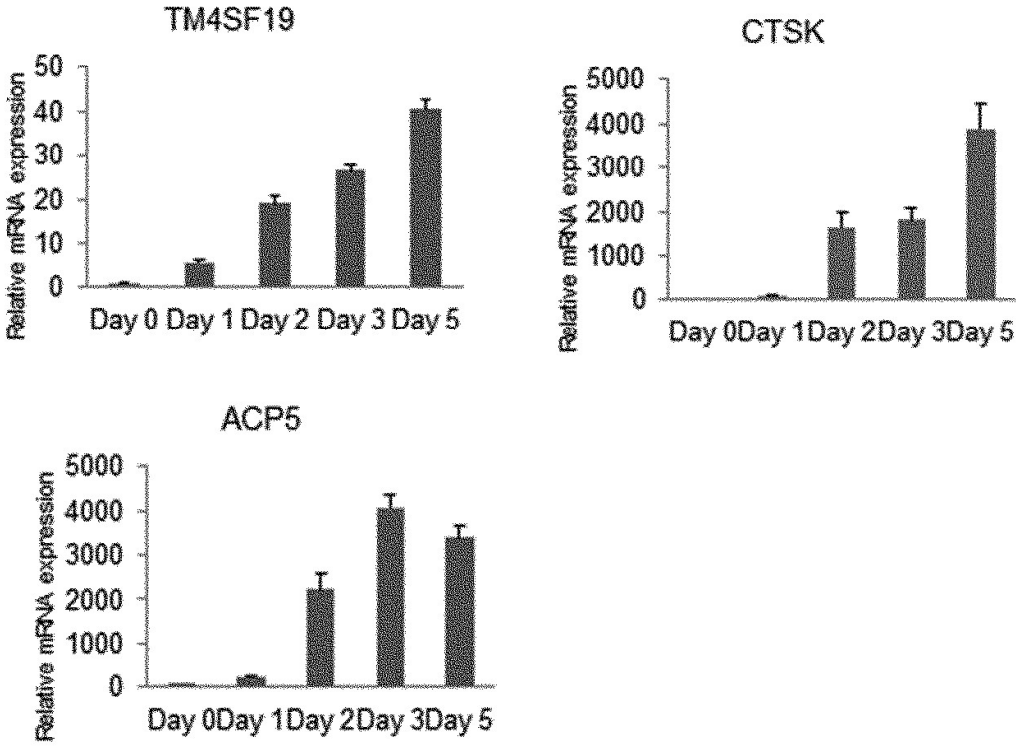
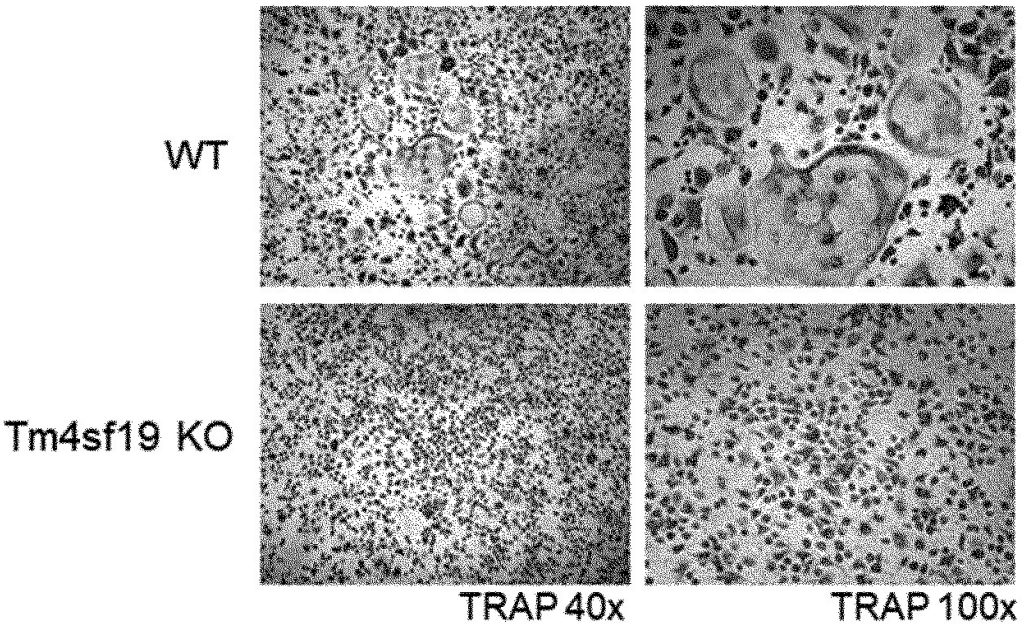
DRAWINGS

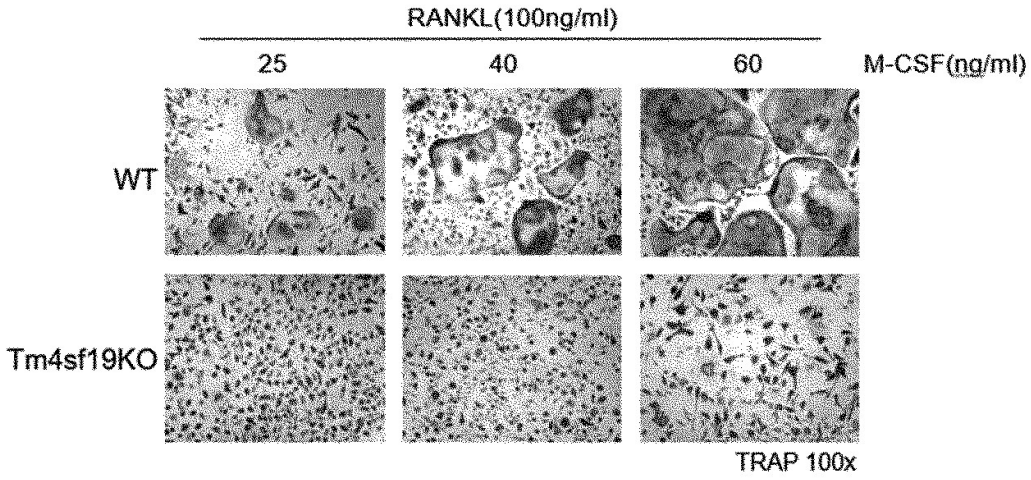
【FIG. 1】



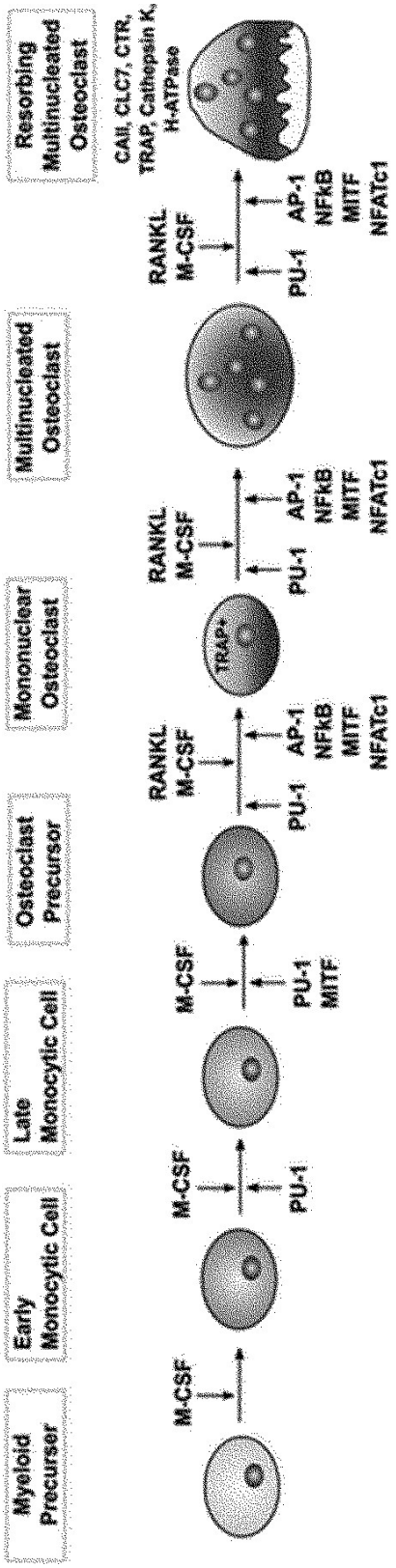
【FIG. 2A】



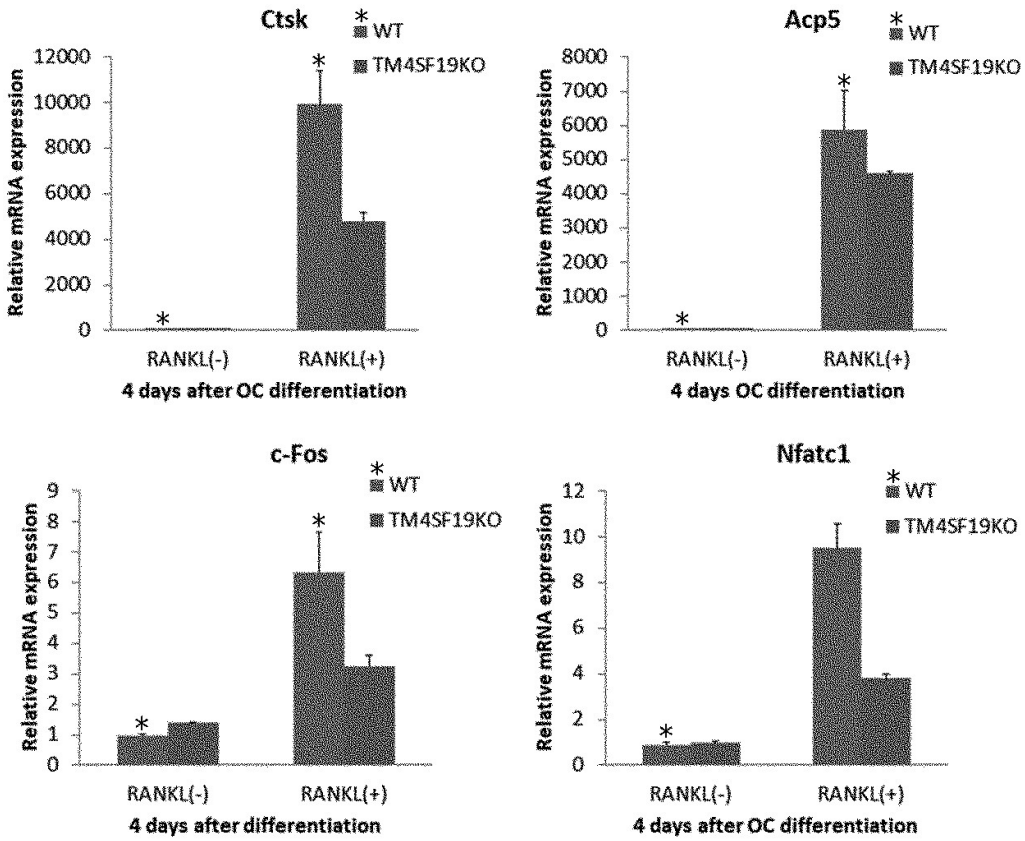
【FIG. 2B】



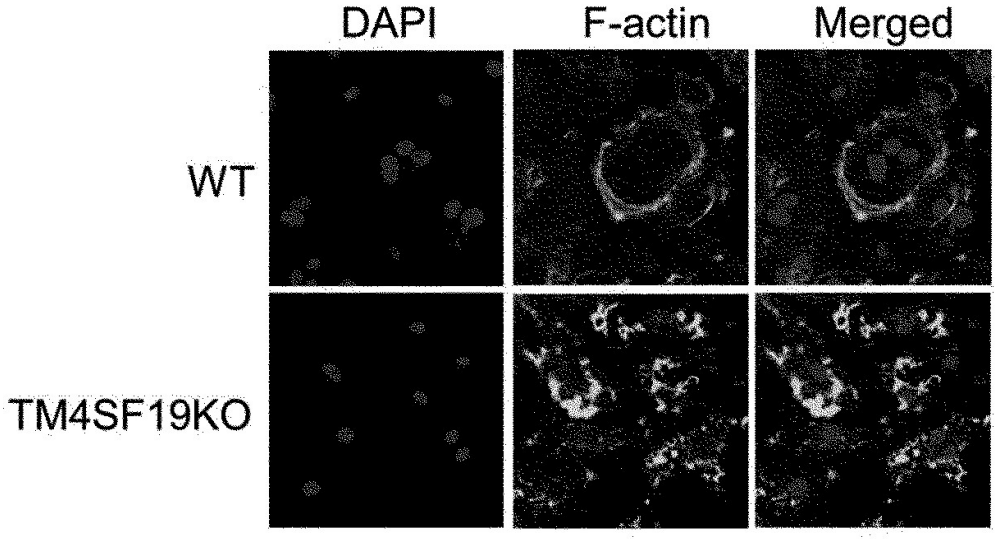
【FIG. 2c】


Myeloid Precursor
Early Monocytic Cell
Late Monocytic Cell
Osteoclast Precursor
Mononuclear Osteoclast
Multinucleated Osteoclast
Resorbing Multinucleated Osteoclast
M-CSF
PU-1
M-CSF
PU-1
MITF
M-CSF
PU-1
MITF
RANKL
M-CSF
PU-1
AP-1
NFkB
MITF
NFATc1
TRAP+
RANKL
M-CSF
PU-1
AP-1
NFkB
MITF
NFATc1
RANKL
M-CSF
PU-1
AP-1
NFkB
MITF
NFATc1
CAII, CLC7, CTR, TRAP, Cathepsin K, H-ATPase

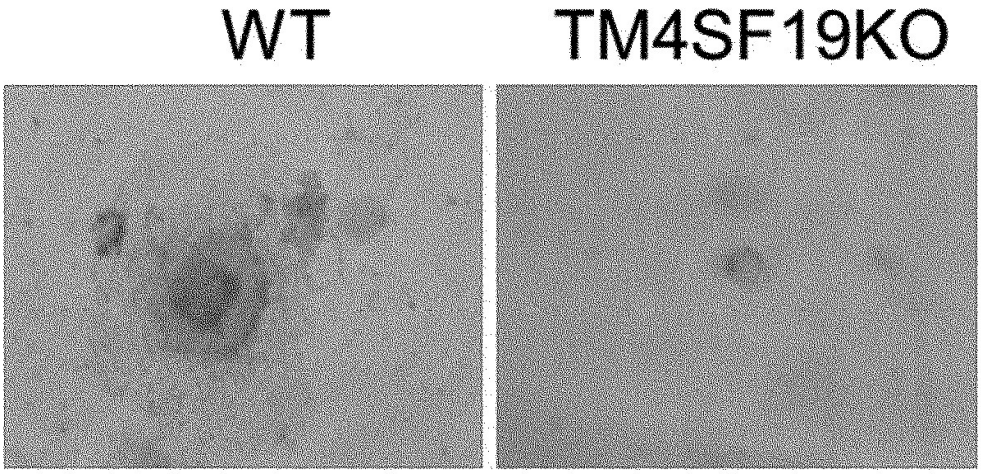
【FIG. 3】


Ctsk
WT
TM4SF19KO
Relative mRNA expression
12000
10000
8000
6000
4000
2000
0
RANKL(-)
RANKL(+)
4 days after OC differentiation
Acp5
WT
TM4SF19KO
Relative mRNA expression
8000
7000
6000
5000
4000
3000
2000
1000
0
RANKL(-)
RANKL(+)
4 days OC differentiation
c-Fos
WT
TM4SF19KO
Relative mRNA expression
9
8
7
6
5
4
3
2
1
0
RANKL(-)
RANKL(+)
4 days after differentiation
Nfatc1
WT
TM4SF19KO
Relative mRNA expression
12
10
8
6
4
2
0
RANKL(-)
RANKL(+)
4 days after OC differentiation

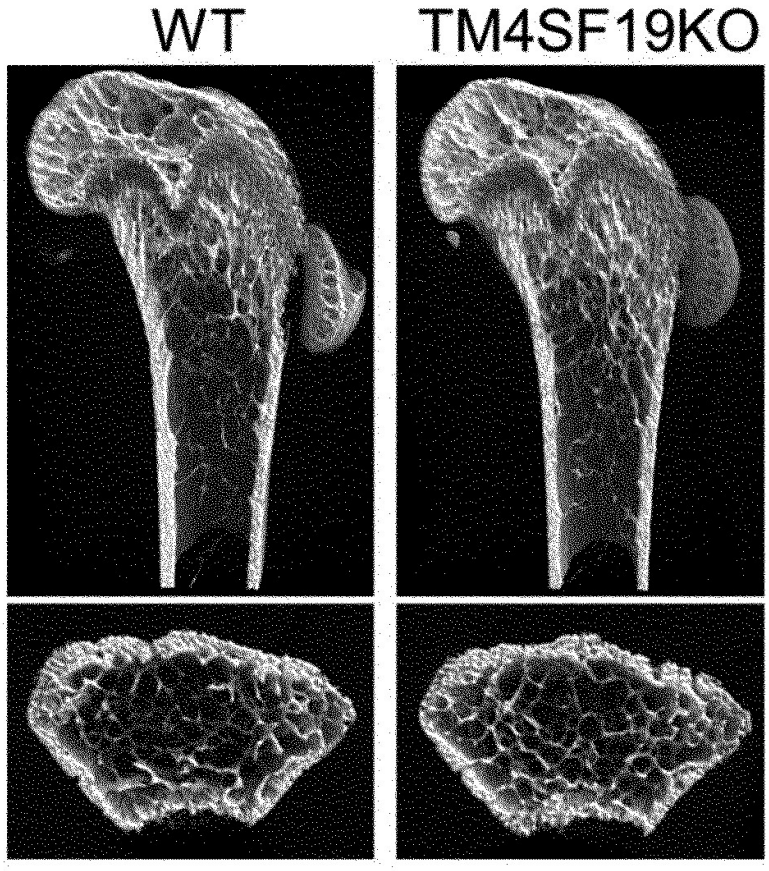
【FIG. 4A】


DAPI
F-actin
Merged
WT
TM4SF19KO

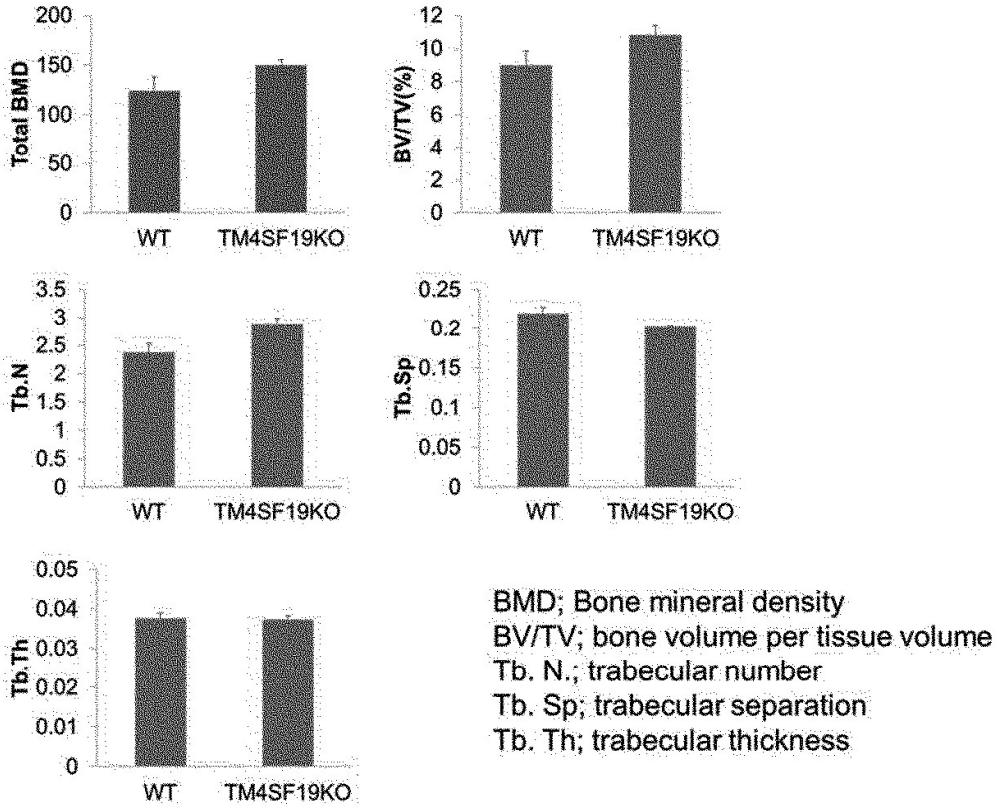
【FIG. 4B】



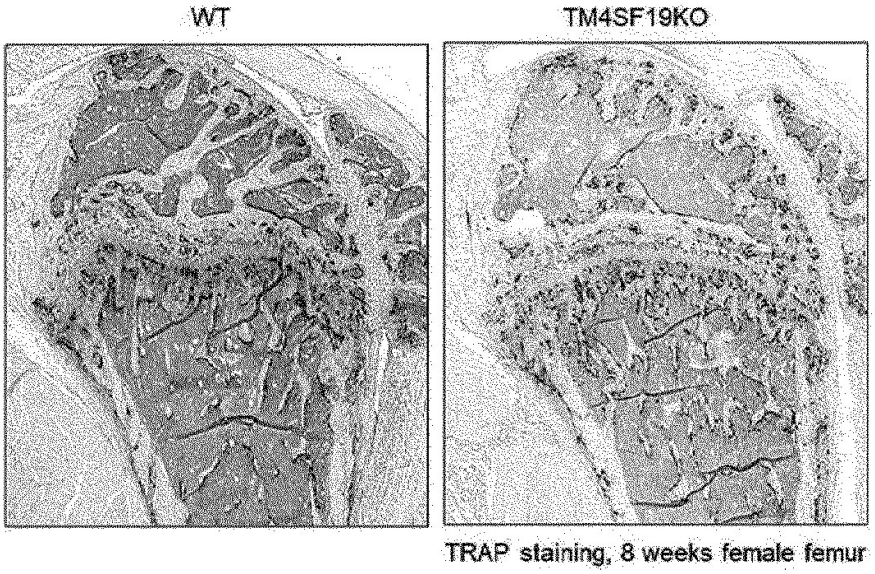
【FIG. 5A】



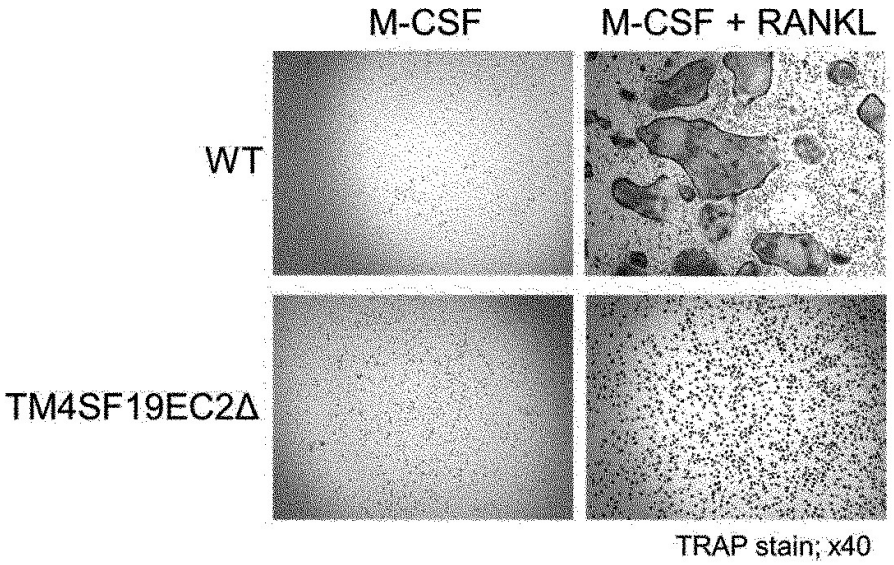
【FIG. 5B】


Total BMD
200
150
100
50
0
WT
TM4SF19KO
BV/TV(%)
12
10
8
6
4
2
0
WT
TM4SF19KO
Tb.N
3.5
3
2.5
2
1.5
1
0.5
0
WT
TM4SF19KO
Tb.Sp
0.25
0.2
0.15
0.1
0.05
0
WT
TM4SF19KO
Tb.Th
0.05
0.04
0.03
0.02
0.01
0
WT
TM4SF19KO
BMD; Bone mineral density
BV/TV; bone volume per tissue volume
Tb. N.; trabecular number
Tb. Sp; trabecular separation
Tb. Th; trabecular thickness

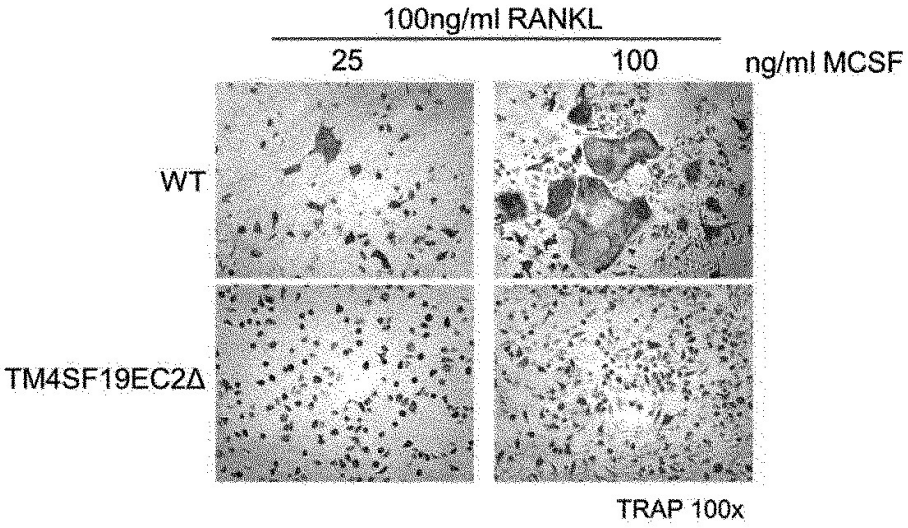
【FIG. 6】


WT
TM4SF19KO
TRAP staining, 8 weeks female femur

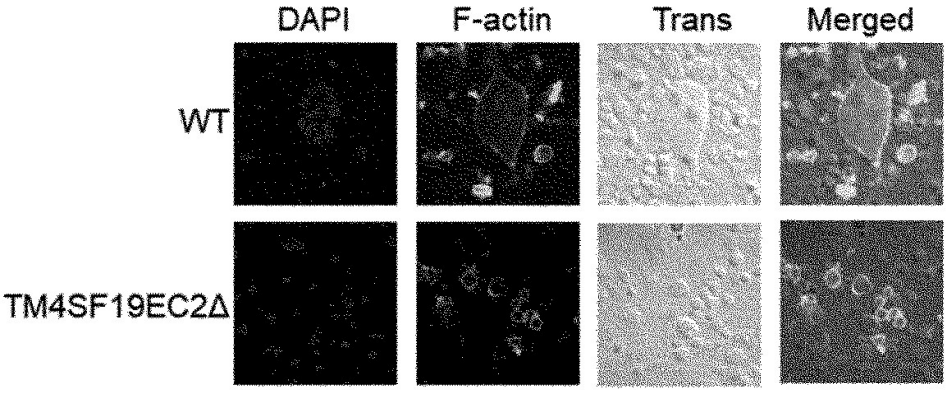
【FIG. 7A】



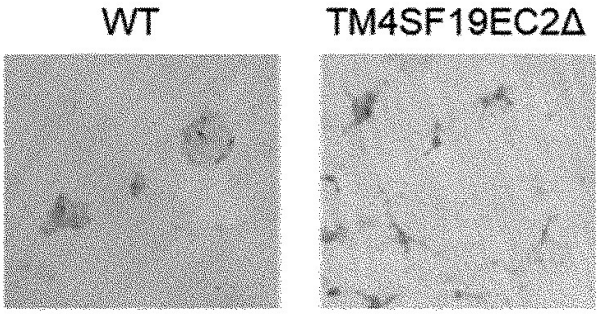
【FIG. 7B】



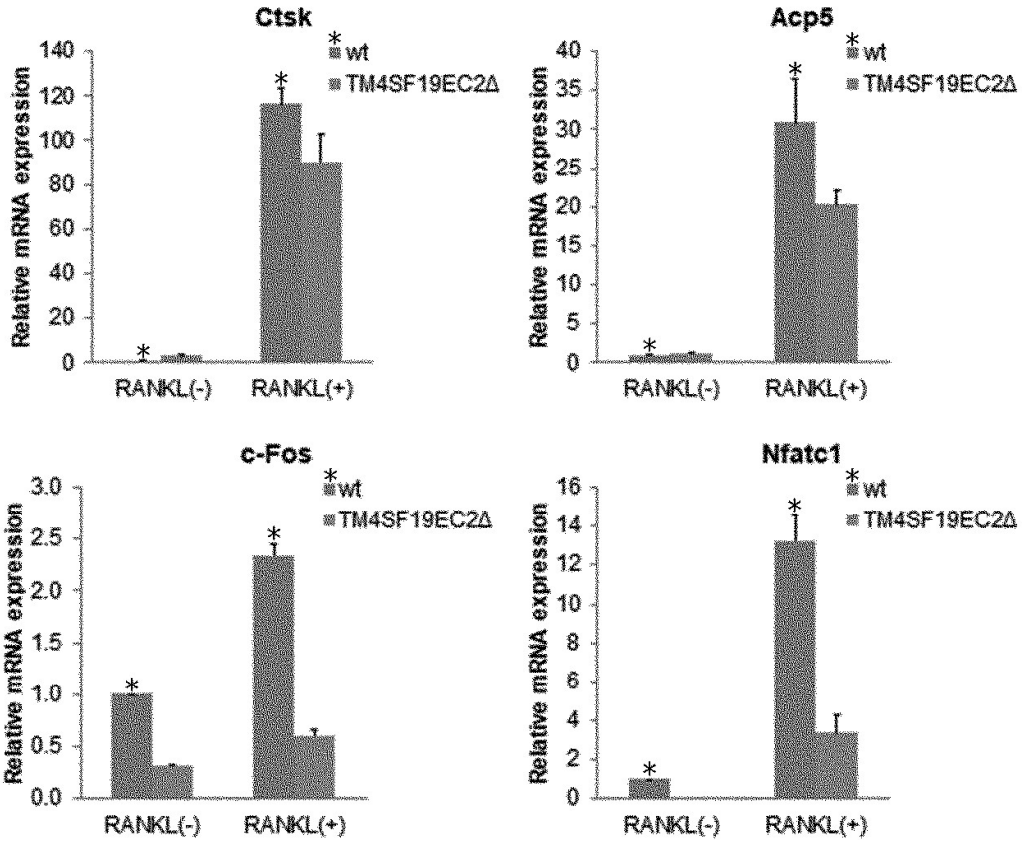
【FIG. 7C】



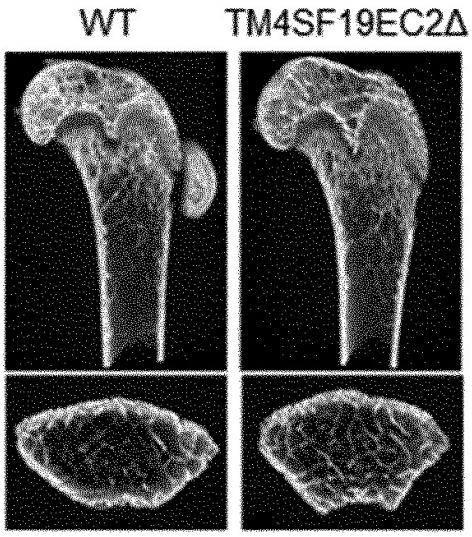
【FIG. 7D】


WT
TM4SF19EC2Δ

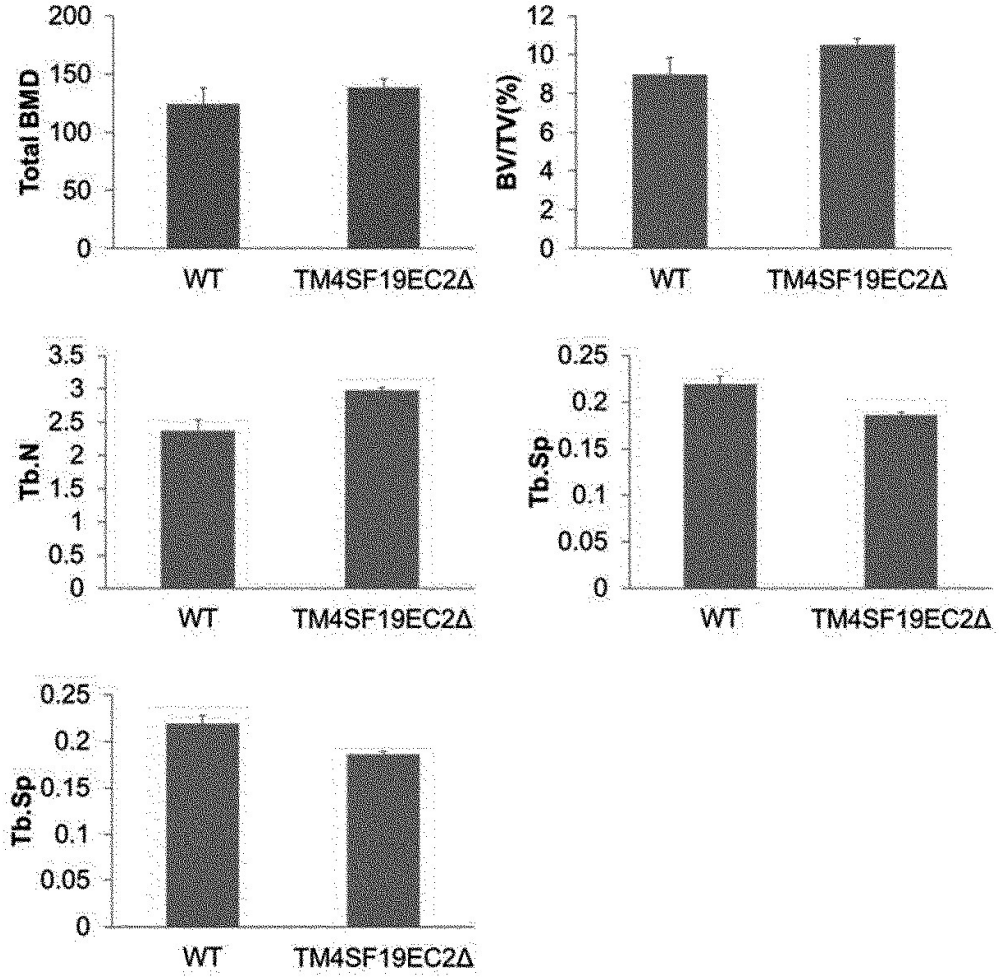
【FIG. 8】


Ctsk
Acp5
c-Fos
Nfatc1
wt
TM4SF19EC2Δ
Relative mRNA expression
RANKL(-)
RANKL(+)

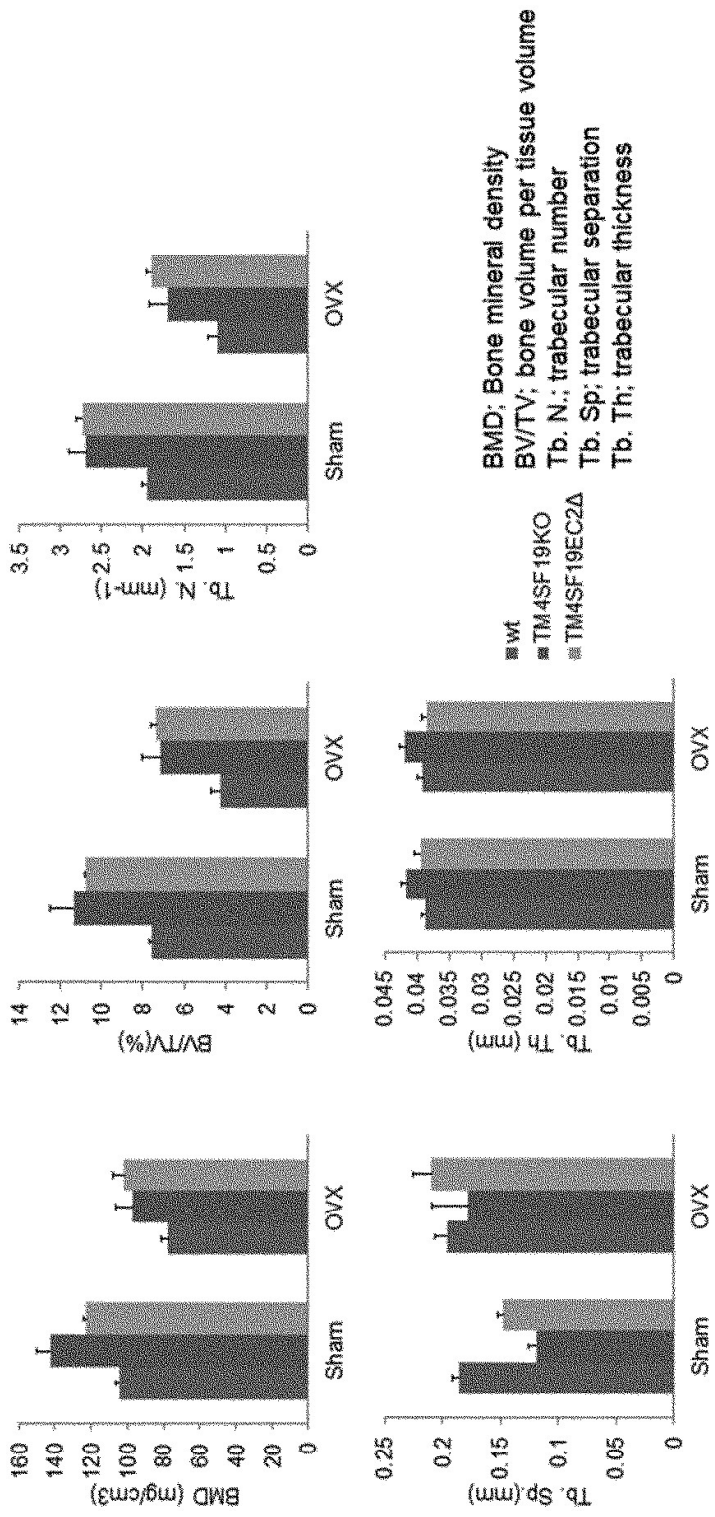
【FIG. 9A】


WT
TM4SF19EC2Δ

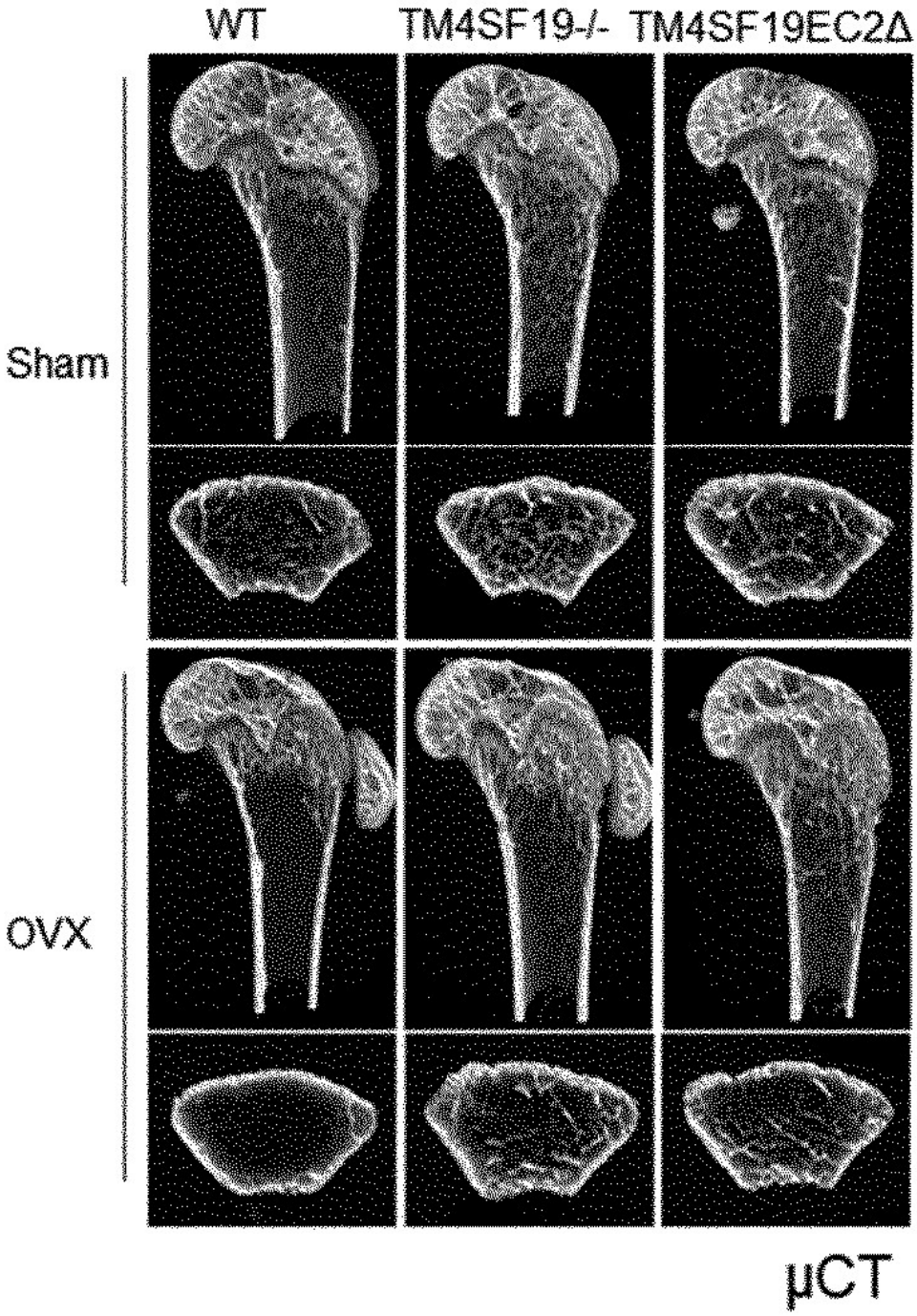
【FIG. 9B】


Total BMD
200
150
100
50
0
WT
TM4SF19EC2Δ
BV/TV(%)
12
10
8
6
4
2
0
WT
TM4SF19EC2Δ
Tb.N
3.5
3
2.5
2
1.5
1
0.5
0
WT
TM4SF19EC2Δ
Tb.Sp
0.25
0.2
0.15
0.1
0.05
0
WT
TM4SF19EC2Δ
Tb.Sp
0.25
0.2
0.15
0.1
0.05
0
WT
TM4SF19EC2Δ

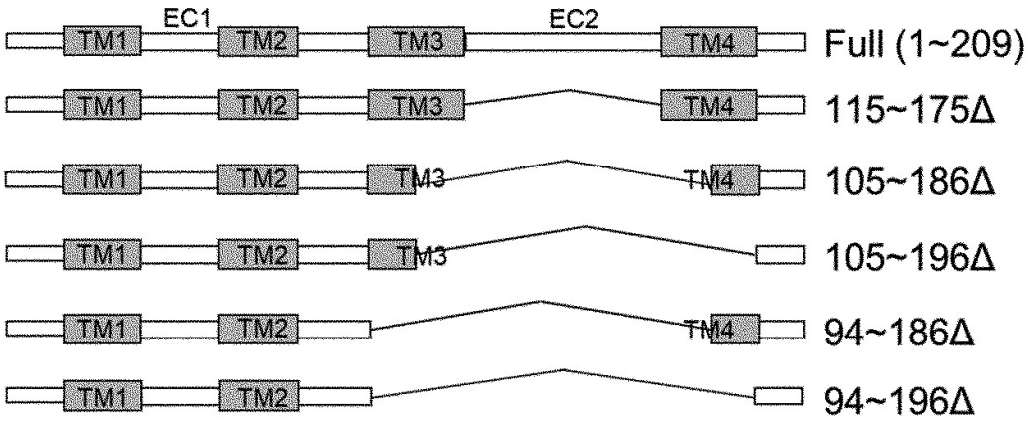
【FIG. 10】


BMD (mg/cm3)
Tb. Sp.(mm)
BV/TV(%)
Tb. Th (mm)
Tb. N. (mm-1)
Sham
OVX
wt
TM4SF19KO
TM4SF19EC2Δ
BMD; Bone mineral density
BV/TV; bone volume per tissue volume
Tb. N.; trabecular number
Tb. Sp; trabecular separation
Tb. Th; trabecular thickness

【FIG. 11】

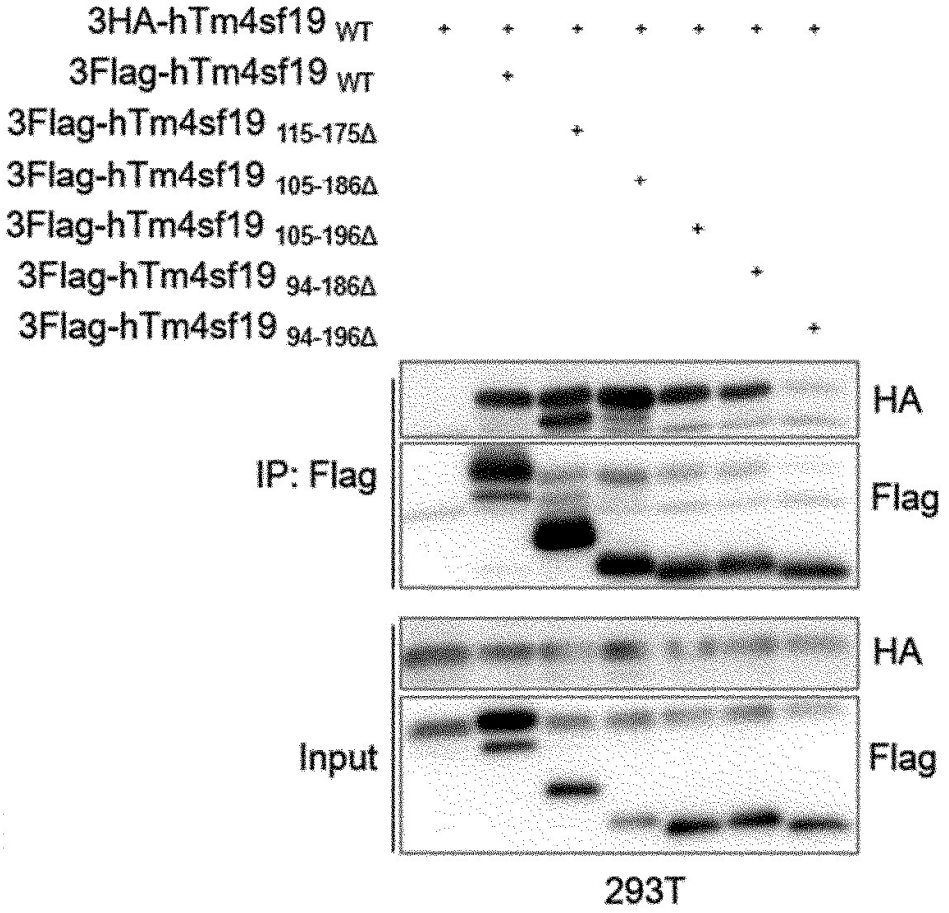


【FIG. 12A】

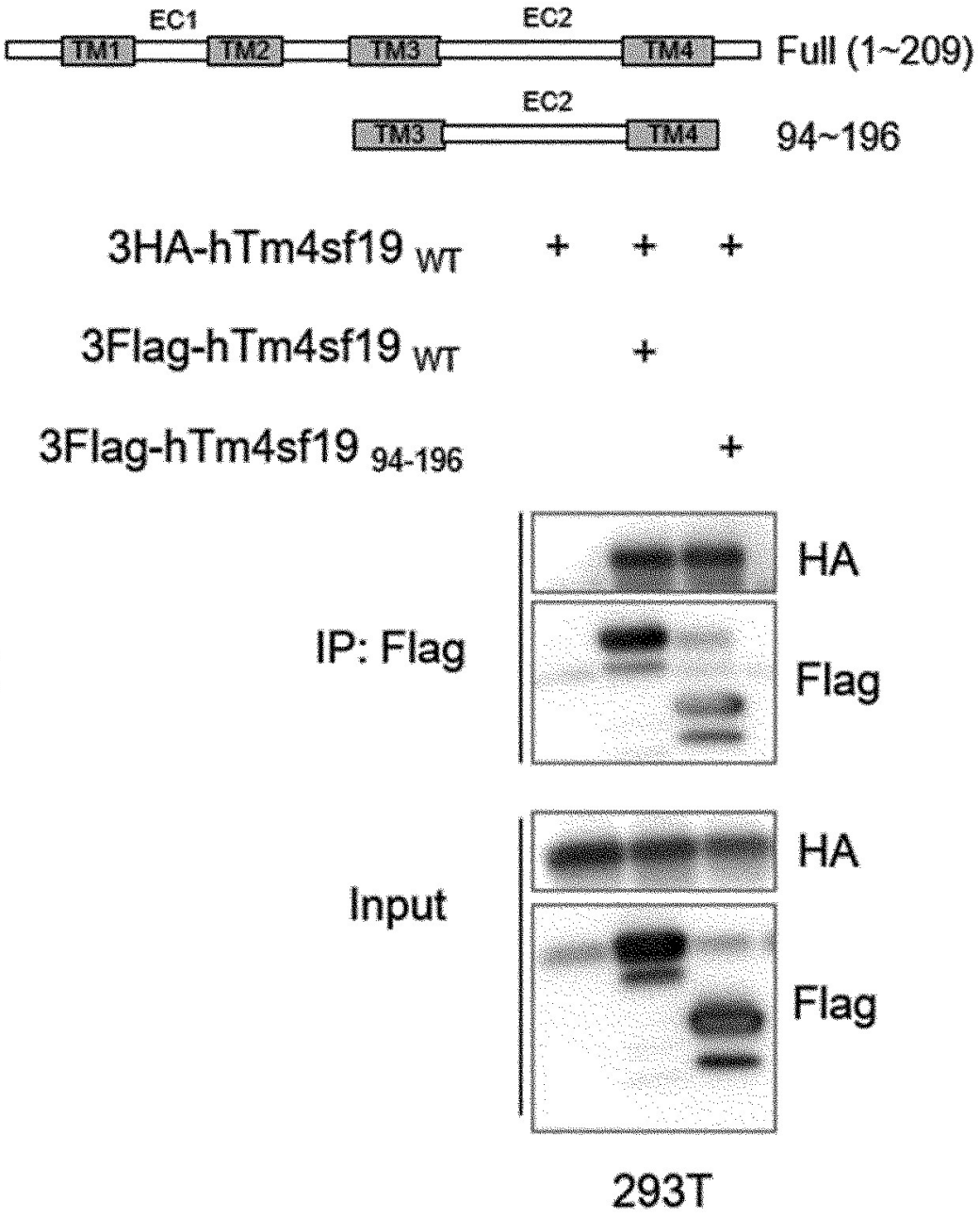


- EC1: Extracellular region 1
- EC2: Extracellular region 2
- TM: Transmembrane

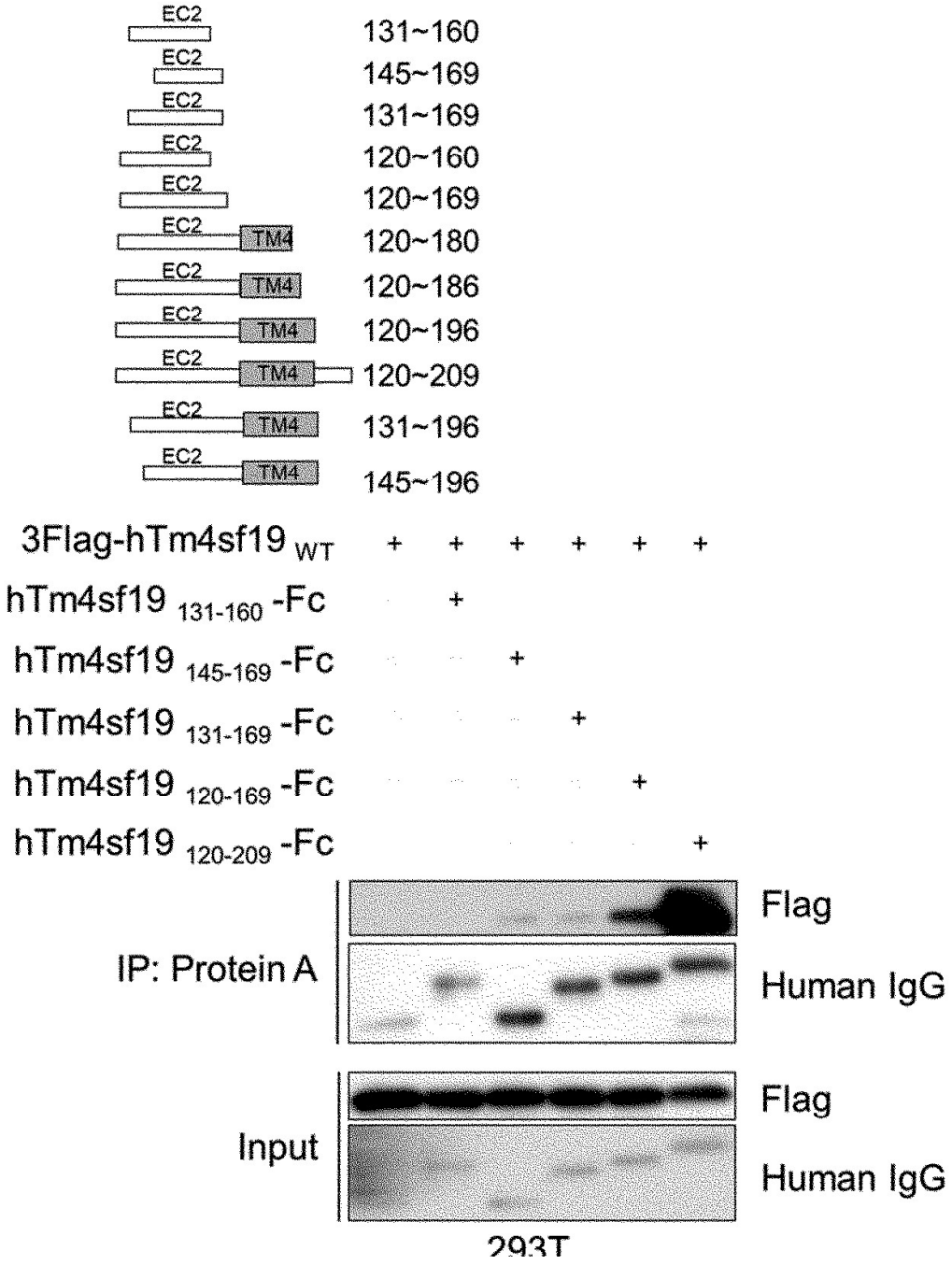
【FIG. 12B】



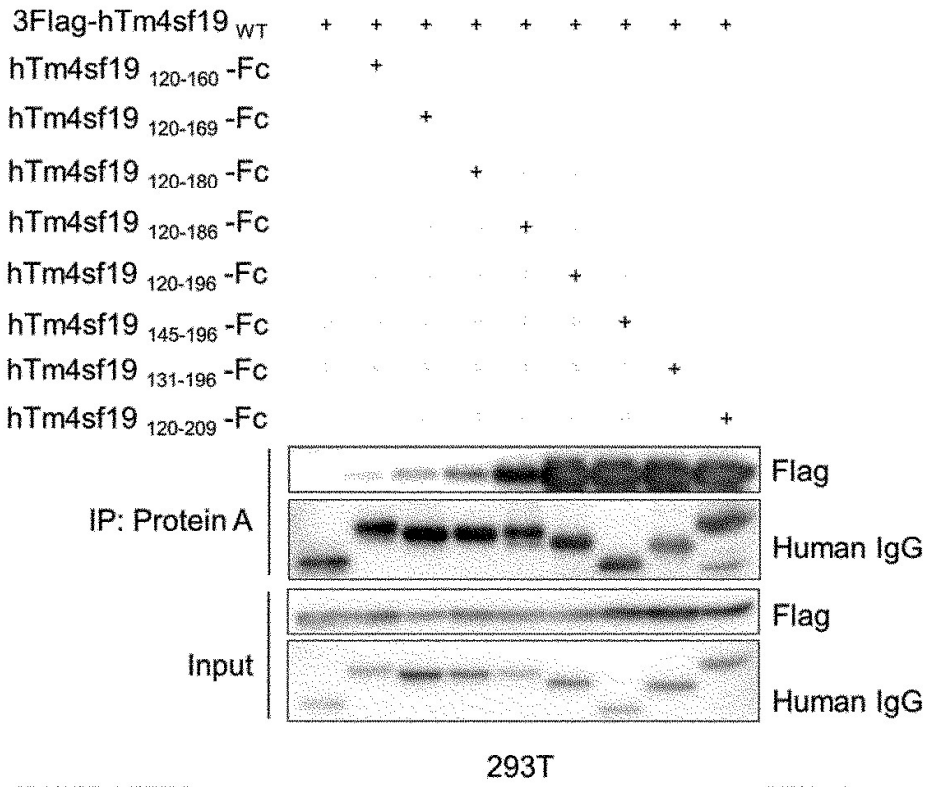
【FIG. 12C】


EC1
EC2
TM1
TM2
TM3
TM4
Full (1~209)
EC2
TM3
TM4
94~196
3HA-hTm4sf19 WT + + +
3Flag-hTm4sf19 WT +
3Flag-hTm4sf19 94-196 +
IP: Flag
HA
Flag
Input
HA
Flag
293T

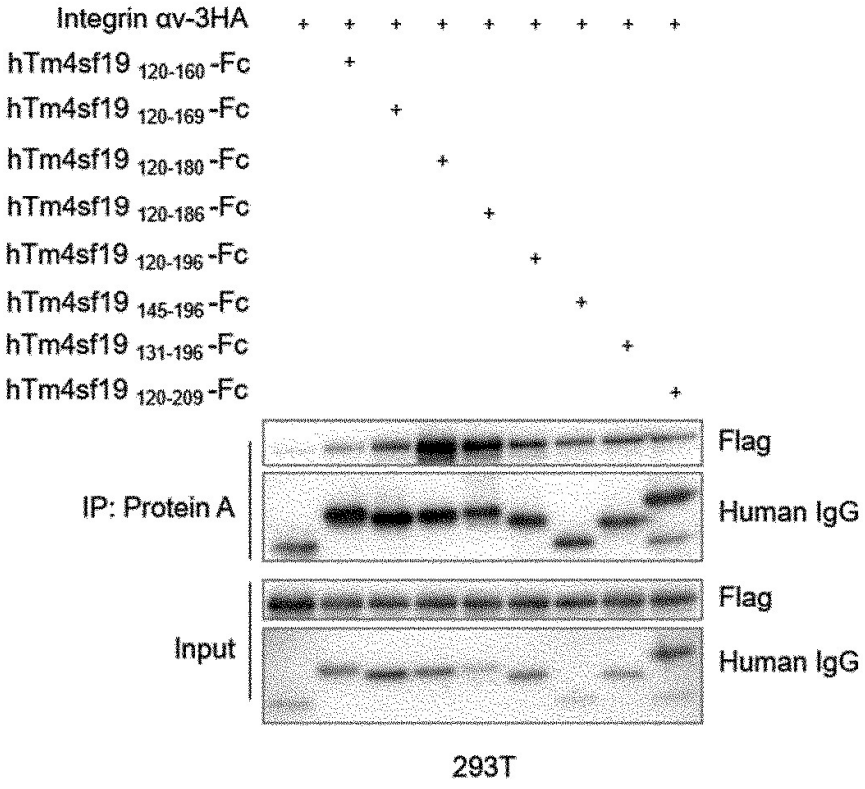
【FIG. 12D】


EC2
TM4
131~160
145~169
131~169
120~160
120~169
120~180
120~186
120~196
120~209
131~196
145~196
3Flag-hTm4sf19 WT
hTm4sf19 131-160 -Fc
hTm4sf19 145-169 -Fc
hTm4sf19 131-169 -Fc
hTm4sf19 120-169 -Fc
hTm4sf19 120-209 -Fc
IP: Protein A
Flag
Human IgG
Input
Flag
Human IgG
293T

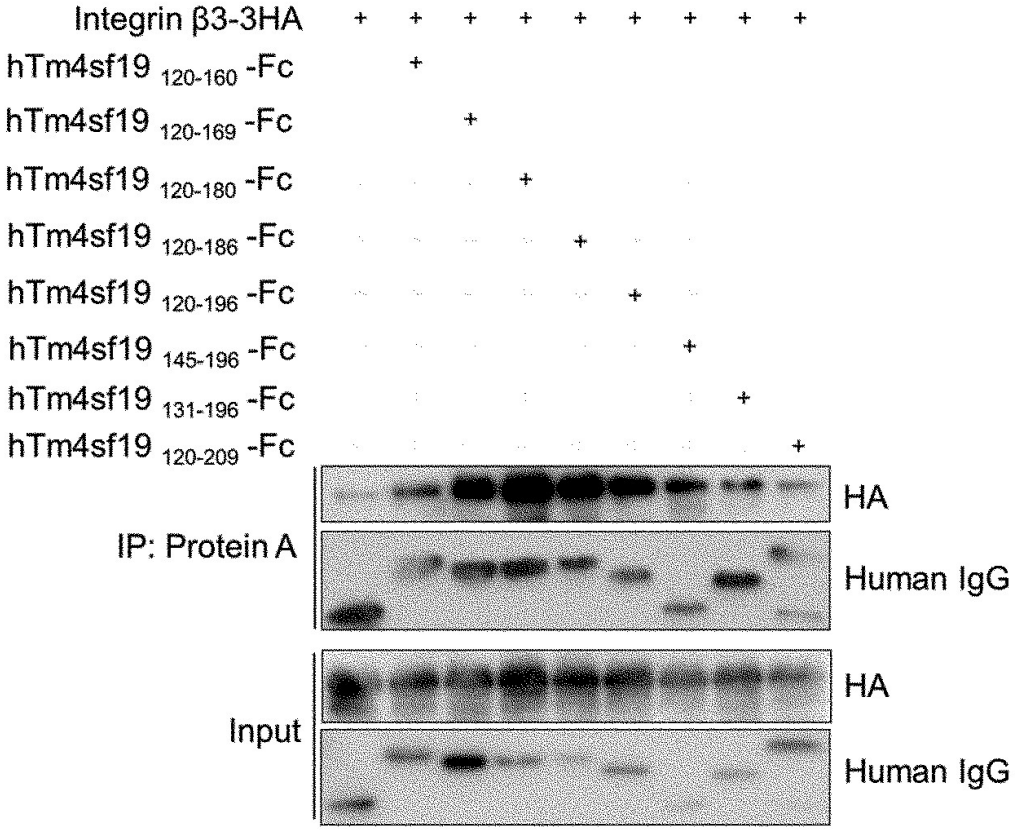
【FIG. 12E】



【FIG. 12F】



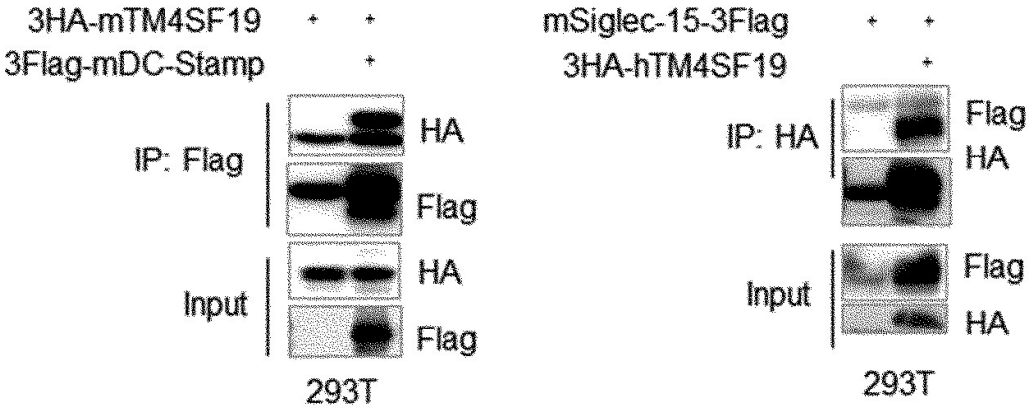
【FIG. 12G】


Integrin β3-3HA + + + + + + + + +
hTm4sf19 120-160 -Fc +
hTm4sf19 120-169 -Fc +
hTm4sf19 120-180 -Fc +
hTm4sf19 120-186 -Fc +
hTm4sf19 120-196 -Fc +
hTm4sf19 145-196 -Fc +
hTm4sf19 131-196 -Fc +
hTm4sf19 120-209 -Fc +
IP: Protein A
HA
Human IgG
Input
HA
Human IgG

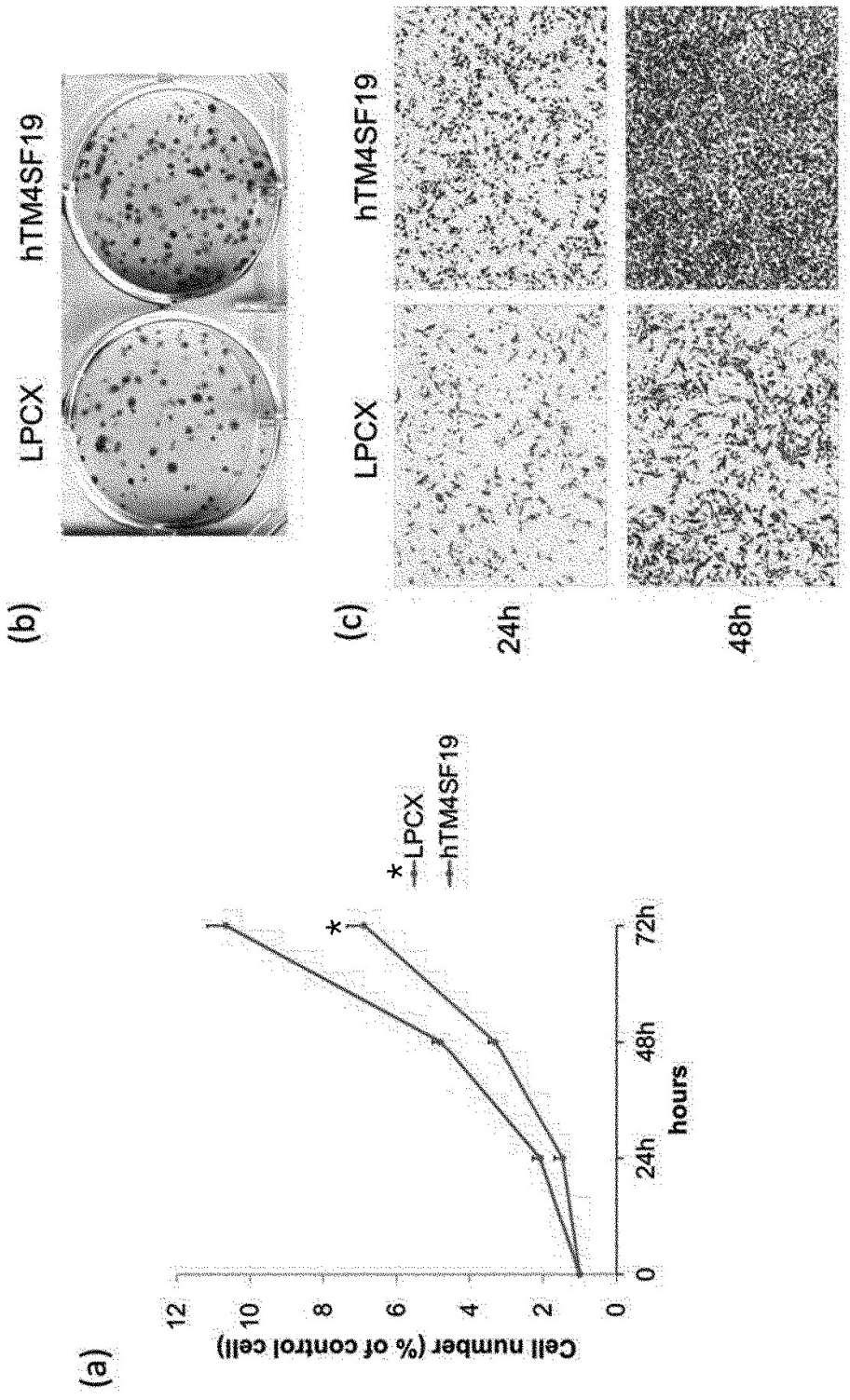
【FIG. 12H】

Integrin αv-3Flag + + +
3HA-hTm4sf19 +
IP: HA
Flag
HA
Input
Flag
HA
293T
Integrin αv-3Flag + + +
3HA-hTm4sf19 +
IP: HA
Flag
HA
Input
Flag
HA
Raw 264.7
Integrin β3-3HA + + +
3Flag-hTm4sf19 +
IP: Flag
Integrin β3
TM4SF19
Input
anti-Integrin β3
anti-TM4SF19
anti-Integrin αv
293T
Integrin αv-3HA + + +
3Flag-TM4SF19WT +
3Flag-TM4SF19 115-175Δ +
IP: Flag
HA
Flag
Input
HA
Flag
Integrin β3-3HA + + +
3Flag-TM4SF19WT +
3Flag-TM4SF19 115-175Δ +
IP: Flag
HA
Flag
Input
HA
Flag

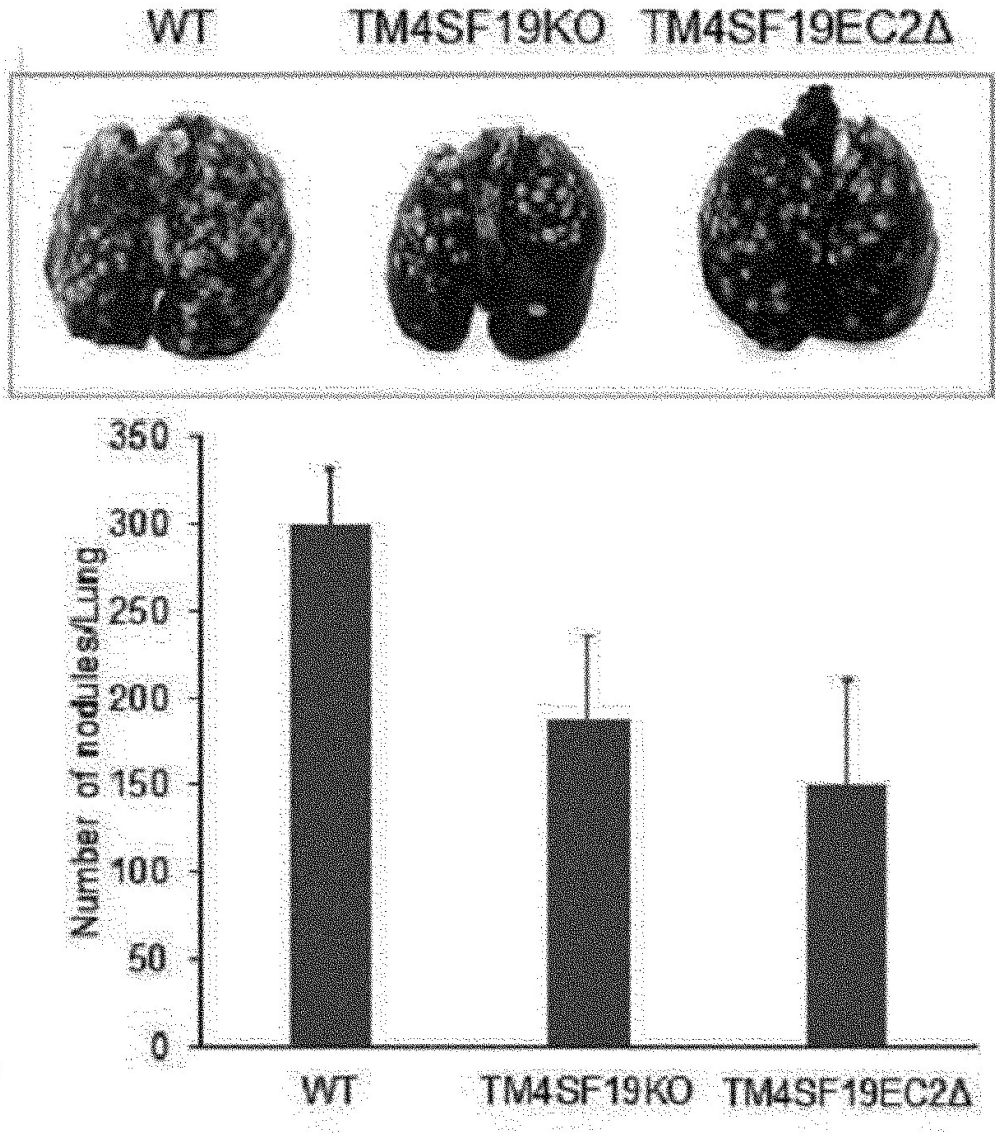
【FIG. 12I】


3HA-mTM4SF19
3Flag-mDC-Stamp
IP: Flag
HA
Flag
Input
HA
Flag
293T
mSiglec-15-3Flag
3HA-hTM4SF19
IP: HA
Flag
HA
Input
Flag
HA
293T

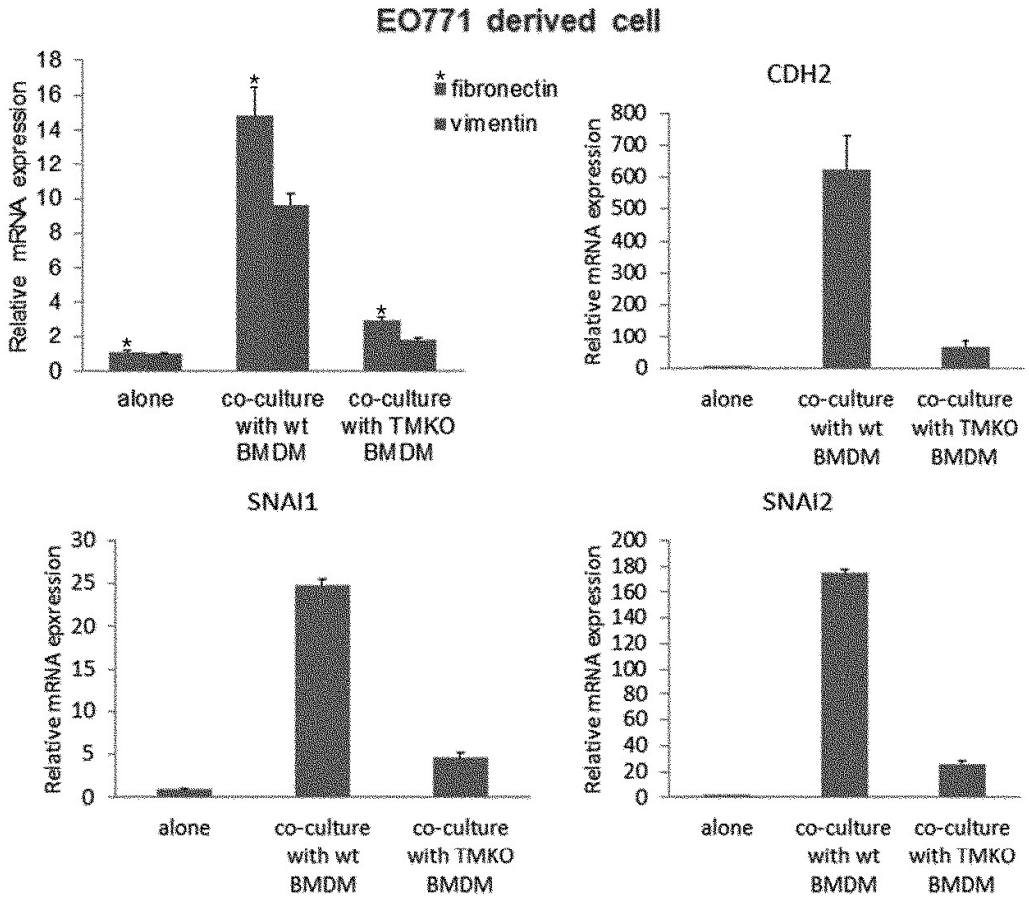
【FIG. 13】


(a)
Cell number (% of control cell)
12
10
8
6
4
2
0
0
24h
48h
72h
hours
*
*LPCX
hTM4SF19
(b)
LPCX
hTM4SF19
(c)
LPCX
hTM4SF19
24h
48h

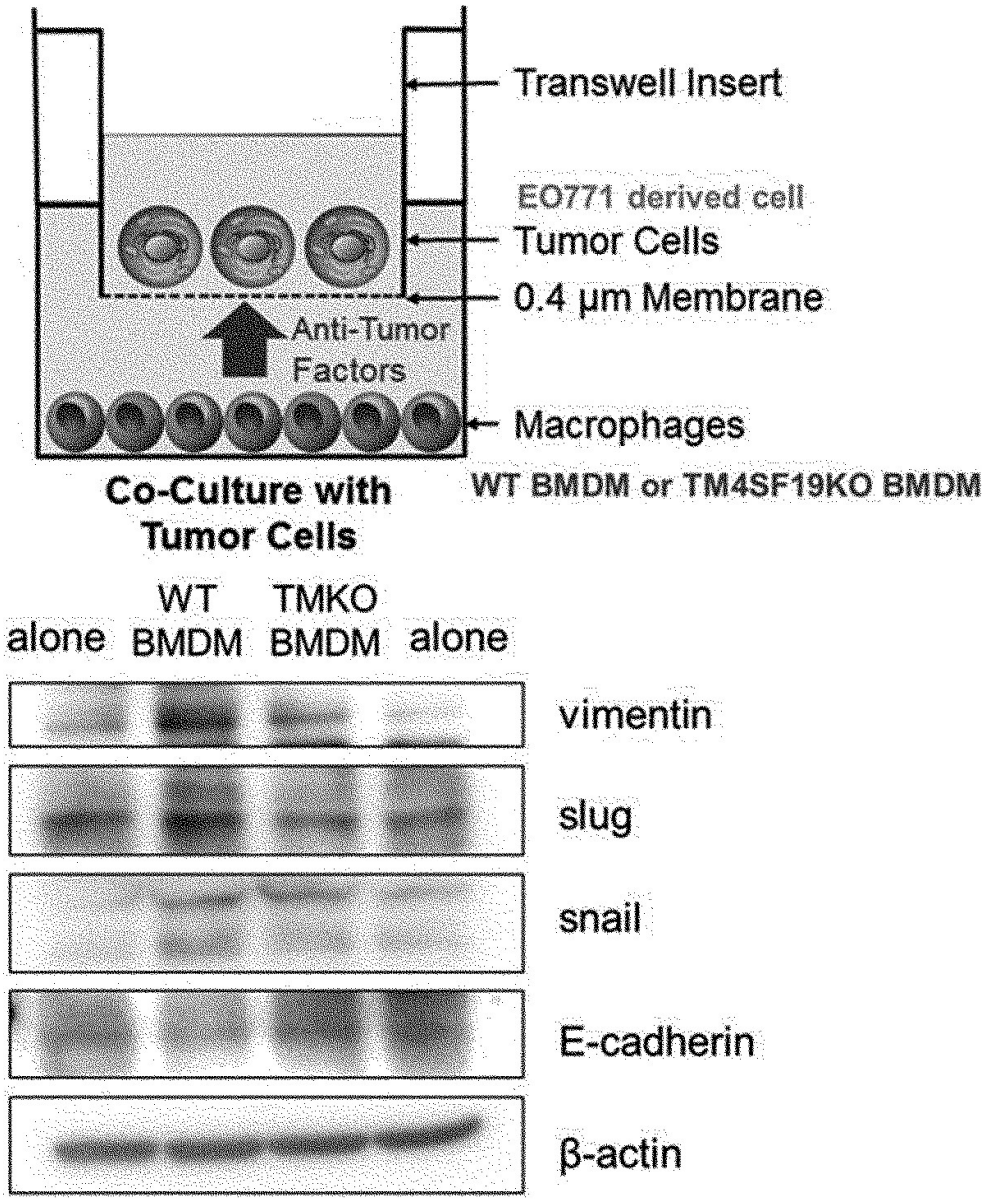
【FIG. 14】


WT
TM4SF19KO
TM4SF19EC2Δ
Number of nodules/Lung
350
300
250
200
150
100
50
0
WT
TM4SF19KO
TM4SF19EC2Δ

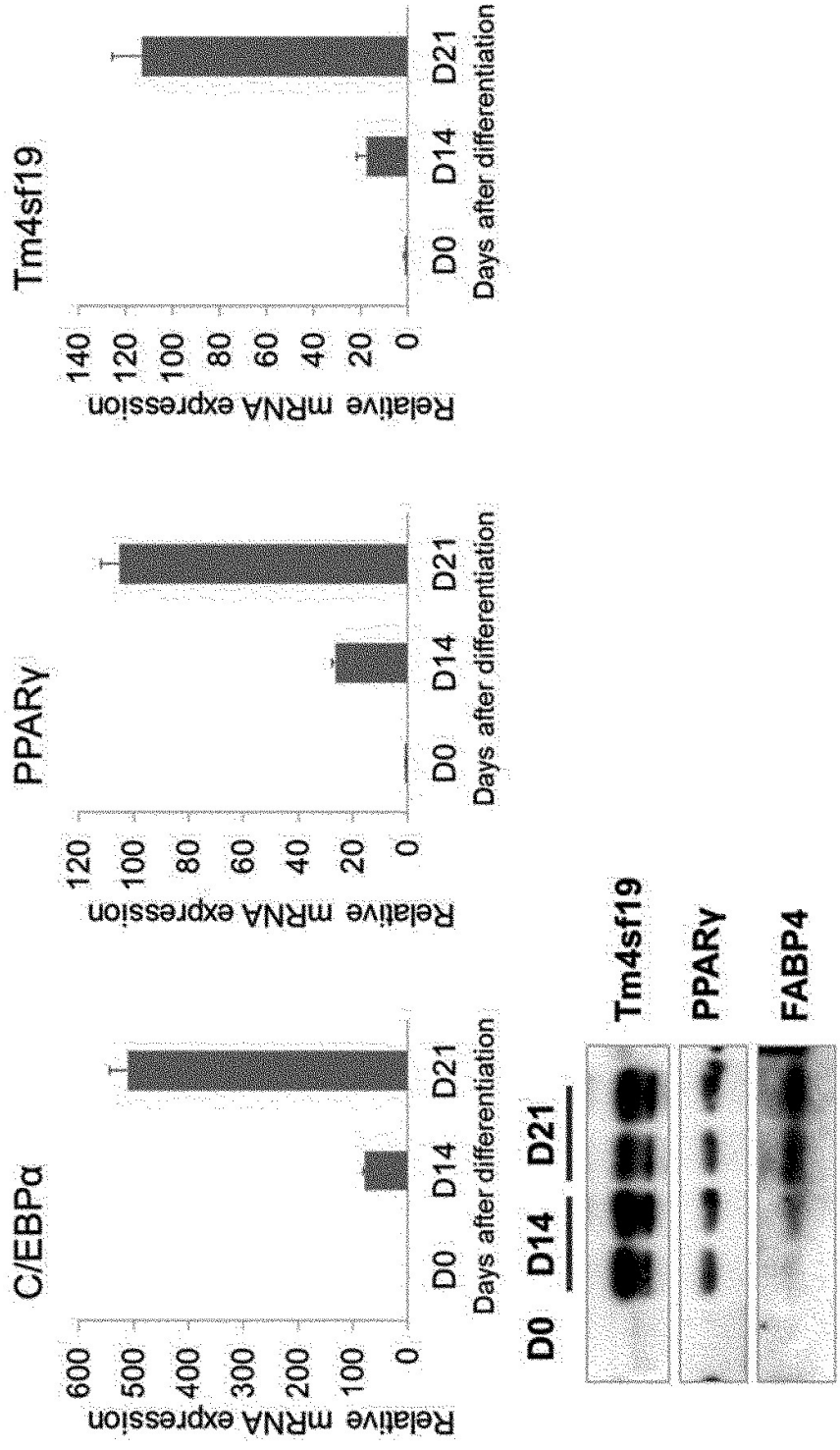
【FIG. 15A】


EO771 derived cell
Relative mRNA expression
fibronectin
vimentin
alone
co-culture with wt BMDM
co-culture with TMKO BMDM
CDH2
SNAI1
SNAI2

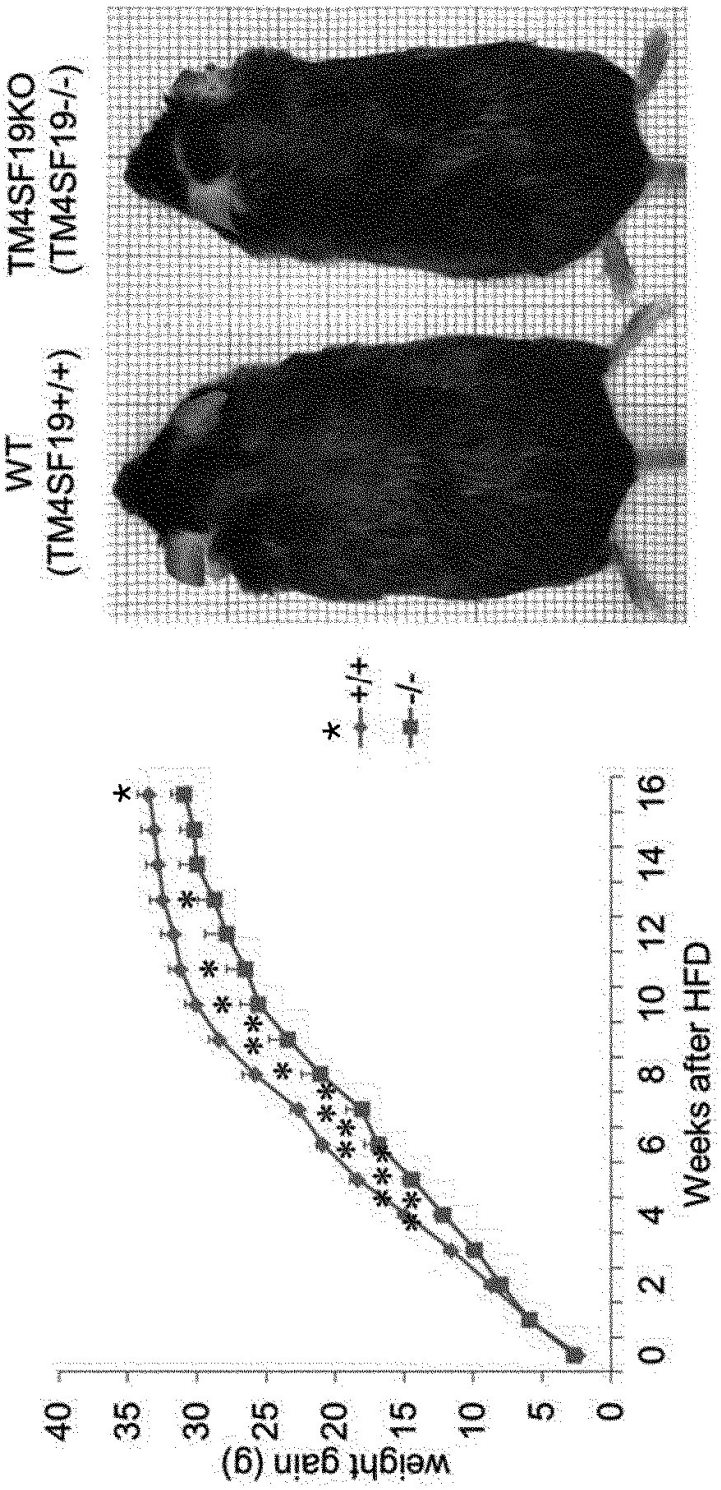
【FIG. 15B】


Transwell Insert
EO771 derived cell
Tumor Cells
0.4 μm Membrane
Anti-Tumor Factors
Macrophages
WT BMDM or TM4SF19KO BMDM
Co-Culture with Tumor Cells
alone
WT BMDM
TMKO BMDM
alone
vimentin
slug
snail
E-cadherin
β-actin

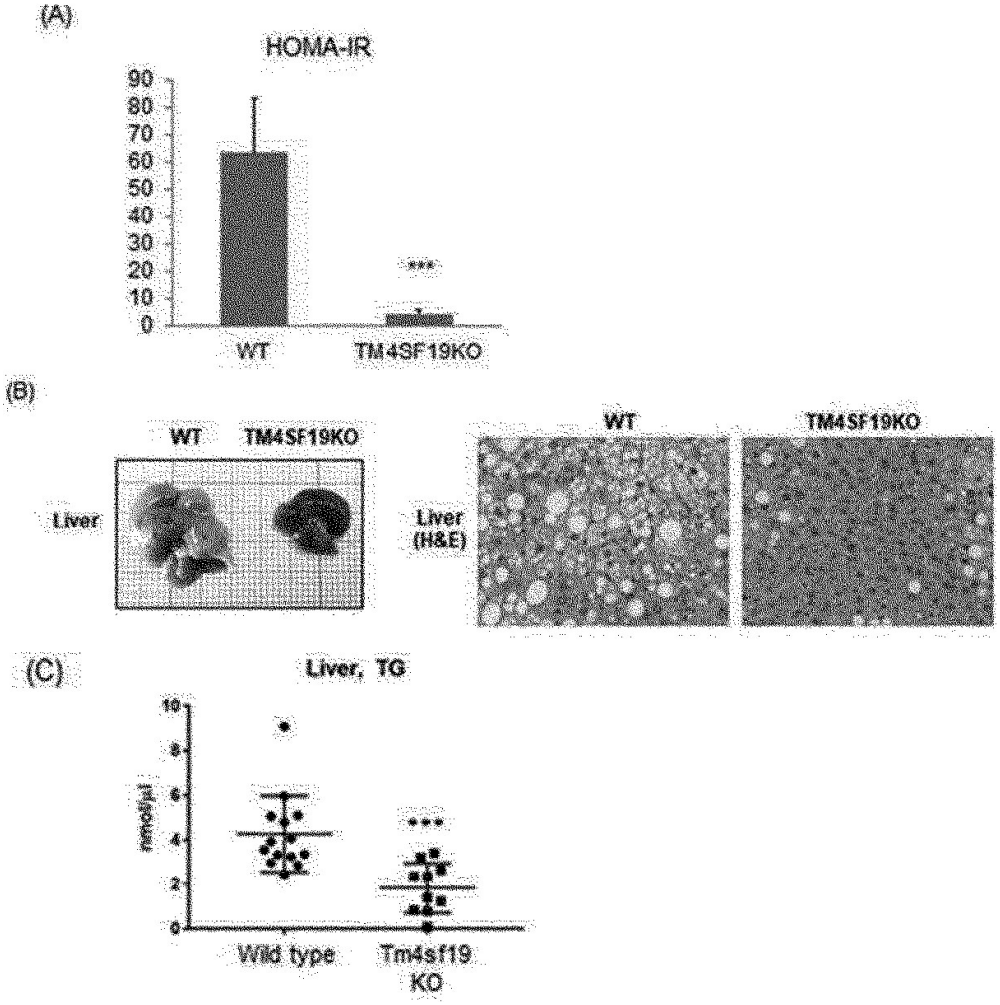
【FIG. 16】


C/EBPα
Relative mRNA expression
600
500
400
300
200
100
0
D0 D14 D21
Days after differentiation
PPARγ
Relative mRNA expression
120
100
80
60
40
20
0
D0 D14 D21
Days after differentiation
Tm4sf19
Relative mRNA expression
140
120
100
80
60
40
20
0
D0 D14 D21
Days after differentiation
D0 D14 D21
Tm4sf19
PPARγ
FABP4

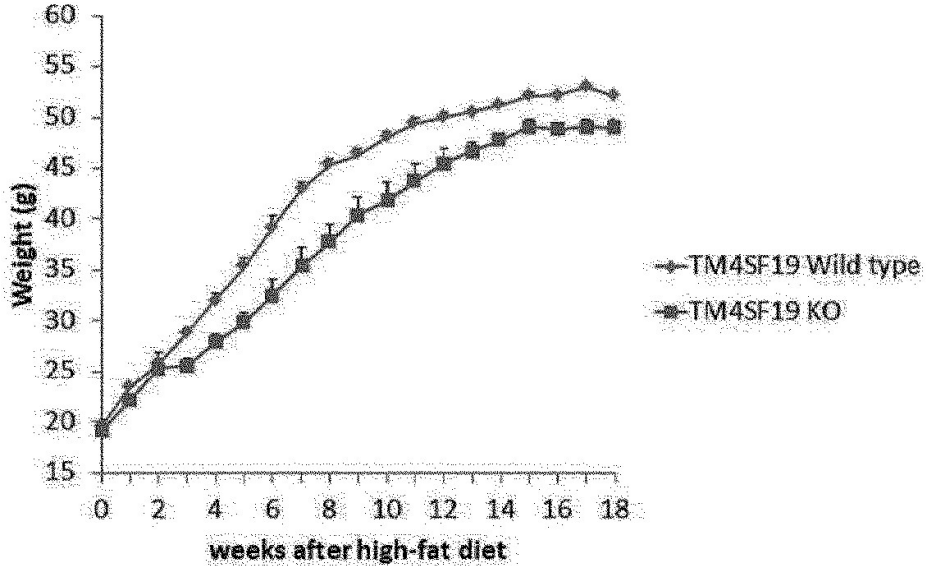
【FIG. 17】


WT
(TM4SF19+/+)
TM4SF19KO
(TM4SF19-/-)
+/+
-/-
weight gain (g)
Weeks after HFD
0
5
10
15
20
25
30
35
40
0
2
4
6
8
10
12
14
16

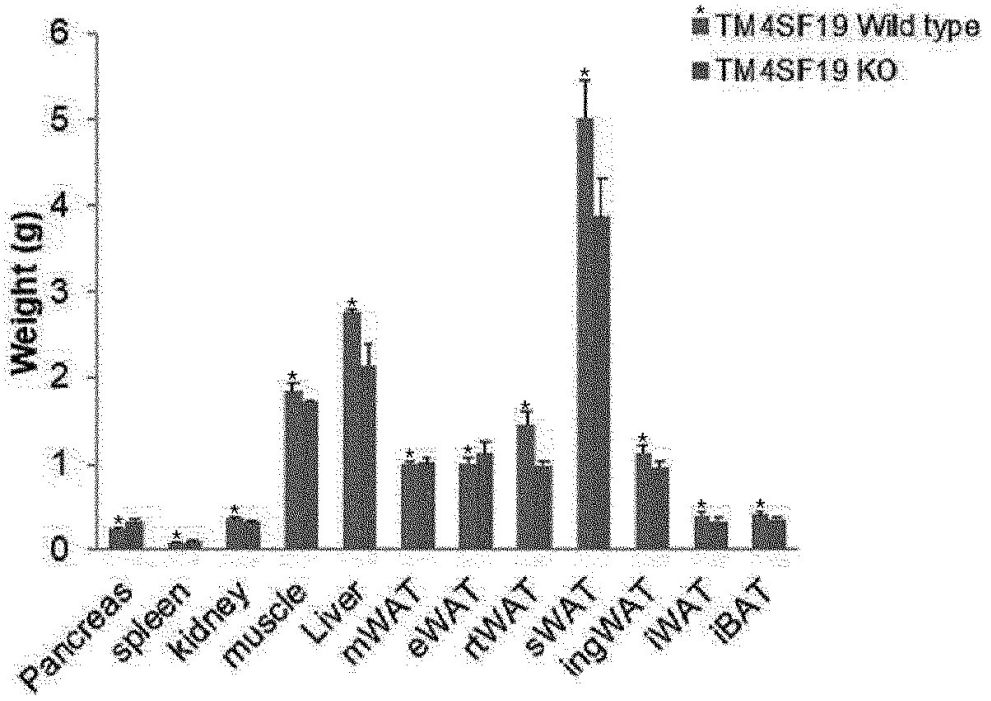
【FIG. 18】



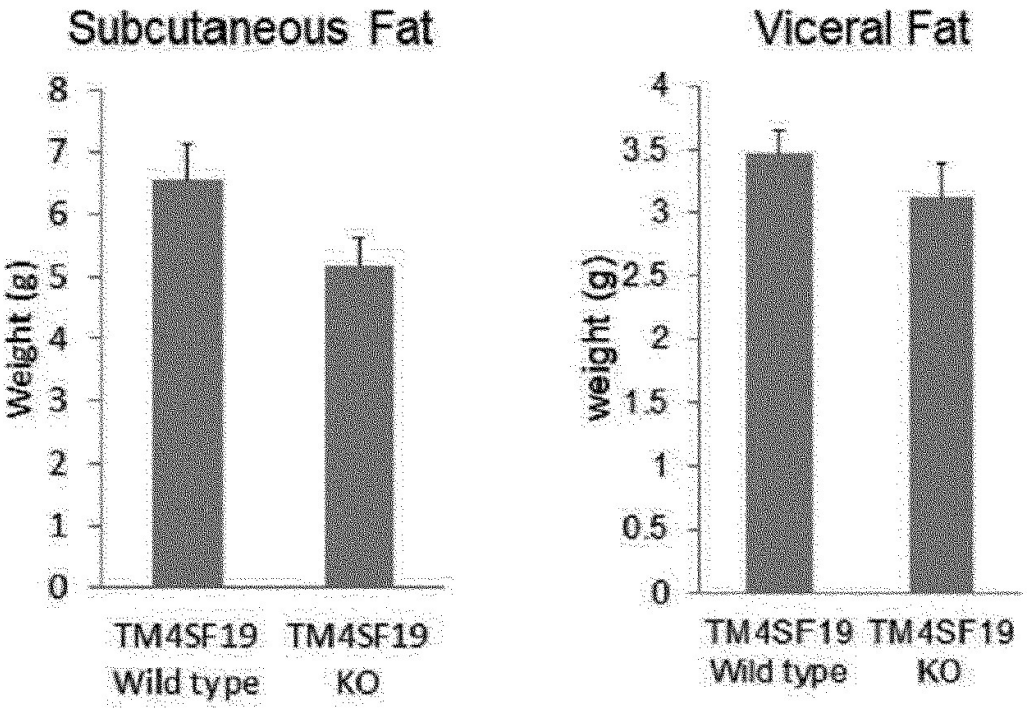
【FIG. 19A】



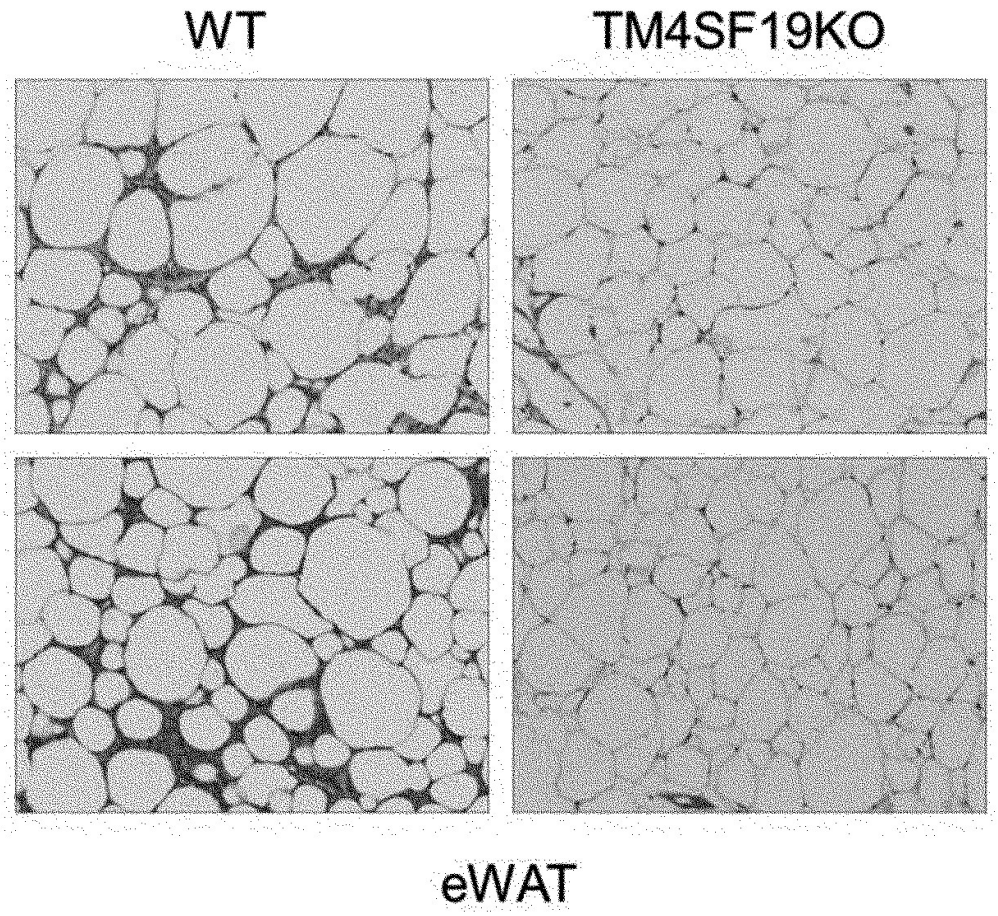
【FIG. 19B】



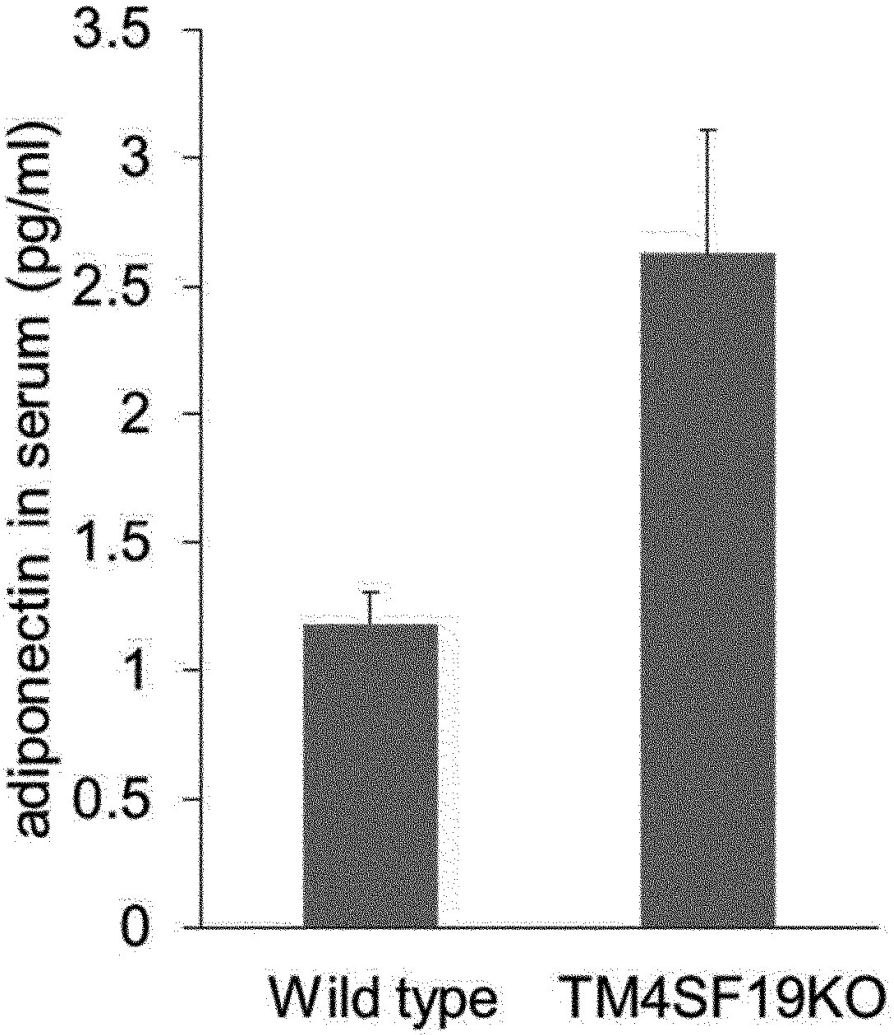
【FIG. 19C】



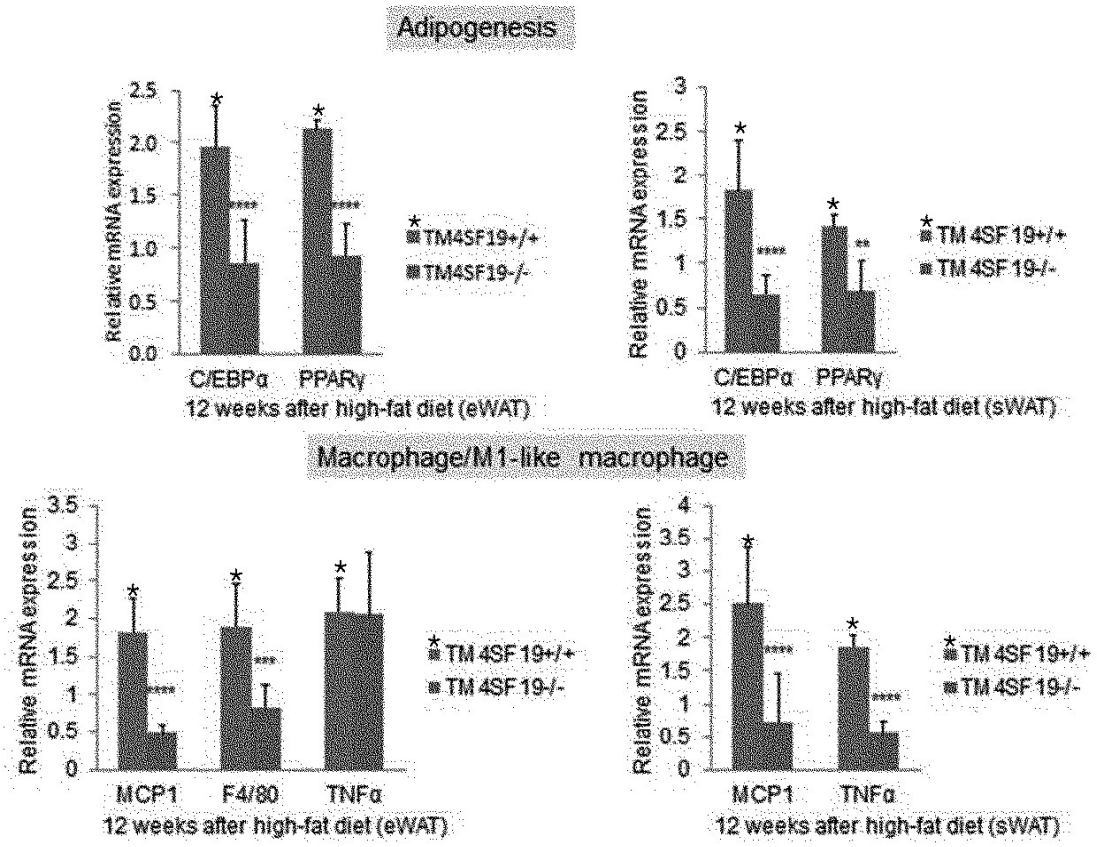
【FIG. 19D】



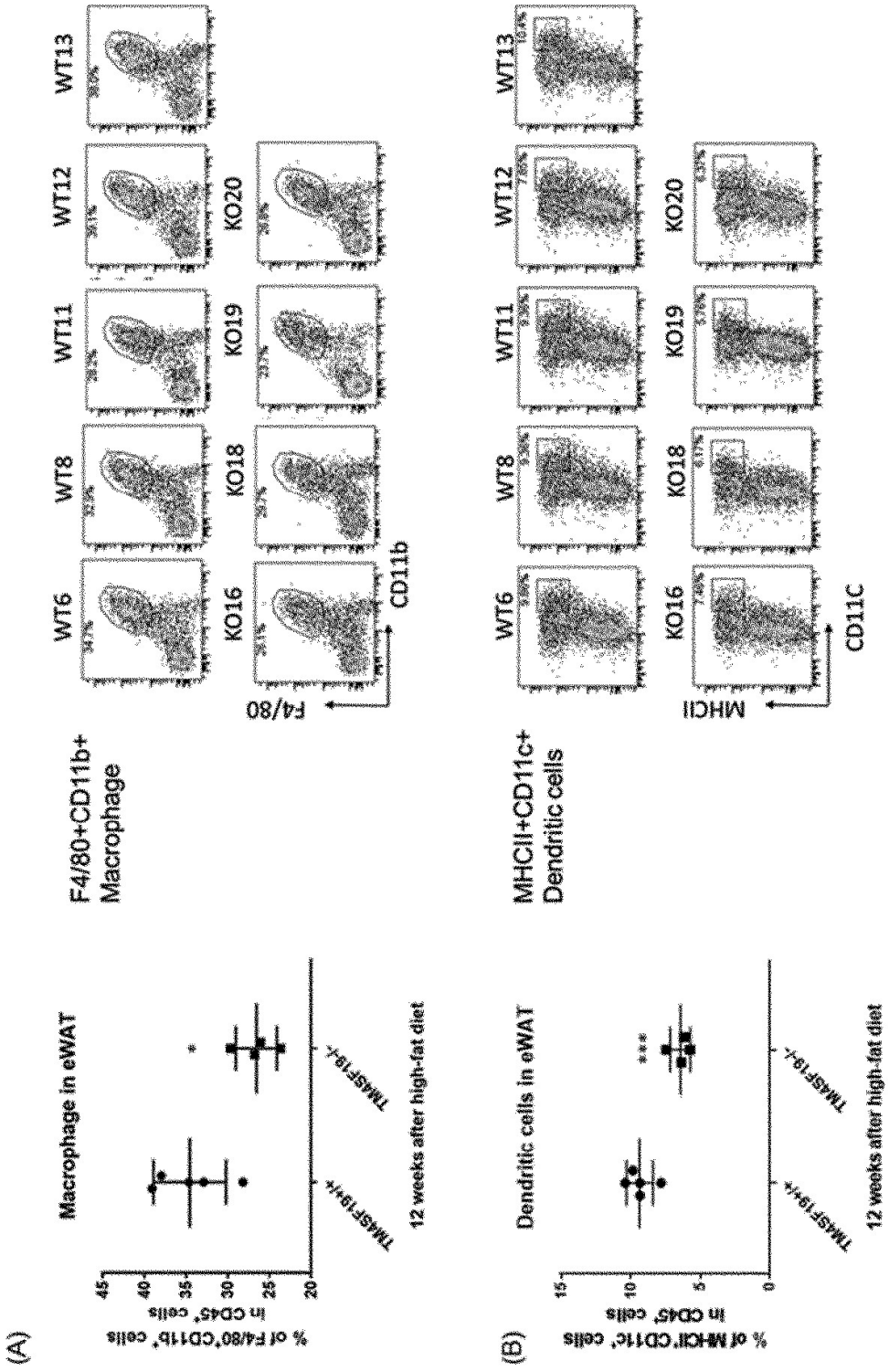
【FIG. 19E】


adiponectin in serum (pg/ml)
3.5
3
2.5
2
1.5
1
0.5
0
Wild type
TM4SF19KO

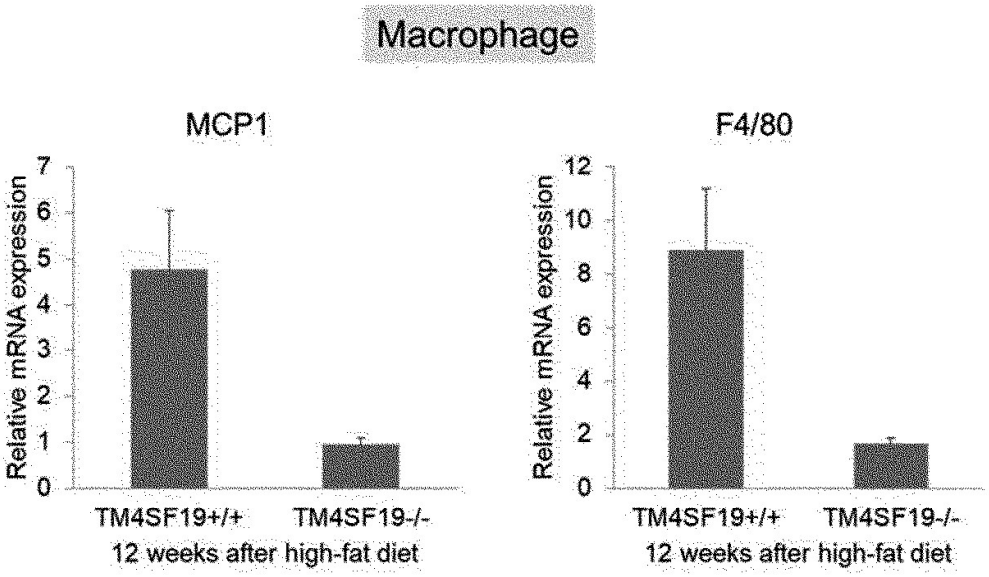
【FIG. 20】


Adipogenesis
Relative mRNA expression
TM4SF19+/+
TM4SF19-/-
C/EBPα
PPARγ
12 weeks after high-fat diet (eWAT)
12 weeks after high-fat diet (sWAT)
Macrophage/M1-like macrophage
MCP1
F4/80
TNFα

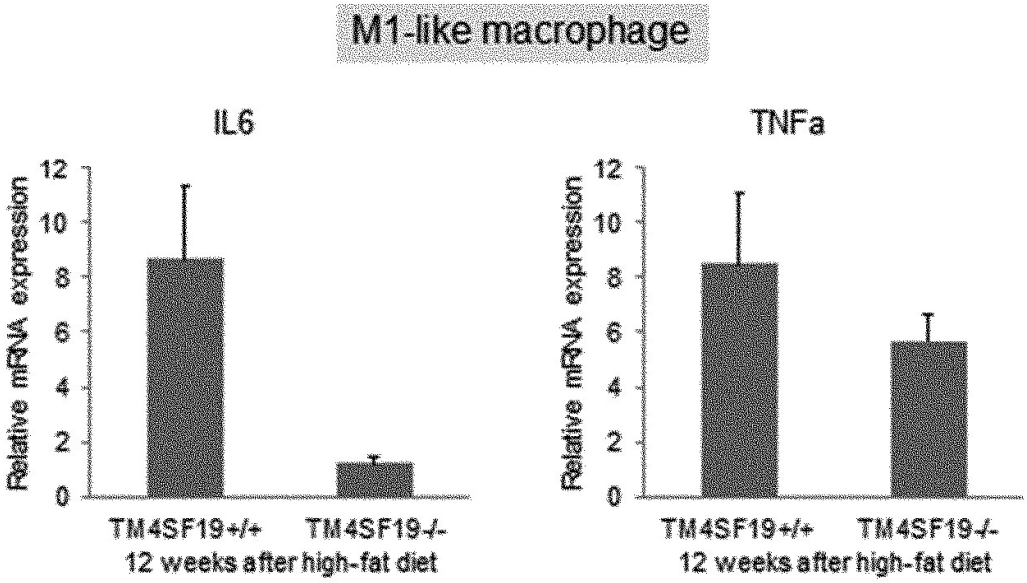
【FIG. 21】


(A)
Macrophage in eWAT
% of F4/80+CD11b+ cells in CD45+ cells
TMASF19+/+
TMASF19+/-
12 weeks after high-fat diet
F4/80+CD11b+
Macrophage
WT6
WT8
WT11
WT12
WT13
KO16
KO18
KO19
KO20
F4/80
CD11b
(B)
Dendritic cells in eWAT
% of MHCII+CD11c+ cells in CD45+ cells
TMASF19+/+
TMASF19+/-
12 weeks after high-fat diet
MHCII+CD11c+
Dendritic cells
WT6
WT8
WT11
WT12
WT13
KO16
KO18
KO19
KO20
MHCII
CD11C

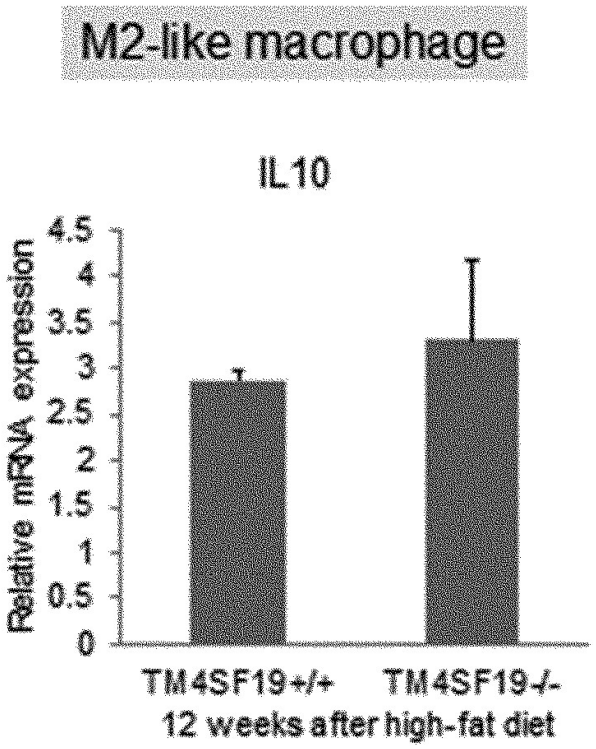
【FIG. 22A】



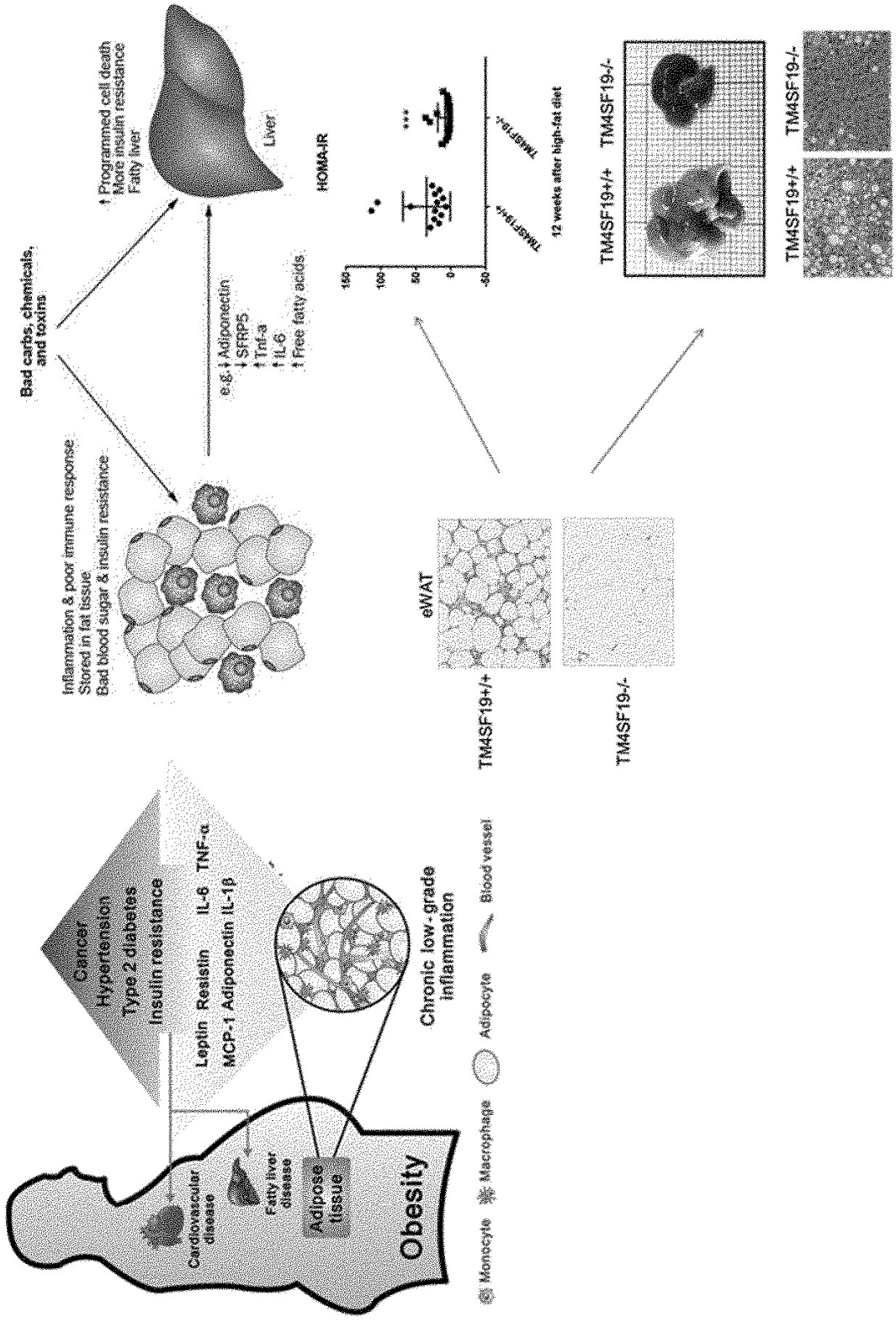
【FIG. 22B】



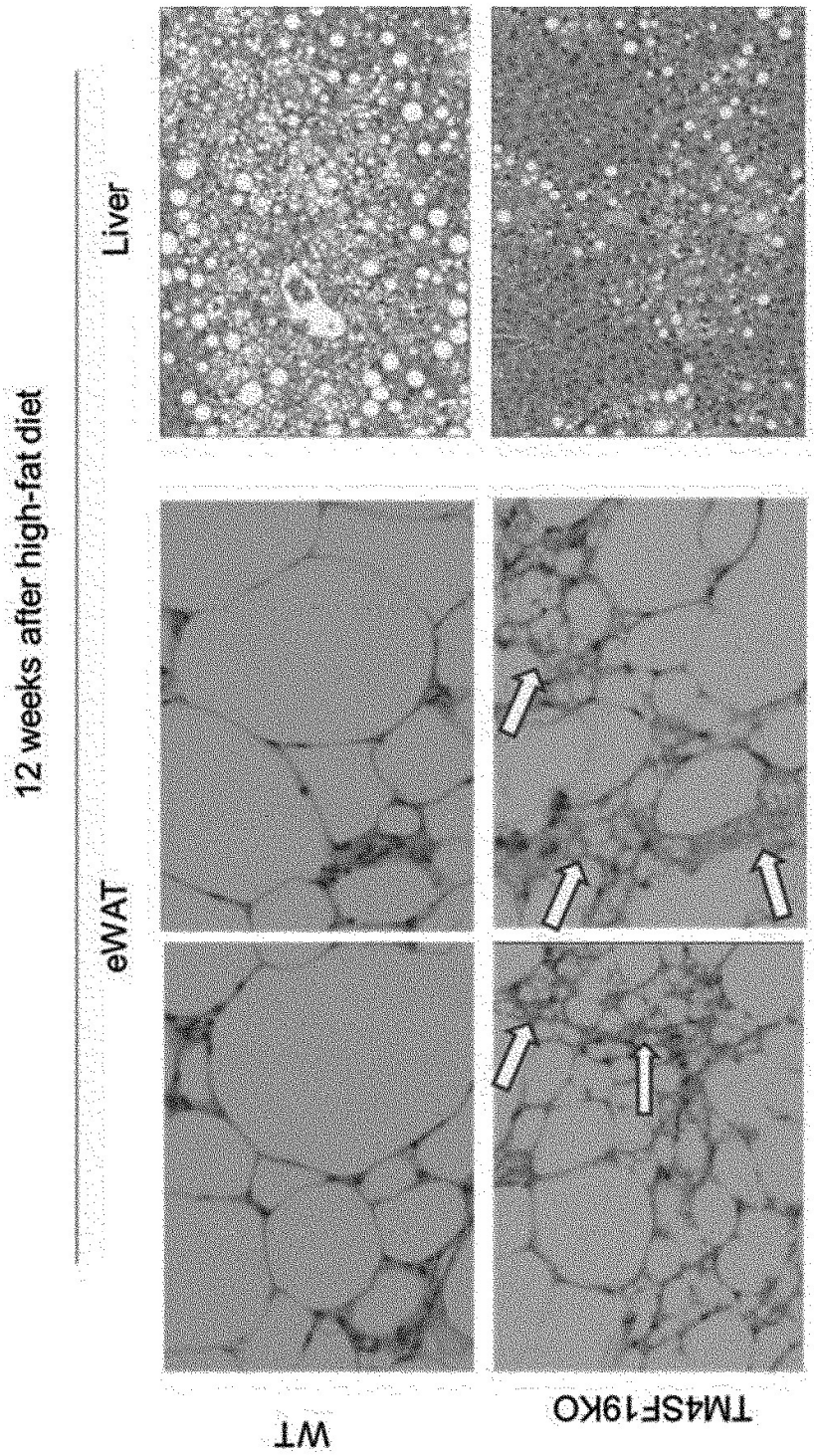
【FIG. 22C】


M2-like macrophage
IL10
Relative mRNA expression
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
TM4SF19+/+
TM4SF19-/-
12 weeks after high-fat diet

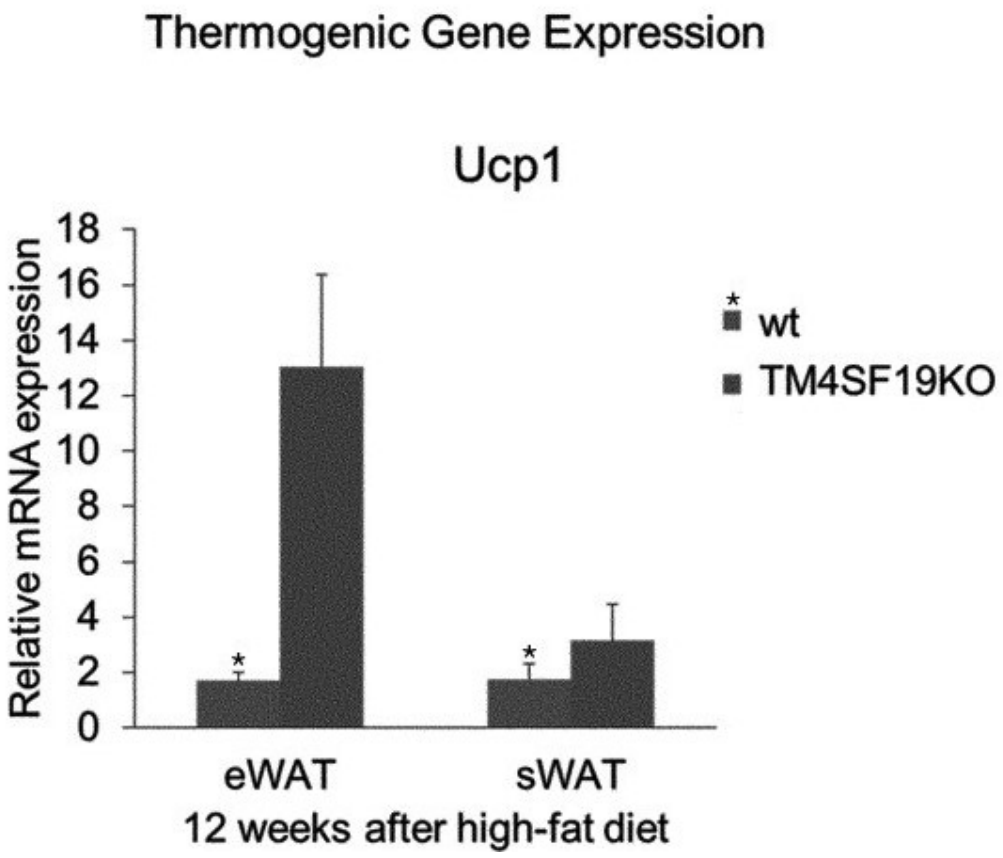
【FIG. 23】


Bad carbs, chemicals, and toxins
↑ Programmed cell death
More insulin resistance
Fatty liver
Liver
Inflammation & poor immune response
Stored in fat tissue
Bad blood sugar & insulin resistance
e.g. ↓ Adiponectin
↑ SFRP5
↑ Tnf-a
↑ IL-6
↑ Free fatty acids
HOMA-IR
150
100
50
0
-50
***
TM4SF19+/+
TM4SF19-/-
12 weeks after high-fat diet
eWAT
TM4SF19+/+
TM4SF19-/-
TM4SF19+/+
TM4SF19-/-
TM4SF19+/+
TM4SF19-/-
Cancer
Hypertension
Type 2 diabetes
Insulin resistance
Leptin Resistin IL-6 TNF-α
MCP-1 Adiponectin IL-1β
Chronic low-grade inflammation
Cardiovascular disease
Fatty liver disease
Adipose tissue
Obesity
Monocyte
Macrophage
Adipocyte
Blood vessel

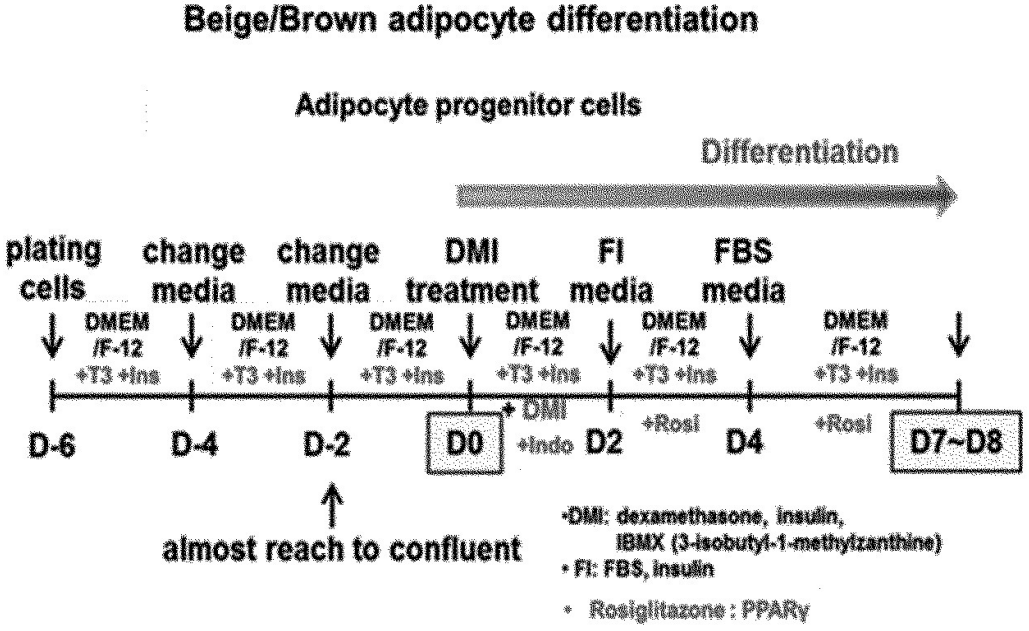
【FIG. 24A】



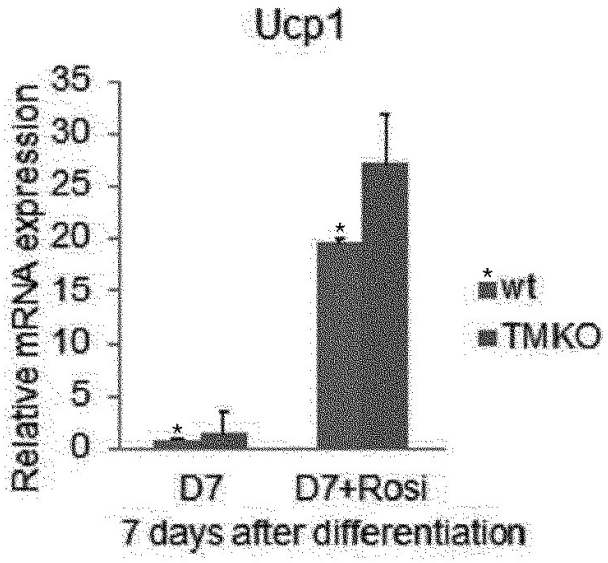
【FIG. 24B】



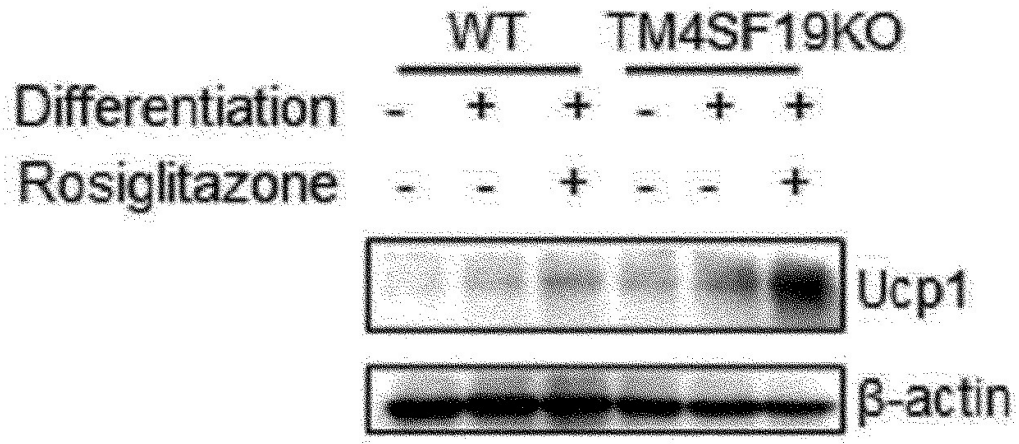
【FIG. 24C】



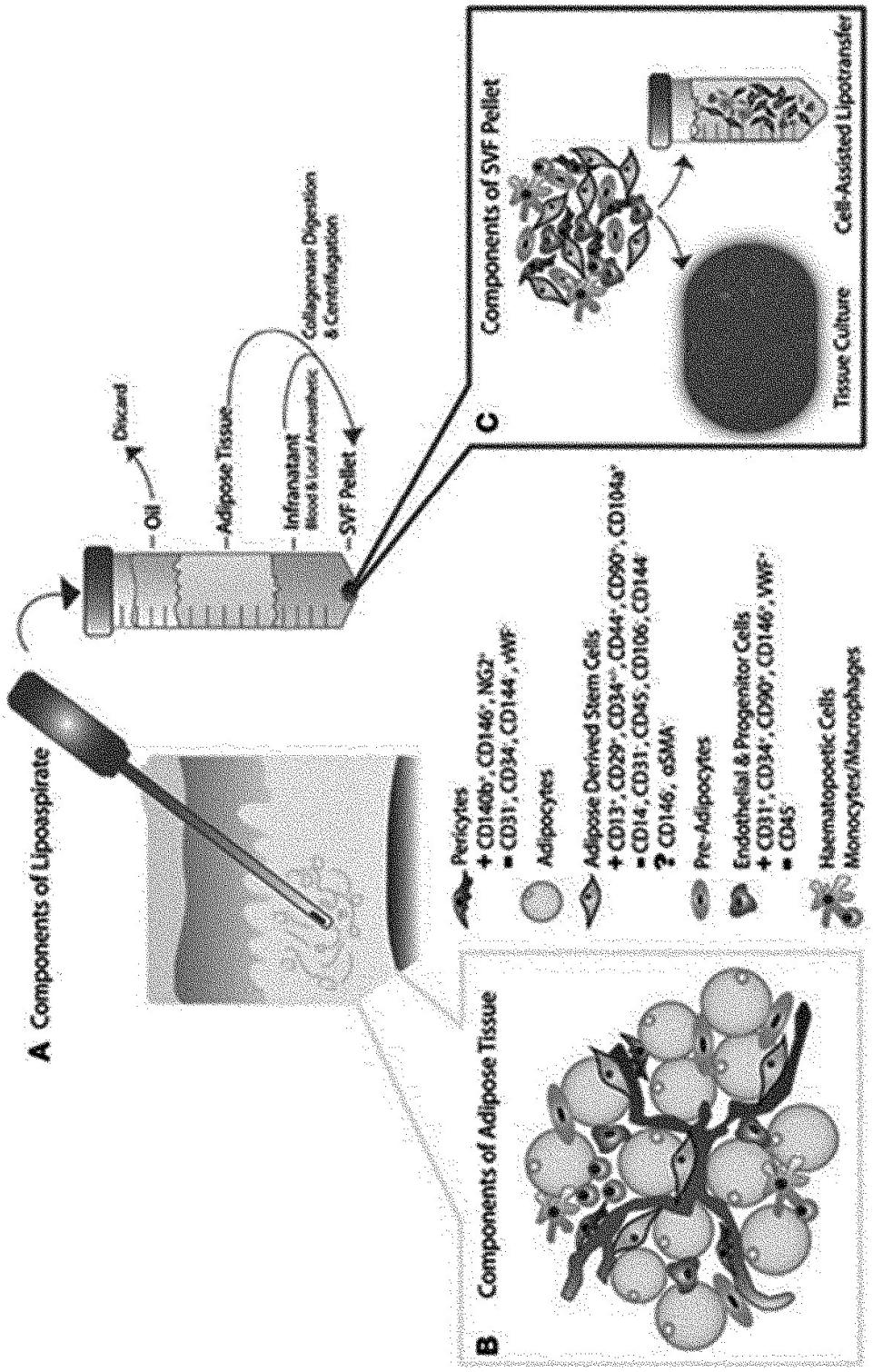
【FIG. 24D】



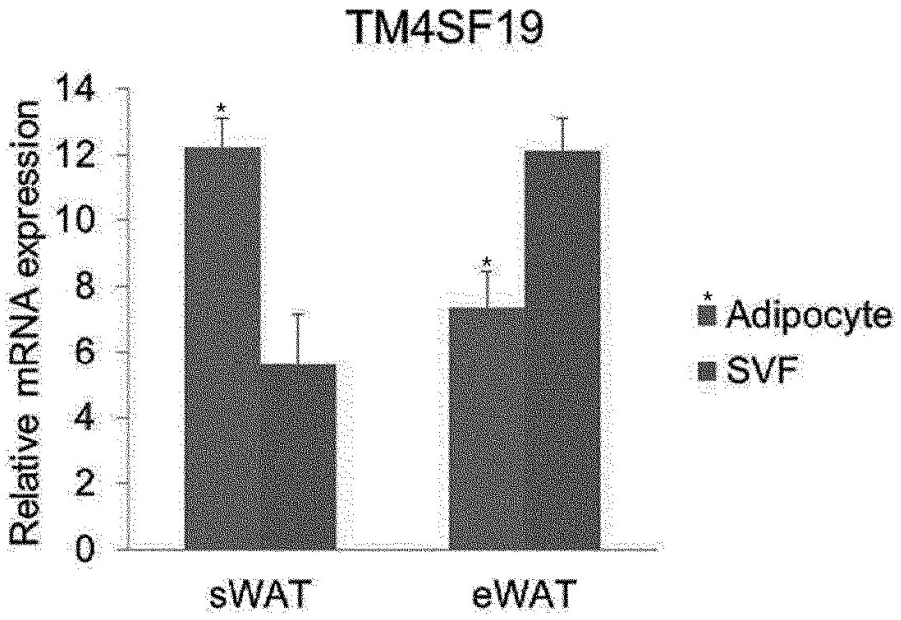
【FIG. 24E】



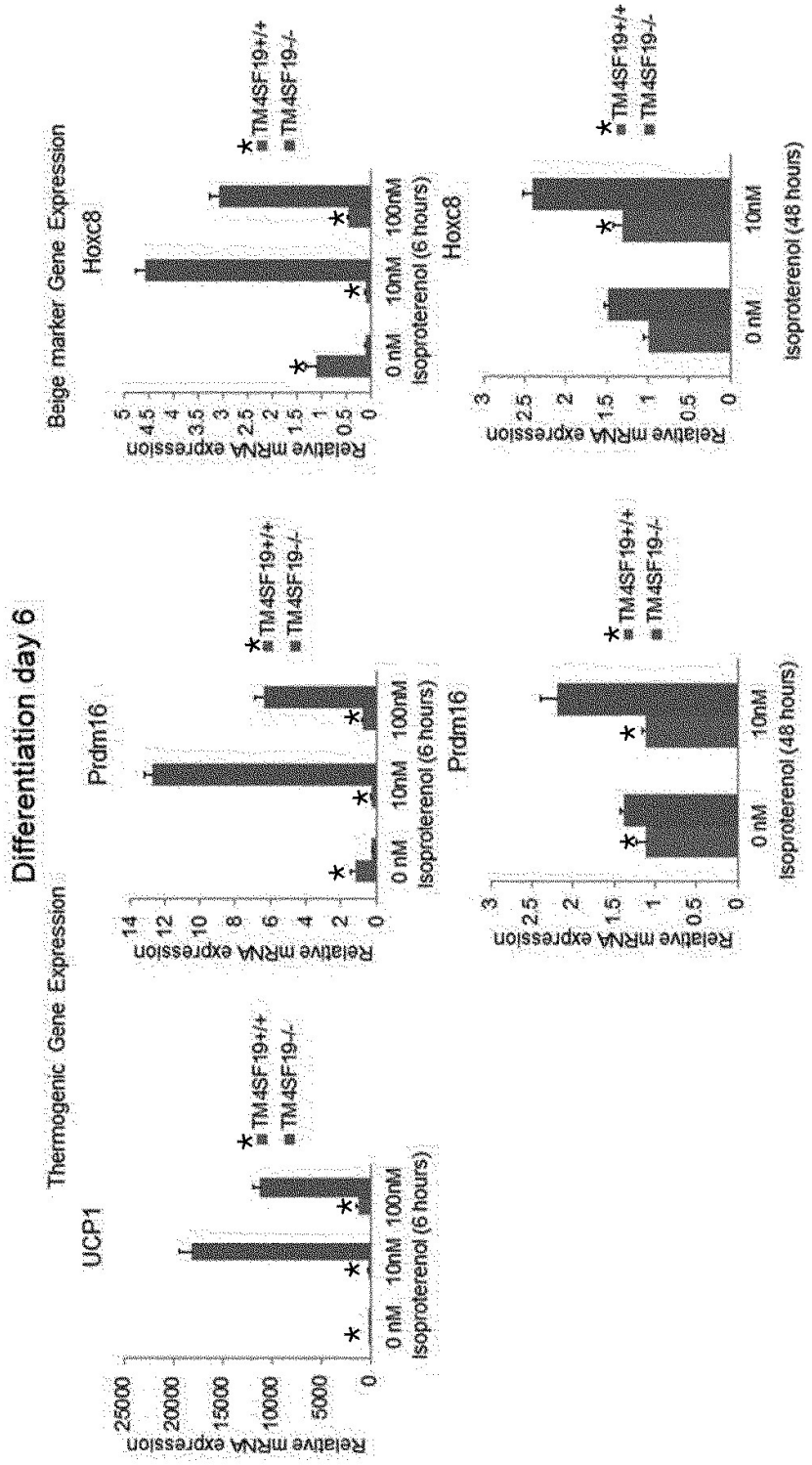
【FIG. 25A】


A Components of Lipospirate
Oil
Discard
Adipose Tissue
Infranatant
Blood & Local Anesthetic
Collagenase Digestion
& Centrifugation
SVF Pellet
B Components of Adipose Tissue
Pericytes
+ CD140b+, CD146+, NG2+
- CD31-, CD34-, CD144-, vWF-
Adipocytes
Adipose Derived Stem Cells
+ CD13+, CD29+, CD34+/-, CD44+, CD90+, CD104+
- CD14-, CD31-, CD45-, CD106-, CD144-
? CD146-, αSMA-
Pre-Adipocytes
Endothelial & Progenitor Cells
+ CD31+, CD34+, CD90+, CD146+, vWF+
- CD45-
Haematopoetic Cells
Monocytes/Macrophages
C Components of SVF Pellet
Tissue Culture
Cell-Assisted Lipotransfer

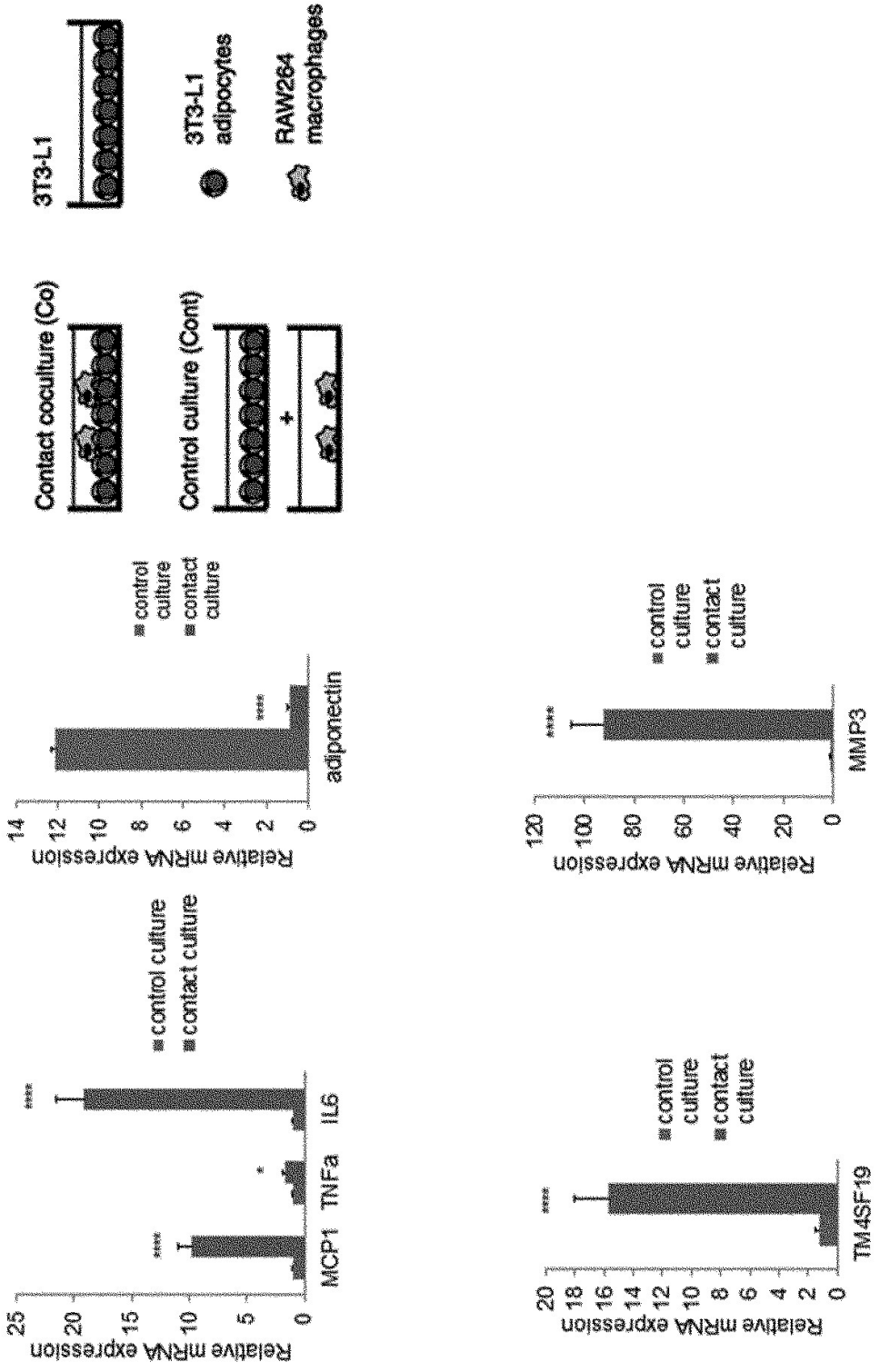
【FIG. 25b】


TM4SF19
Relative mRNA expression
14
12
10
8
6
4
2
0
*
*
sWAT
eWAT
* Adipocyte
SVF

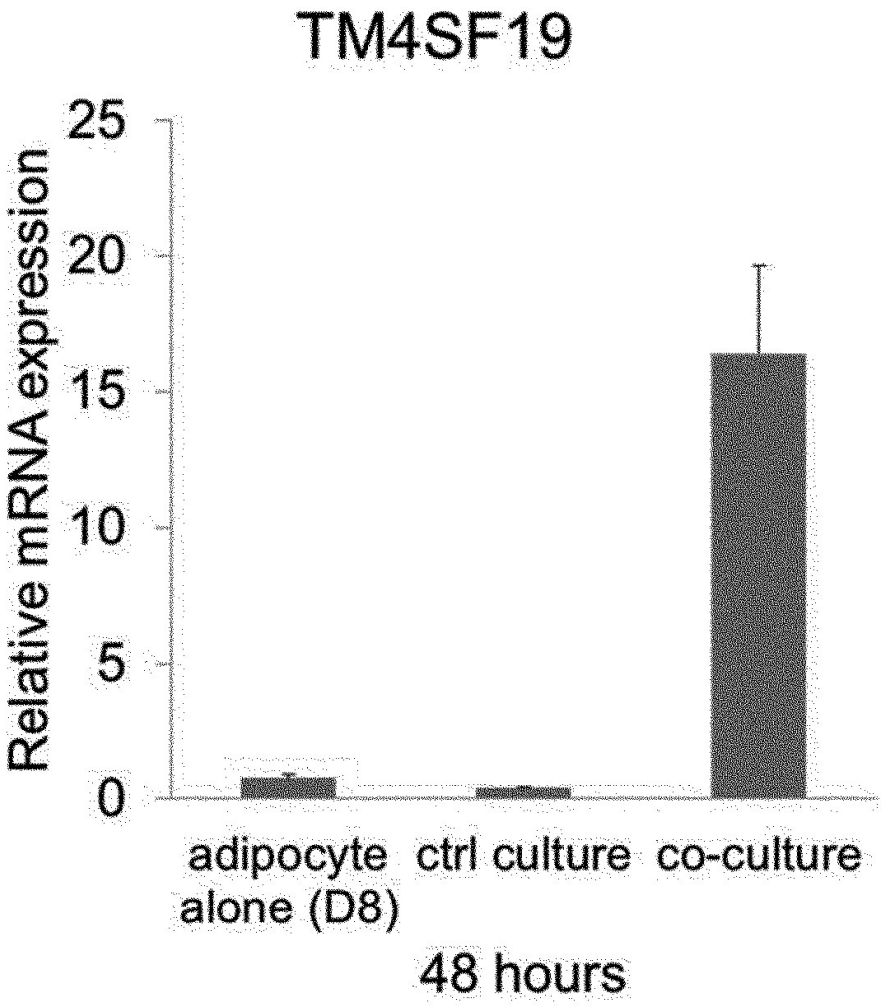
【FIG. 26】


Differentiation day 6
Thermogenic Gene Expression
UCP1
Relative mRNA expression
25000
20000
15000
10000
5000
0
0 nM 10nM 100nM
Isoproterenol (6 hours)
*TM4SF19+/+
TM4SF19-/-
Prdm16
Relative mRNA expression
14
12
10
8
6
4
2
0
0 nM 10nM 100nM
Isoproterenol (6 hours)
*TM4SF19+/+
TM4SF19-/-
Beige marker Gene Expression
Hoxc8
Relative mRNA expression
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 nM 10nM 100nM
Isoproterenol (6 hours)
*TM4SF19+/+
TM4SF19-/-
Prdm16
Relative mRNA expression
3
2.5
2
1.5
1
0.5
0
0 nM 10nM
Isoproterenol (48 hours)
*TM4SF19+/+
TM4SF19-/-
Hoxc8
Relative mRNA expression
3
2.5
2
1.5
1
0.5
0
0 nM 10nM
Isoproterenol (48 hours)
*TM4SF19+/+
TM4SF19-/-

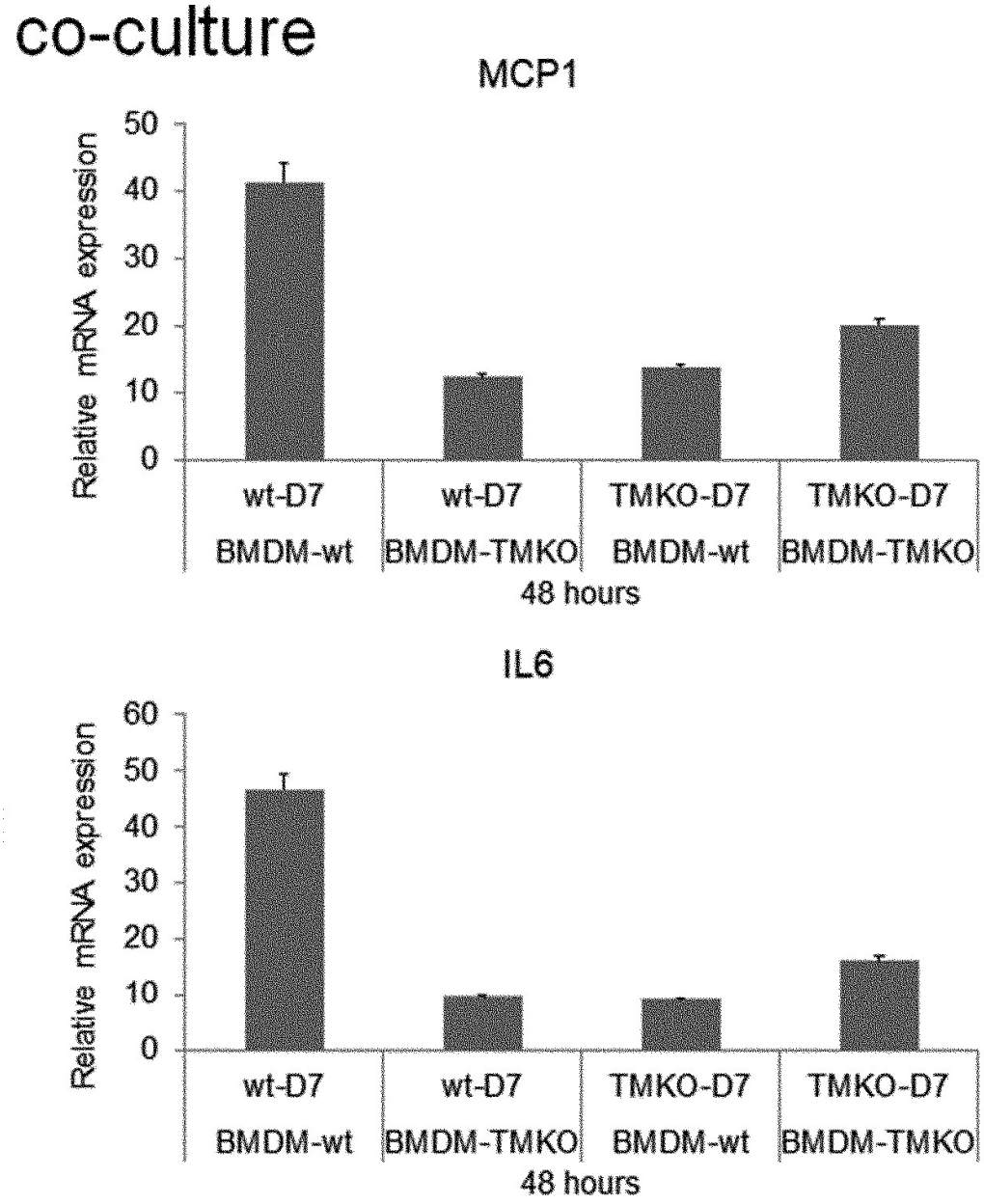
【FIG. 27】


3T3-L1
3T3-L1 adipocytes
RAW264 macrophages
Contact coculture (Co)
Control culture (Cont)
control culture
contact culture
Relative mRNA expression
adiponectin
MCP1
TNFa
IL6
TM4SF19
MMP3

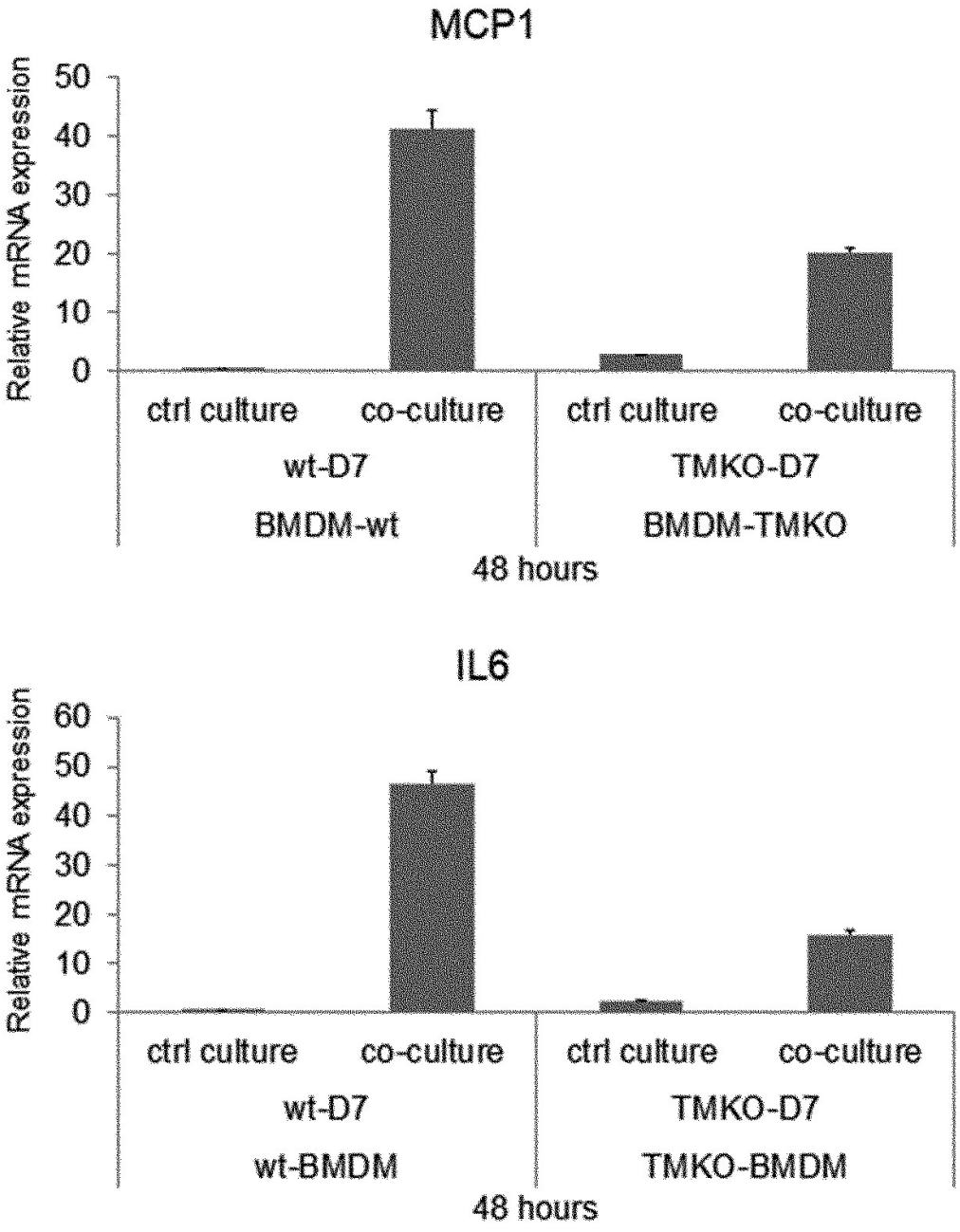
【FIG. 28】


TM4SF19
Relative mRNA expression
25
20
15
10
5
0
adipocyte alone (D8)
ctrl culture
co-culture
48 hours

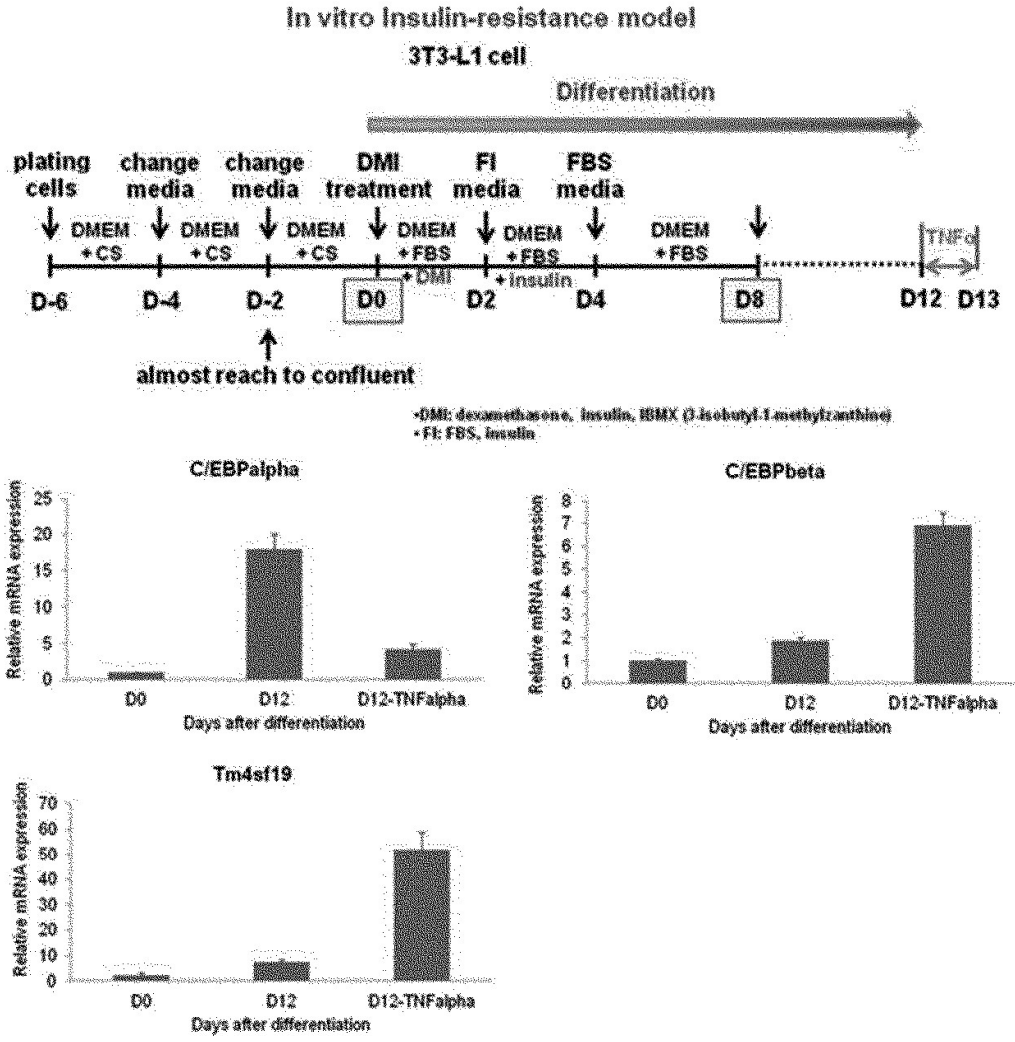
【FIG. 29】


co-culture
MCP1
Relative mRNA expression
50
40
30
20
10
0
wt-D7
BMDM-wt
wt-D7
BMDM-TMKO
TMKO-D7
BMDM-wt
TMKO-D7
BMDM-TMKO
48 hours
IL6
Relative mRNA expression
60
50
40
30
20
10
0
wt-D7
BMDM-wt
wt-D7
BMDM-TMKO
TMKO-D7
BMDM-wt
TMKO-D7
BMDM-TMKO
48 hours

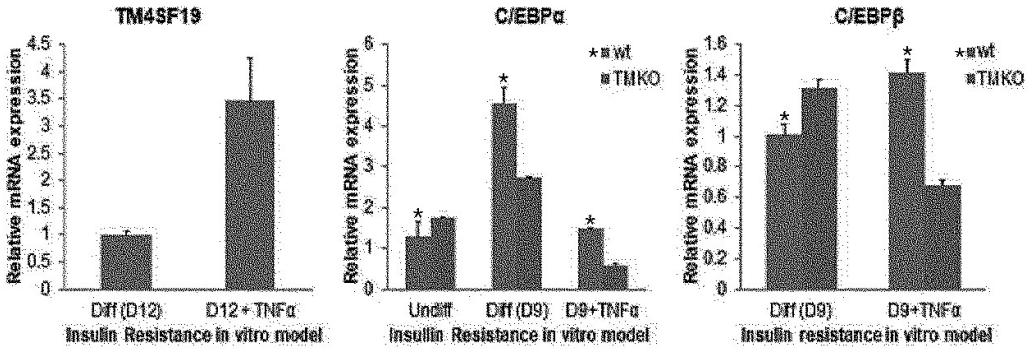
【FIG. 30】


MCP1
Relative mRNA expression
50
40
30
20
10
0
ctrl culture
co-culture
ctrl culture
co-culture
wt-D7
TMKO-D7
BMDM-wt
BMDM-TMKO
48 hours
IL6
Relative mRNA expression
60
50
40
30
20
10
0
ctrl culture
co-culture
ctrl culture
co-culture
wt-D7
TMKO-D7
wt-BMDM
TMKO-BMDM
48 hours

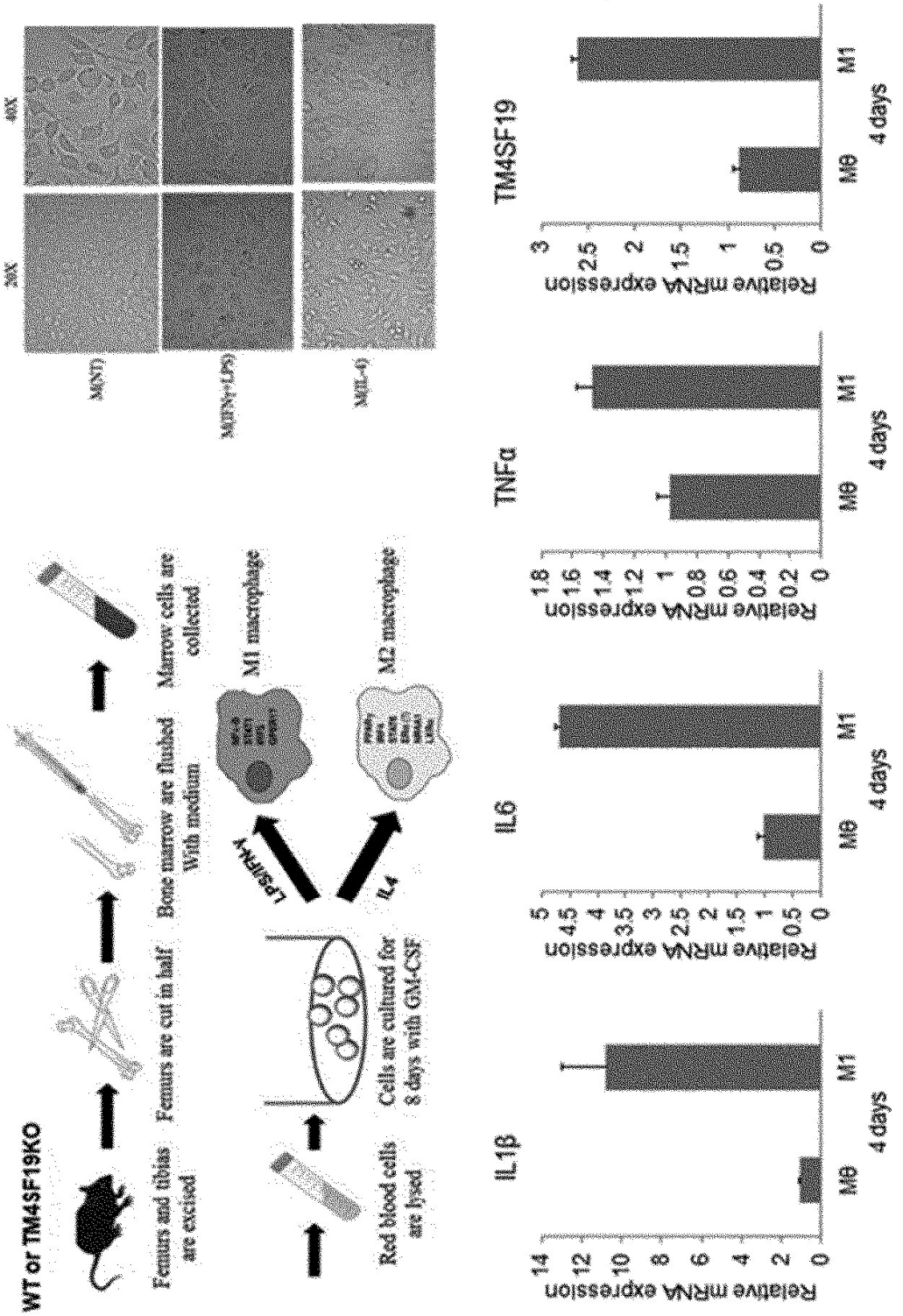
【FIG. 31】


In vitro Insulin-resistance model
3T3-L1 cell
Differentiation
plating cells
change media
change media
DMI treatment
FI media
FBS media
DMEM +CS
DMEM +FBS
+DMI
+insulin
TNFα
D-6
D-4
D-2
D0
D2
D4
D8
D12
D13
almost reach to confluent
•DMI: dexamethasone, insulin, IBMX (3-isobutyl-1-methylxanthine)
•FI: FBS, insulin
C/EBPalpha
C/EBPbeta
Tm4sf19
Relative mRNA expression
D0
D12
D12-TNFalpha
Days after differentiation

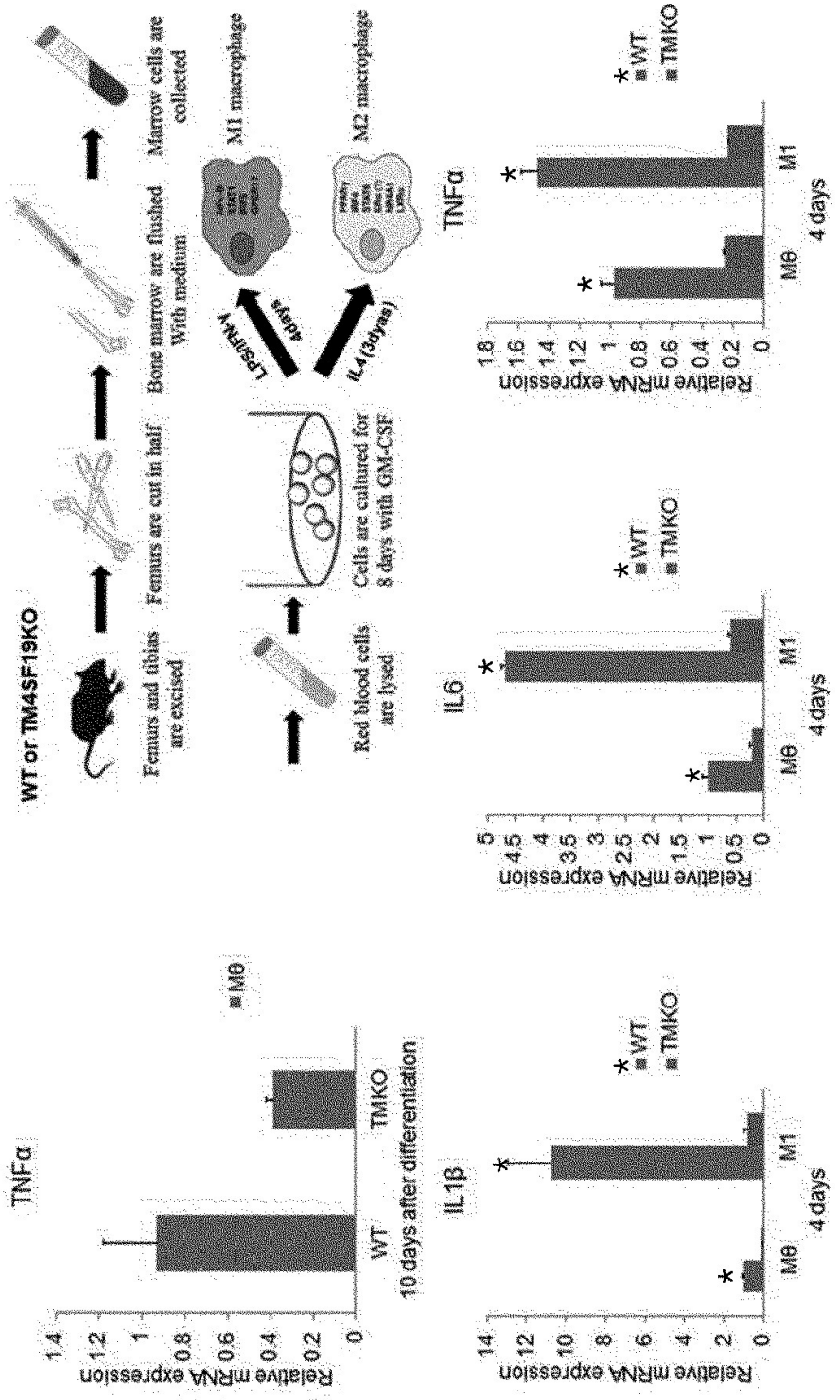
【FIG. 32】


TM4SF19
C/EBPα
C/EBPβ
Relative mRNA expression
wt
TMKO
Diff (D12)
D12+TNFα
Insulin Resistance in vitro model
Undiff
Diff (D9)
D9+TNFα
Insullin Resistance in vitro model
Insulin resistance in vitro model

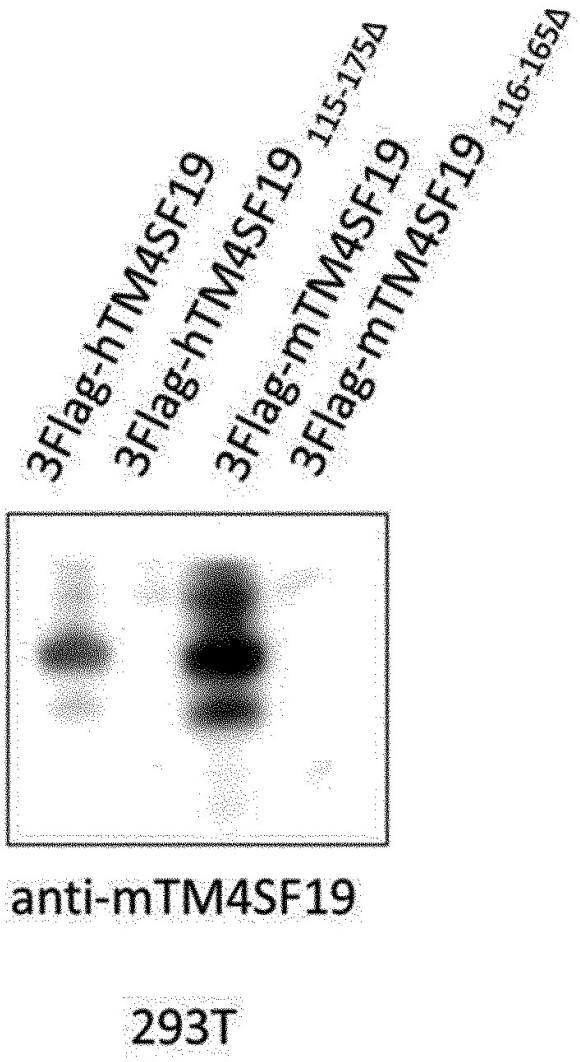
【FIG. 33】


WT or TM4SF19KO
Femurs and tibias are excised
Femurs are cut in half
Bone marrow are flushed With medium
Marrow cells are collected
Red blood cells are lysed
Cells are cultured for 8 days with GM-CSF
LPS/IFN-γ
IL4
M1 macrophage
M2 macrophage
M(Ø)
M(IFN-γ+LPS)
M(IL-4)
20X
40X
IL1β
IL6
TNFα
TM4SF19
Relative mRNA expression
Mø
M1
4 days

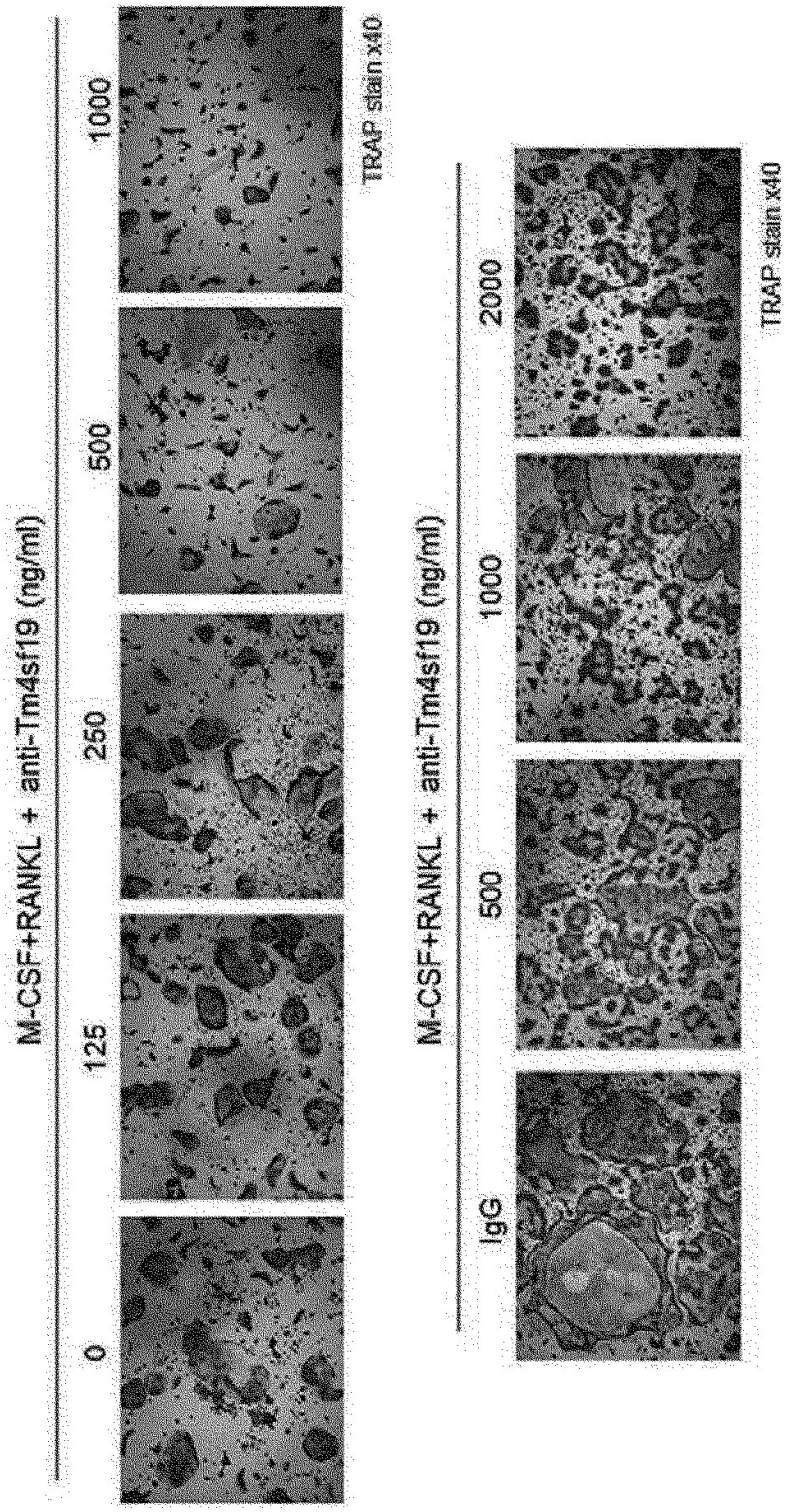
【FIG. 34】


WT or TM4SF19KO
Femurs and tibias are excised
Femurs are cut in half
Bone marrow are flushed With medium
Marrow cells are collected
Red blood cells are lysed
Cells are cultured for 8 days with GM-CSF
LPS/IFN-γ
4days
IL4 (3days)
M1 macrophage
M2 macrophage
TNFα
IL6
IL1β
Relative mRNA expression
WT
TMKO
MΘ
M1
4 days
10 days after differentiation

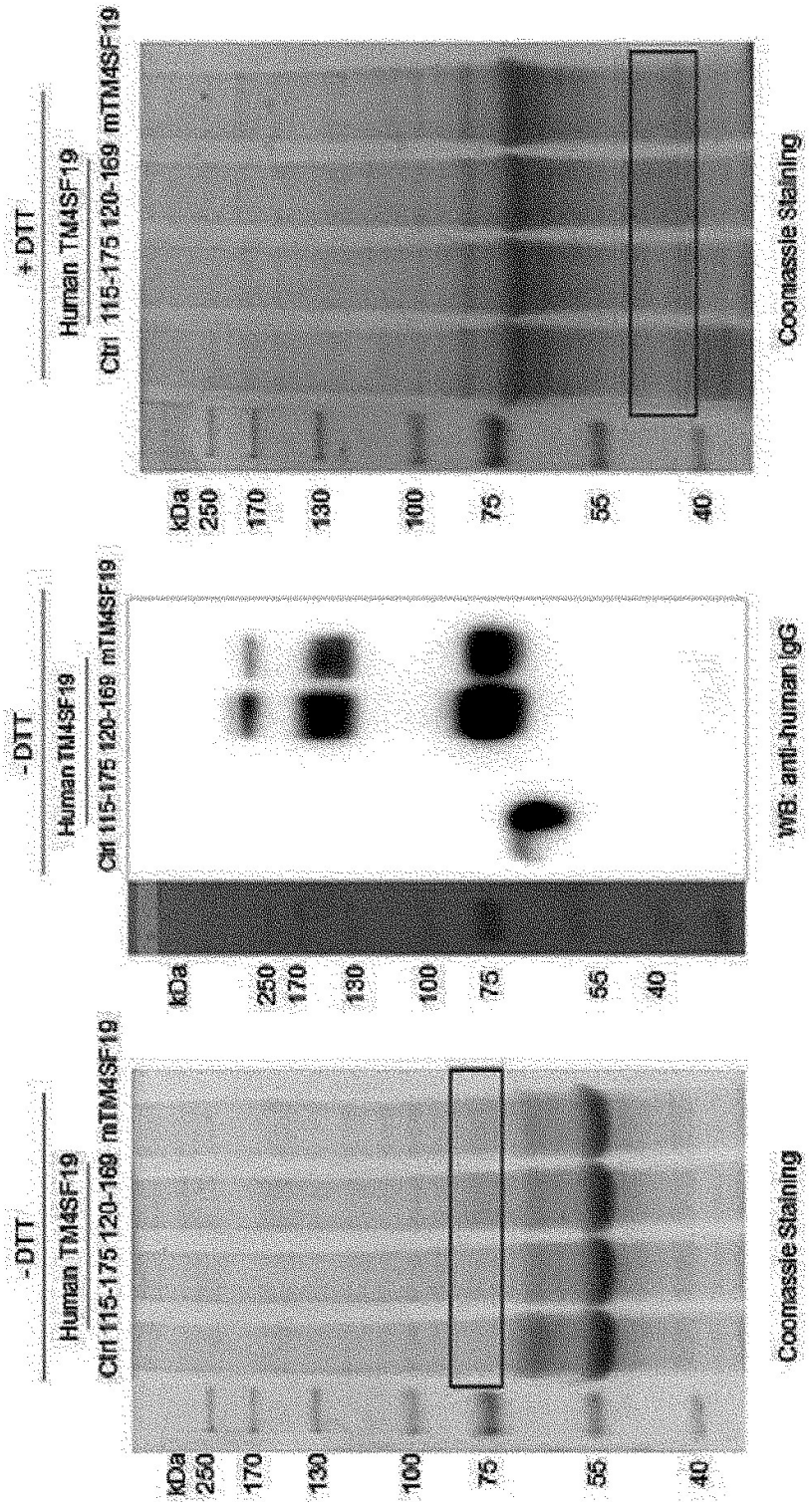
【FIG. 35】


3Flag-hTM4SF19
3Flag-hTM4SF19 115-175Δ
3Flag-mTM4SF19
3Flag-mTM4SF19 116-165Δ
anti-mTM4SF19
293T

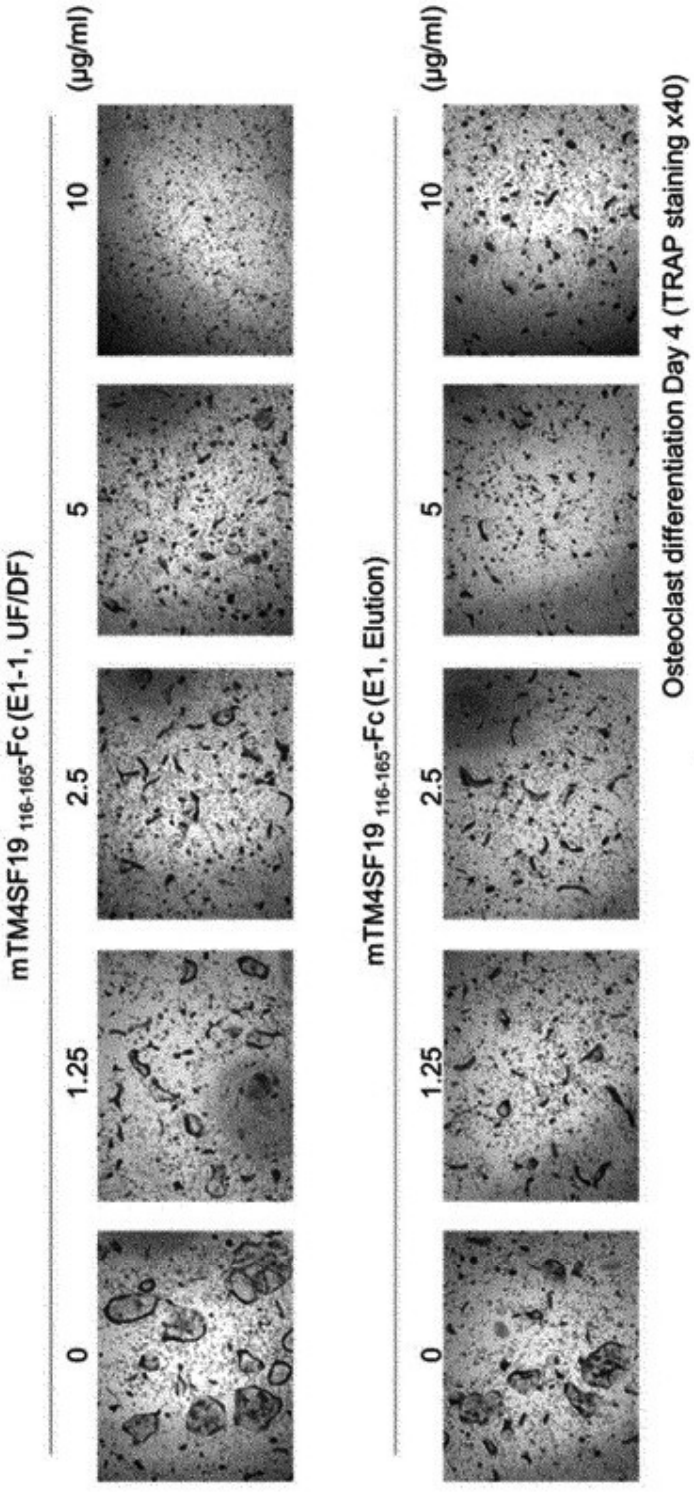
【FIG. 36】


M-CSF+RANKL + anti-Tm4sf19 (ng/ml)
0
125
250
500
1000
TRAP stain x40
M-CSF+RANKL + anti-Tm4sf19 (ng/ml)
IgG
500
1000
2000
TRAP stain x40

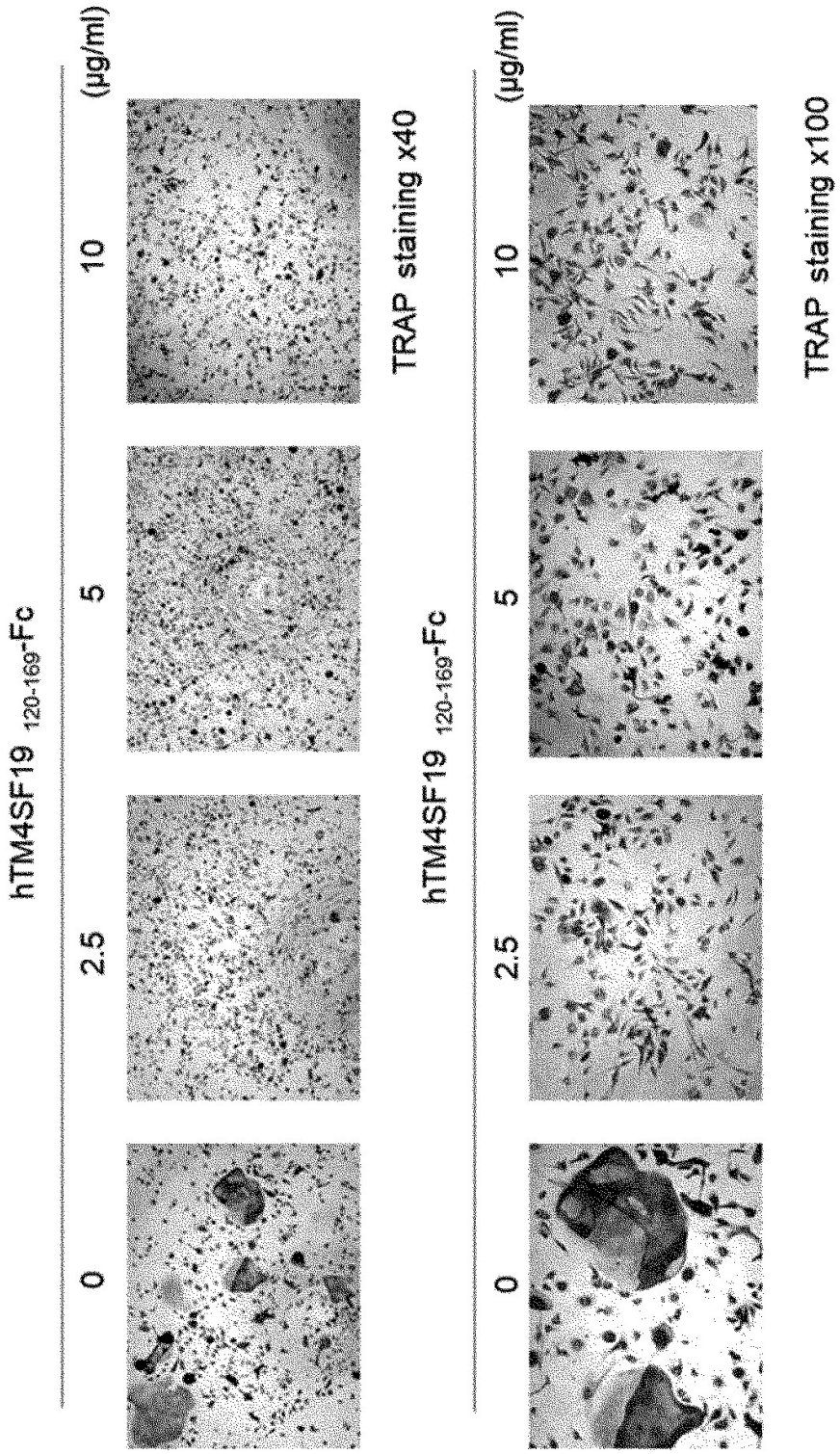
【FIG. 37】


- DTT
Human TM4SF19
Ctrl 115-175 120-169 mTM4SF19
kDa
250
170
130
100
75
55
40
Coomassie Staining
- DTT
Human TM4SF19
Ctrl 115-175 120-169 mTM4SF19
kDa
250
170
130
100
75
55
40
WB: anti-human IgG
+ DTT
Human TM4SF19
Ctrl 115-175 120-169 mTM4SF19
kDa
250
170
130
100
75
55
40
Coomassie Staining

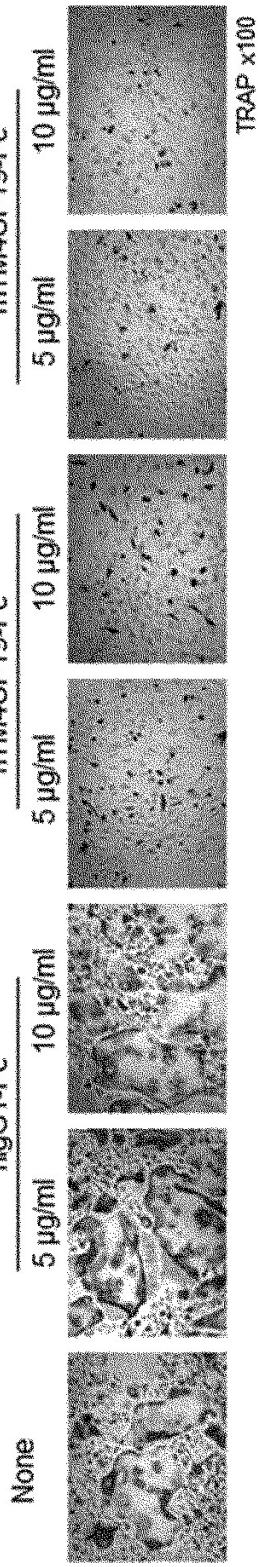
【FIG. 38A】


mTM4SF19 116-165-Fc (E1-1, UF/DF)
mTM4SF19 116-165-Fc (E1, Elution)
0
1.25
2.5
5
10
(μg/ml)
Osteoclast differentiation Day 4 (TRAP staining x40)

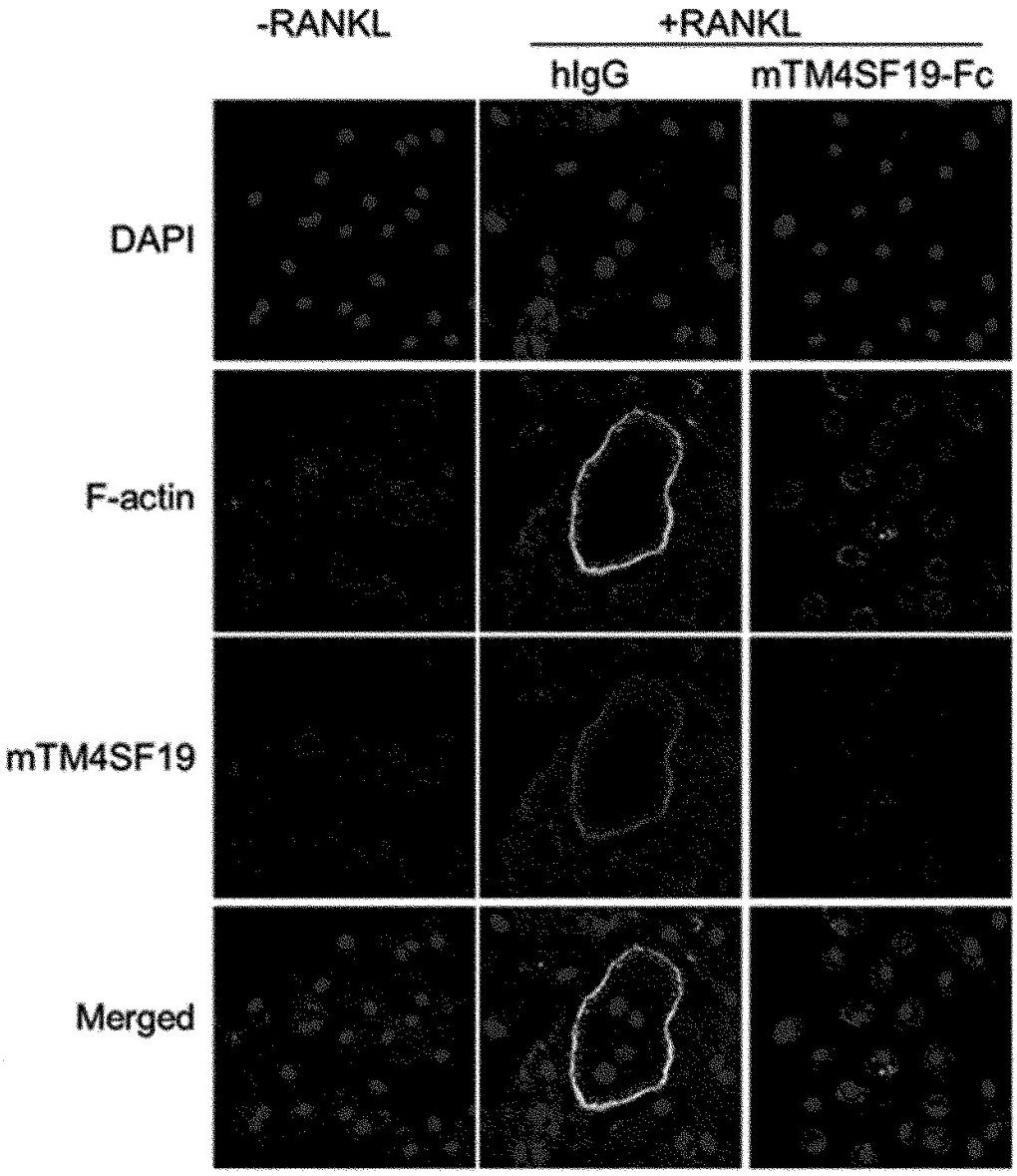
【FIG. 38B】


hTM4SF19 120-169-Fc
0
2.5
5
10
(μg/ml)
TRAP staining x40
hTM4SF19 120-169-Fc
0
2.5
5
10
(μg/ml)
TRAP staining x100

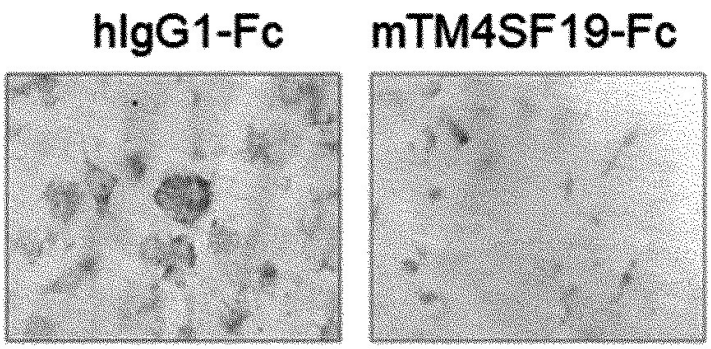
【FIG. 38C】


None
hIgG1-Fc
5 μg/ml
10 μg/ml
hTM4SF19-Fc
5 μg/ml
10 μg/ml
mTM4SF19-Fc
5 μg/ml
10 μg/ml
TRAP x100

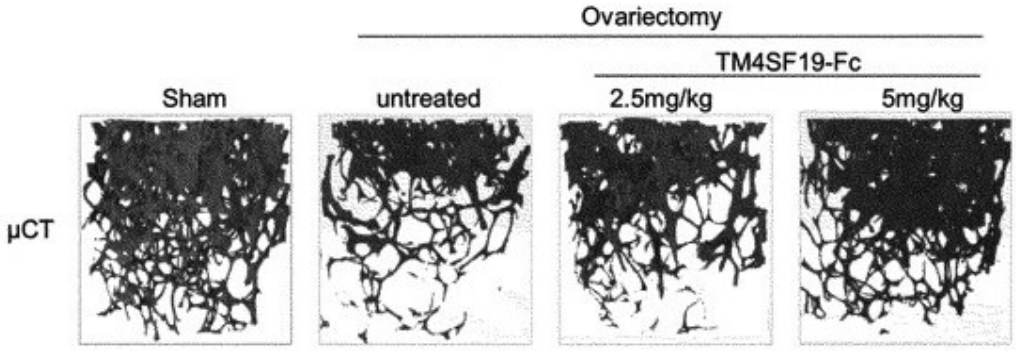
【FIG. 38D】



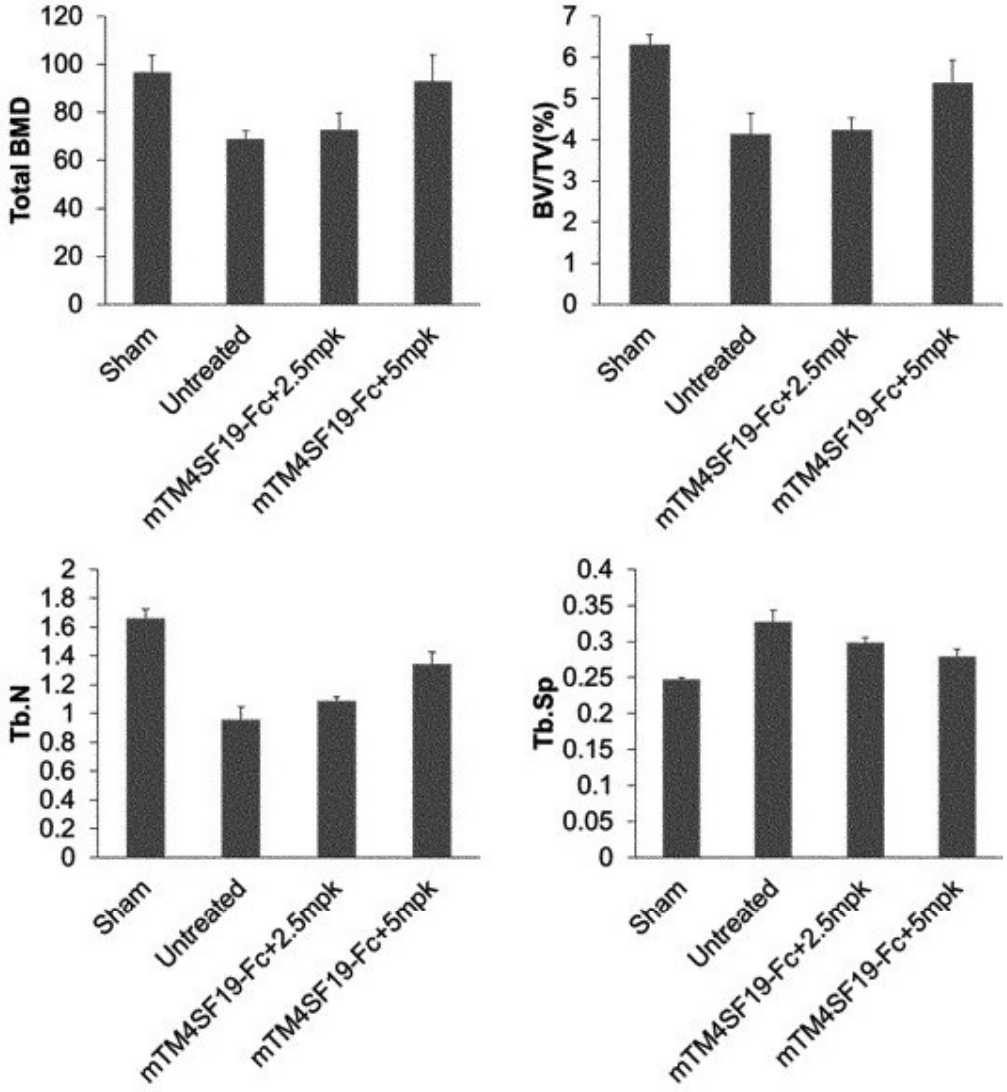
【FIG. 38E】



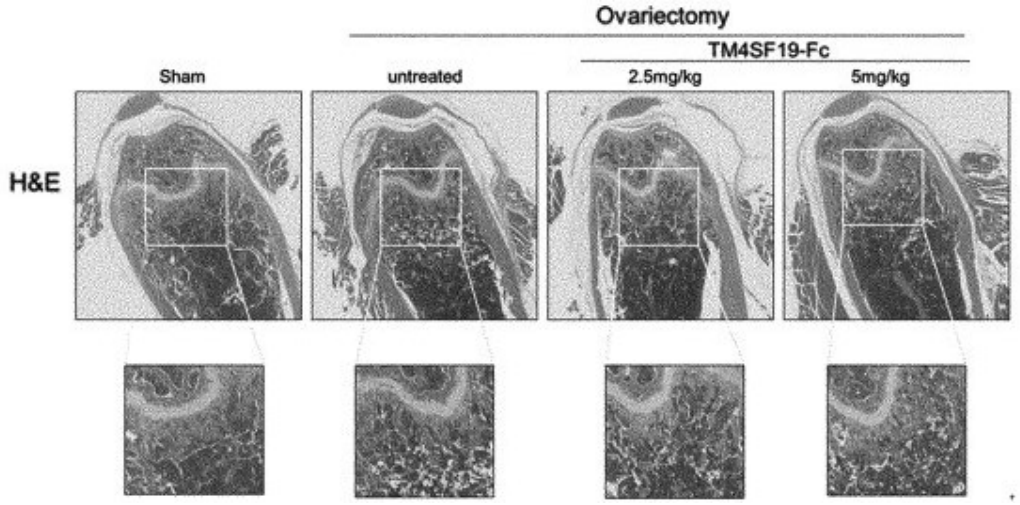
【FIG. 39A】



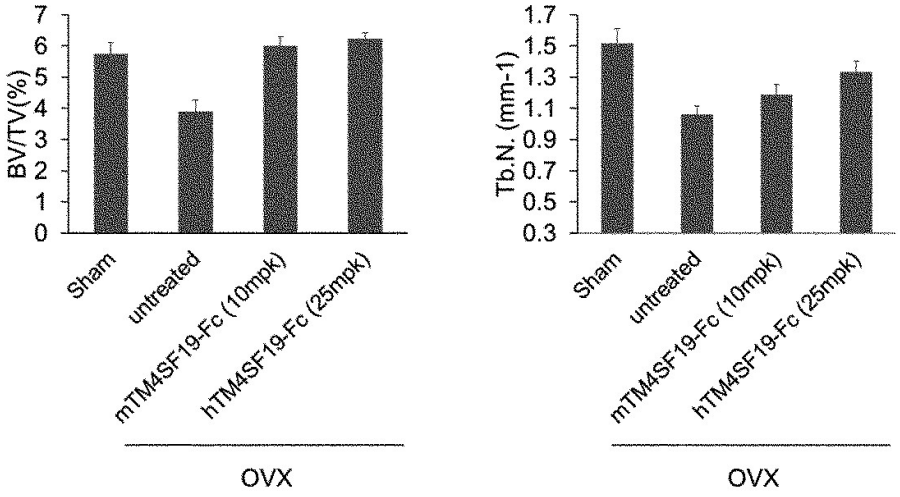
【FIG. 39B】



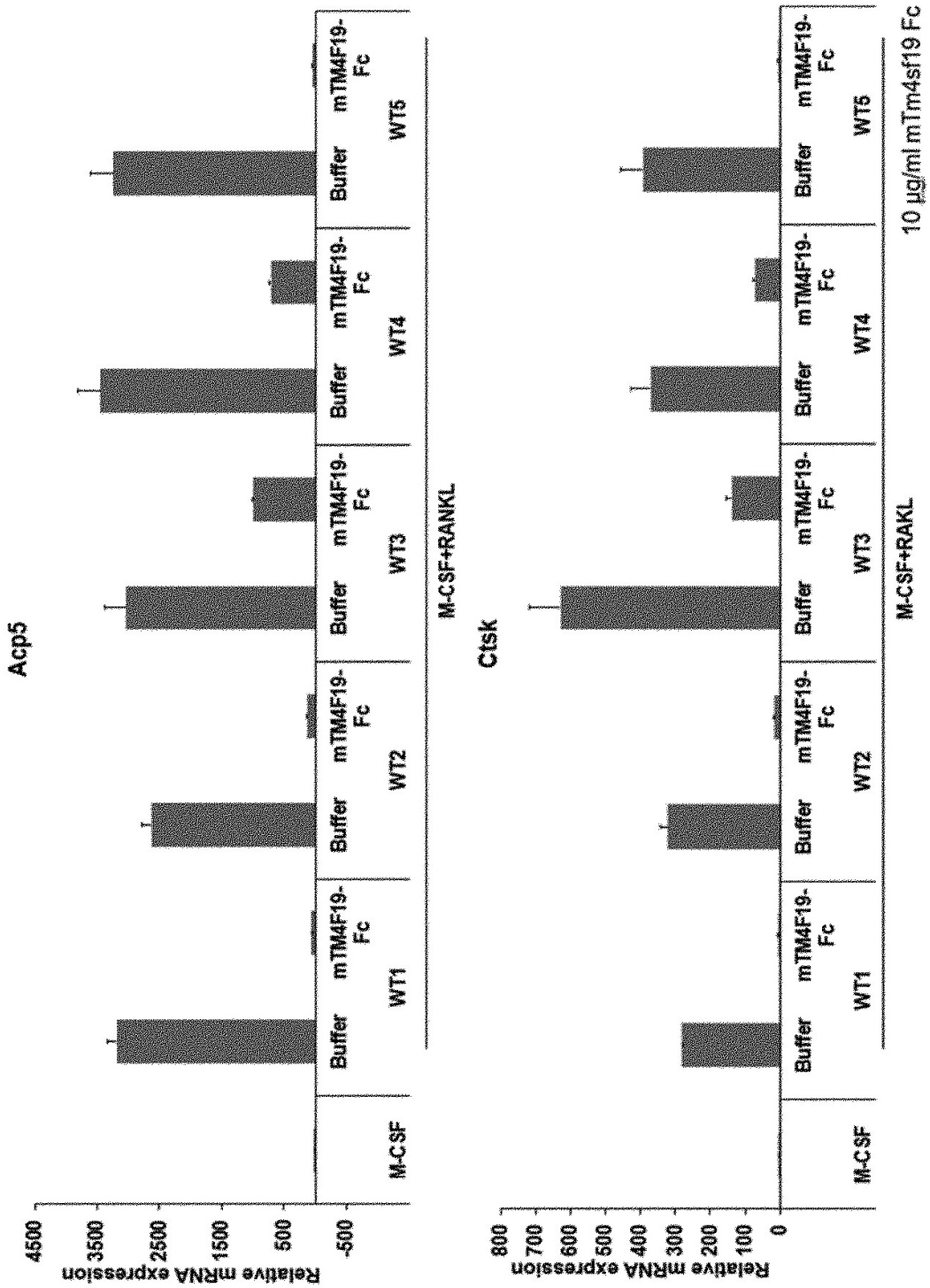
【FIG. 39C】



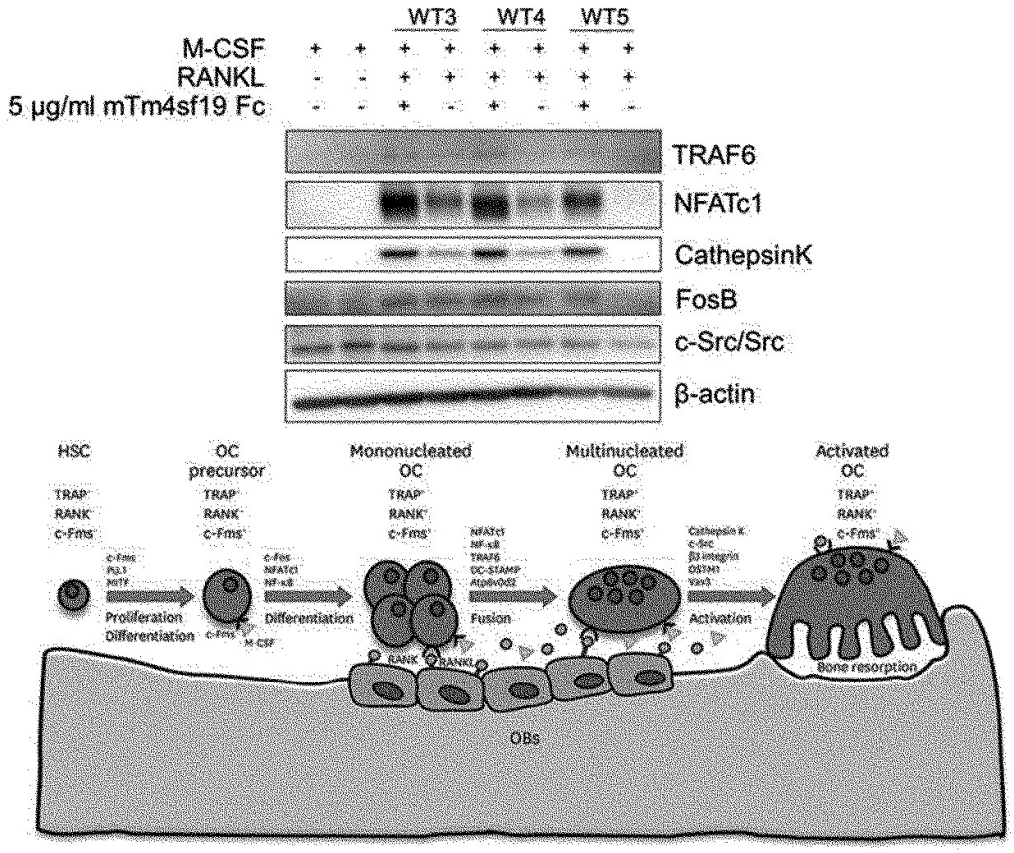
【FIG. 39D】



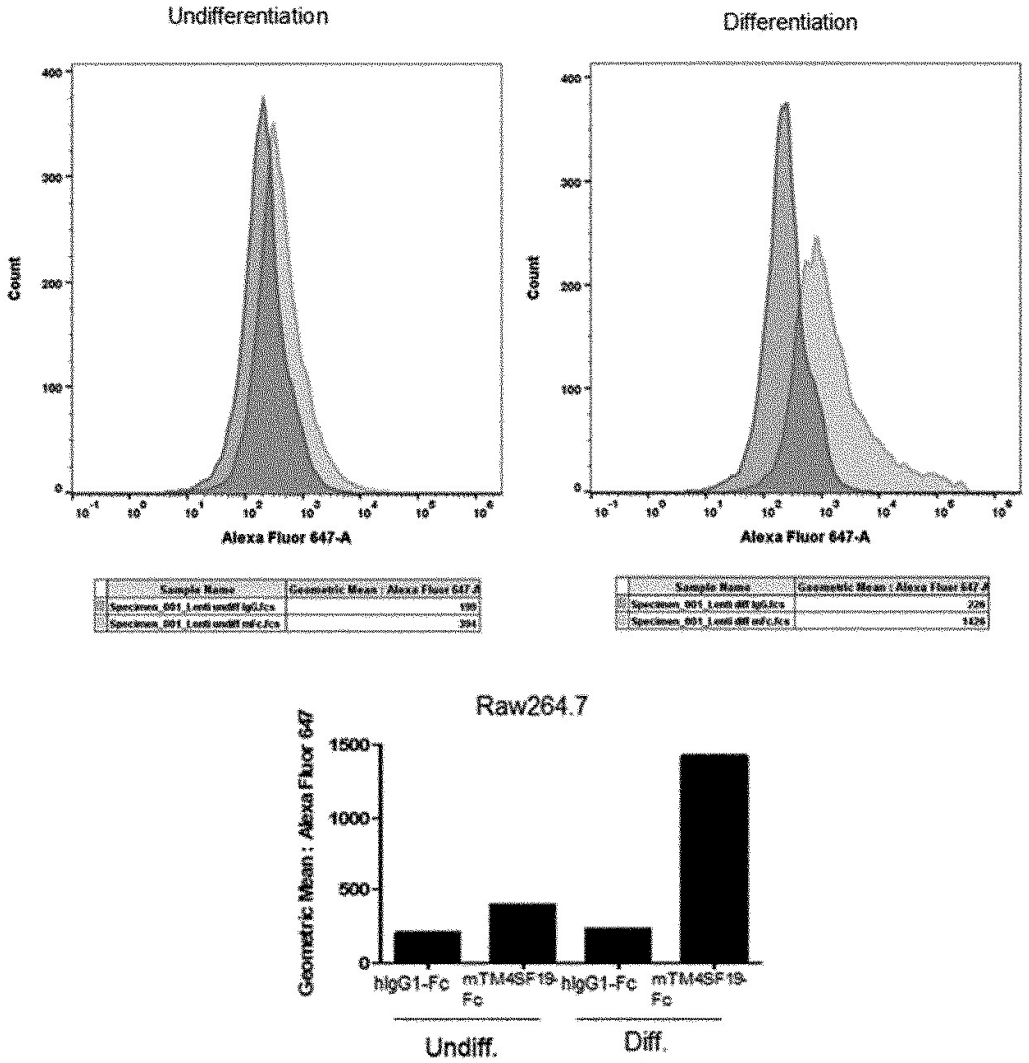
【FIG. 40A】


Acp5
Relative mRNA expression
4500
3500
2500
1500
500
-500
M-CSF
Buffer
mTM4F19-Fc
WT1
WT2
WT3
WT4
WT5
M-CSF+RANKL
Ctsk
800
700
600
500
400
300
200
100
0
M-CSF+RAKL
10 μg/ml mTm4sf19 Fc

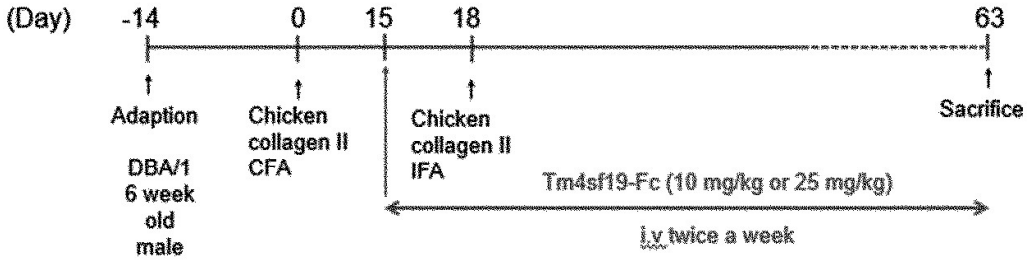
【FIG. 40B】


WT3
WT4
WT5
M-CSF
RANKL
5 μg/ml mTm4sf19 Fc
TRAF6
NFATc1
CathepsinK
FosB
c-Src/Src
β-actin
HSC
OC precursor
Mononucleated OC
Multinucleated OC
Activated OC
TRAP
RANK
c-Fms
Proliferation
Differentiation
Fusion
Activation
Bone resorption
RANK
RANKL
OBs

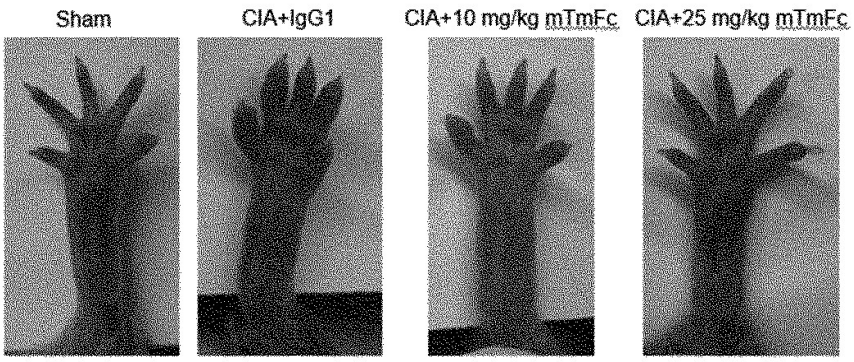
【FIG. 41】



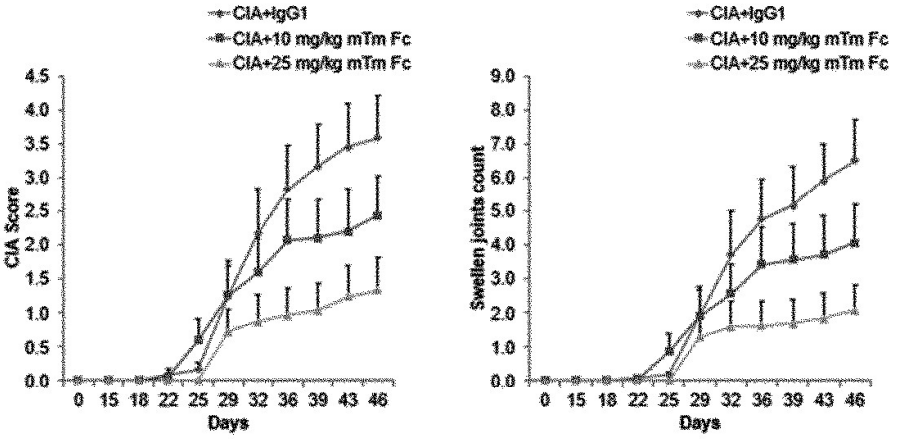
【FIG. 42A】



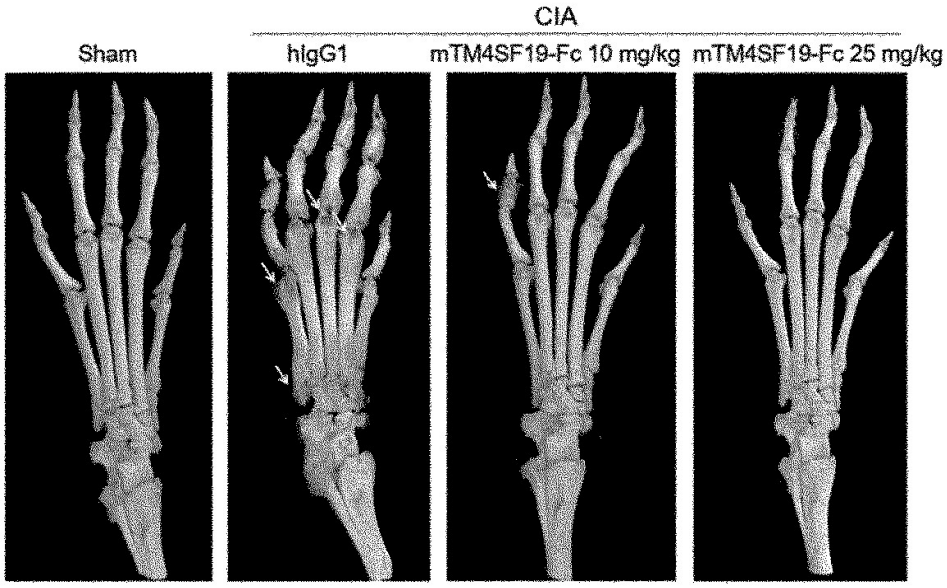
【FIG. 42B】



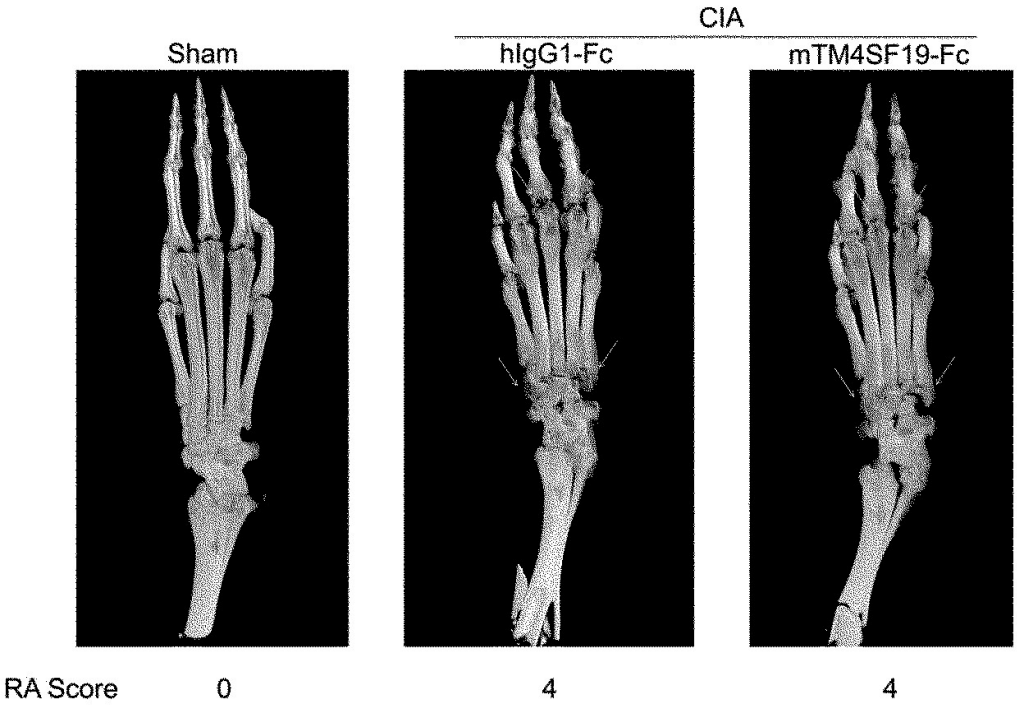
【FIG. 42C】



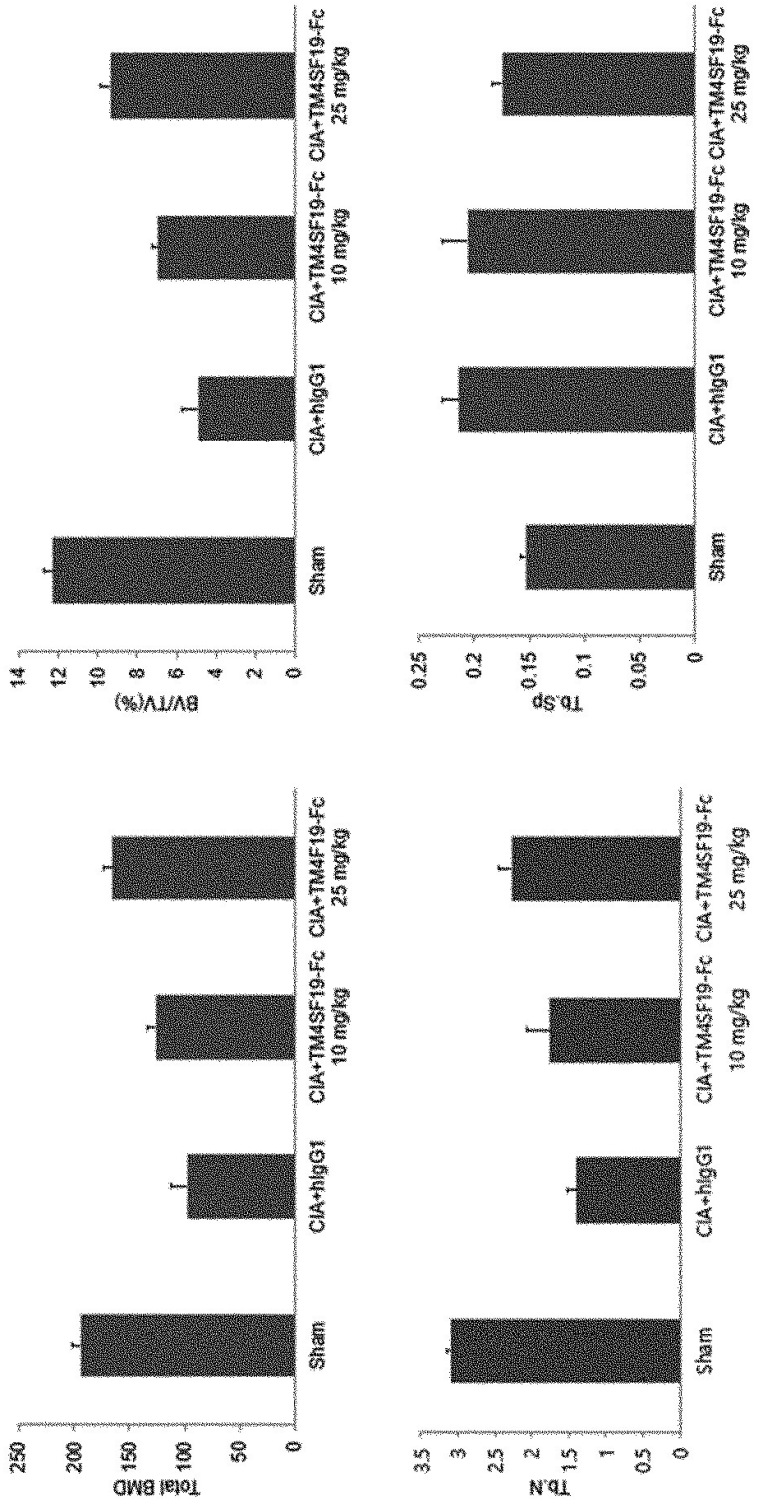
【FIG. 42D】



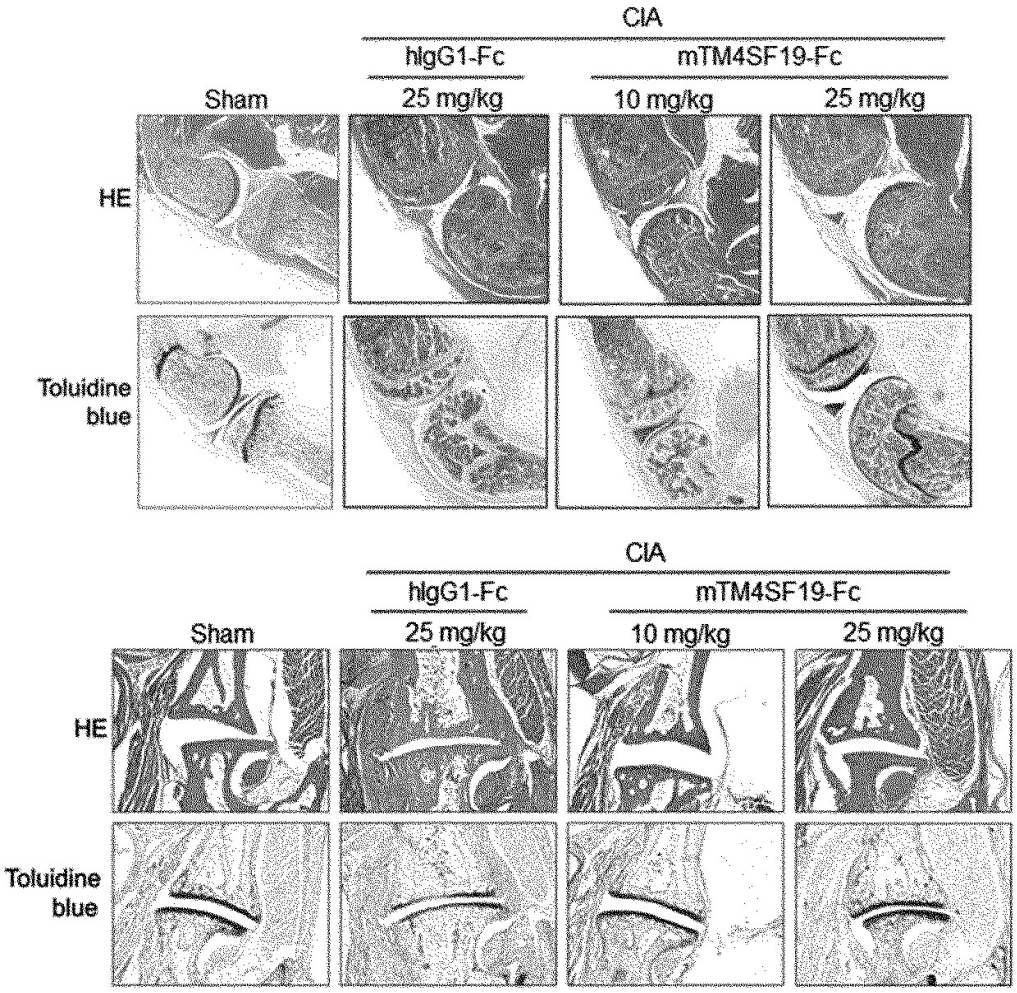
【FIG. 42E】



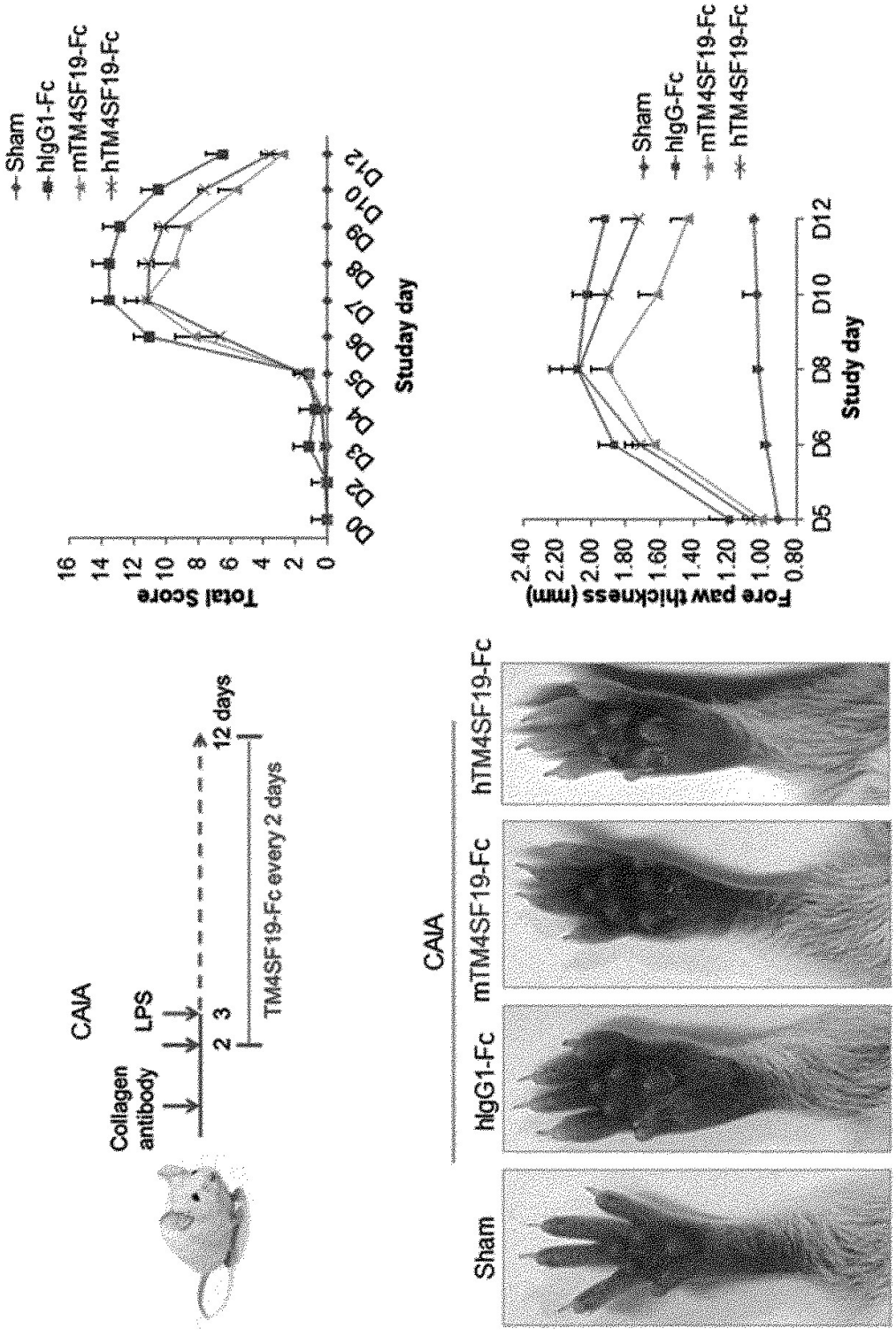
【FIG. 42F】


BV/TV(%)
Tb.Sp
Total BMD
Tb.N
Sham
CIA+hIgG1
CIA+TM4SF19-Fc 10 mg/kg
CIA+TM4SF19-Fc 25 mg/kg

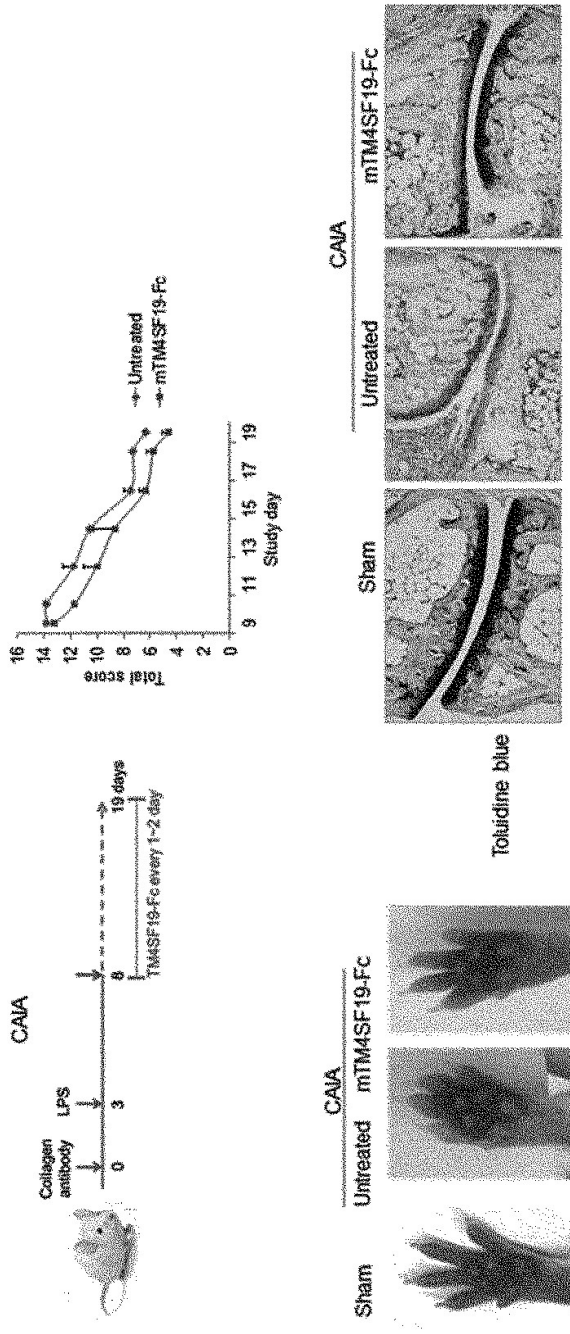
【FIG. 42g】


CIA
hIgG1-Fc
mTM4SF19-Fc
Sham
25 mg/kg
10 mg/kg
25 mg/kg
HE
Toluidine blue
CIA
hIgG1-Fc
mTM4SF19-Fc
Sham
25 mg/kg
10 mg/kg
25 mg/kg
HE
Toluidine blue

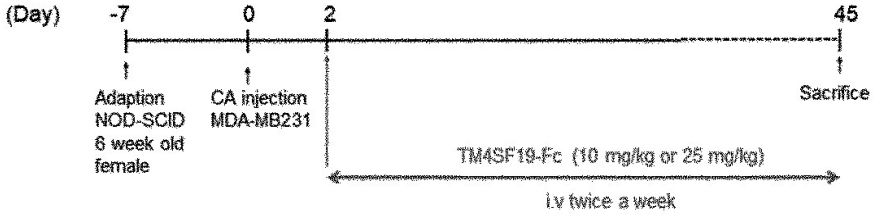
【FIG. 42H】


CAIA
Collagen antibody
LPS
2 3
12 days
TM4SF19-Fc every 2 days
Total Score
Studay day
Sham
hIgG1-Fc
mTM4SF19-Fc
hTM4SF19-Fc
Fore paw thickness (mm)
Study day
Sham
hIgG-Fc
mTM4SF19-Fc
hTM4SF19-Fc
CAIA
Sham
hIgG1-Fc
mTM4SF19-Fc
hTM4SF19-Fc

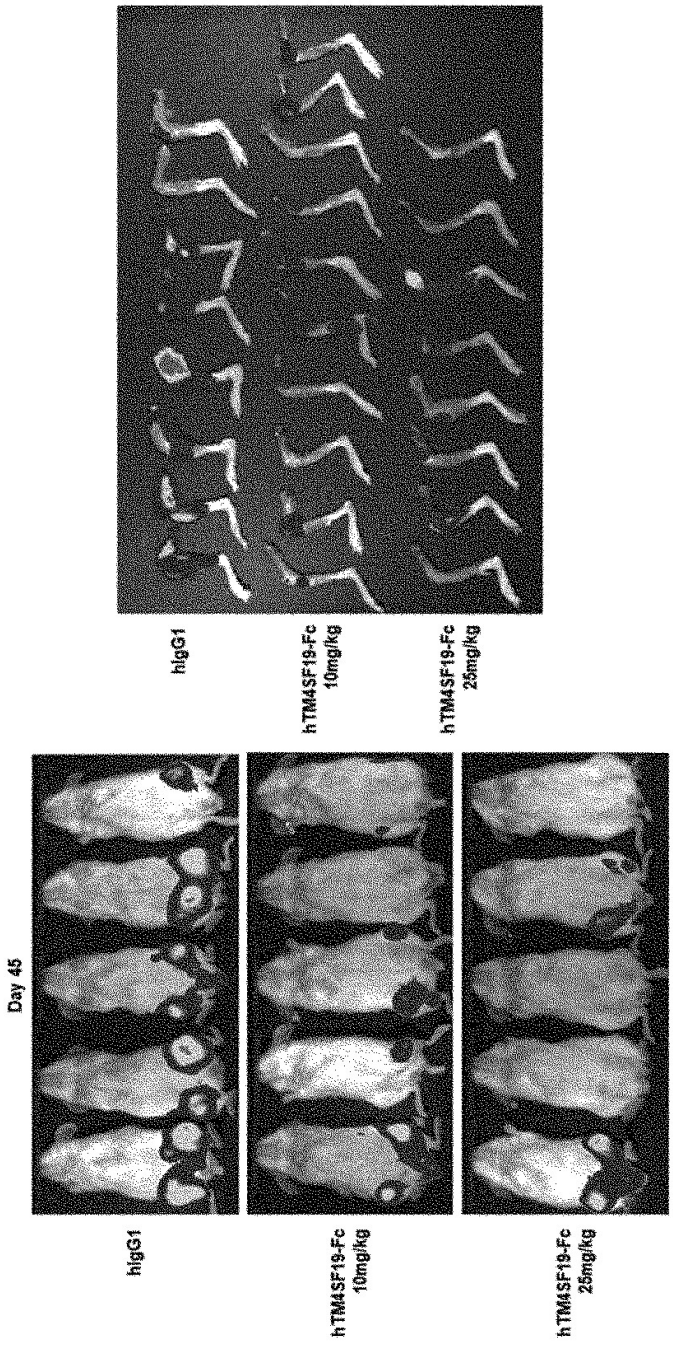
【FIG. 42I】



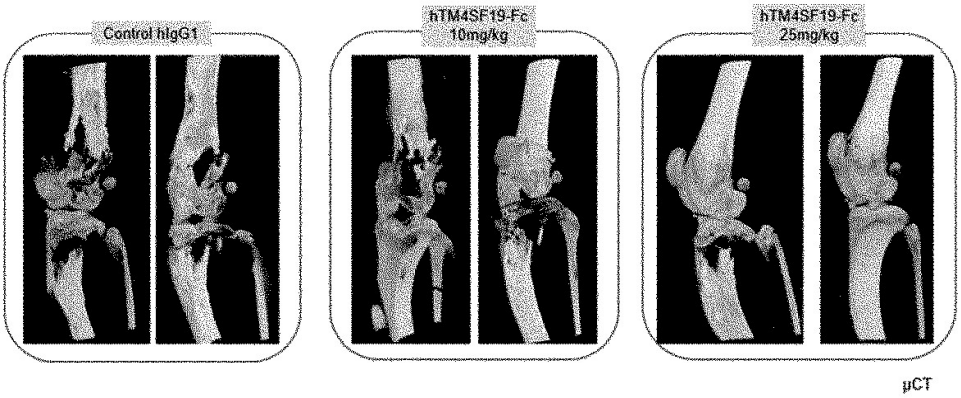
【FIG. 43A】



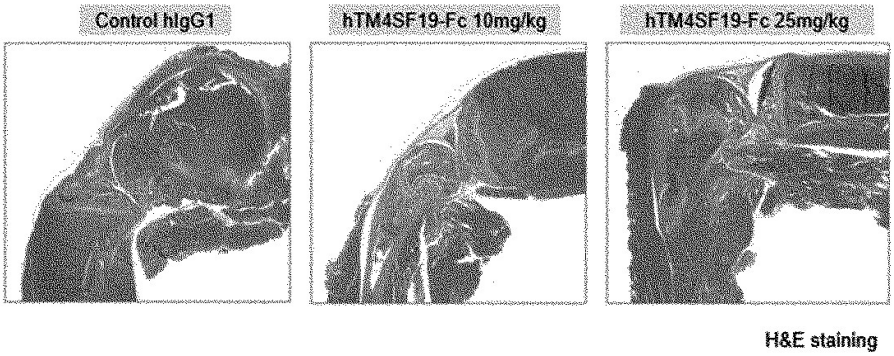
【FIG. 43B】


Day 45
hIgG1
hTM4SF19-Fc 10mg/kg
hTM4SF19-Fc 25mg/kg
hIgG1
hTM4SF19-Fc 10mg/kg
hTM4SF19-Fc 25mg/kg

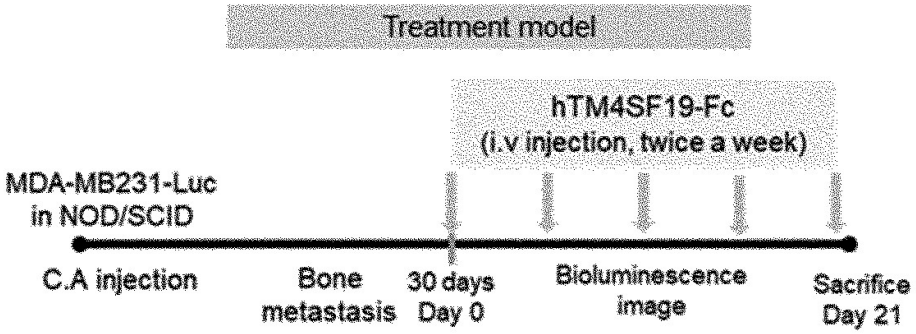
【FIG. 43C】



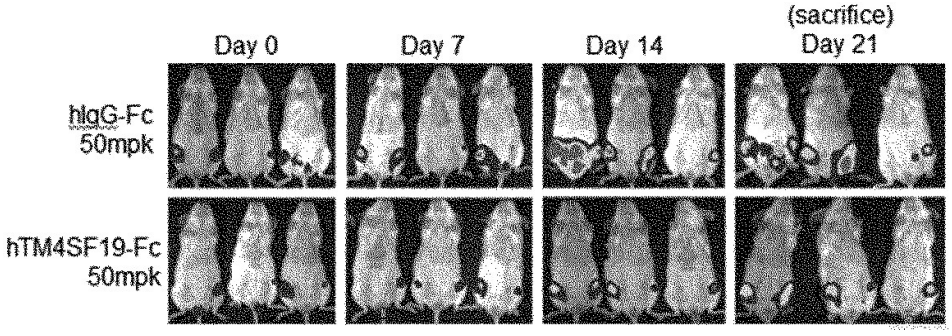
【FIG. 43D】



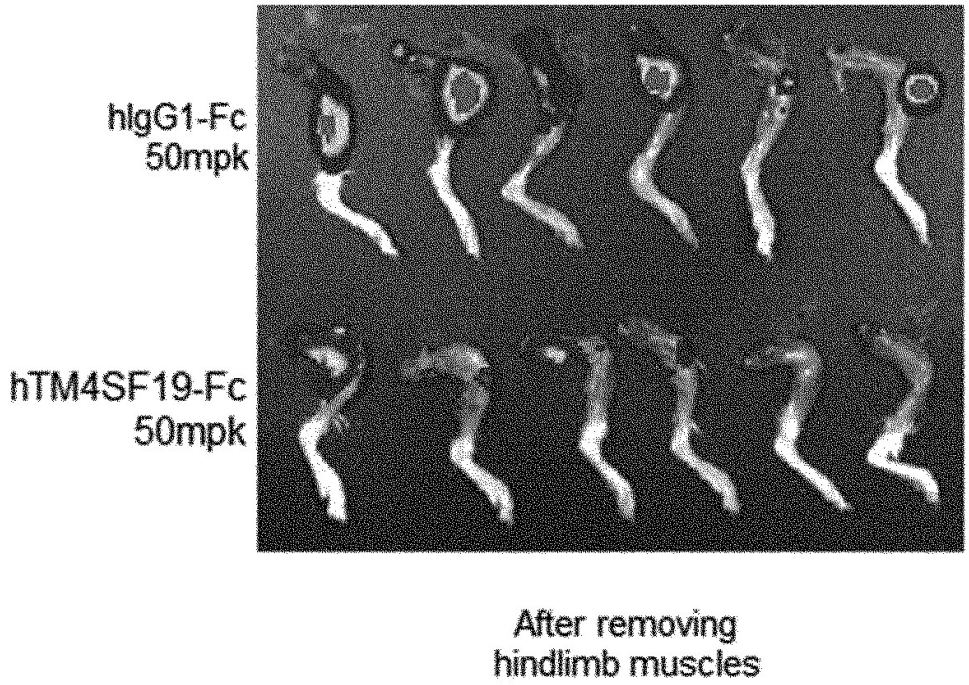
【FIG. 44A】



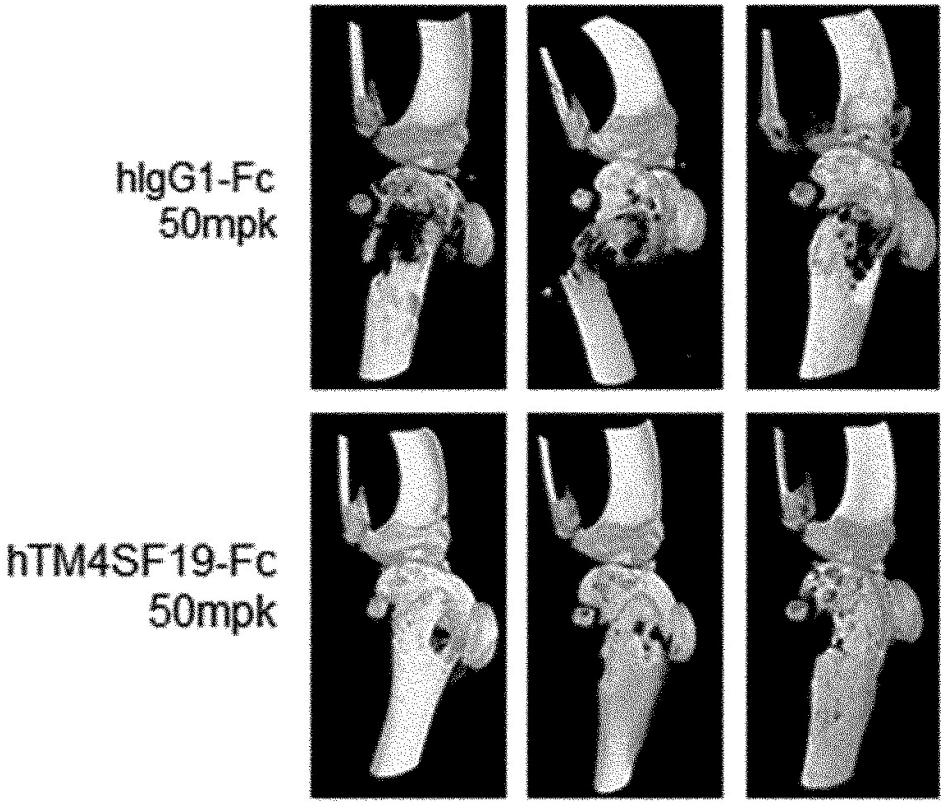
【FIG. 44B】



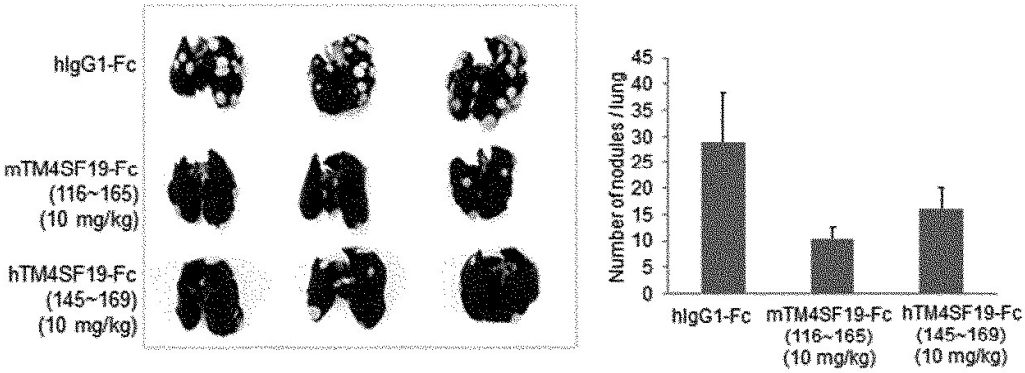
【FIG. 44C】



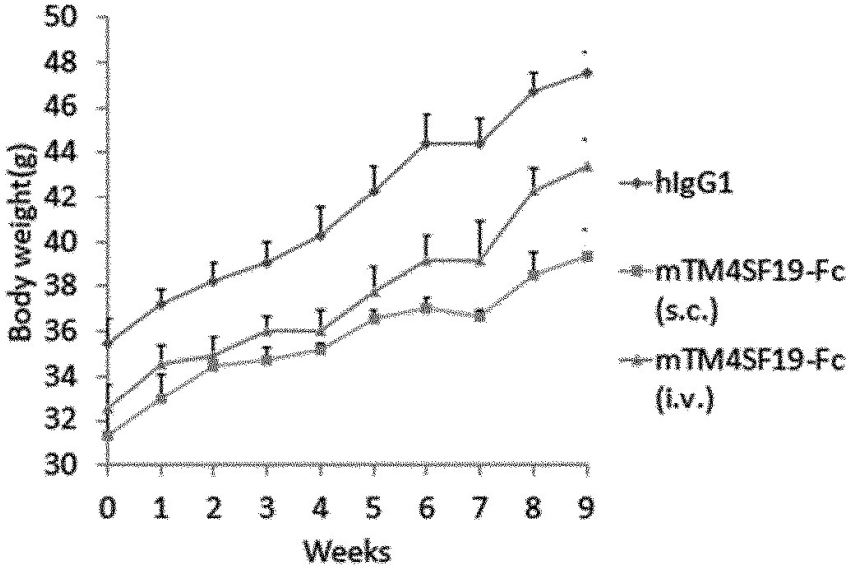
【FIG. 44D】

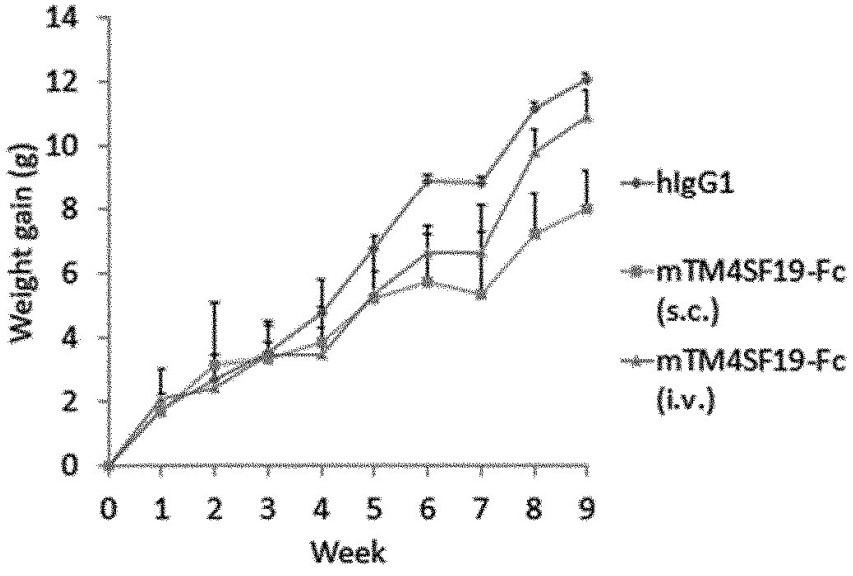


【FIG. 45】

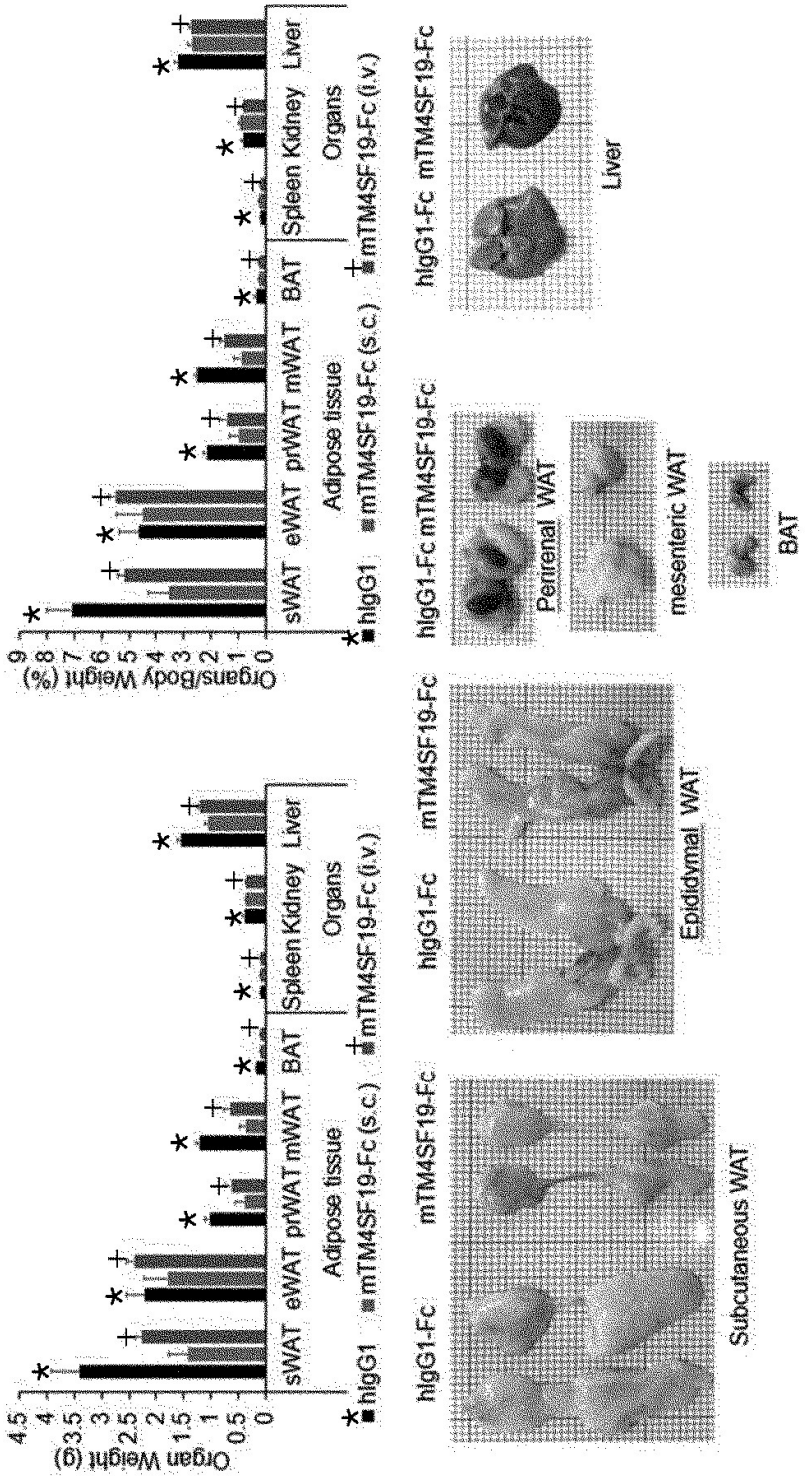


【FIG. 46A】

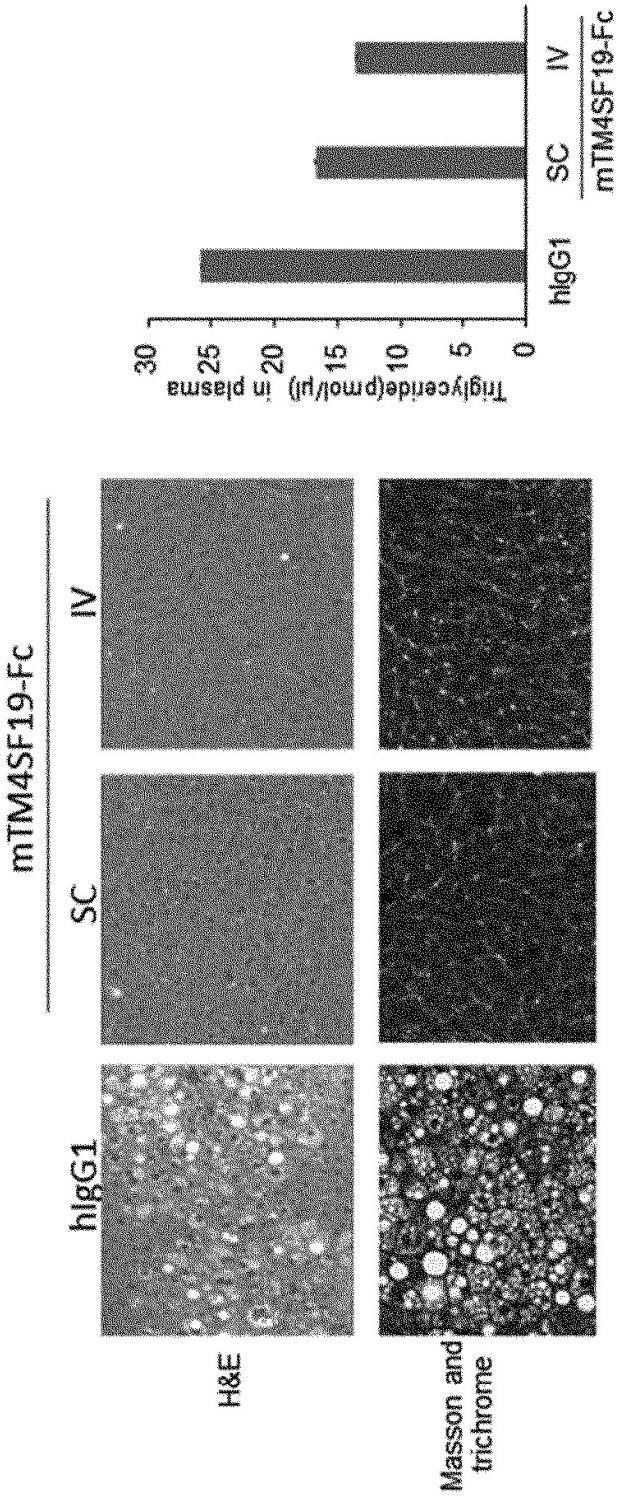




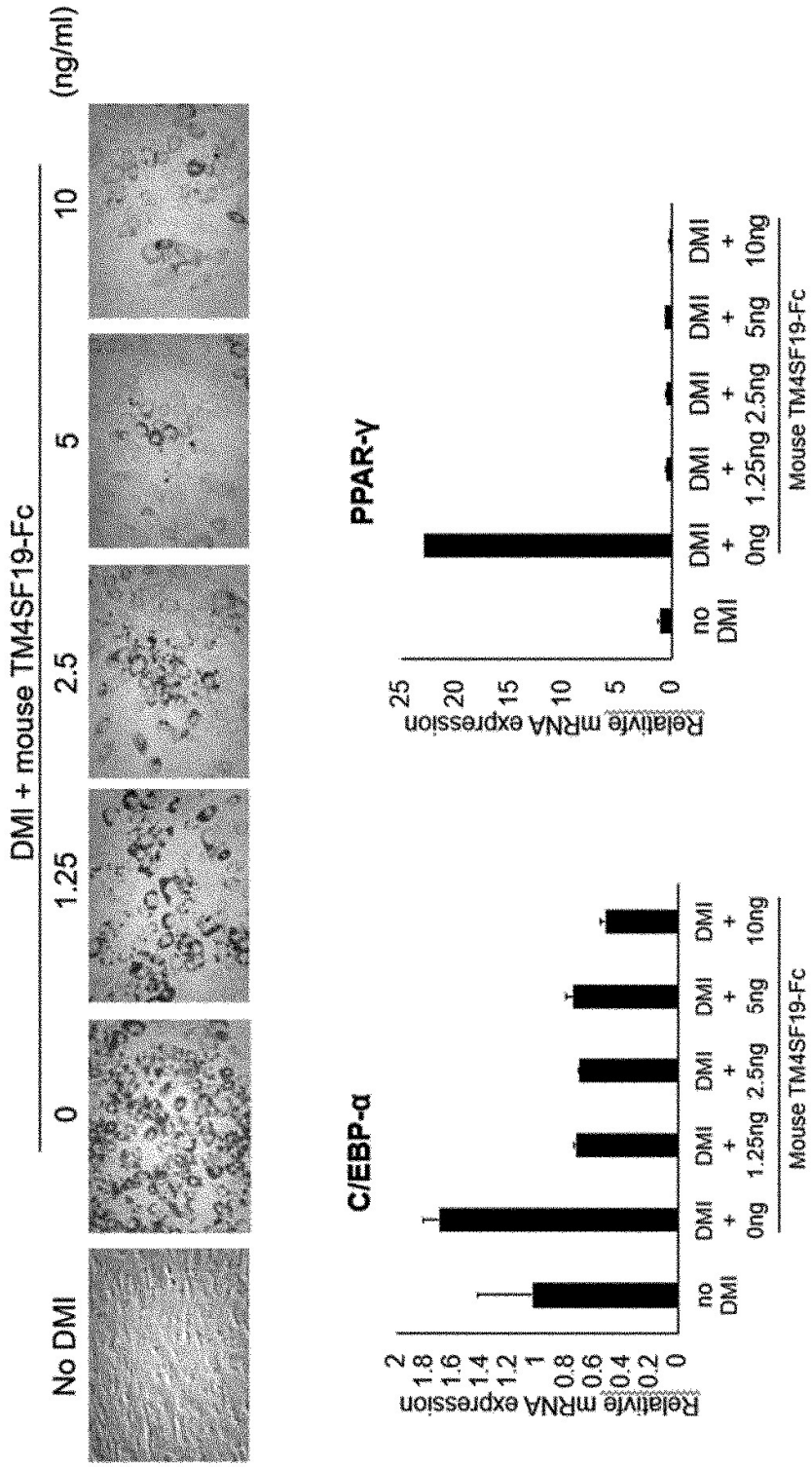
【FIG. 46B】


Organs/Body Weight (%)
Organ Weight (g)
sWAT
eWAT
prWAT
mWAT
BAT
Spleen
Kidney
Liver
Adipose tissue
Organs
hIgG1
mTM4SF19-Fc (s.c.)
mTM4SF19-Fc (i.v.)
hIgG1-Fc
mTM4SF19-Fc
Subcutaneous WAT
Epididymal WAT
Perirenal WAT
mesenteric WAT
BAT
Liver

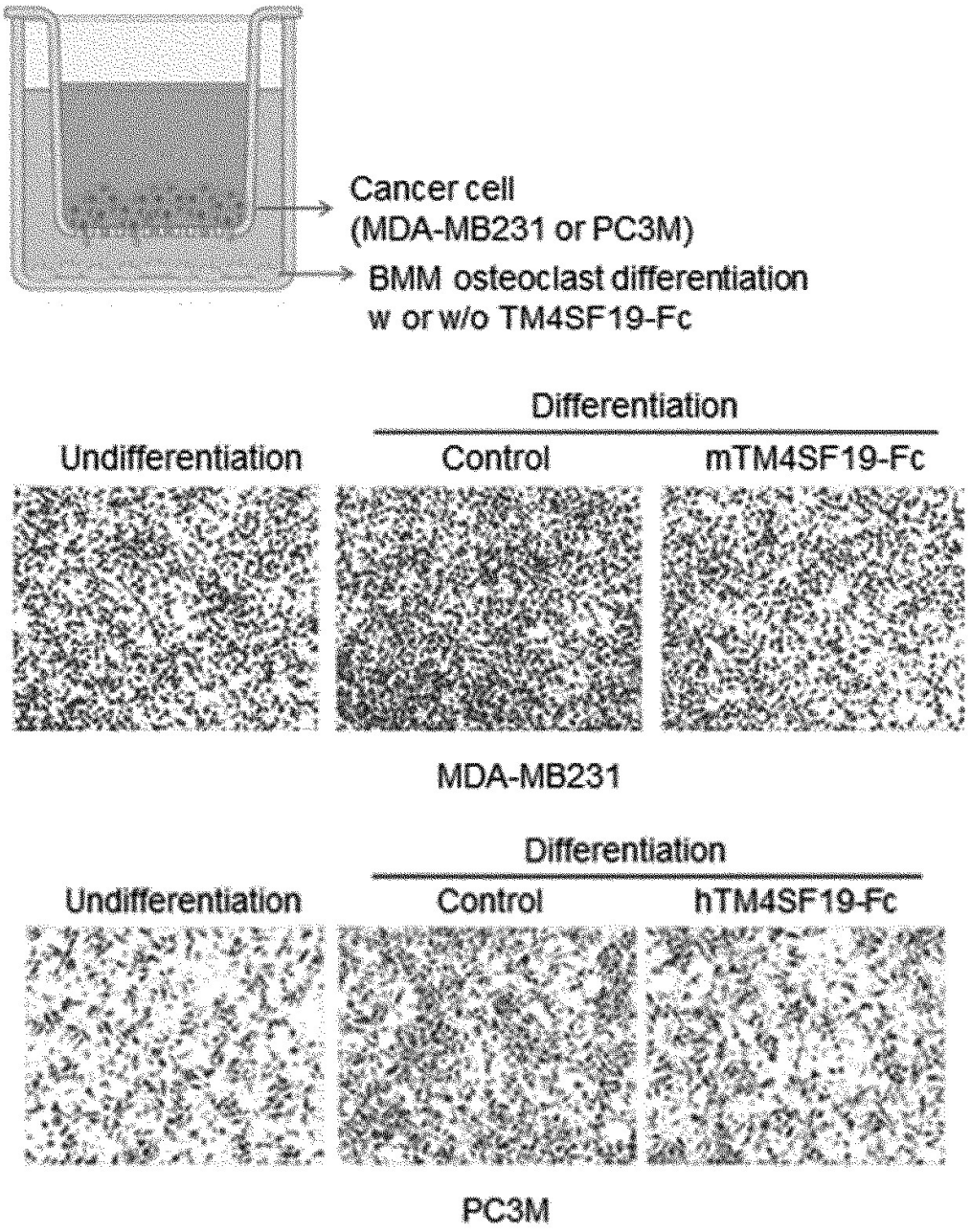
【FIG. 47】


mTM4SF19-Fc
hIgG1
SC
IV
H&E
Masson and trichrome
Triglyceride(pmol/μl) in plasma
30
25
20
15
10
5
0
hIgG1
SC
IV
mTM4SF19-Fc

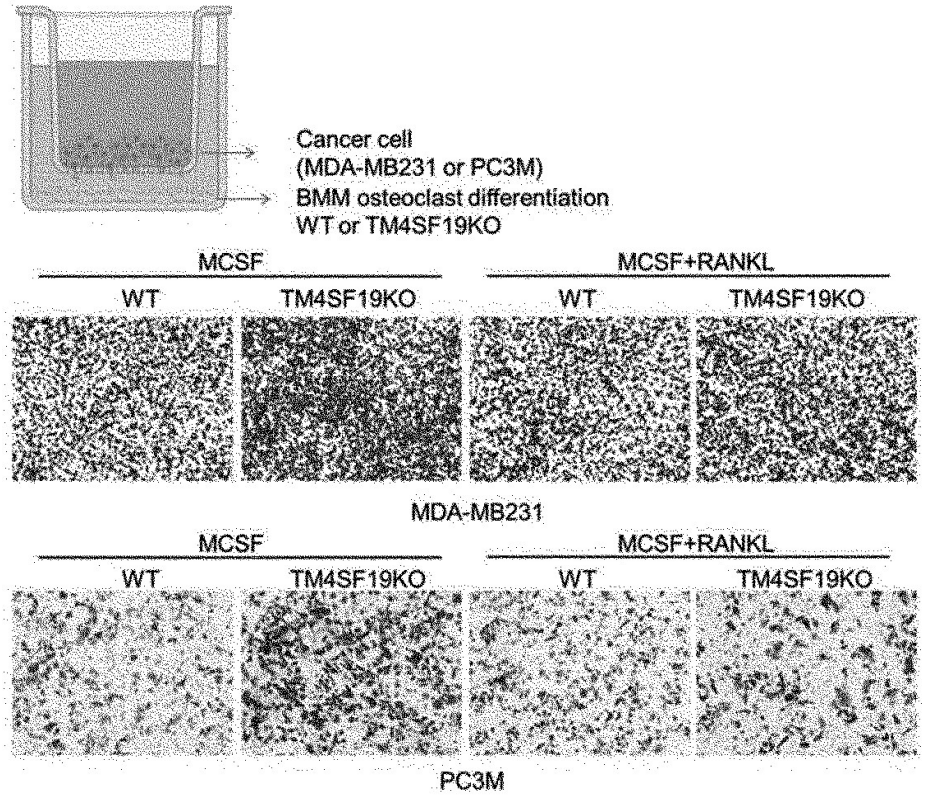
【FIG. 48】


No DMI
DMI + mouse TM4SF19-Fc
0
1.25
2.5
5
10
(ng/ml)
C/EBP-α
Relative mRNA expression
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
no DMI
DMI + 0ng
DMI + 1.25ng
DMI + 2.5ng
DMI + 5ng
DMI + 10ng
Mouse TM4SF19-Fc
PPAR-γ
Relative mRNA expression
25
20
15
10
5
0
no DMI
DMI + 0ng
DMI + 1.25ng
DMI + 2.5ng
DMI + 5ng
DMI + 10ng
Mouse TM4SF19-Fc

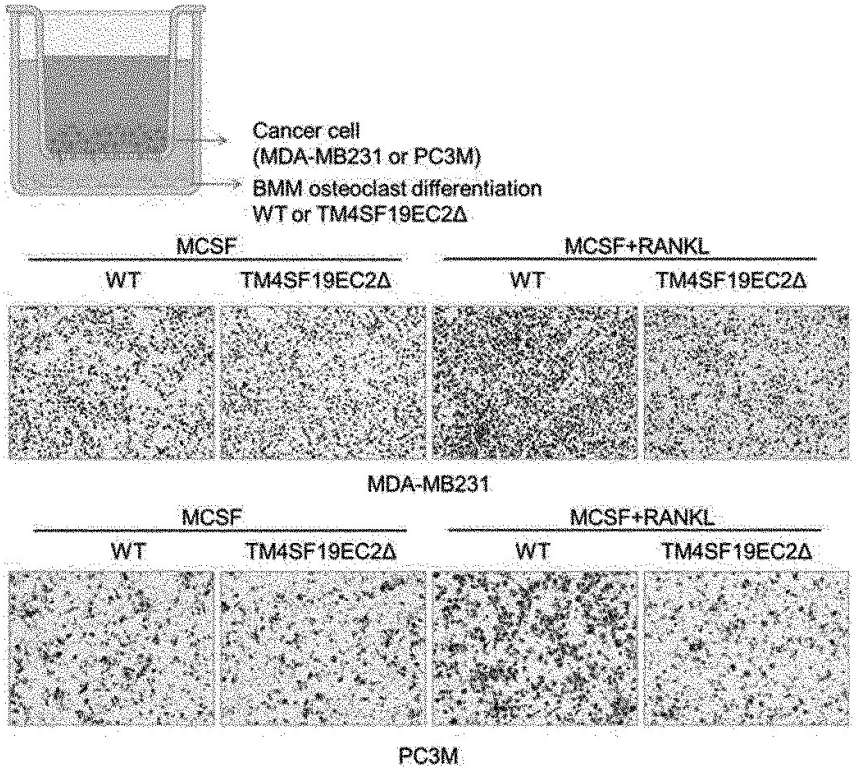
【FIG. 49】


Cancer cell
(MDA-MB231 or PC3M)
BMM osteoclast differentiation
w or w/o TM4SF19-Fc
Differentiation
Undifferentiation
Control
mTM4SF19-Fc
MDA-MB231
Differentiation
Undifferentiation
Control
hTM4SF19-Fc
PC3M

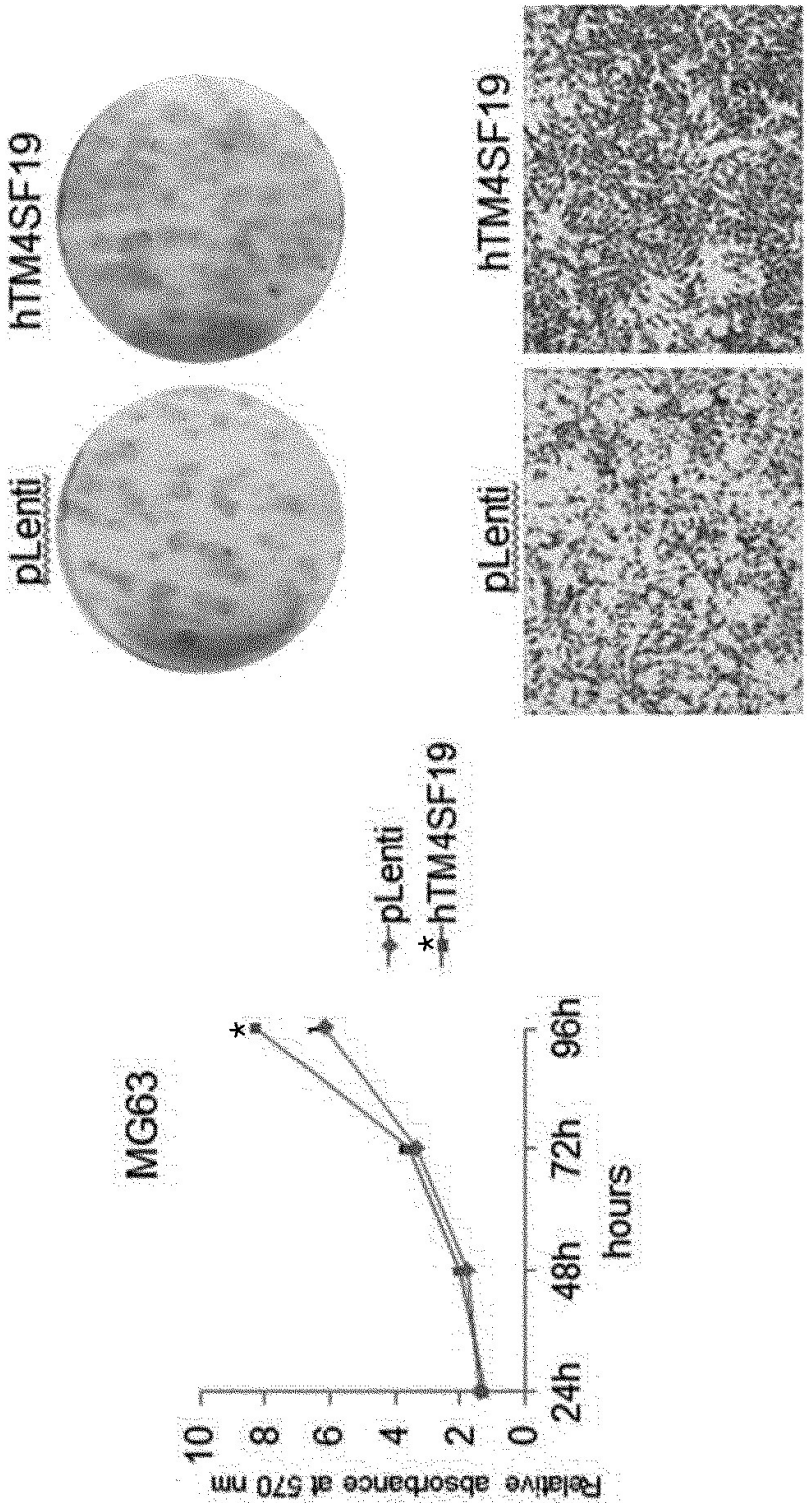
【FIG. 50A】



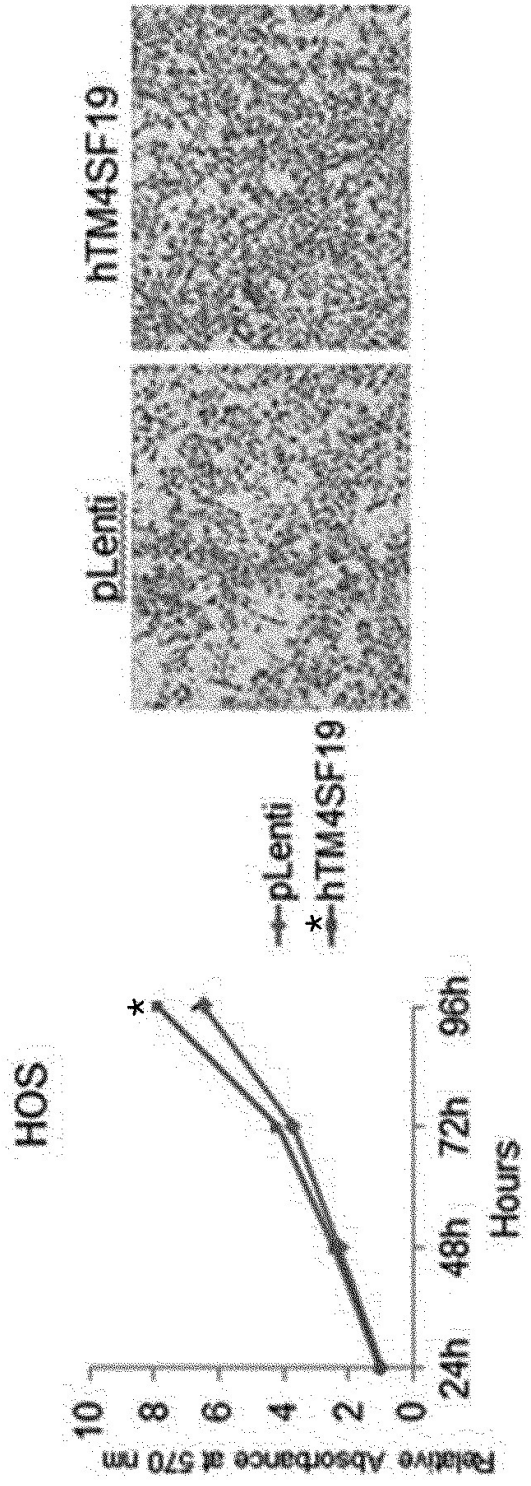
【FIG. 50B】



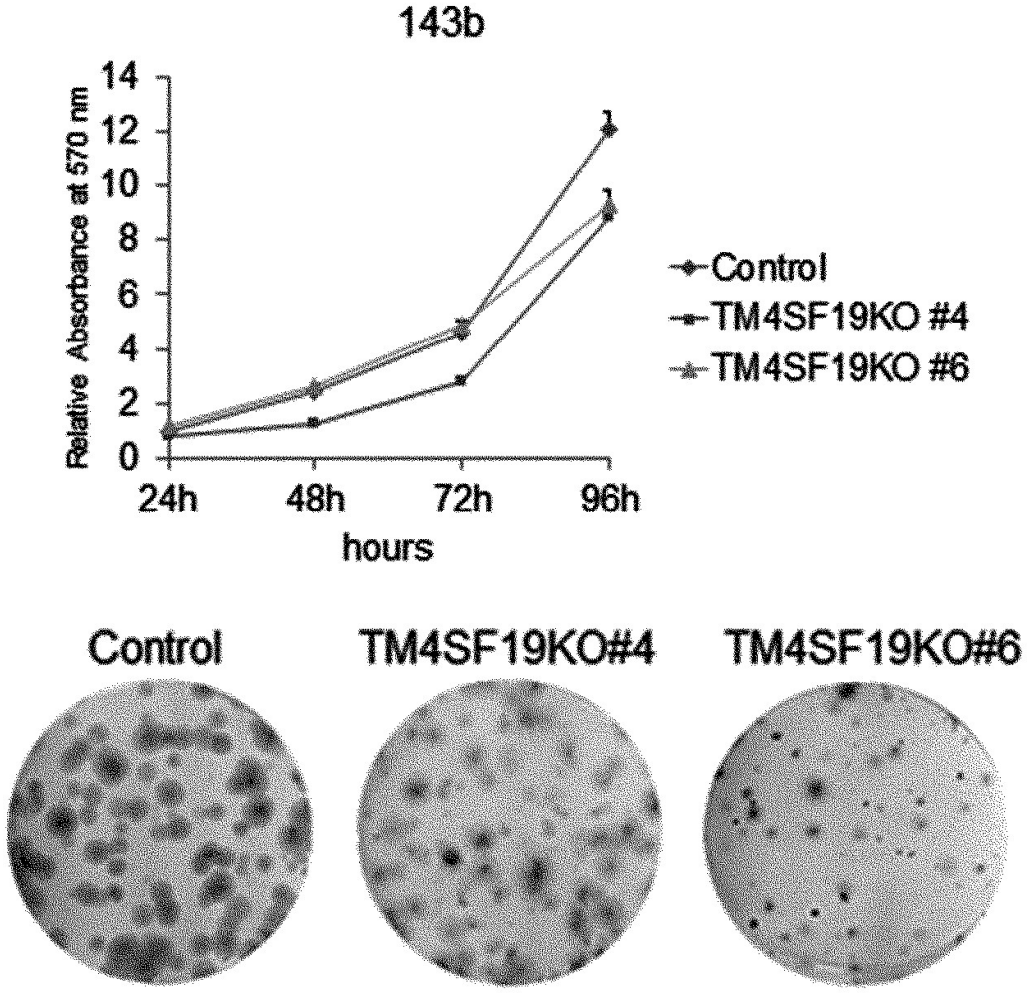
【FIG. 51】


hTM4SF19
pLenti
hTM4SF19
pLenti
MG63
pLenti
*hTM4SF19
Relative absorbance at 570 nm
10
8
6
4
2
0
24h
48h
72h
96h
hours
*

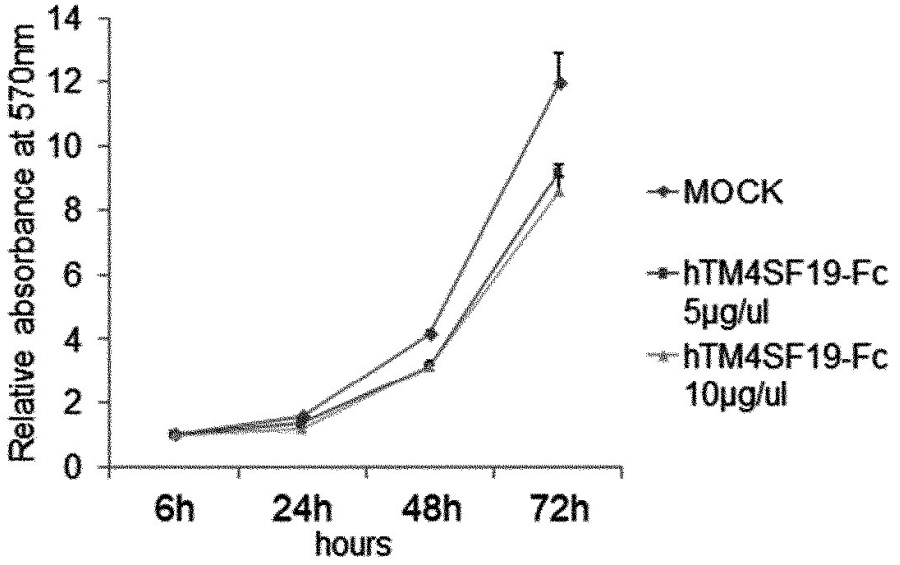
【FIG. 52】


hTM4SF19
pLenti
pLenti
hTM4SF19
HOS
Relative Absorbance at 570 nm
10
8
6
4
2
0
24h
48h
72h
96h
Hours
*
*

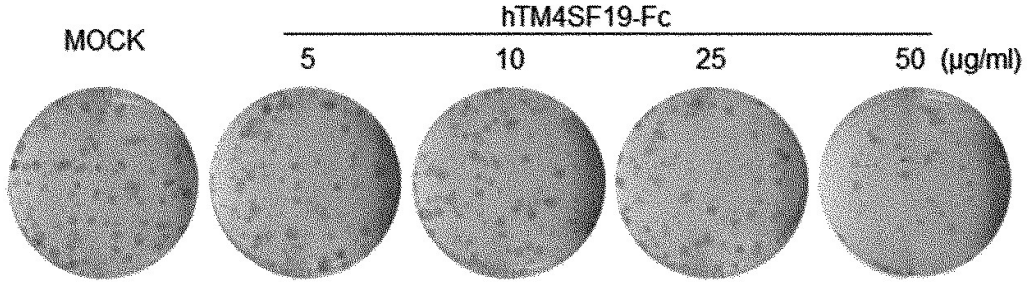
【FIG. 53】



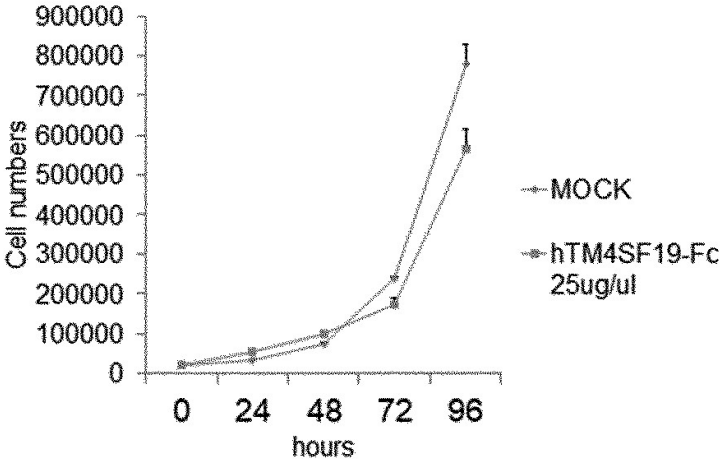
【FIG. 54A】



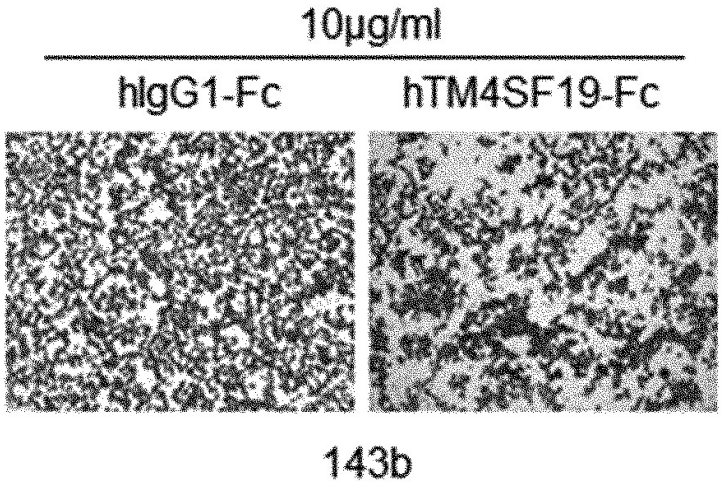
【FIG. 54B】



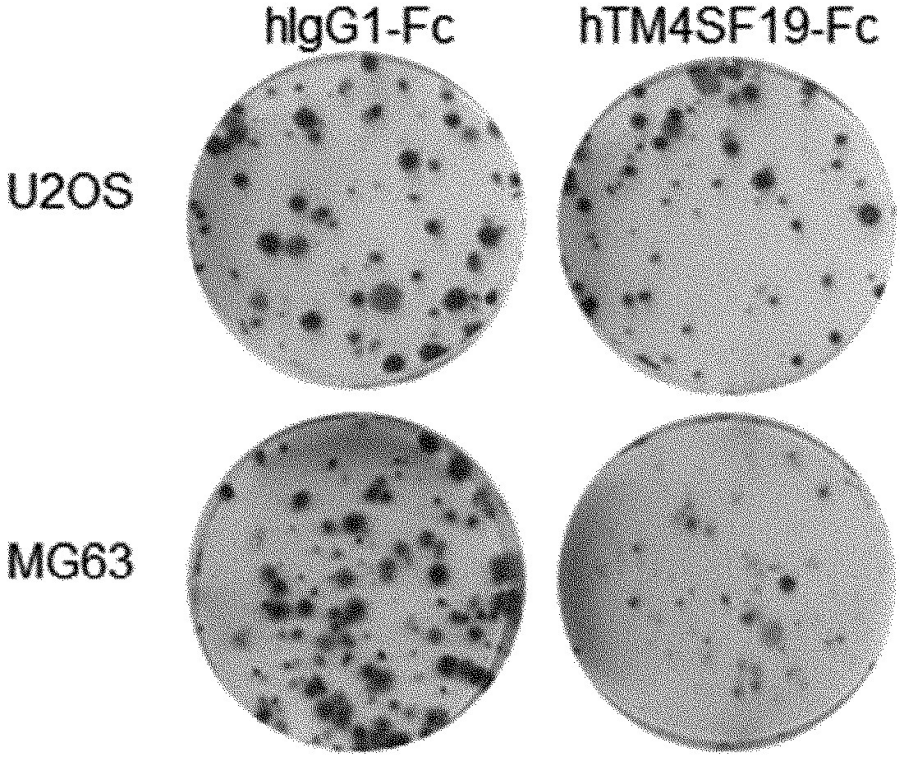
【FIG. 54C】



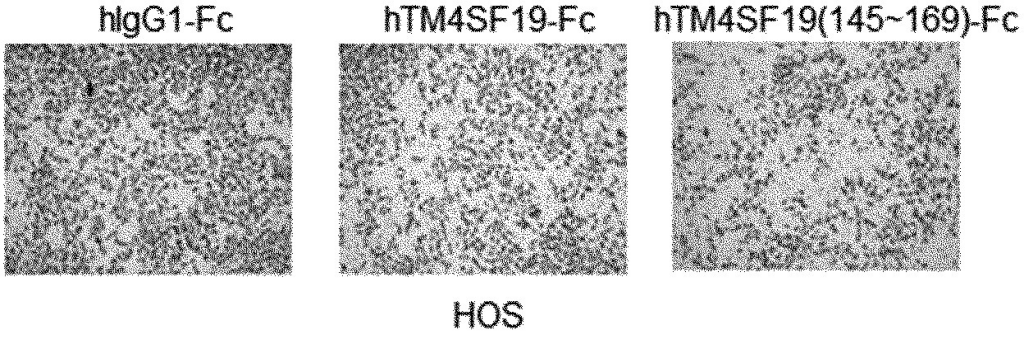
【FIG. 54D】



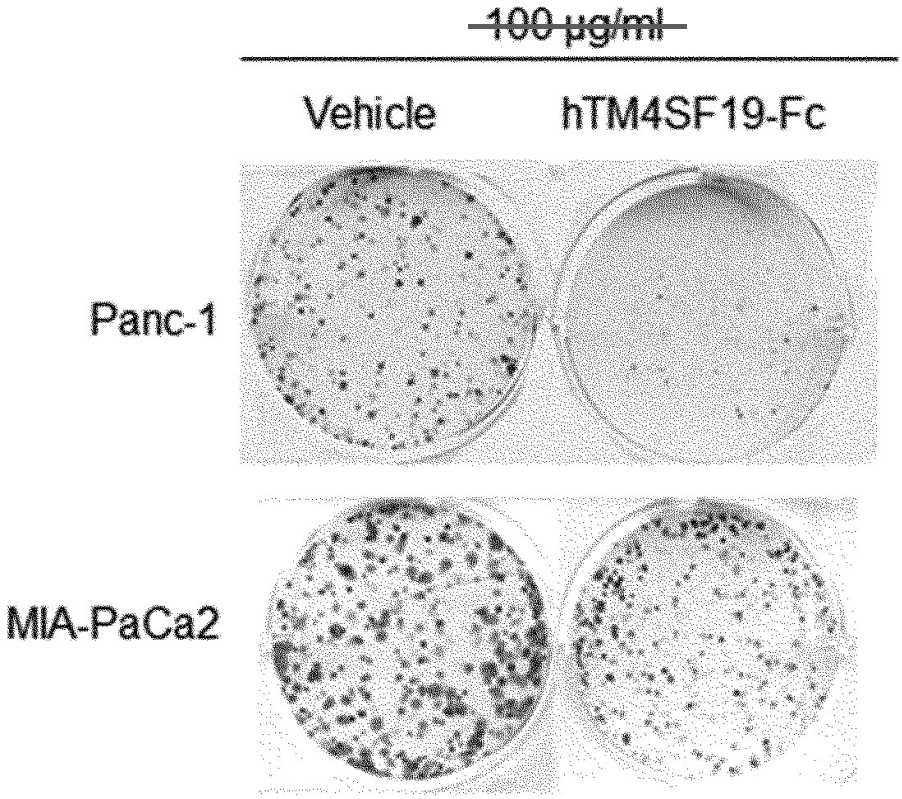
【FIG. 55】


hIgG1-Fc
hTM4SF19-Fc
U2OS
MG63

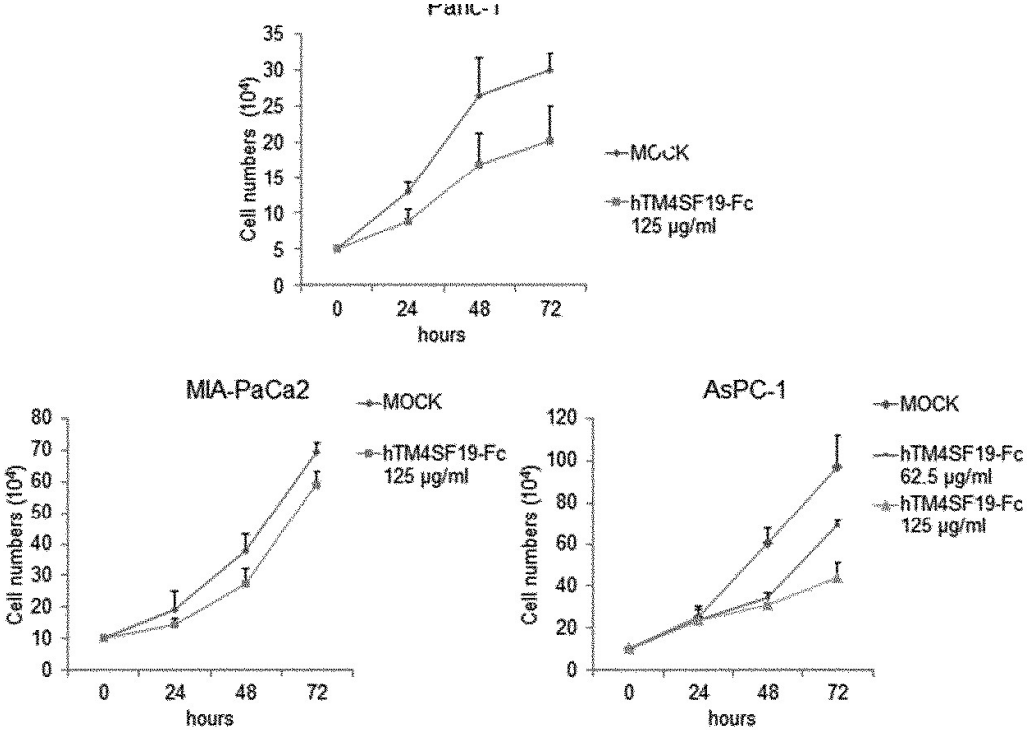
【FIG. 56】


hIgG1-Fc
hTM4SF19-Fc
hTM4SF19(145~169)-Fc
HOS

【FIG. 57A】



【FIG. 57B】



【FIG. 58A】

Mouse TM4SF19$_{116-165}$-Fc : SEQ ID NO: 10

Target Sequence: SEQ ID NO: 8

Enzyme Site

hIgG1-Fc : SEQ ID NO: 9

Mouse 116-165 amino acid seq

KDGPFCMFDVSSFNQTQAWKFGYPFKDLHNRNYLYDRSLWTSVCLEPSKATSEPKSCDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

Nucleotides encoding Mouse TM4SF19$_{116-165}$-Fc : SEQ ID NO: 11

**AAAGATGGTCCCTTTTGCATGTTTGATGTCTCATCCTTCAATCAGACACAAGCTTGGAAATTCGG
CTATCCCTTTAAAGATCTACACAACAGGAATTATCTGTATGACCGTTCACTTTGGACCTCCGTTT
GCCTGGAGCCCTCTAAGGCT**ACTAGTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGT
GCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC
TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
CAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGC
AAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAA
GCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAA
GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GA

【FIG. 58B】

Human TM4SF19$_{120-169}$-Fc : SEQ ID NO: 13

Target Sequence : SEQ ID NO: 12

Enzyme Site

hIgG1-Fc : SEQ ID NO: 9

KDGPFCMFDVSSFNQTQAWKYGYPFKDLHSRNYLYDRSLWNSVCLEPSAATSEPKSCDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

Nucleotides encoding Human TM4SF19$_{120-169}$-Fc : SEQ ID NO: 14

**AAAGATGGTCCTTTTTGCATGTTTGATGTTTCATCCTTCAATCAGACACAAGCTTGGAAATATGG
TTACCCATTCAAAGACCTGCATAGTAGGAATTATCTGTATGACCGTTCGCTCTGGAACTCCGTCT
GCCTGGAGCCCTCTGCAGCT**ACTAGTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGT
GCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC
TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
CAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGC
AAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAA
GCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAA
GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GA

【FIG. 58C】

Human TM4SF19$_{145-169}$-Fc : SEQ ID NO: 16

Target Sequence : SEQ ID NO: 15

Enzyme Site

hIgG1-Fc: SEQ ID NO: 9

KDLHSRNYLYDRSLWNSVCLEPSAATSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Nucleotides encoding Human Human TM4SF19$_{145-169}$-Fc : SEQ ID NO: 17

**AAAGACCTGCATAGTAGGAATTATCTGTATGACCGTTCGCTCTGGAACTCCGTCTGCCTGGAGC
CCTCTGCAGCT**ACTAGTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCAC
CTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTC
CCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCA
ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGG
CAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG
GCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

【FIG. 58D】

Human TM4SF19$_{131-169}$-Fc : SEQ ID NO: 19

Target Sequence : SEQ ID NO: 18

Enzyme Site

hIgG1-Fc : SEQ ID NO: 9

SFNQTQAWKYGYPFKDLHSRNYLYDRSLWNSVCLEPSAATSEPKSCDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Nucleotides encoding Human TM4SF19$_{131-169}$-Fc SEQ ID NO: 20

TCCTTCAATCAGACACAAGCTTGGAAATATGGTTACCCATTCAAAGACCTGCATAGTAGGAATT
ATCTGTATGACCGTTCGCTCTGGAACTCCGTCTGCCTGGAGCCCTCTGCAGCTACTAGTGAGCCC
AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCA
GTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCG
TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG
GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGT
CCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT
ACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG
GCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG
ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGA
GCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA
CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

Human TM4SF19 extracellular loop 2, 115~175, 60 aa: SEQ ID NO: 21

SGVALKDGPFCMFDVSSFNQTQAWKYGYPFKDLHSRNYLYDRSLWNSVCLEPSAAVVWHVS