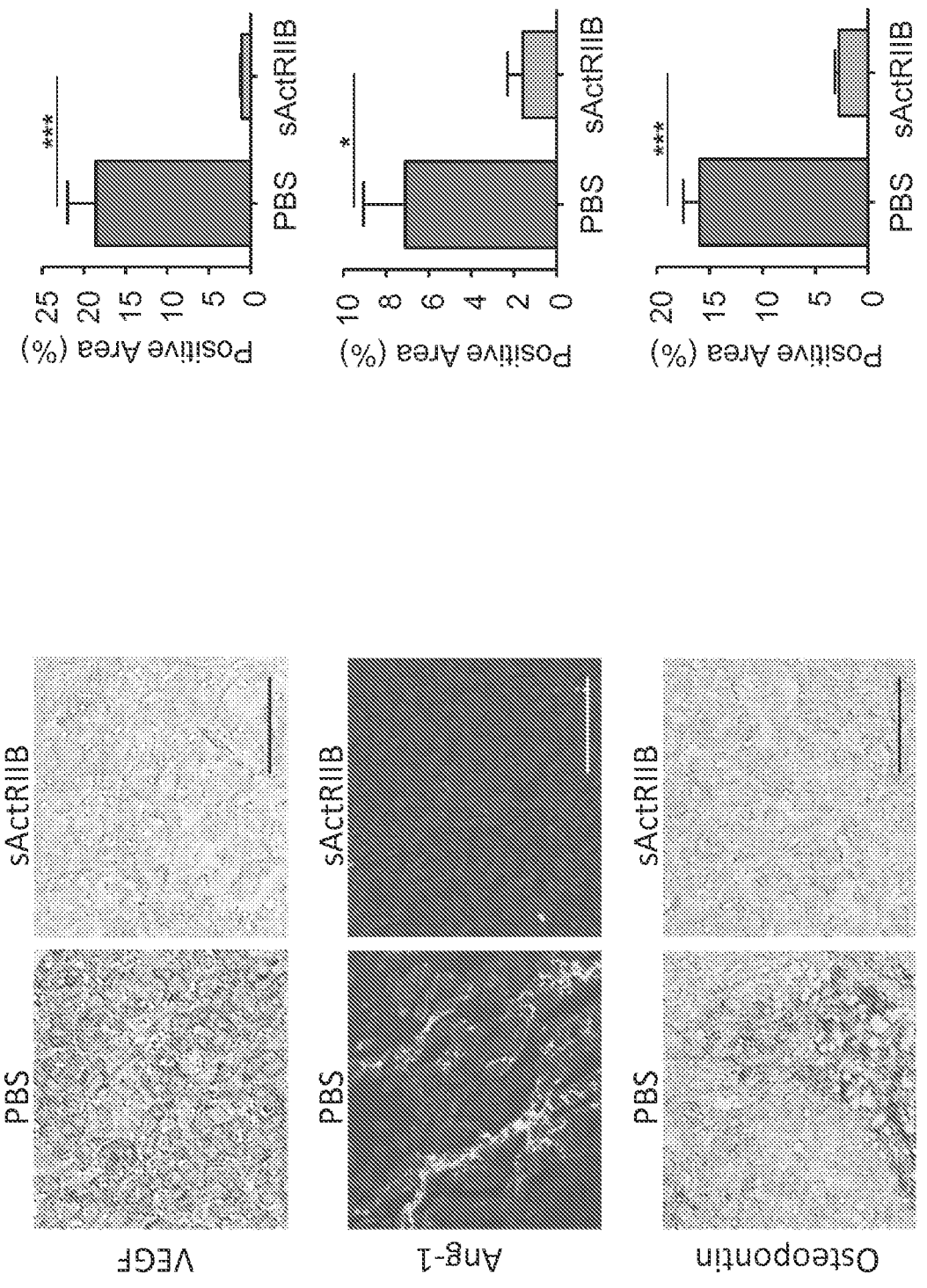


FIG. 15A

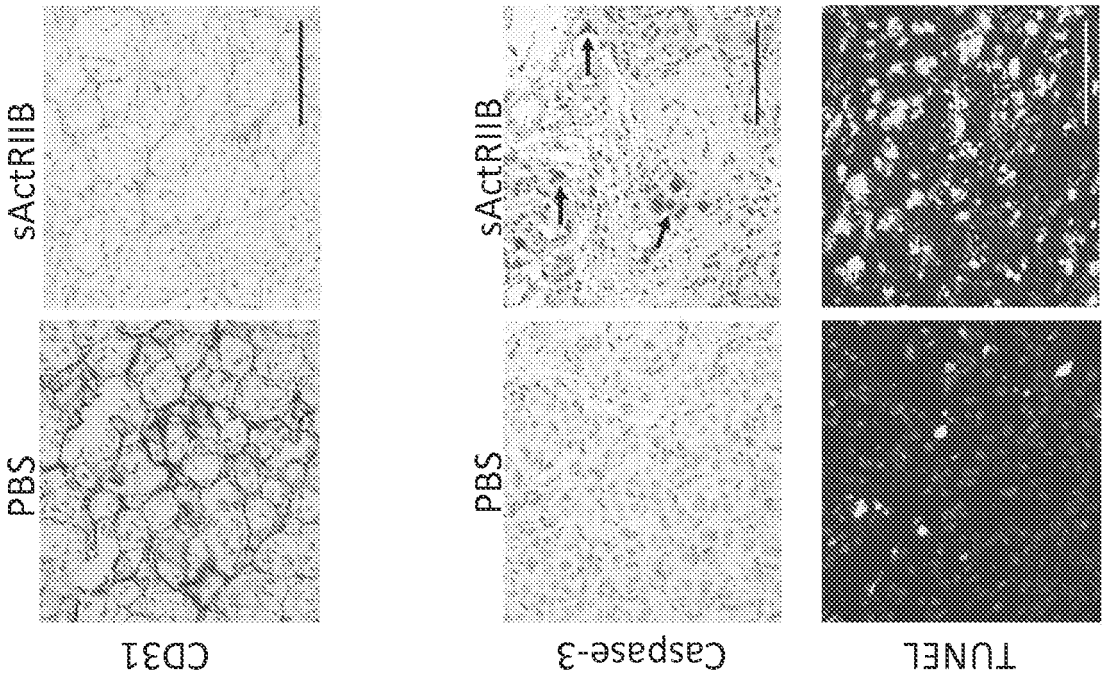


FIG. 15B

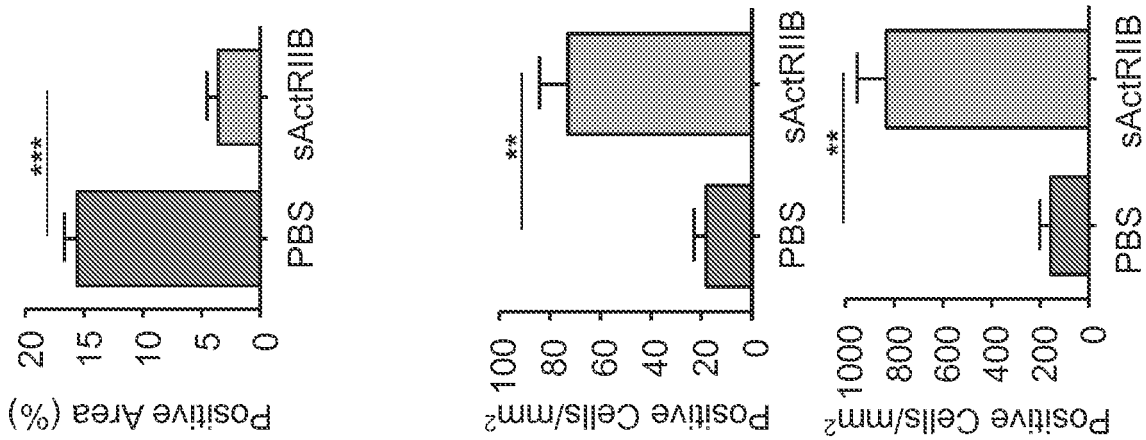


FIG. 15C

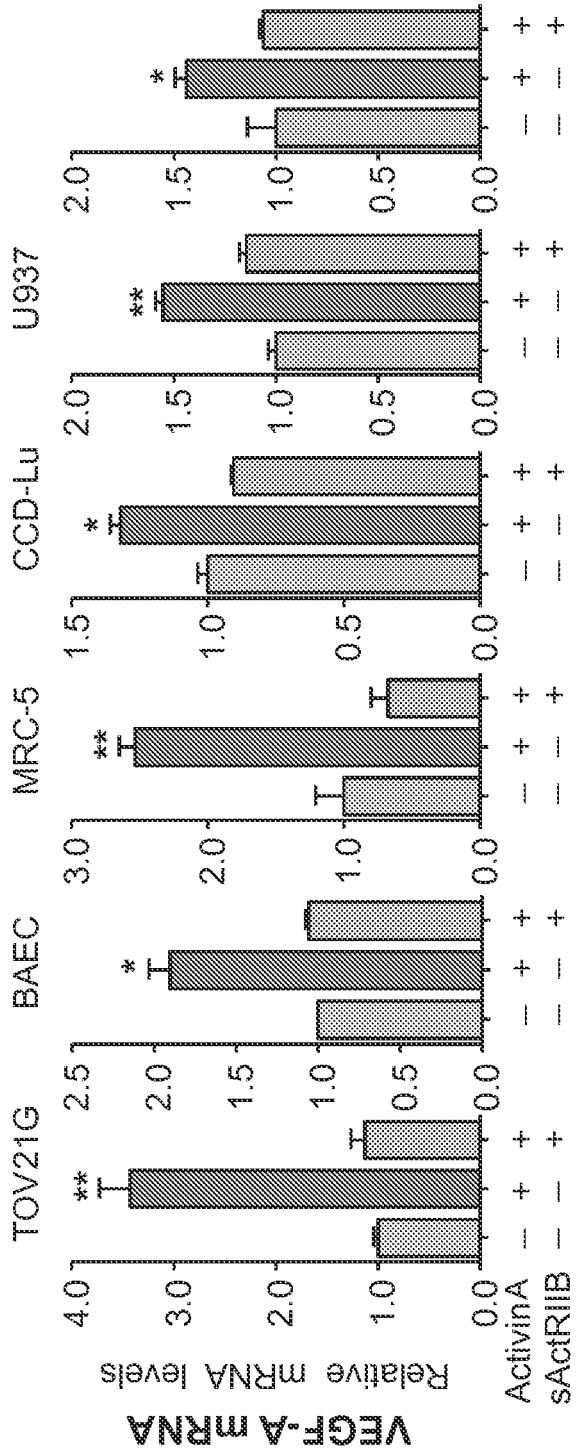


FIG. 16A

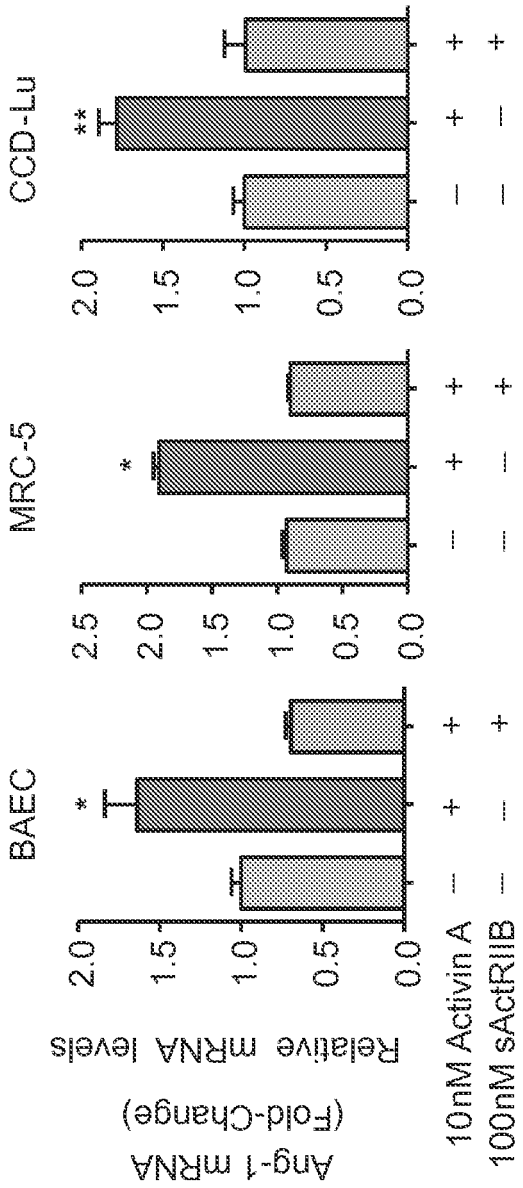


FIG. 16B

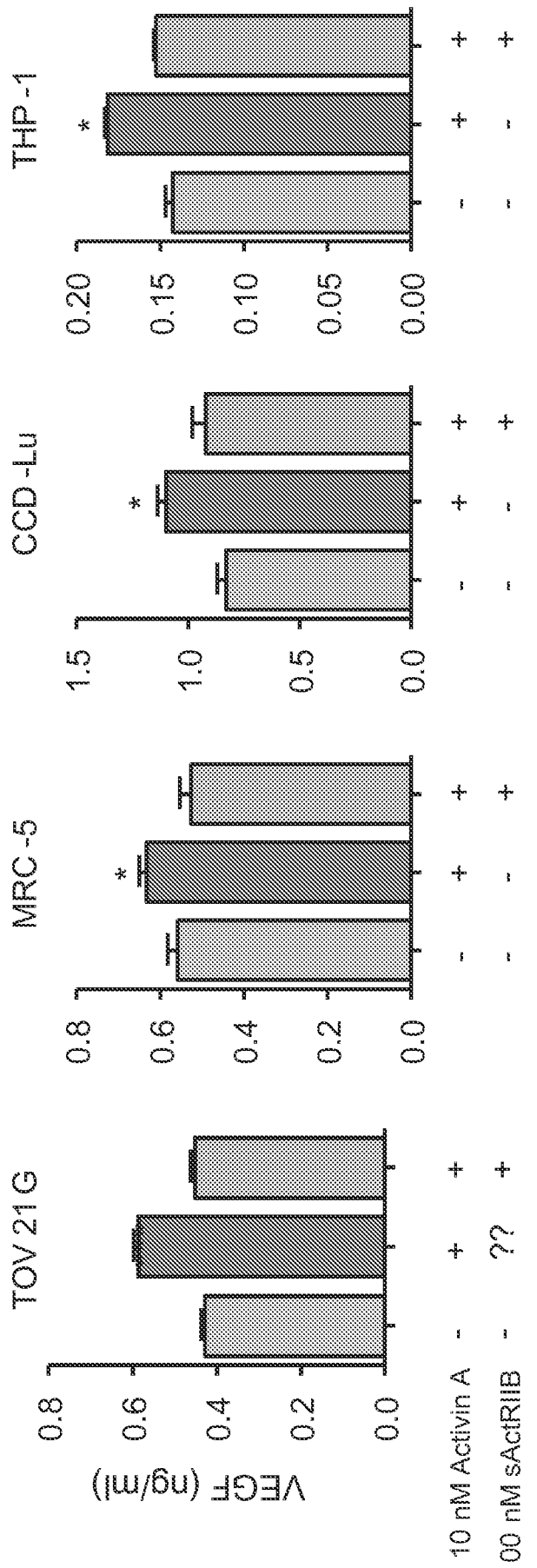


FIG. 17A

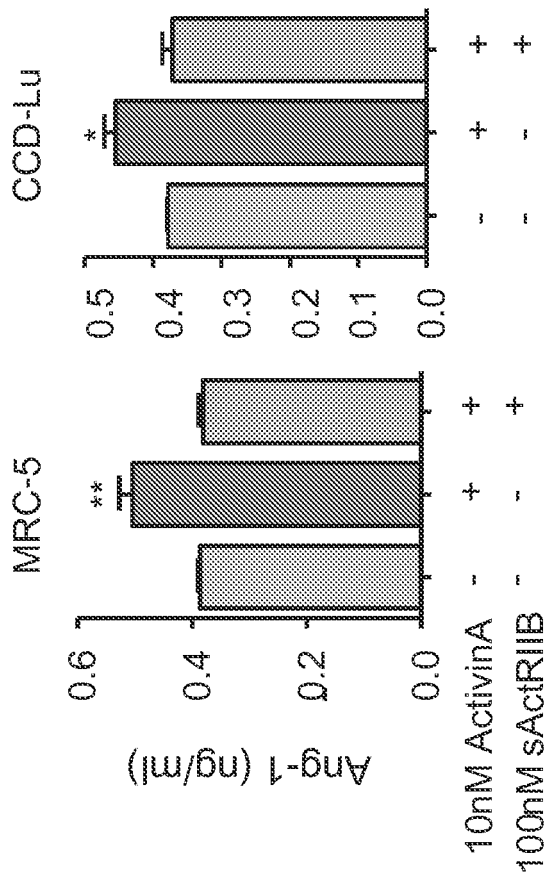


FIG. 17B

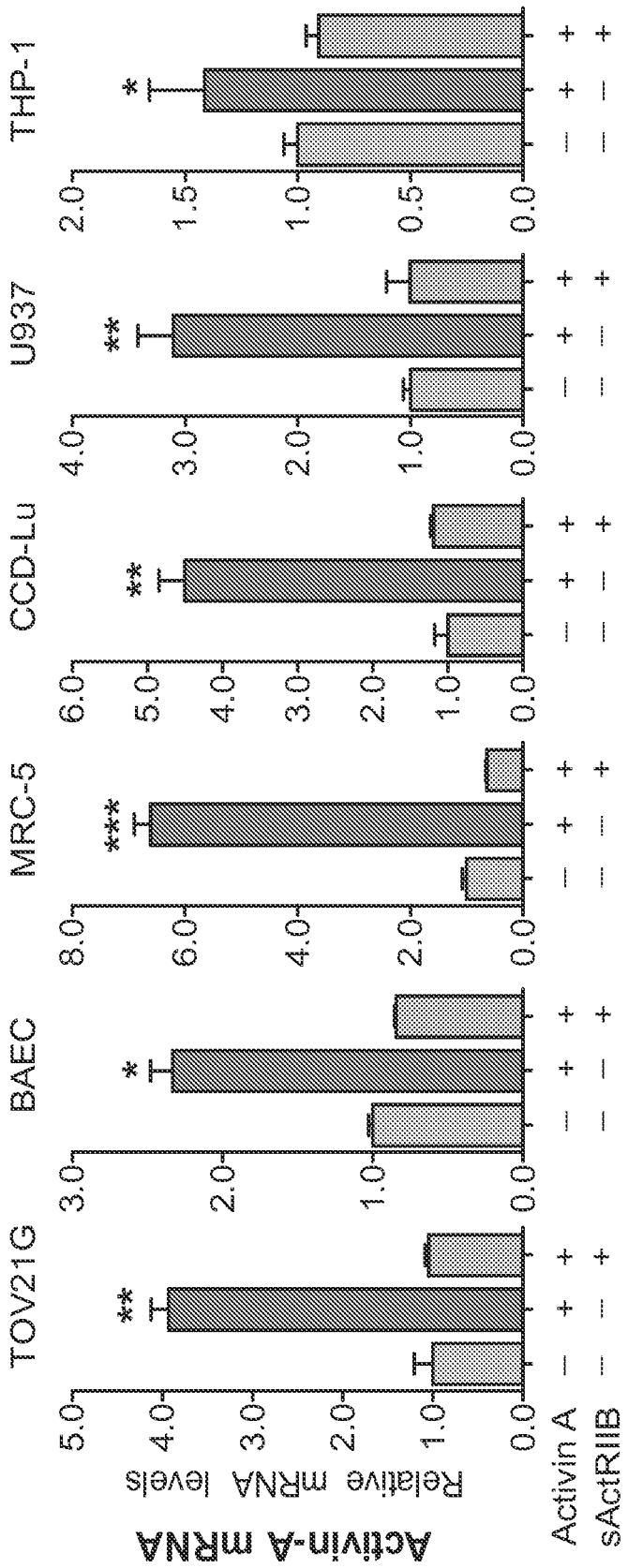

Activin-A mRNA
Relative mRNA levels
TOV21G
BAEC
MRC-5
CCD-Lu
U937
THP-1
Activin A
sActRIIB

FIG. 18

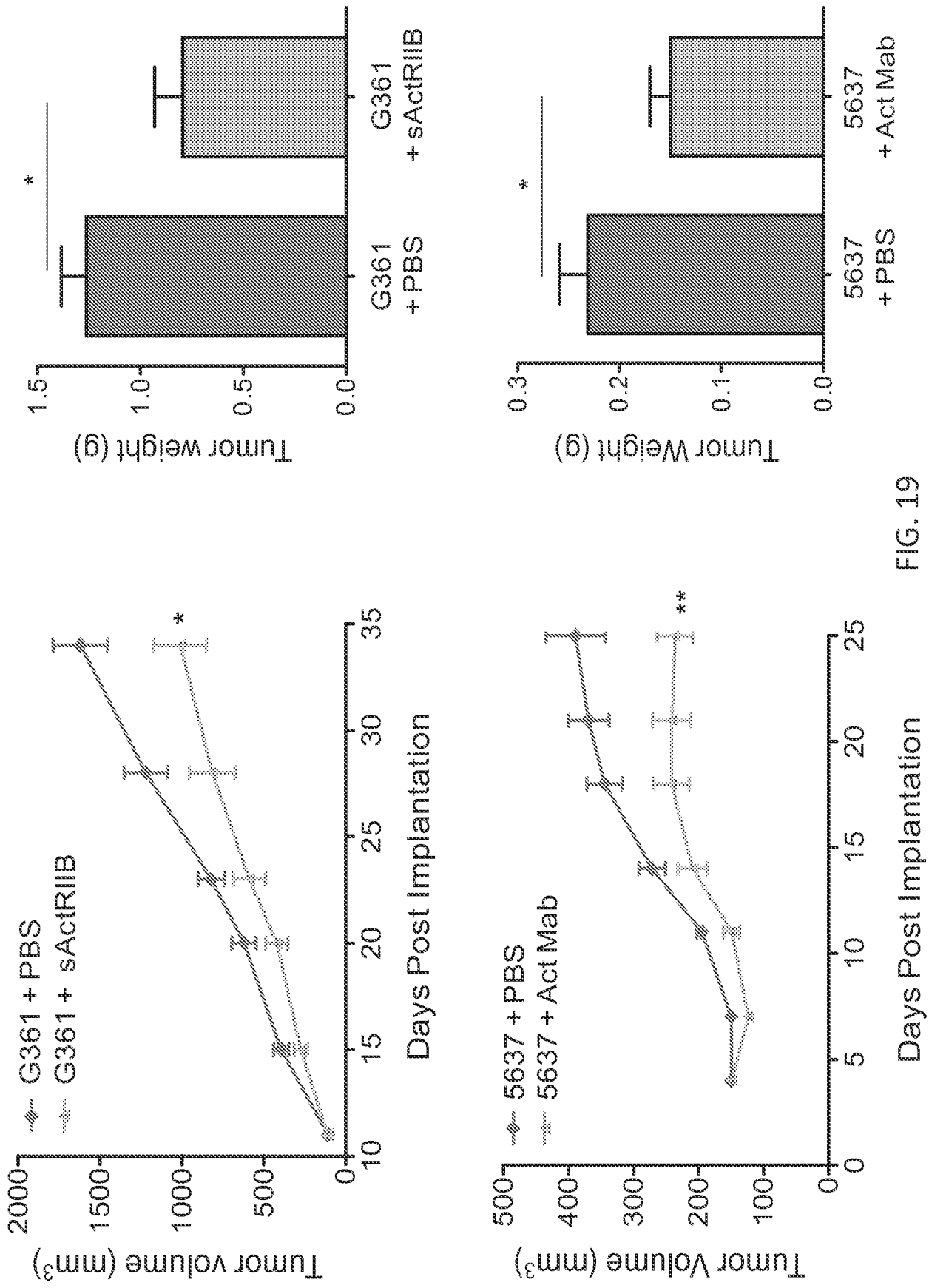

Tumor weight (g)
1.5
1.0
0.5
0.0
*
G361 + PBS
G361 + sActRIIB
Tumor Weight (g)
0.3
0.2
0.1
0.0
*
5637 + PBS
5637 + Act Mab
Tumor volume (mm3)
2000
1500
1000
500
0
10
15
20
25
30
35
*
G361 + PBS
G361 + sActRIIB
Days Post Implantation
Tumor Volume (mm3)
500
400
300
200
100
0
0
5
10
15
20
25
**
5637 + PBS
5637 + Act Mab
Days Post Implantation

FIG. 19

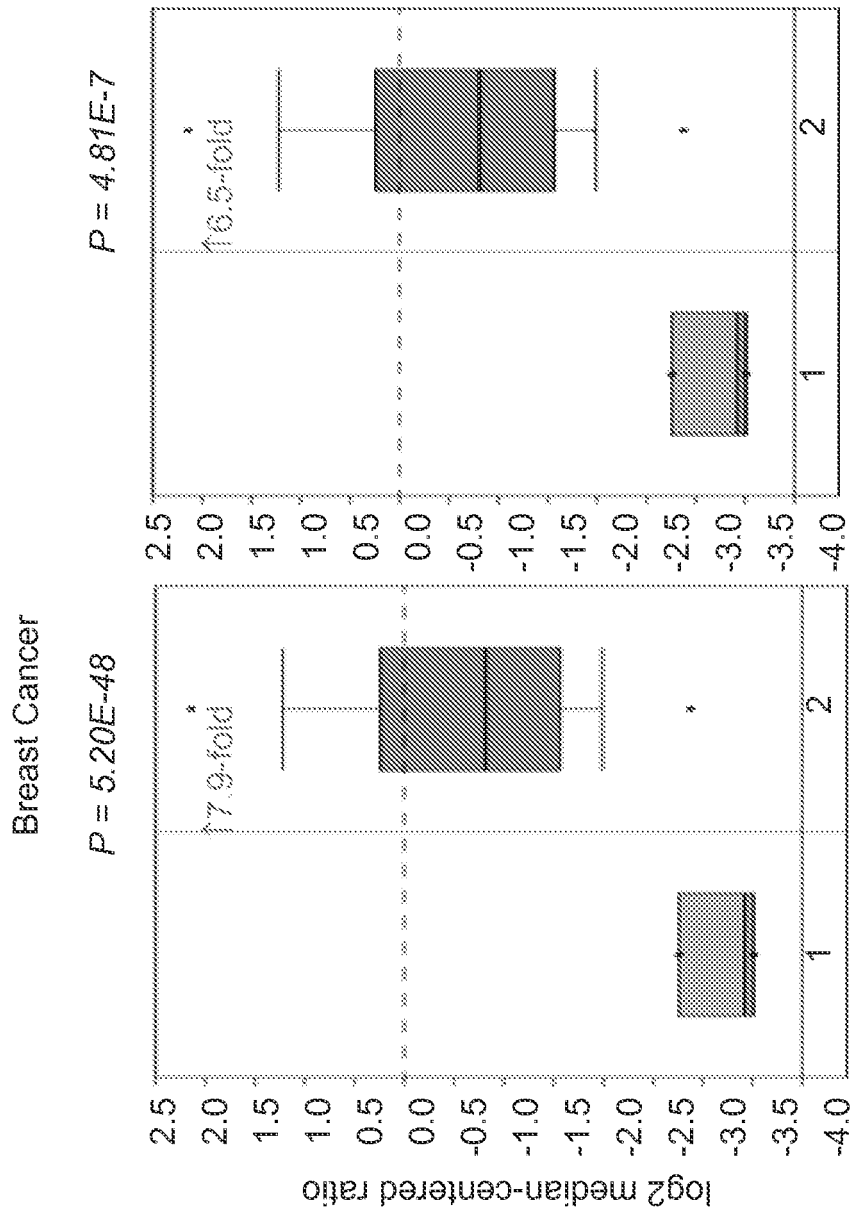

Breast Cancer
P = 5.20E-48
17.9-fold
P = 4.81E-7
16.5-fold
log2 median-centered ratio
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
1
2
Breast (n = 61)
Ductal Carcinoma (n = 392)
Breast (n = 4)
Ductal Carcinoma (n = 64)
Cancer Genome Atlas (2011)
Sorlie et al. (2001)

FIG. 20

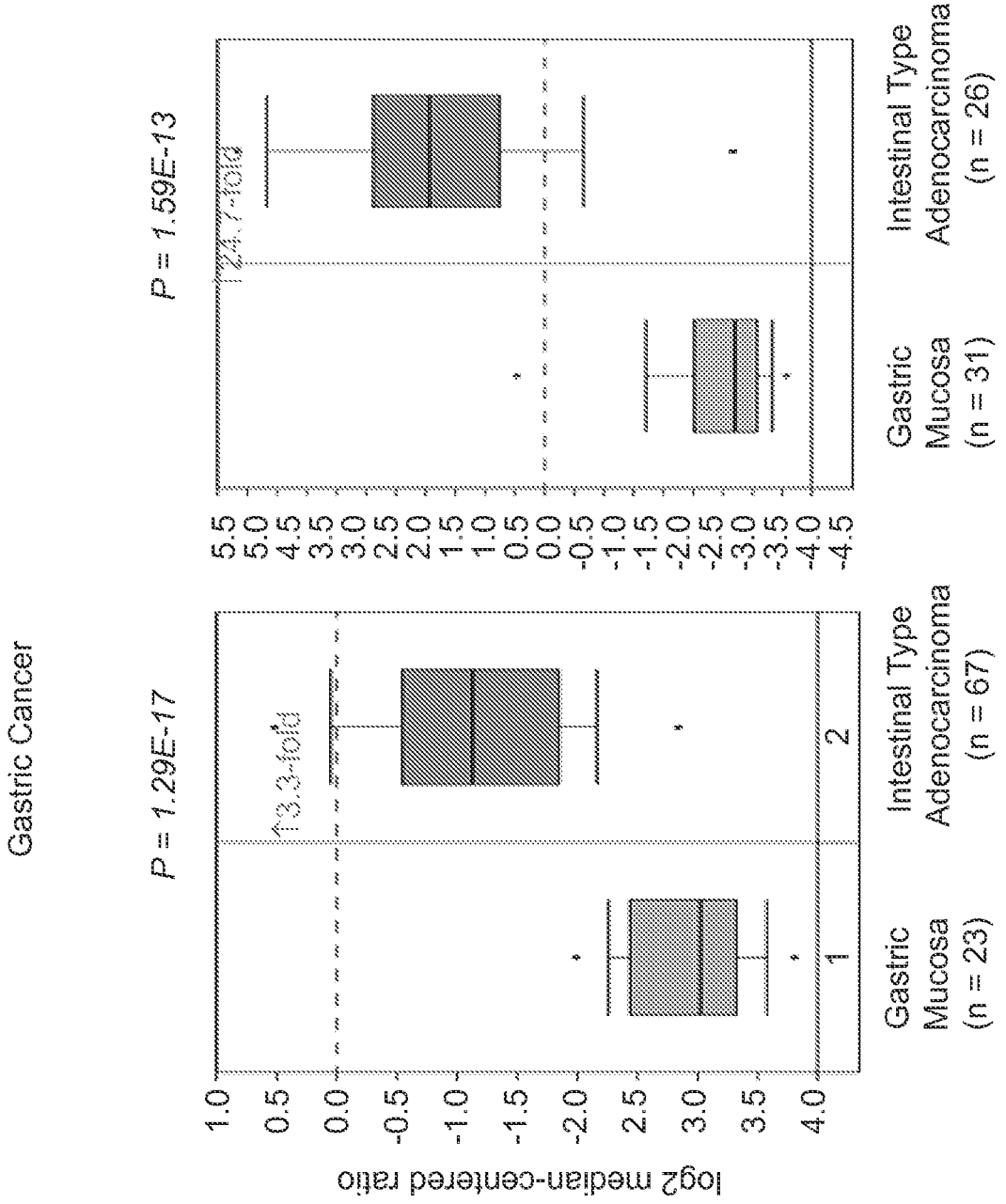

Gastric Cancer
P = 1.29E-17
13.3-fold
P = 1.59E-13
124.7-fold
log2 median-centered ratio
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
2.5
3.0
3.5
4.0
5.5
5.0
4.5
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
1
2
Gastric Mucosa (n = 23)
Intestinal Type Adenocarcinoma (n = 67)
Gastric Mucosa (n = 31)
Intestinal Type Adenocarcinoma (n = 26)
Chen et al. (2003)
D'Errico et al. (2010)

FIG. 20 (Cont.)

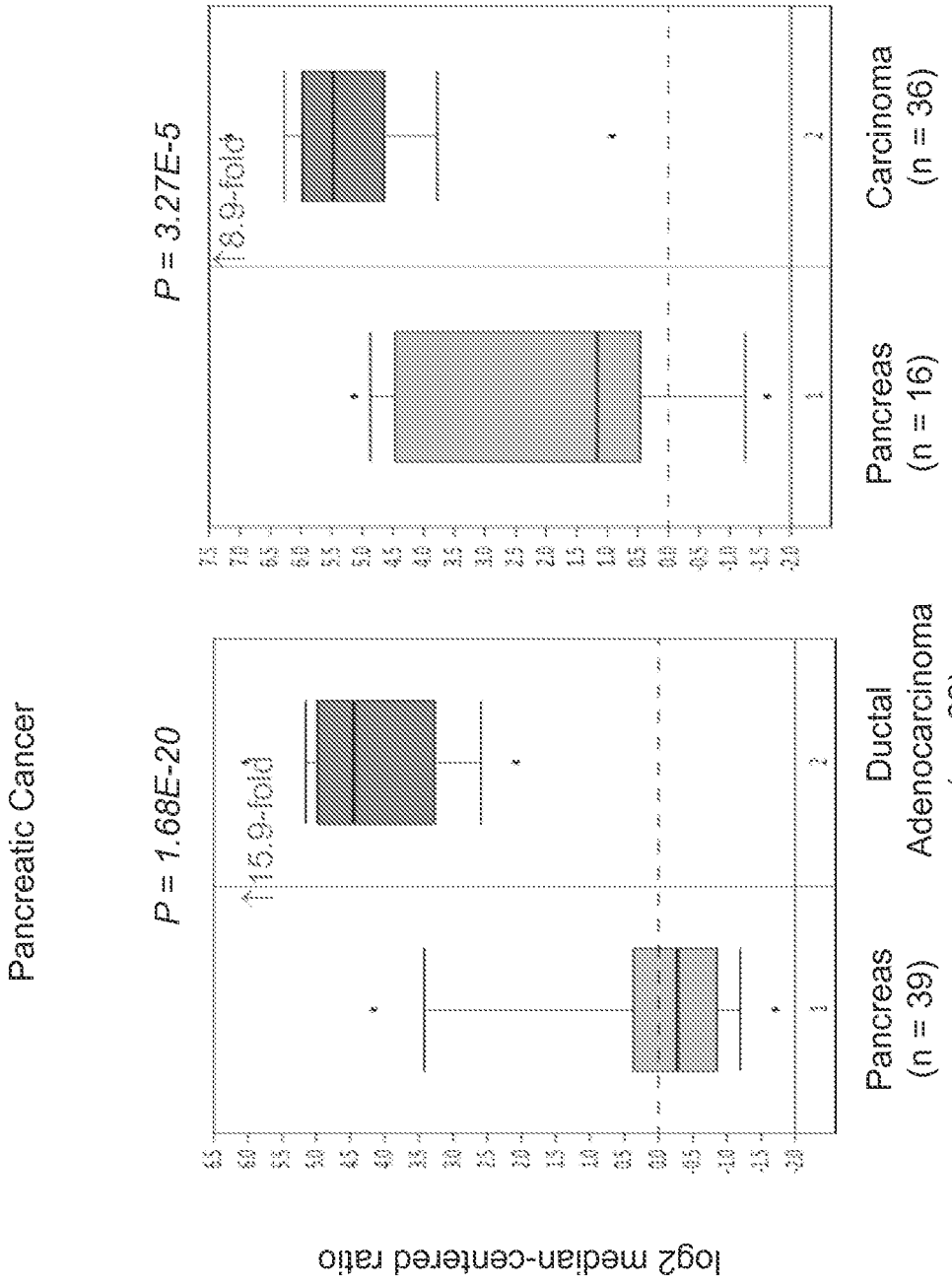

Pancreatic Cancer
P = 1.68E-20
↑15.9-fold
Pancreas (n = 39)
Ductal Adenocarcinoma (n = 39)
Badea et al. (2010)
P = 3.27E-5
↑8.9-fold
Pancreas (n = 16)
Carcinoma (n = 36)
Pei et al. (2009)
log2 median-centered ratio

FIG. 20 (Cont.)

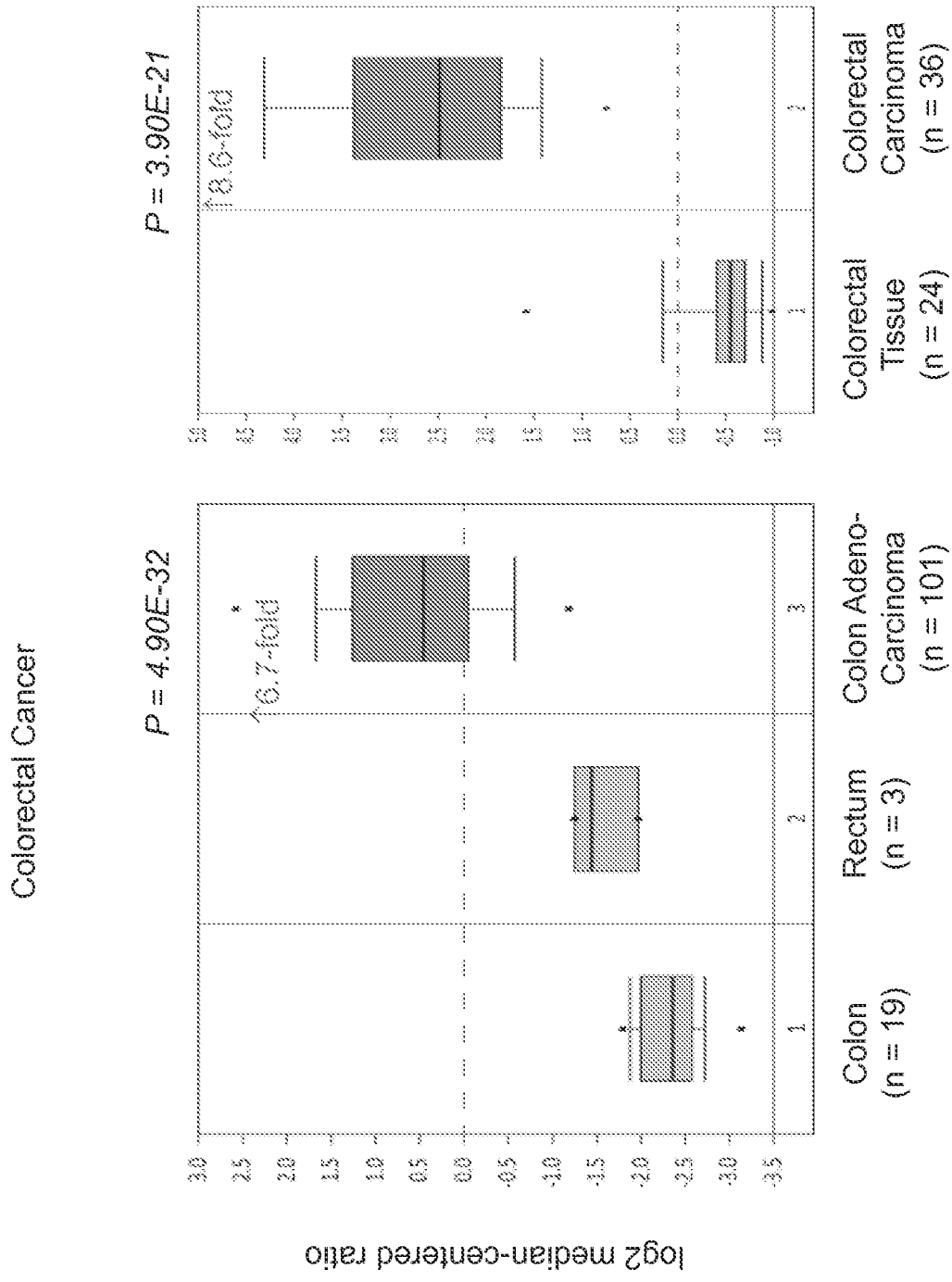

Colorectal Cancer
P = 4.90E-32
16.7-fold
P = 3.90E-21
18.6-fold
log2 median-centered ratio
Colon (n = 19)
Rectum (n = 3)
Colon Adeno-Carcinoma (n = 101)
Colorectal Tissue (n = 24)
Colorectal Carcinoma (n = 36)
Cancer Genome Atlas (2011)
Skrzypczak et al. (2010)

FIG. 20 (Cont.)

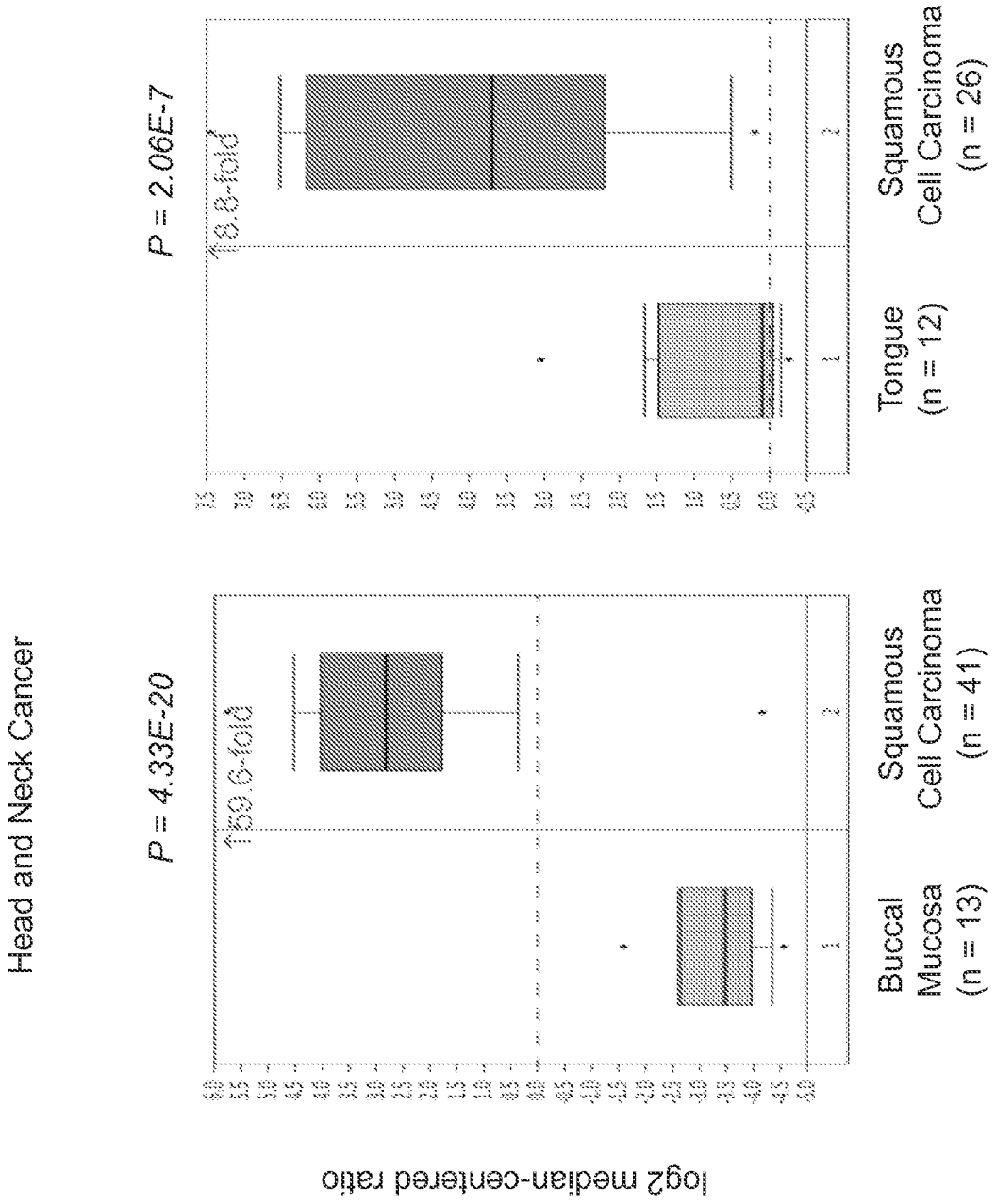

Head and Neck Cancer
P = 4.33E-20
↑59.6-fold
P = 2.06E-7
↑8.8-fold
log2 median-centered ratio
Buccal Mucosa (n = 13)
Squamous Cell Carcinoma (n = 41)
Tongue (n = 12)
Squamous Cell Carcinoma (n = 26)
Ginos et al. (2004)
Ye et al. (2008)

FIG. 20 (Cont.)

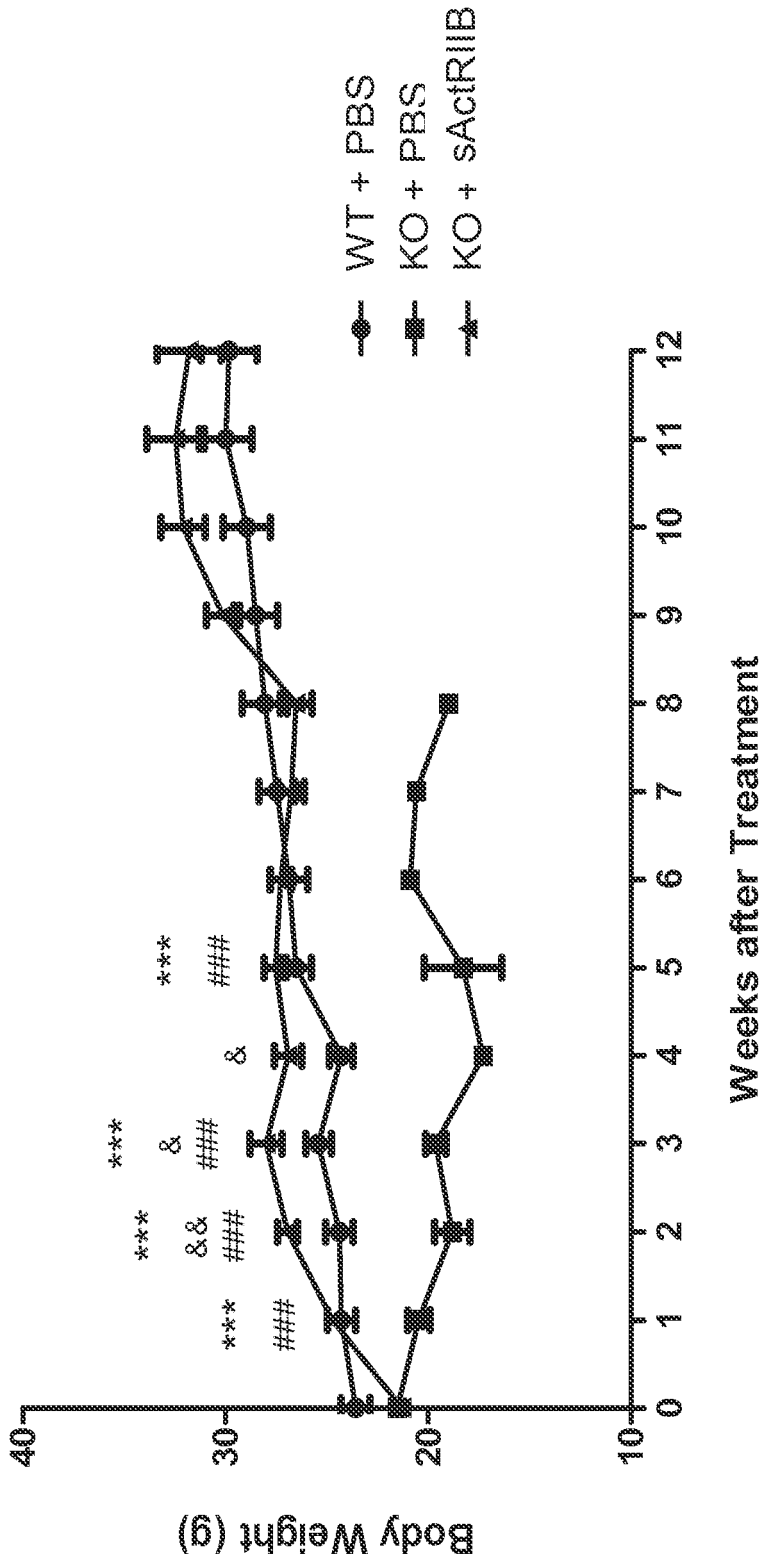

WT + PBS
KO + PBS
KO + sActRIIB
Body Weight (g)
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
Weeks after Treatment
***
***
***
***
&
&&
&
###
###
###
###

FIG. 21

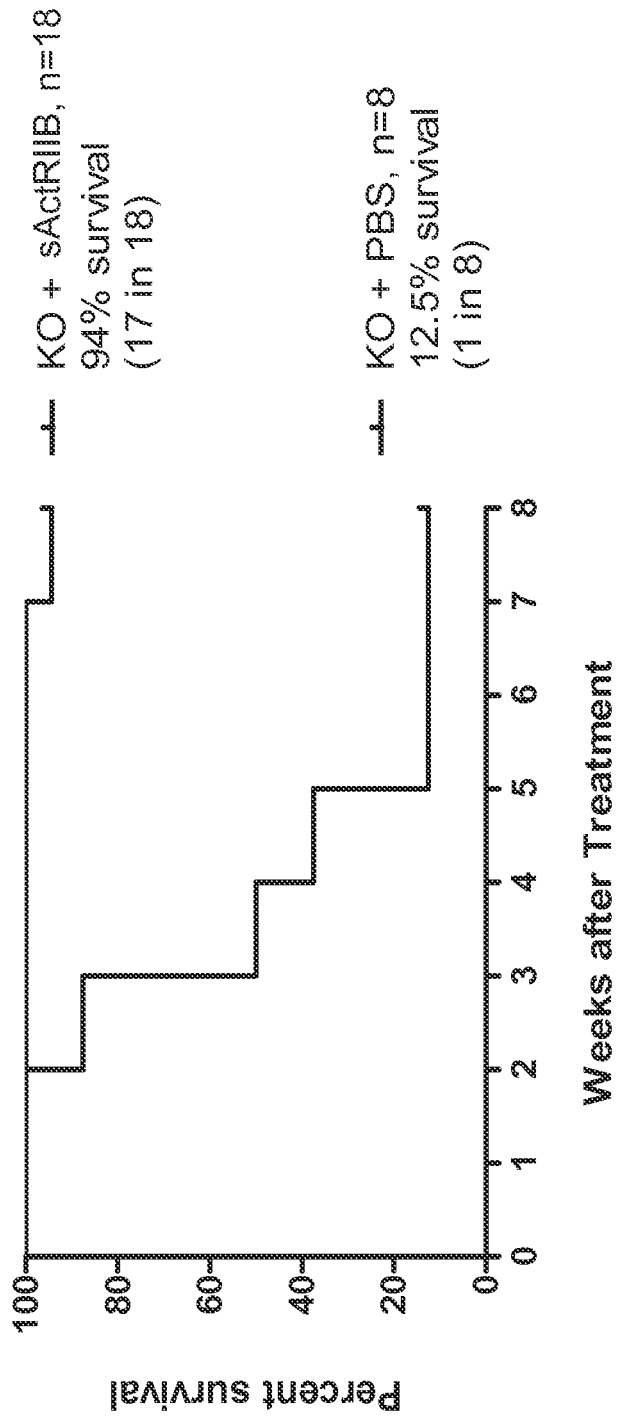

KO + sActRIIB, n=18
94% survival
(17 in 18)
KO + PBS, n=8
12.5% survival
(1 in 8)
Percent survival
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
Weeks after Treatment

FIG. 22

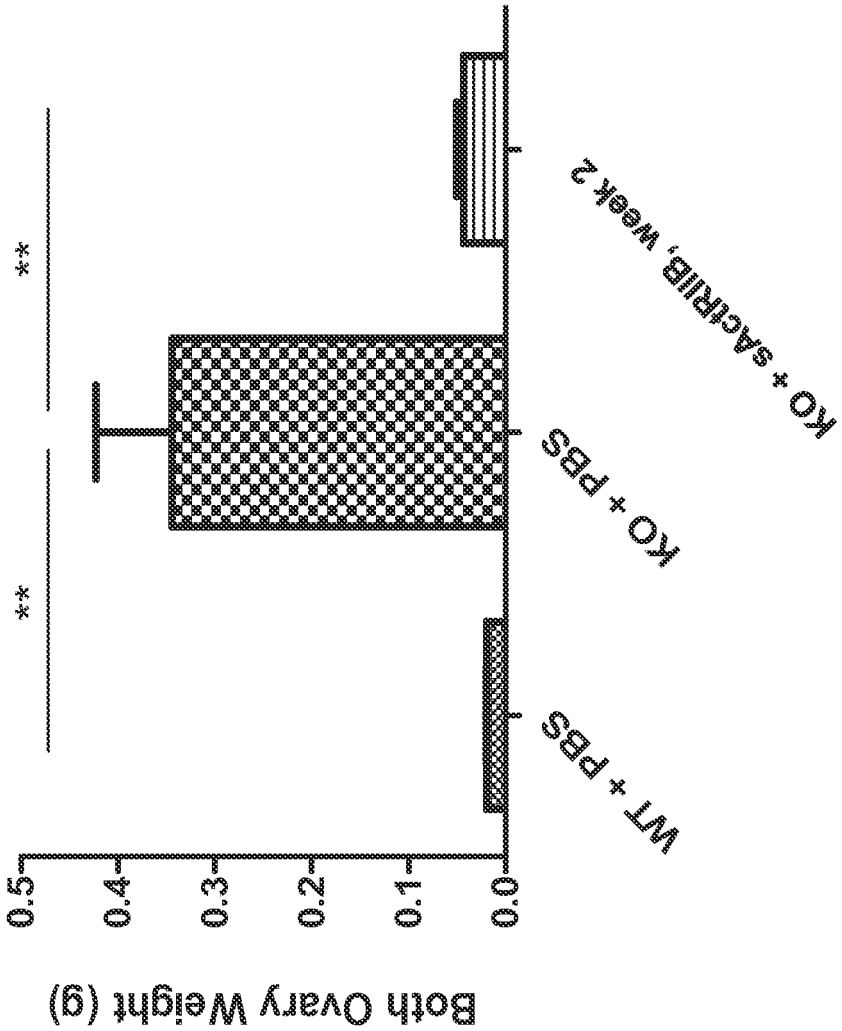

Both Ovary Weight (g)
0.5
0.4
0.3
0.2
0.1
0.0
**
**
WT + PBS
KO + PBS
KO + sAcrRIIB, week 2

FIG. 23

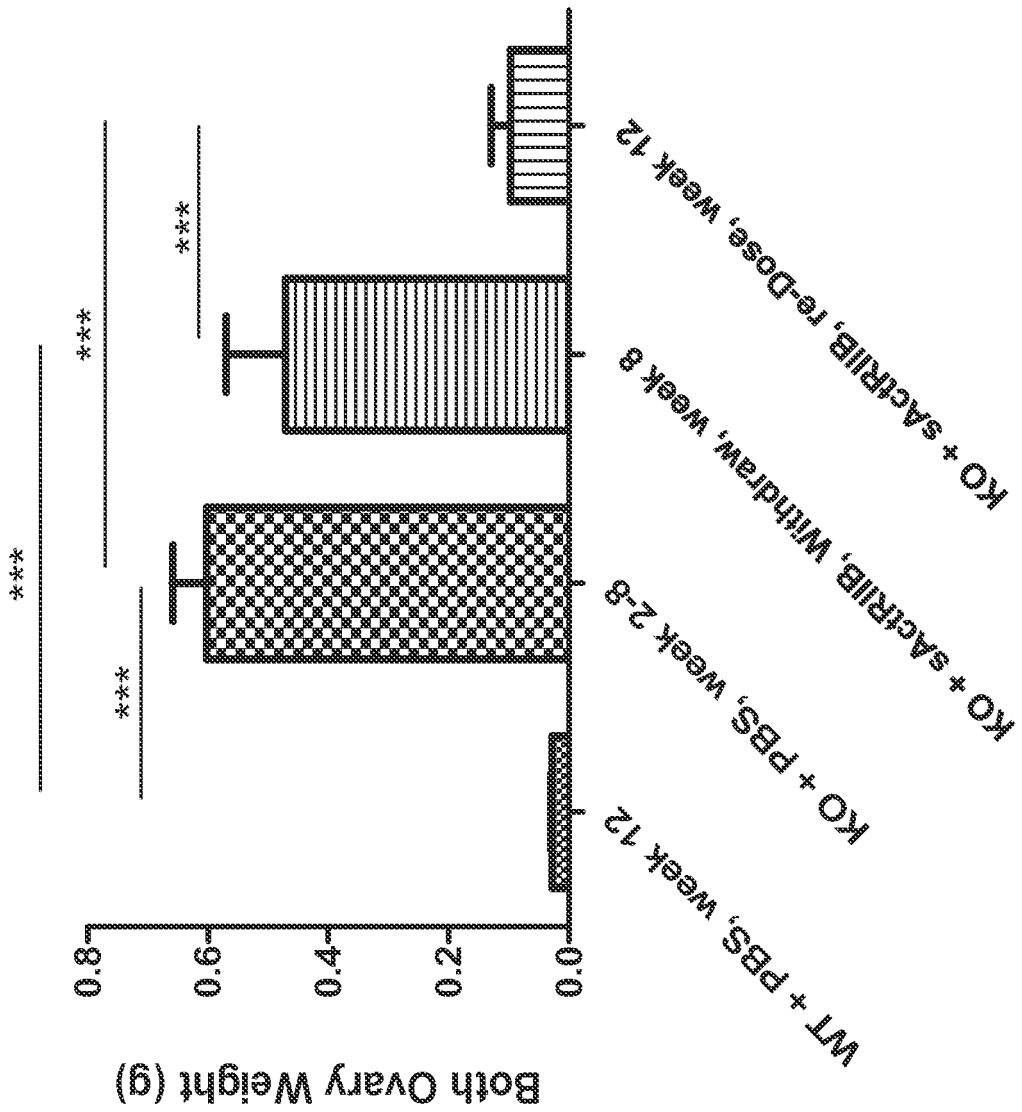

Both Ovary Weight (g)
0.0
0.2
0.4
0.6
0.8
***
***
***
***
WT + PBS, week 12
KO + PBS, week 2-8
KO + SACTRIIB, Withdraw, week 8
KO + SACTRIIB, re-Dose, week 12

FIG. 24

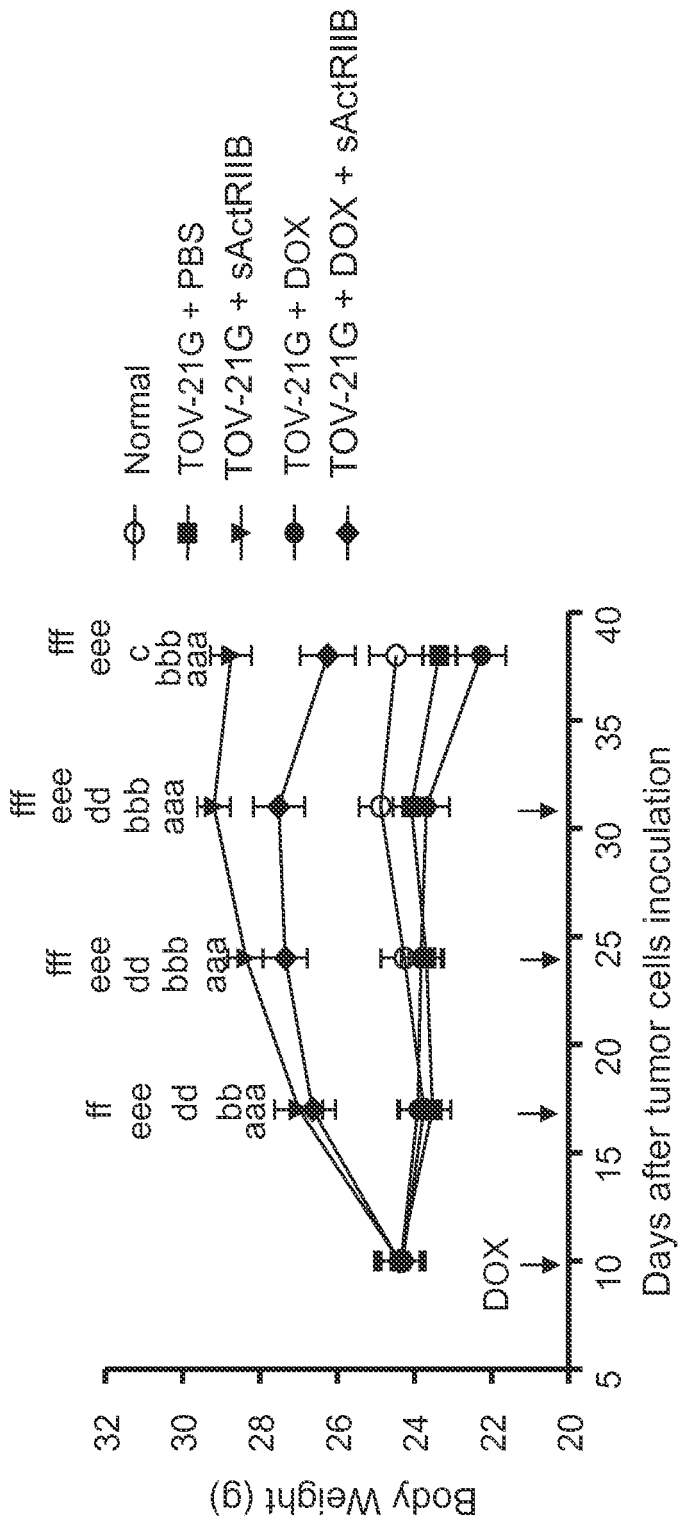

Normal
TOV-21G + PBS
TOV-21G + sActRIIB
TOV-21G + DOX
TOV-21G + DOX + sActRIIB
Body Weight (g)
Days after tumor cells inoculation
DOX

FIG. 25

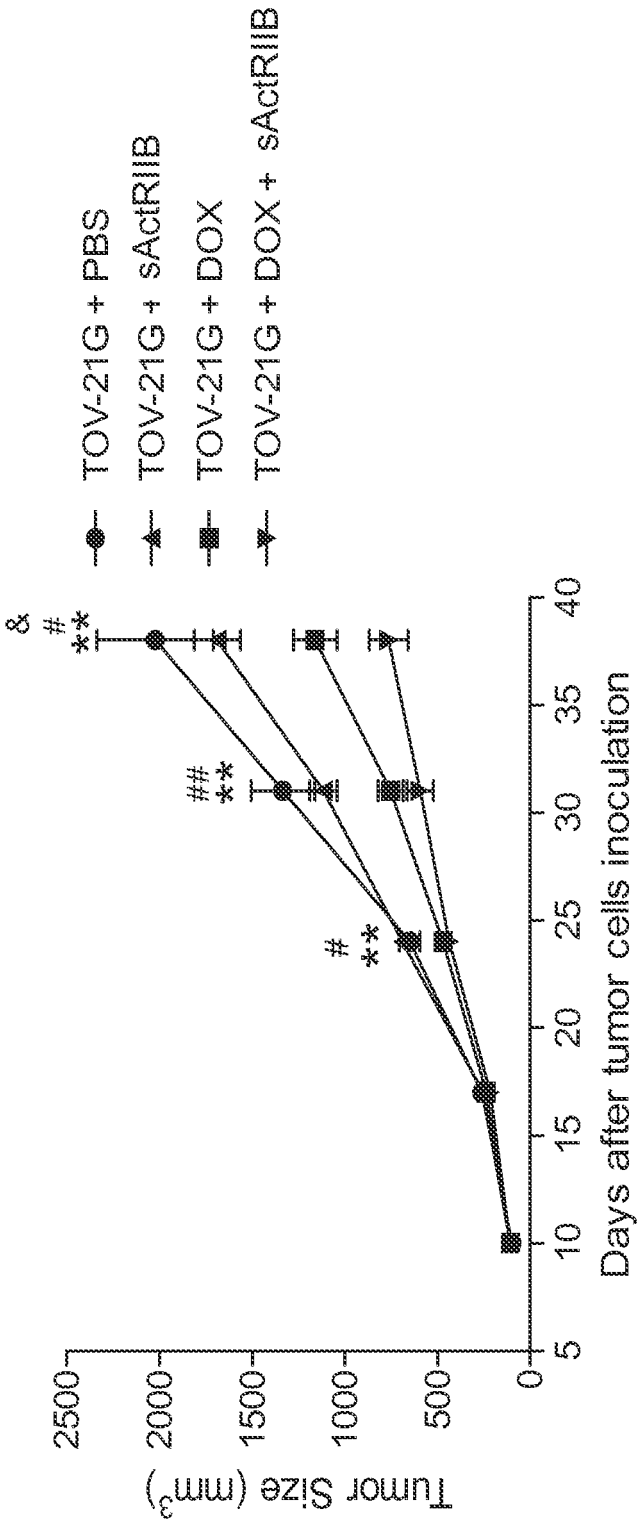

TOV-21G + PBS
TOV-21G + sActRIIB
TOV-21G + DOX
TOV-21G + DOX + sActRIIB
Tumor Size (mm3)
Days after tumor cells inoculation
0
500
1000
1500
2000
2500
5
10
15
20
25
30
35
40
&
#
**
##
**
#
**

FIG. 26

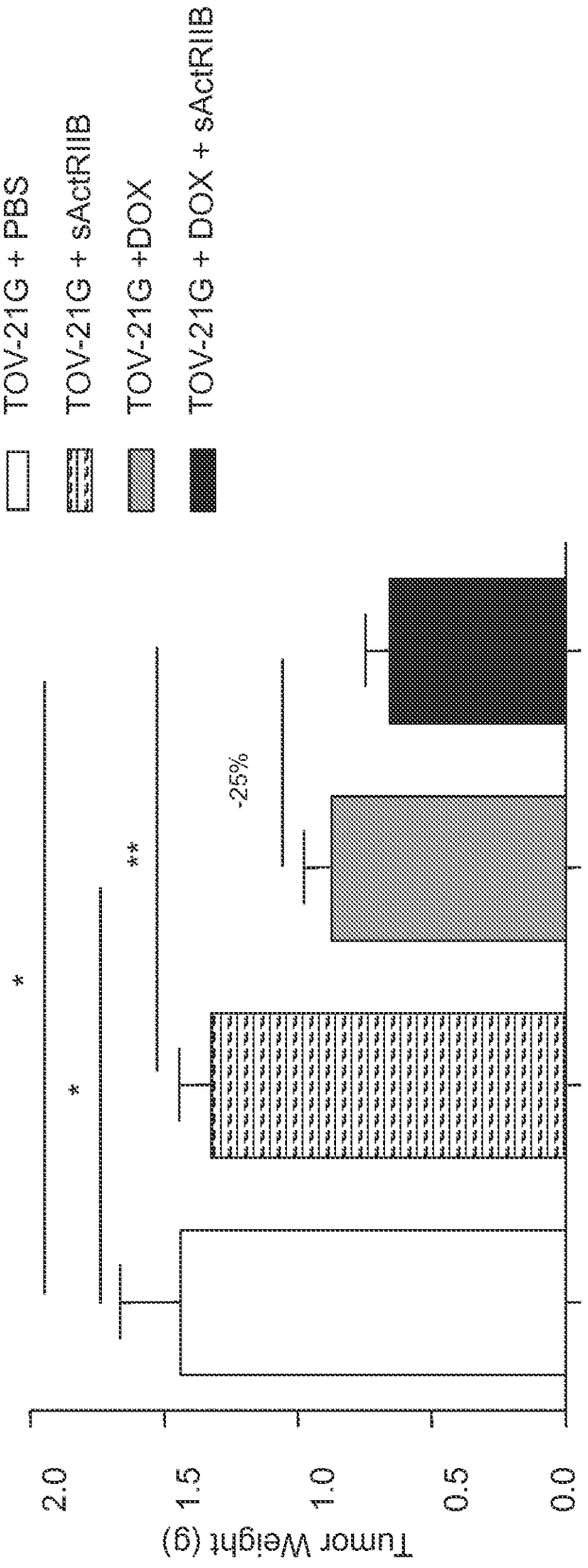

TOV-21G + PBS
TOV-21G + sActRIIB
TOV-21G +DOX
TOV-21G + DOX + sActRIIB
Tumor Weight (g)
2.0
1.5
1.0
0.5
0.0
*
*
**
-25%

FIG. 26 (Cont.)

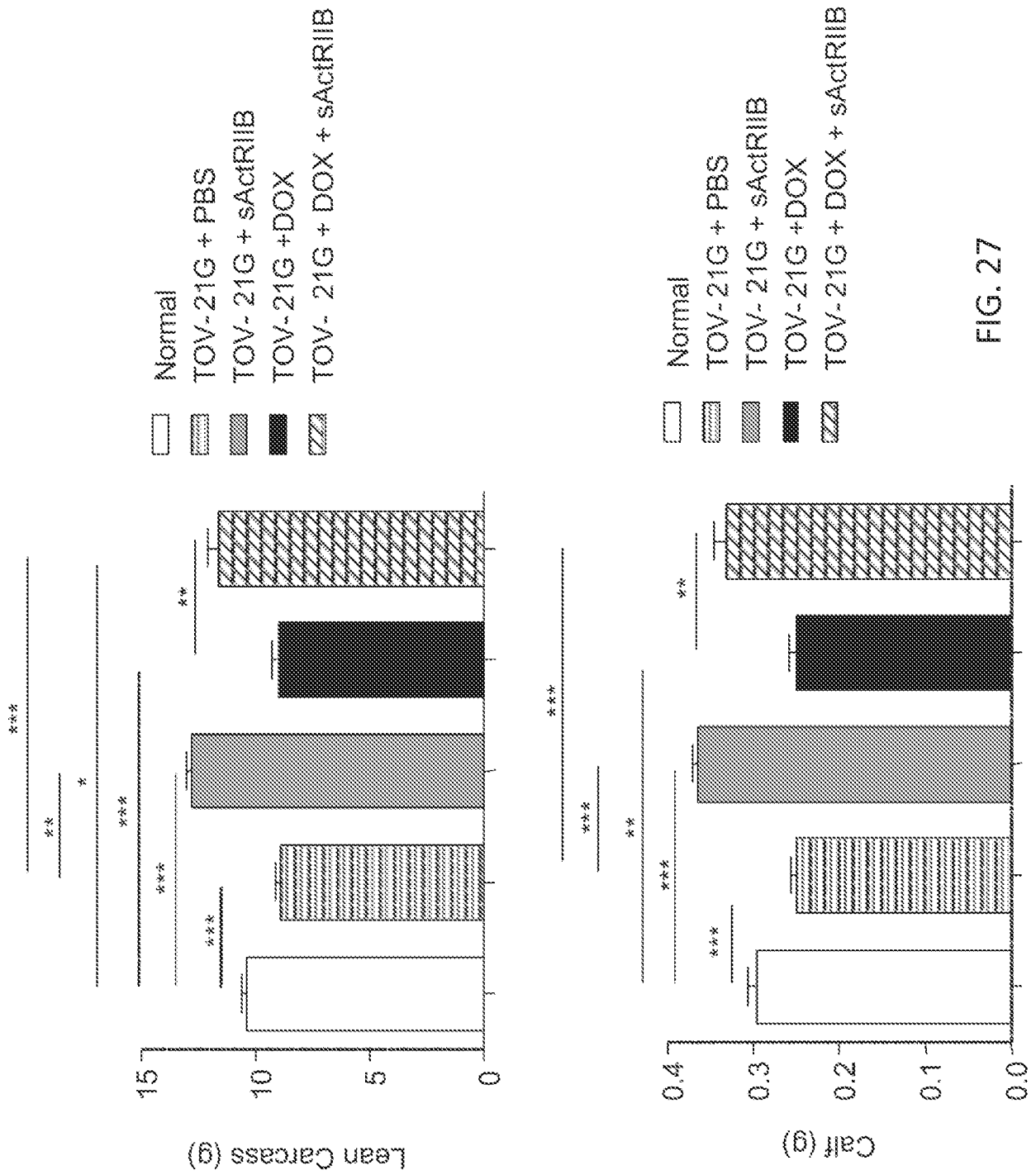

Normal
TOV-21G + PBS
TOV- 21G + sActRIIB
TOV-21G +DOX
TOV- 21G + DOX + sActRIIB
Lean Carcass (g)
Calf (g)
0
5
10
15
0.0
0.1
0.2
0.3
0.4
*
**
***

FIG. 27

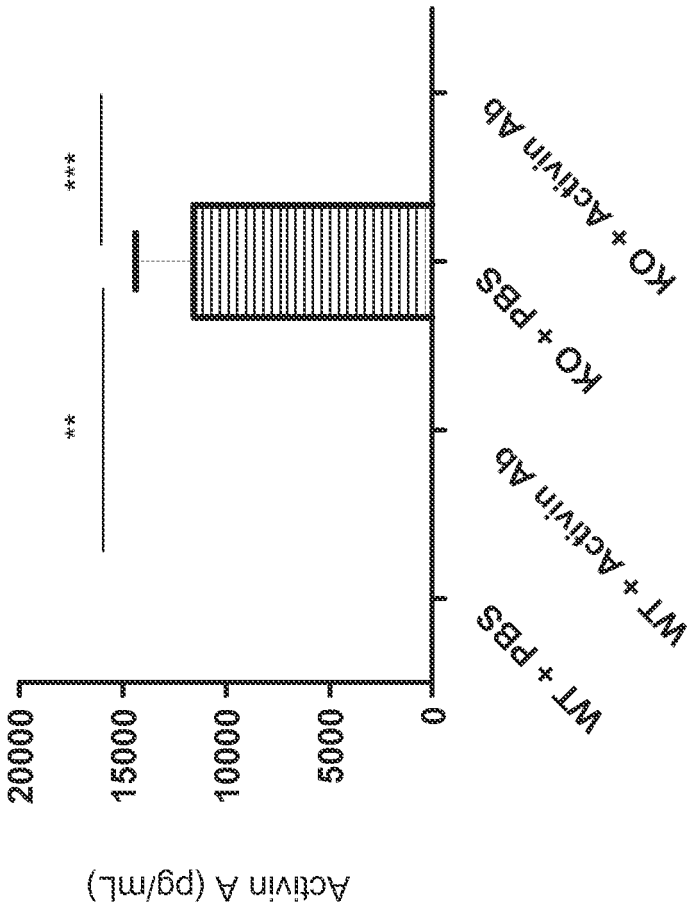

Activin A (pg/mL)
20000
15000
10000
5000
0
WT + PBS
WT + Activin Ab
KO + PBS
KO + Activin Ab
**
***

FIG. 28

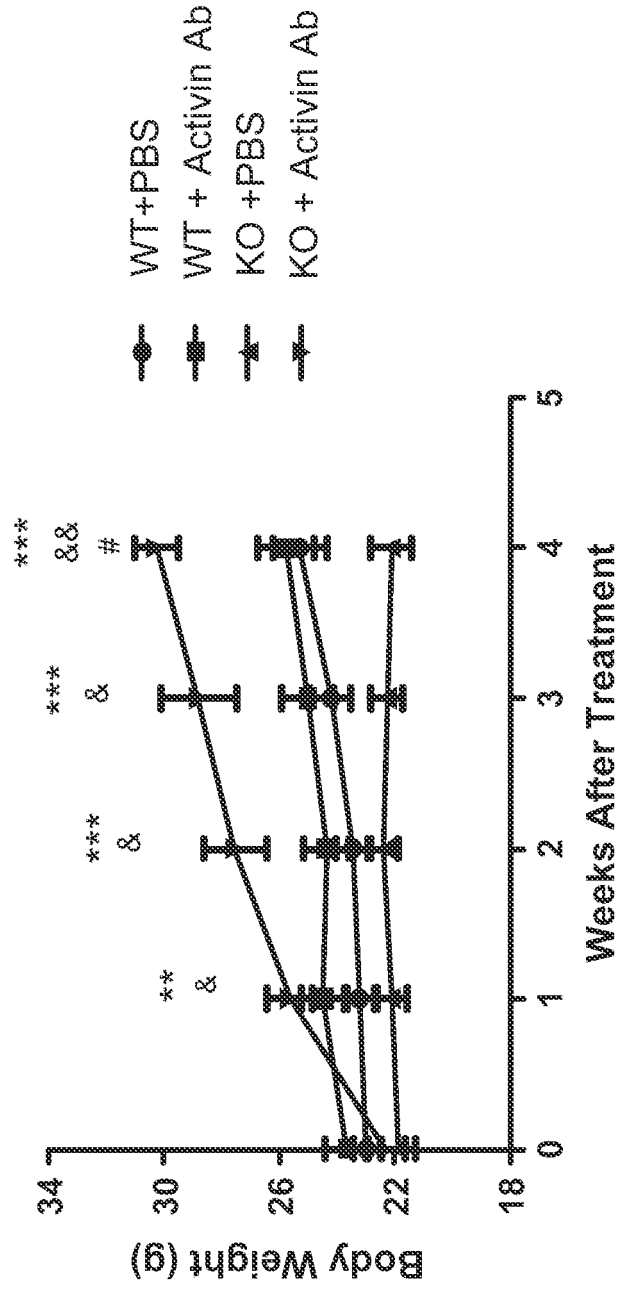

WT+PBS
WT + Activin Ab
KO +PBS
KO + Activin Ab
Body Weight (g)
34
30
26
22
18
0
1
2
3
4
5
Weeks After Treatment
**
&
***
&
***
&
***
&&
#

FIG. 29

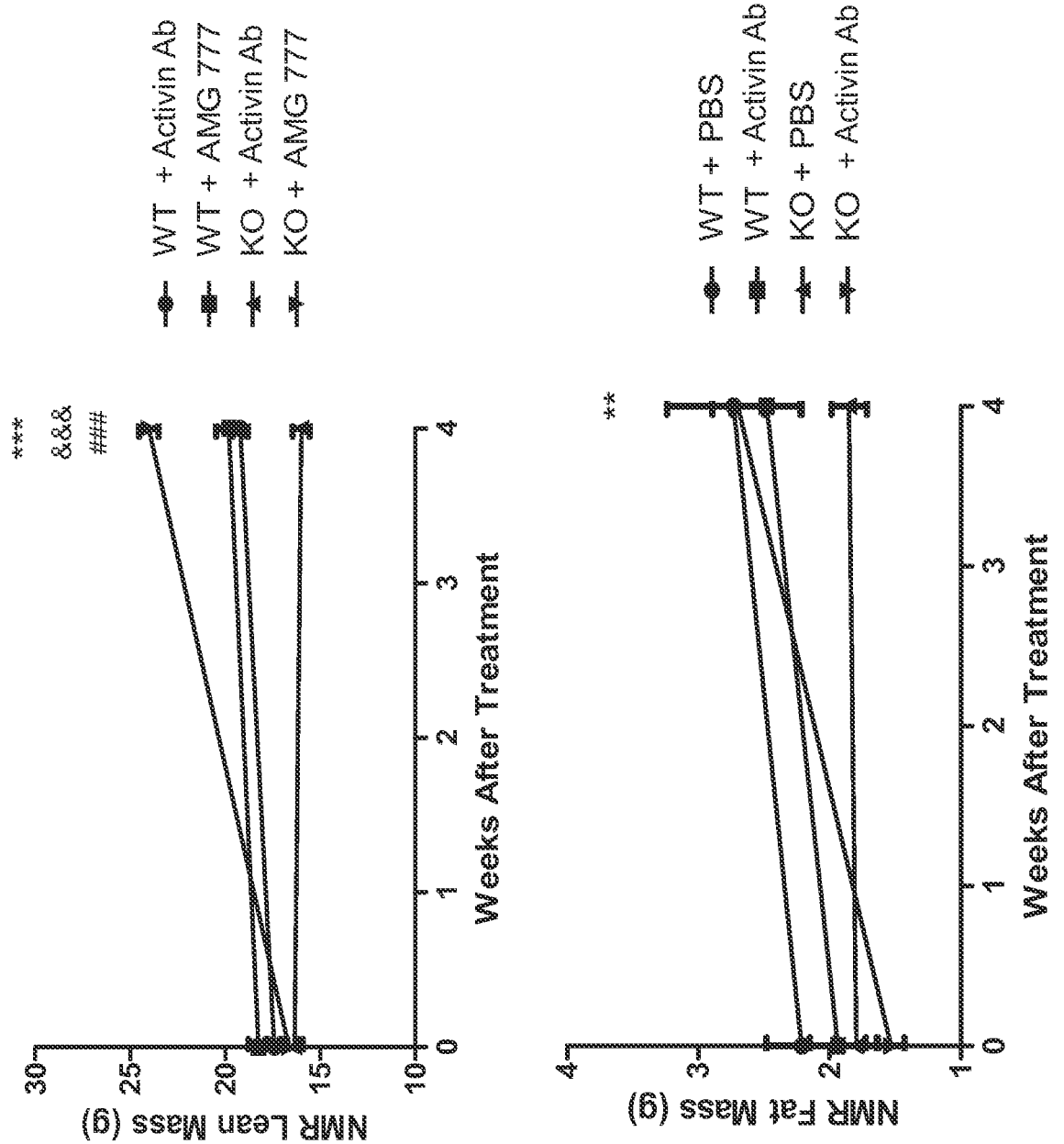

WT + Activin Ab
WT + AMG 777
KO + Activin Ab
KO + AMG 777
***
&&&
###
NMR Lean Mass (g)
30
25
20
15
10
0
1
2
3
4
Weeks After Treatment
WT + PBS
WT + Activin Ab
KO + PBS
KO + Activin Ab
**
NMR Fat Mass (g)
4
3
2
1
0
1
2
3
4
Weeks After Treatment

FIG. 30

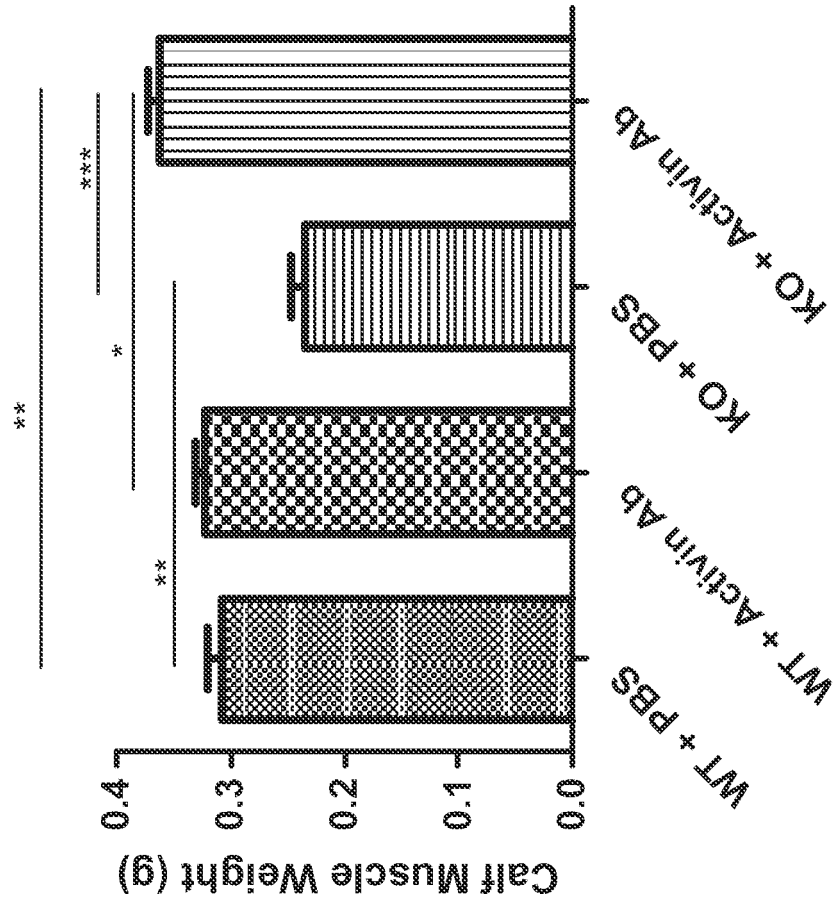

Calf Muscle Weight (g)
0.4
0.3
0.2
0.1
0.0
WT + PBS
WT + Activin Ab
KO + PBS
KO + Activin Ab
**
*
**
***

FIG. 31

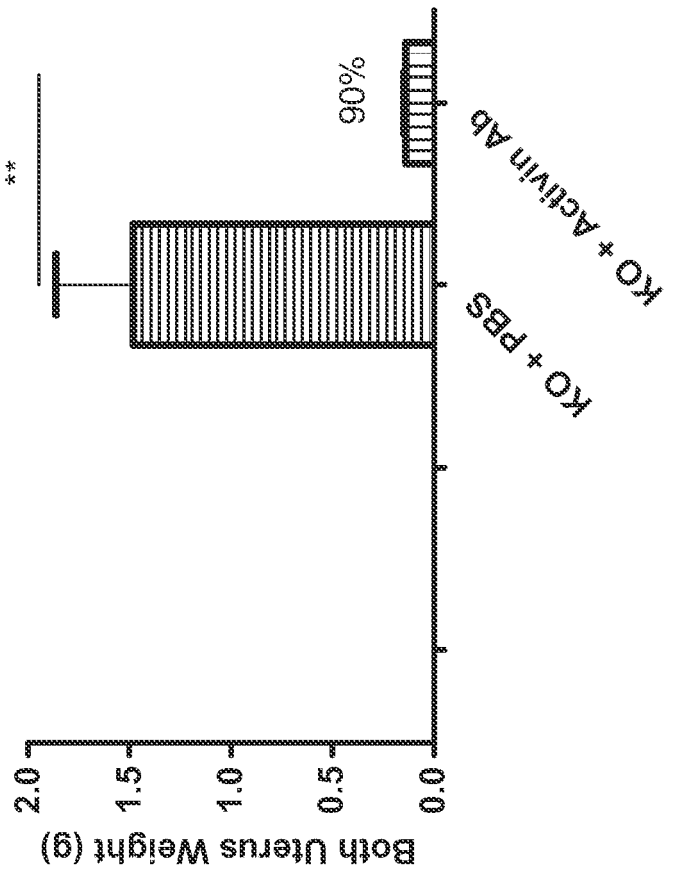


FIG. 32B

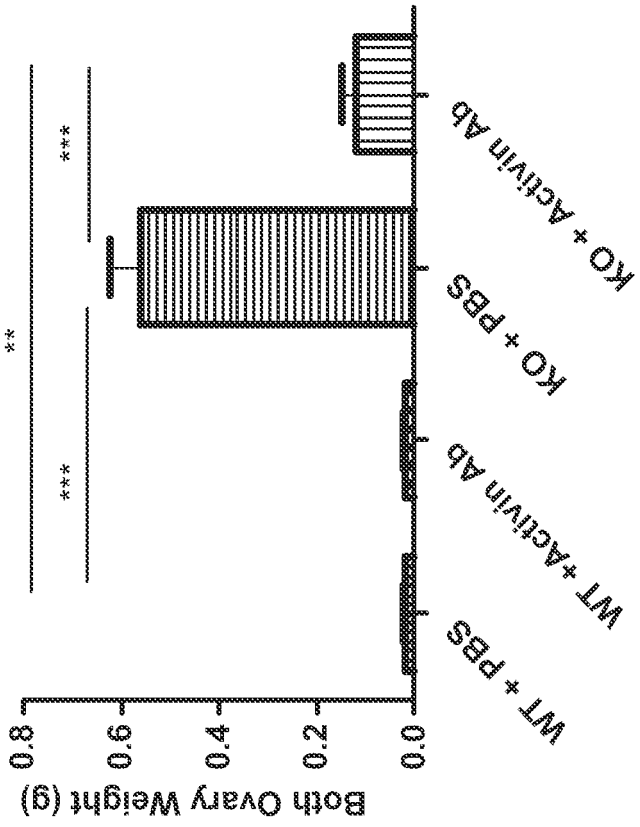


FIG. 32A

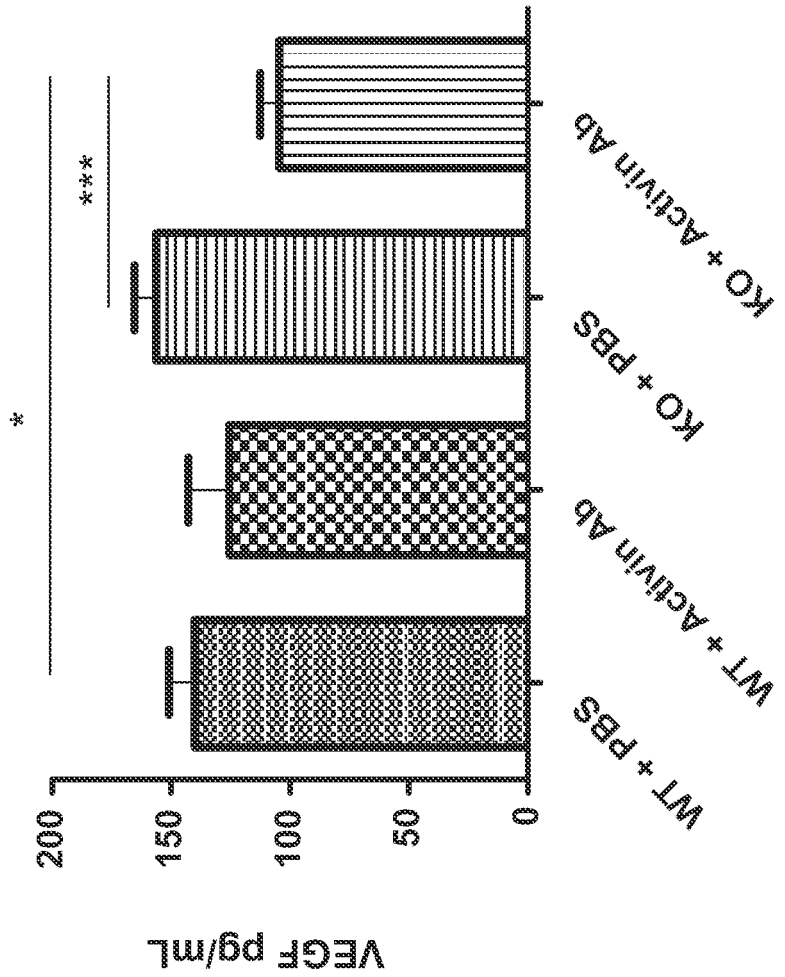

VEGF pg/mL
200
150
100
50
0
WT + PBS
WT + Activin Ab
KO + PBS
KO + Activin Ab
*
***

FIG. 33

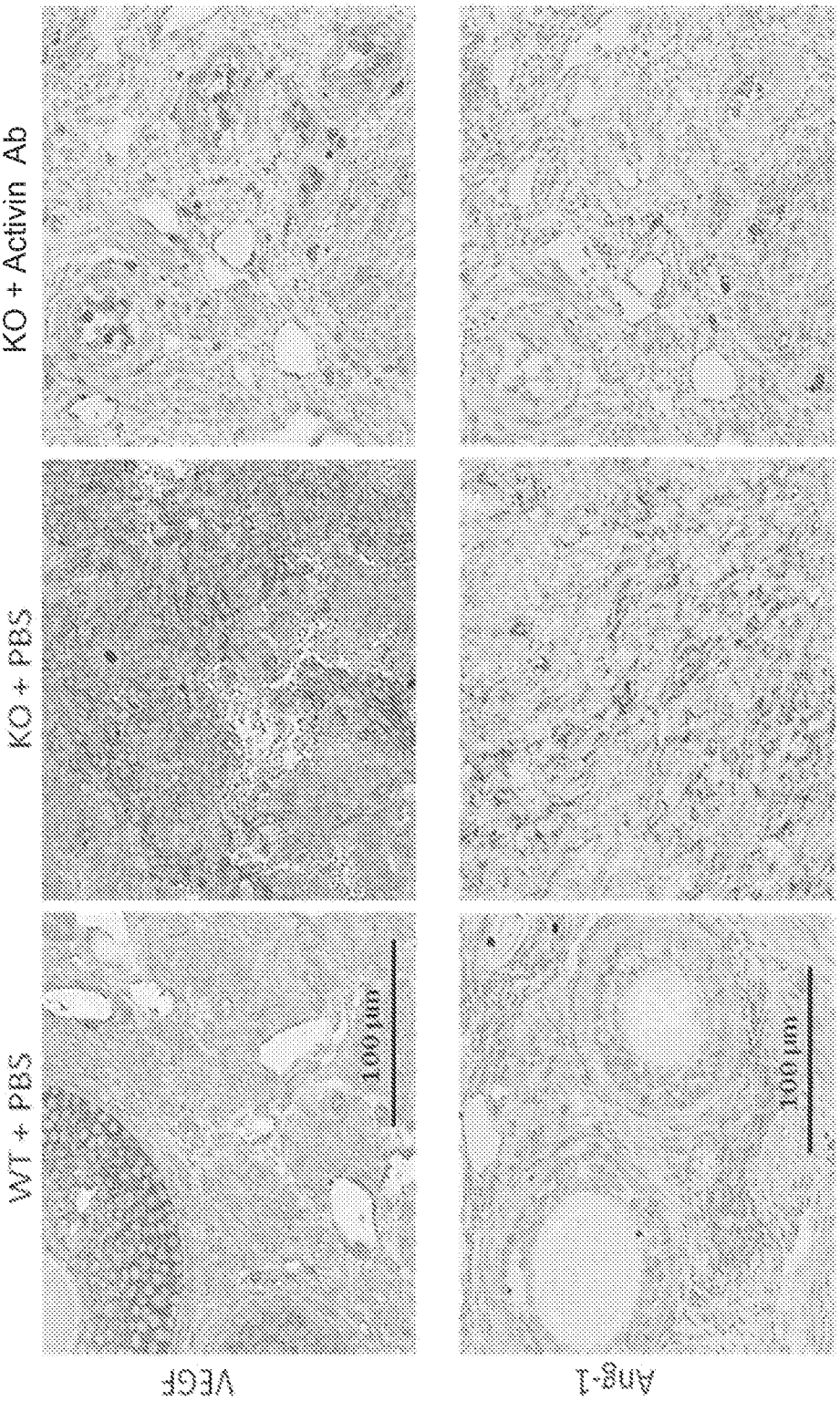
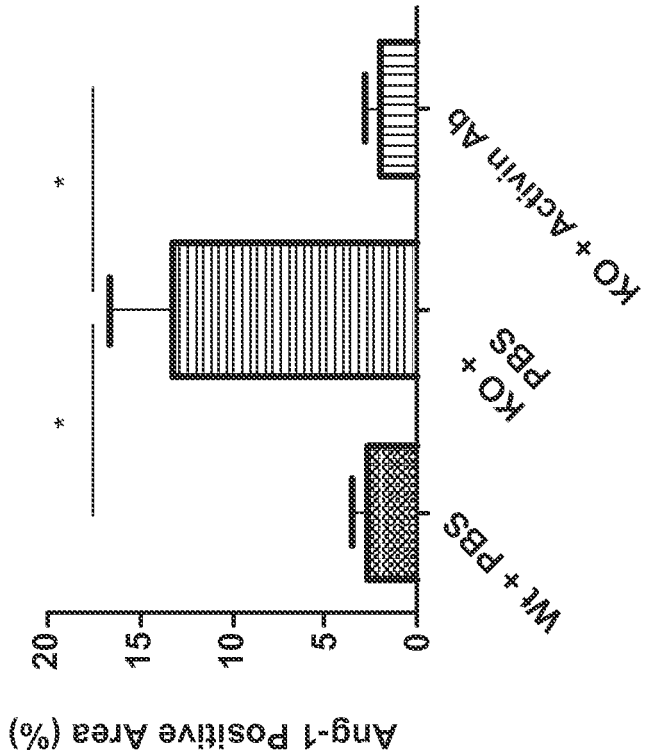


FIG. 34


Ang-1 Positive Area (%)
20
15
10
5
0
Wt + PBS
KO + PBS
KO + Activin Ab
*
*

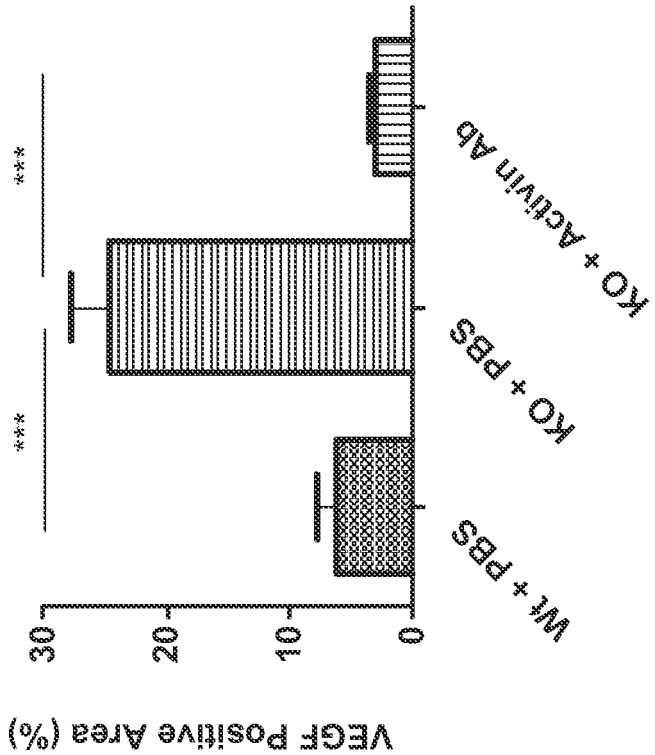

VEGF Positive Area (%)
30
20
10
0
Wt + PBS
KO + PBS
KO + Activin Ab
***
***

FIG. 34 (Cont.)

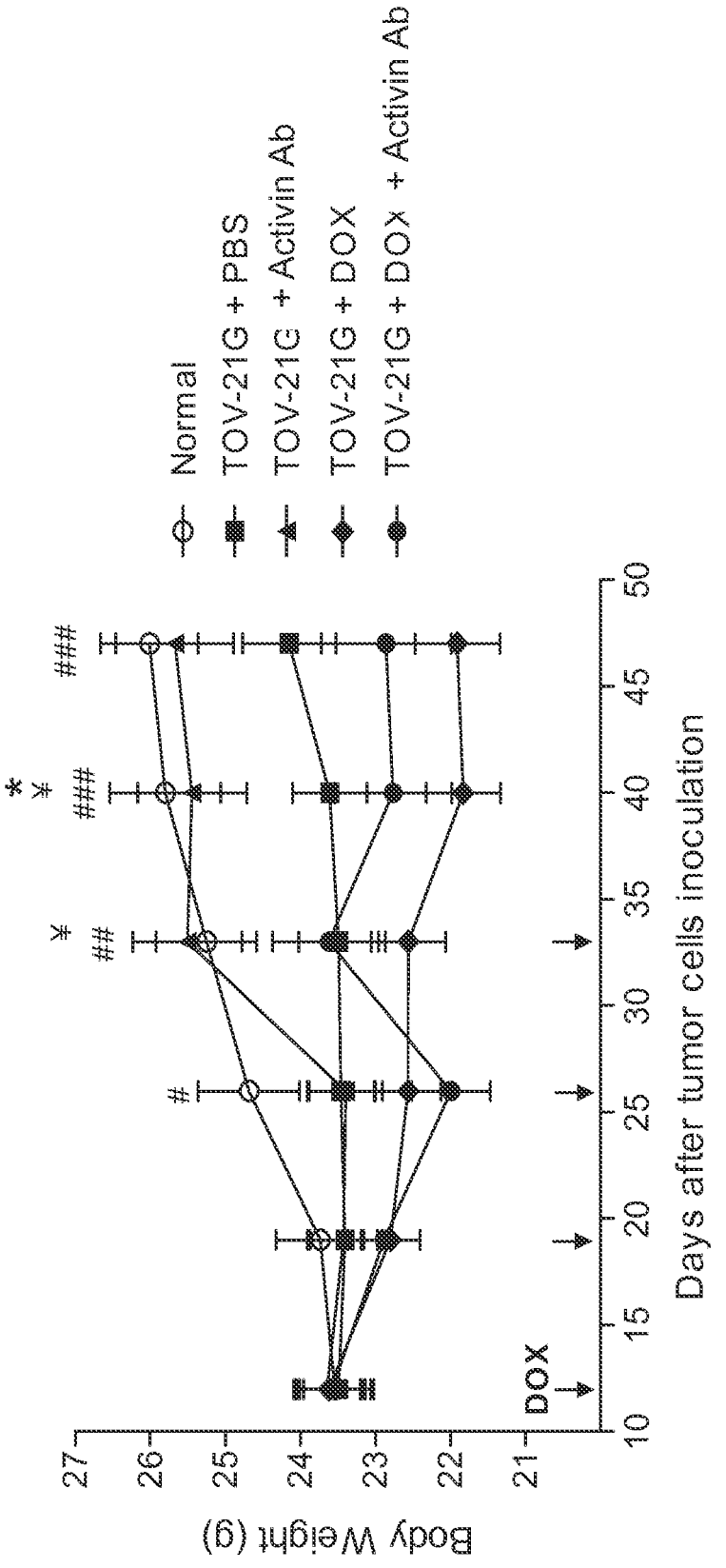

Normal
TOV-21G + PBS
TOV-21G + Activin Ab
TOV-21G + DOX
TOV-21G + DOX + Activin Ab
Body Weight (g)
Days after tumor cells inoculation
DOX
#
##
###
###
*
*

FIG. 35

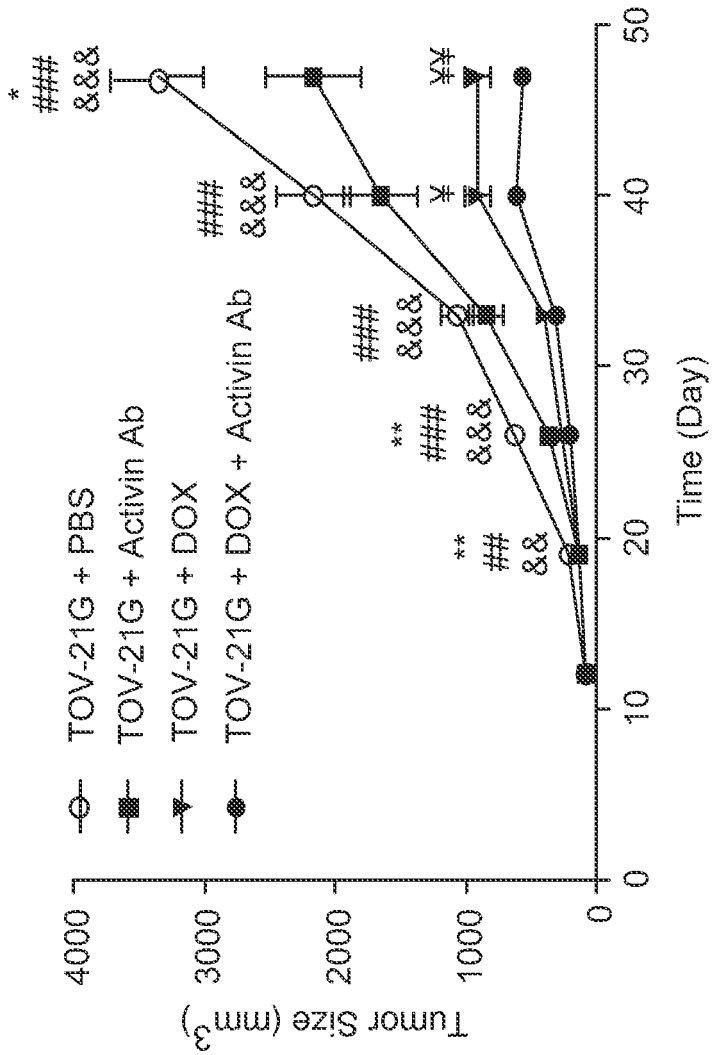

TOV-21G + PBS
TOV-21G + Activin Ab
TOV-21G + DOX
TOV-21G + DOX + Activin Ab
Tumor Size (mm3)
Time (Day)
0
1000
2000
3000
4000
0
10
20
30
40
50
*
###
&&&
**
##
&&
**
###
&&&
###
&&&
*
**

FIG. 36

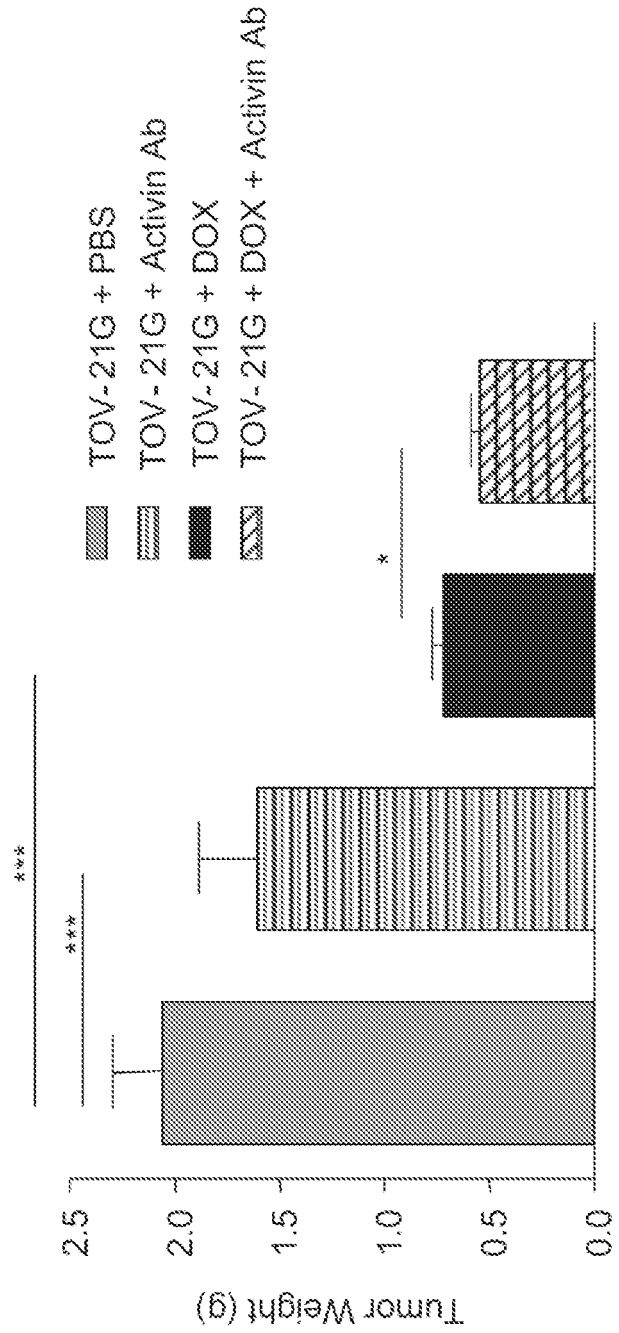

TOV-21G + PBS
TOV-21G + Activin Ab
TOV-21G + DOX
TOV-21G + DOX + Activin Ab
***
***
*
Tumor Weight (g)
2.5
2.0
1.5
1.0
0.5
0.0

FIG. 37

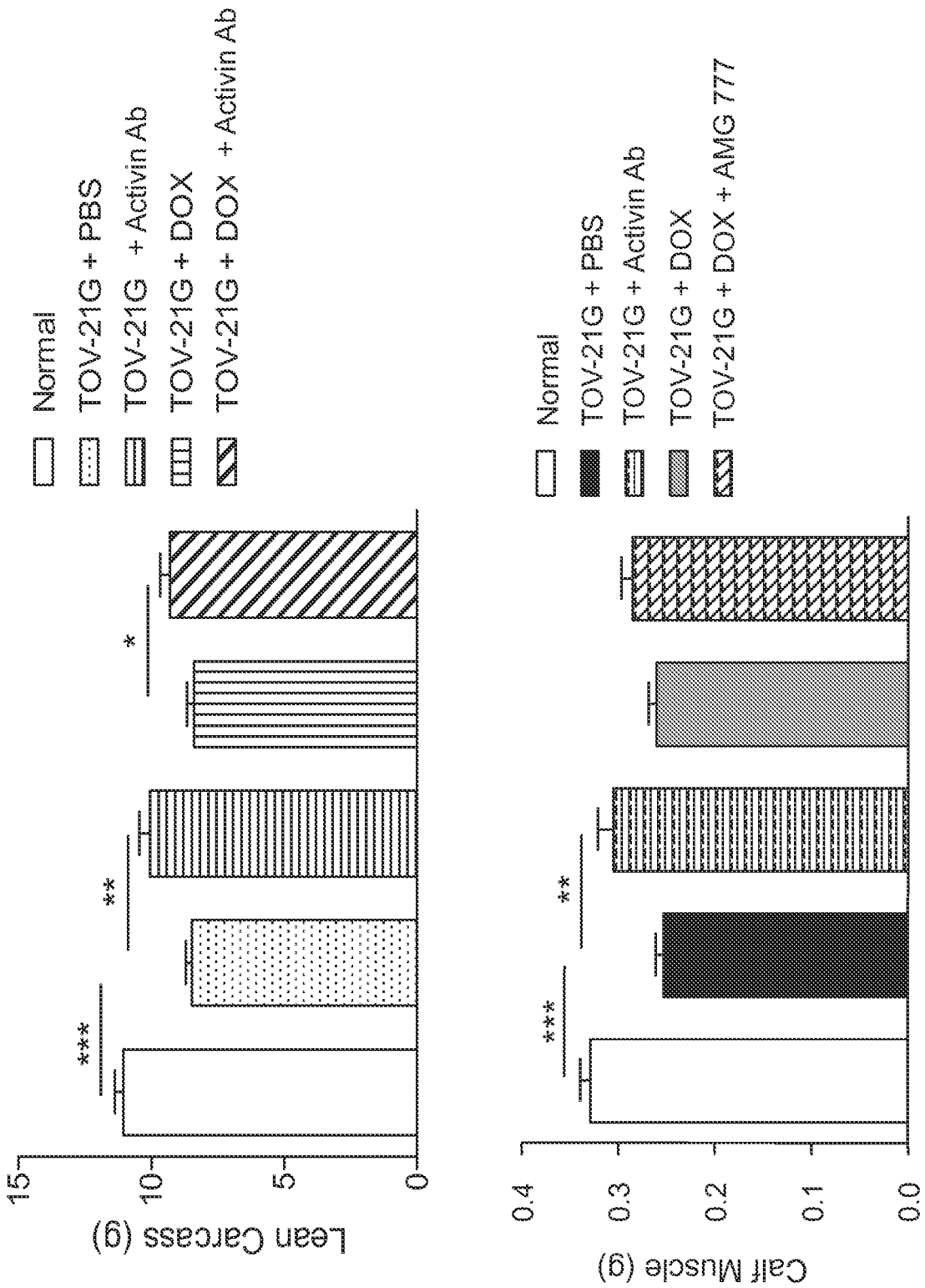

Normal
TOV-21G + PBS
TOV-21G + Activin Ab
TOV-21G + DOX
TOV-21G + DOX + Activin Ab
Lean Carcass (g)
15
10
5
0
***
**
*
Normal
TOV-21G + PBS
TOV-21G + Activin Ab
TOV-21G + DOX
TOV-21G + DOX + AMG 777
Calf Muscle (g)
0.4
0.3
0.2
0.1
0.0
***
**

FIG. 38