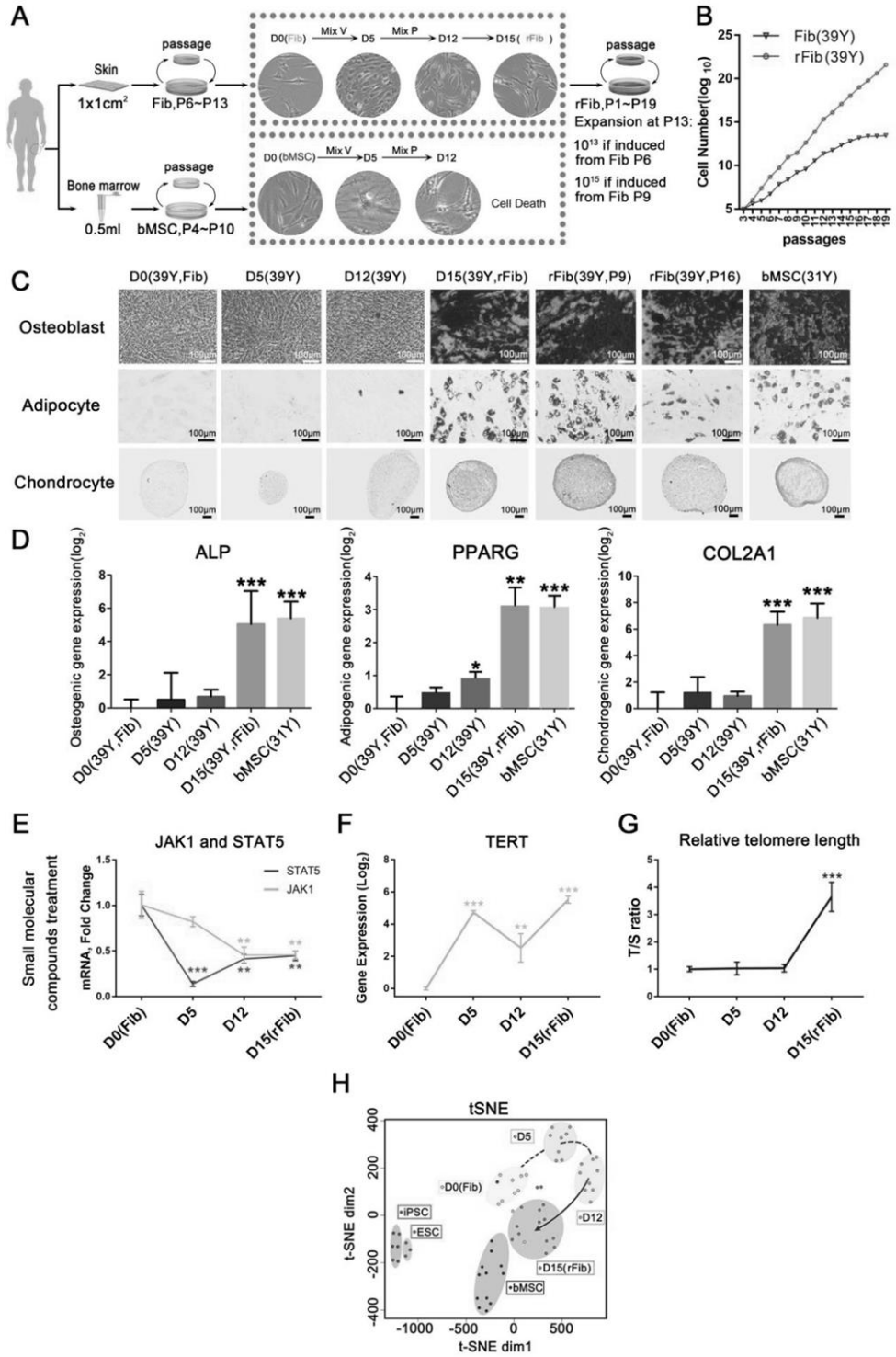

A
Skin
1x1cm²
passage
Fib,P6~P13
Bone marrow
0.5ml
passage
bMSC,P4~P10
D0(Fib)
Mix V
D5
Mix P
D12
D15(rFib)
D0 (bMSC)
Mix V
D5
Mix P
D12
Cell Death
passage
rFib,P1~P19
Expansion at P13:
10¹³ if induced from Fib P6
10¹⁵ if induced from Fib P9
B
Fib(39Y)
rFib(39Y)
Cell Number(log 10)
passages
C
D0(39Y,Fib)
D5(39Y)
D12(39Y)
D15(39Y,rFib)
rFib(39Y,P9)
rFib(39Y,P16)
bMSC(31Y)
Osteoblast
Adipocyte
Chondrocyte
100μm
D
ALP
PPARG
COL2A1
Osteogenic gene expression(log2)
Adipogenic gene expression(log2)
Chondrogenic gene expression(log2)
D0(39Y,Fib)
D5(39Y)
D12(39Y)
D15(39Y,rFib)
bMSC(31Y)
E
JAK1 and STAT5
STAT5
JAK1
Small molecular compounds treatment
mRNA, Fold Change
D0(Fib)
D5
D12
D15(rFib)
F
TERT
Gene Expression (Log2)
G
Relative telomere length
T/S ratio
H
tSNE
D5
D0(Fib)
iPSC
ESC
D12
D15(rFib)
bMSC
t-SNE dim2
t-SNE dim1

FIG. 1

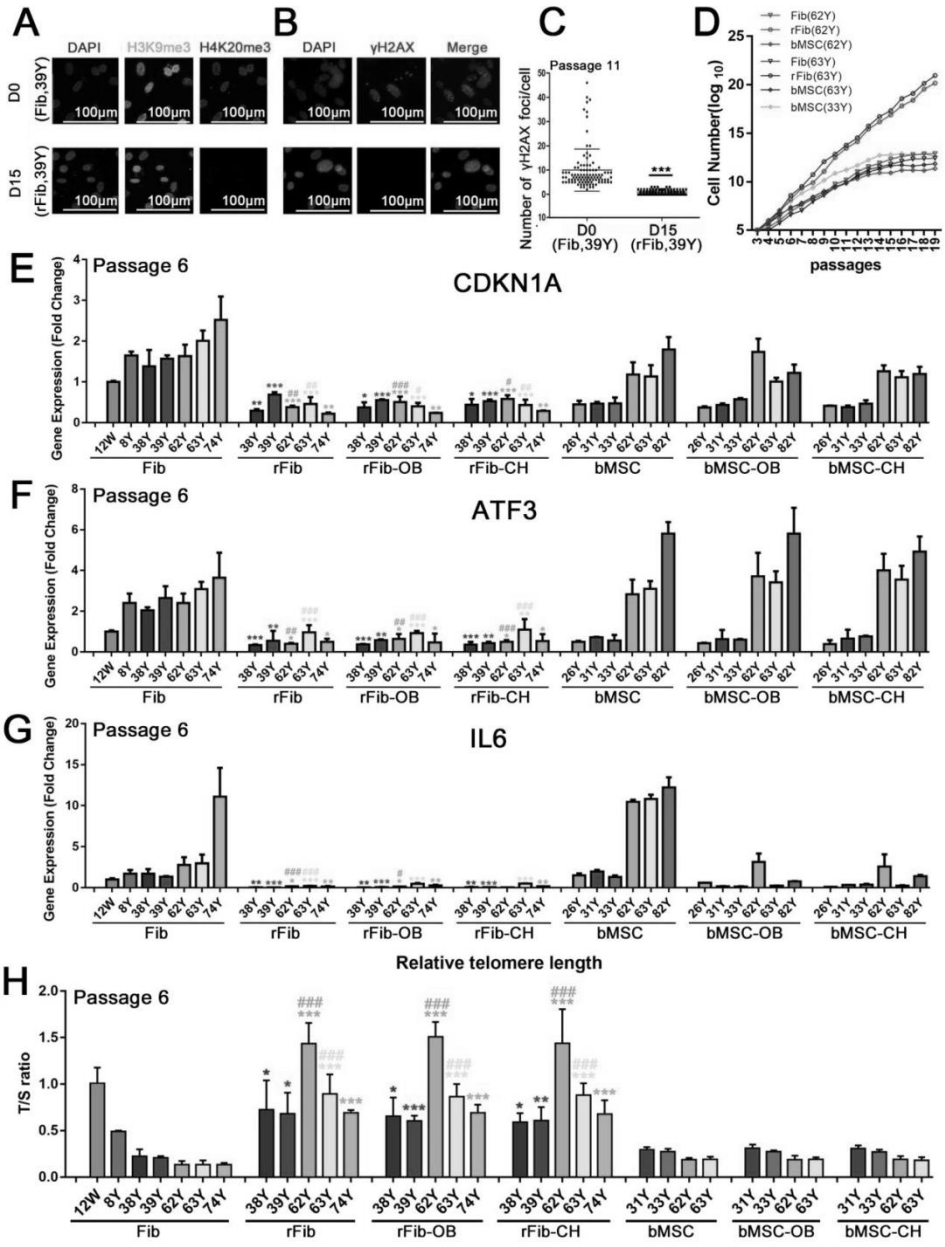

A
DAPI
H3K9me3
H4K20me3
D0
(Fib,39Y)
D15
(rFib,39Y)
100μm
B
DAPI
γH2AX
Merge
C
Passage 11
Number of γH2AX foci/cell
D0
(Fib,39Y)
D15
(rFib,39Y)
***
D
Fib(62Y)
rFib(62Y)
bMSC(62Y)
Fib(63Y)
rFib(63Y)
bMSC(63Y)
bMSC(33Y)
Cell Number(log 10)
passages
E
Passage 6
CDKN1A
Gene Expression (Fold Change)
F
Passage 6
ATF3
Gene Expression (Fold Change)
G
Passage 6
IL6
Gene Expression (Fold Change)
12W 8Y 38Y 39Y 62Y 63Y 74Y
26Y 31Y 33Y 62Y 63Y 82Y
Fib
rFib
rFib-OB
rFib-CH
bMSC
bMSC-OB
bMSC-CH
Relative telomere length
H
Passage 6
T/S ratio

FIG. 2

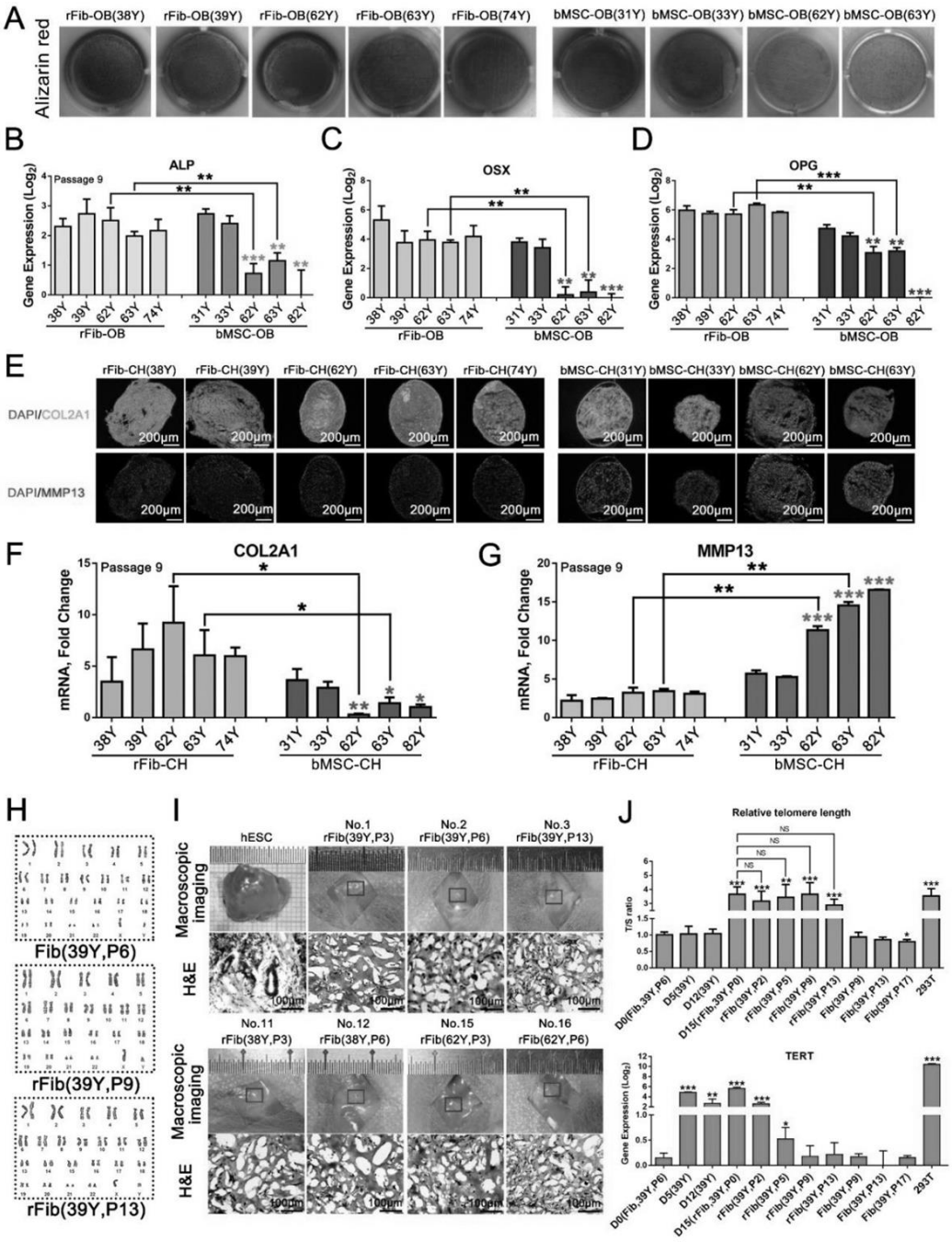

A
Alizarin red
rFib-OB(38Y)
rFib-OB(39Y)
rFib-OB(62Y)
rFib-OB(63Y)
rFib-OB(74Y)
bMSC-OB(31Y)
bMSC-OB(33Y)
bMSC-OB(62Y)
bMSC-OB(63Y)
B
ALP
C
OSX
D
OPG
Gene Expression (Log2)
Passage 9
rFib-OB
bMSC-OB
E
rFib-CH(38Y)
rFib-CH(39Y)
rFib-CH(62Y)
rFib-CH(63Y)
rFib-CH(74Y)
bMSC-CH(31Y)
bMSC-CH(33Y)
bMSC-CH(62Y)
bMSC-CH(63Y)
DAPI/COL2A1
DAPI/MMP13
200μm
F
COL2A1
G
MMP13
mRNA, Fold Change
rFib-CH
bMSC-CH
H
Fib(39Y,P6)
rFib(39Y,P9)
rFib(39Y,P13)
I
hESC
No.1 rFib(39Y,P3)
No.2 rFib(39Y,P6)
No.3 rFib(39Y,P13)
No.11 rFib(38Y,P3)
No.12 rFib(38Y,P6)
No.15 rFib(62Y,P3)
No.16 rFib(62Y,P6)
Macroscopic imaging
H&E
100μm
J
Relative telomere length
T/S ratio
TERT
Gene Expression (Log2)
D0(Fib,39Y,P6)
D5(39Y)
D12(39Y)
D15(rFib,39Y,P0)
rFib(39Y,P2)
rFib(39Y,P5)
rFib(39Y,P9)
rFib(39Y,P13)
Fib(39Y,P9)
Fib(39Y,P13)
Fib(39Y,P17)
293T

FIG. 3

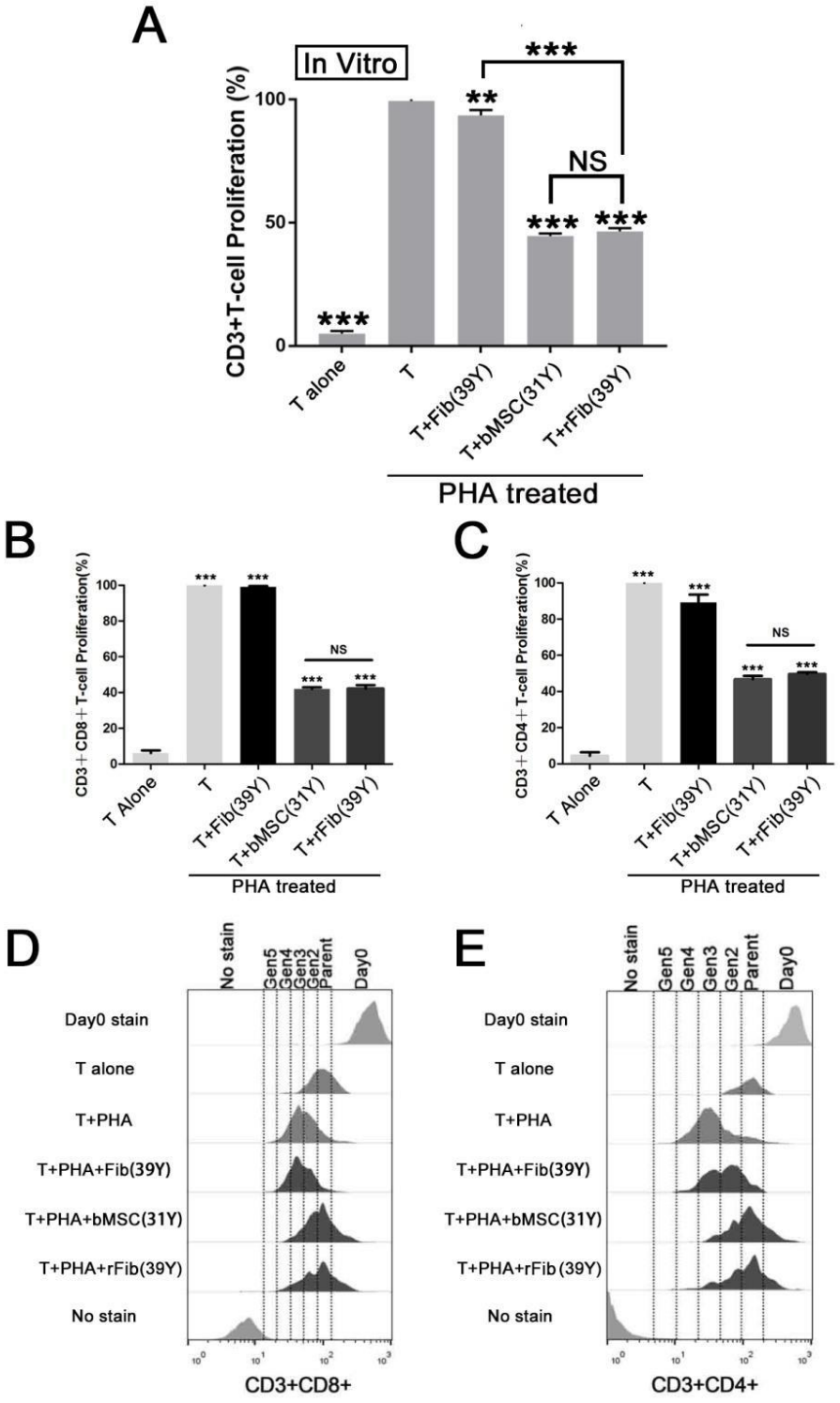

A
In Vitro
CD3+T-cell Proliferation (%)
100
50
0
***
**
***
***
NS
***
T alone
T
T+Fib(39Y)
T+bMSC(31Y)
T+rFib(39Y)
PHA treated
B
CD3+CD8+T-cell Proliferation(%)
T Alone
T
T+Fib(39Y)
T+bMSC(31Y)
T+rFib(39Y)
PHA treated
C
CD3+CD4+T-cell Proliferation(%)
T Alone
T
T+Fib(39Y)
T+bMSC(31Y)
T+rFib(39Y)
PHA treated
D
No stain
Gen5
Gen4
Gen3
Gen2
Parent
Day0
Day0 stain
T alone
T+PHA
T+PHA+Fib(39Y)
T+PHA+bMSC(31Y)
T+PHA+rFib(39Y)
No stain
CD3+CD8+
E
CD3+CD4+

FIG. 4

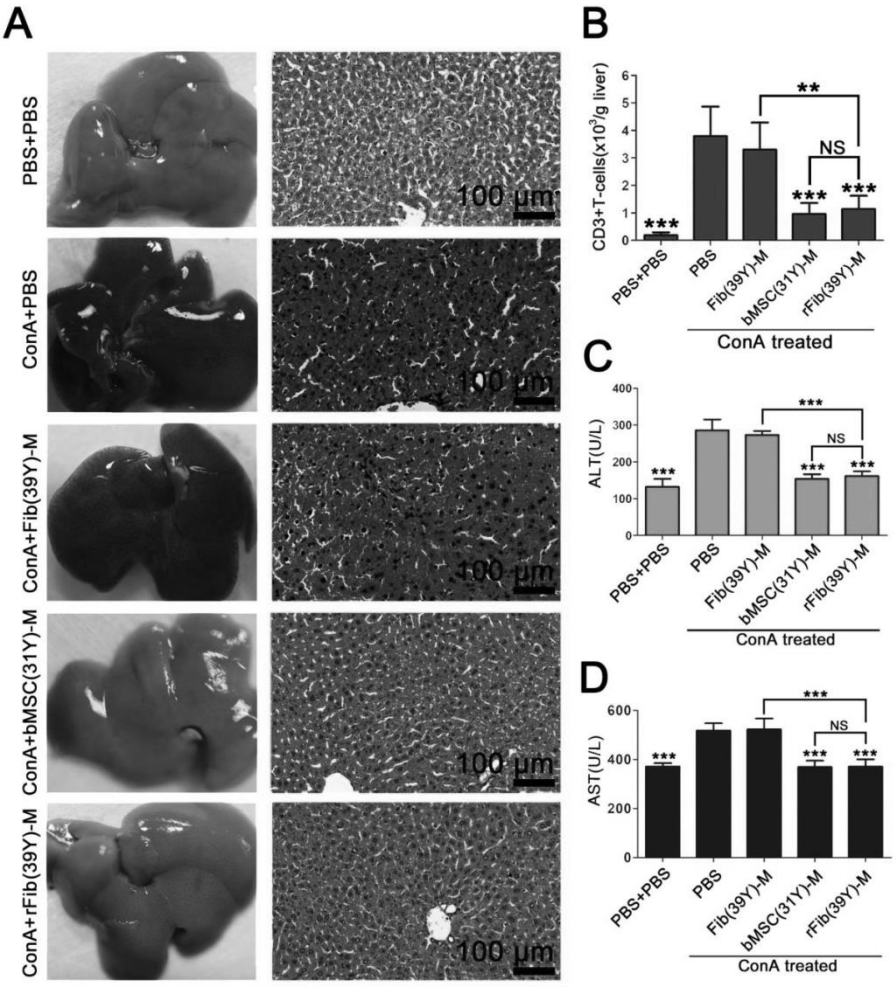

A
PBS+PBS
ConA+PBS
ConA+Fib(39Y)-M
ConA+bMSC(31Y)-M
ConA+rFib(39Y)-M
100 μm
B
CD3+T-cells(x10^3/g liver)
**
NS
***
PBS+PBS
PBS
Fib(39Y)-M
bMSC(31Y)-M
rFib(39Y)-M
ConA treated
C
ALT(U/L)
D
AST(U/L)

FIG. 5

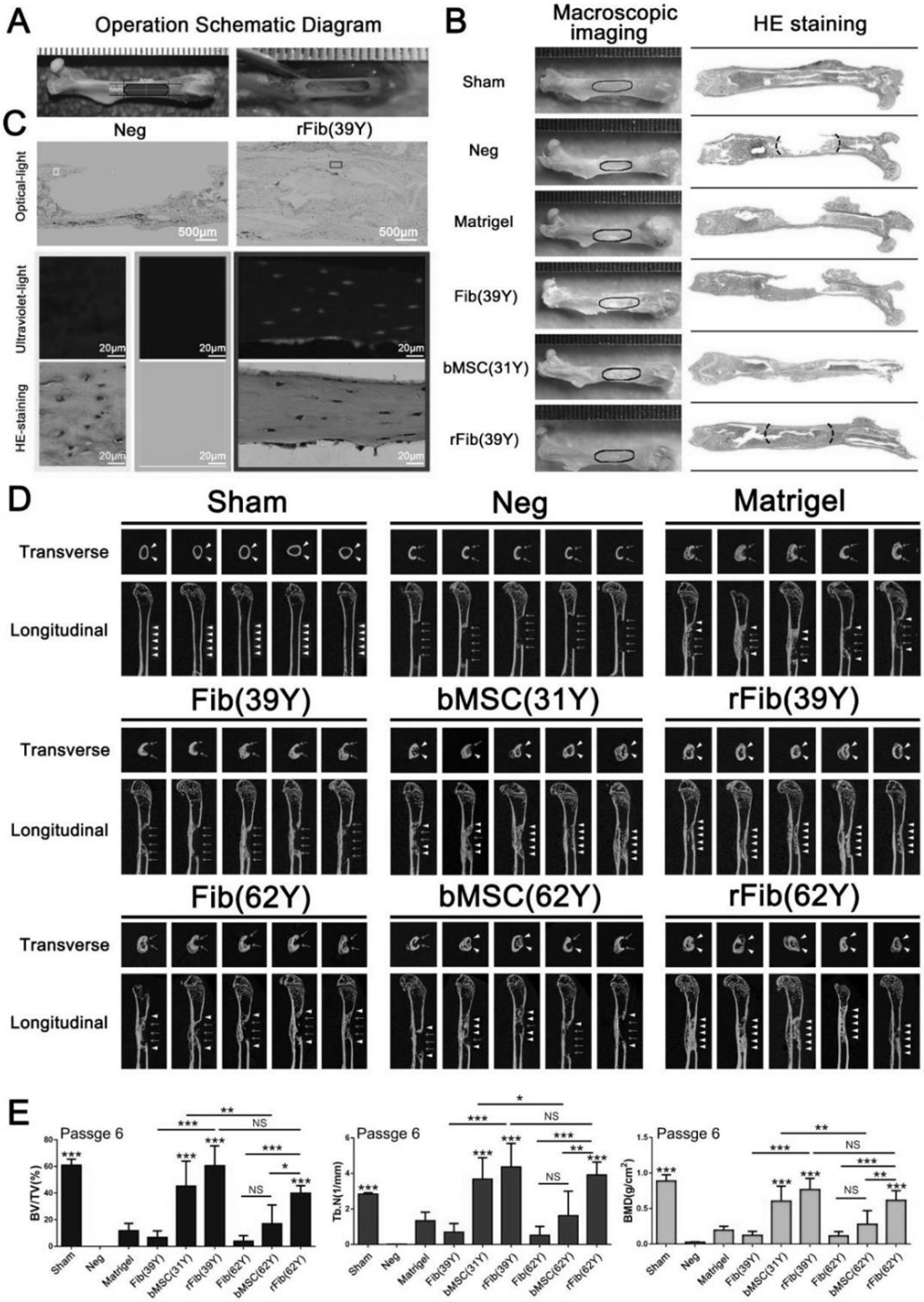

A
Operation Schematic Diagram
B
Macroscopic imaging
HE staining
Sham
Neg
Matrigel
Fib(39Y)
bMSC(31Y)
rFib(39Y)
C
Neg
rFib(39Y)
Optical-light
Ultraviolet-light
HE-staining
500μm
20μm
D
Sham
Neg
Matrigel
Fib(39Y)
bMSC(31Y)
rFib(39Y)
Fib(62Y)
bMSC(62Y)
rFib(62Y)
Transverse
Longitudinal
E
Passge 6
BV/TV(%)
Tb.N(1/mm)
BMD(g/cm²)
NS

FIG. 6

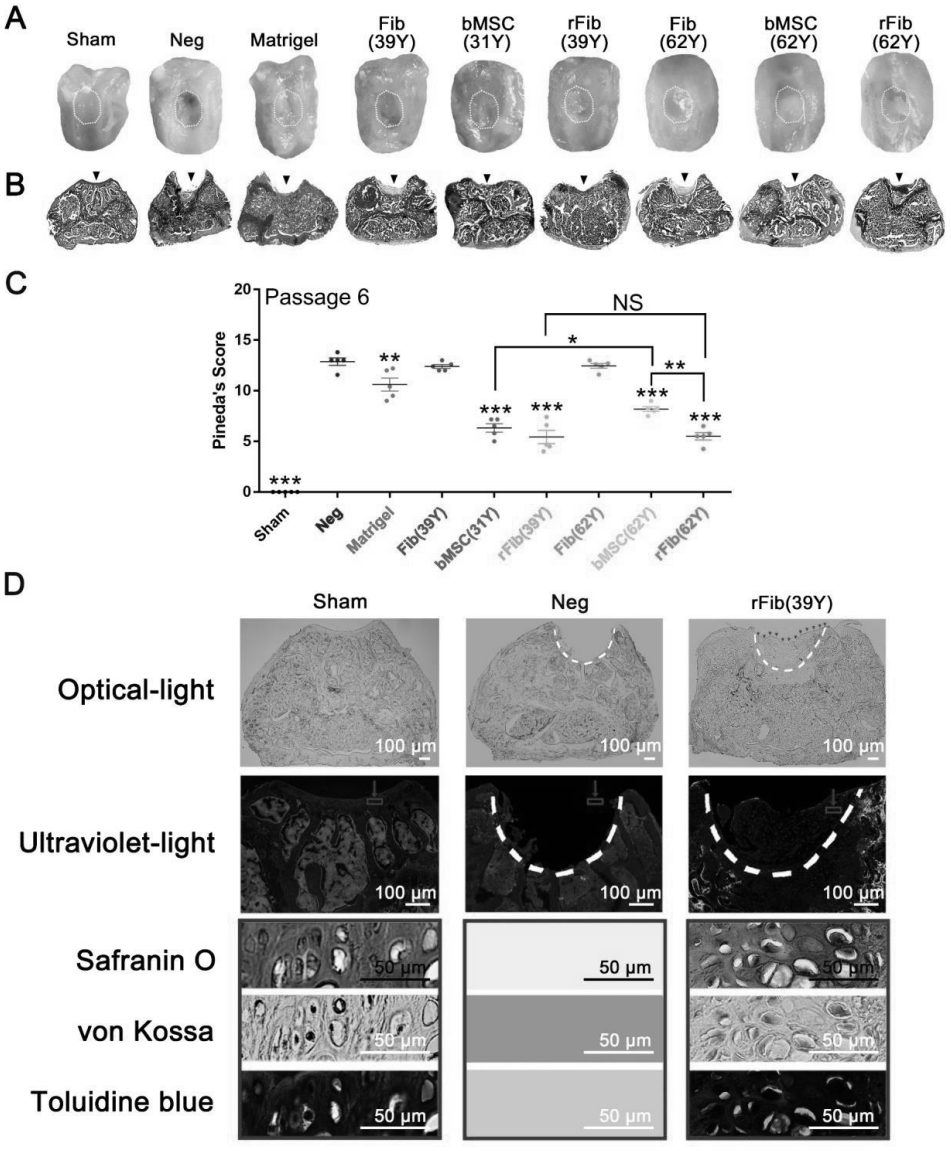

A
Sham
Neg
Matrigel
Fib (39Y)
bMSC (31Y)
rFib (39Y)
Fib (62Y)
bMSC (62Y)
rFib (62Y)
B
C
Passage 6
Pineda's Score
NS
Sham
Neg
Matrigel
Fib(39Y)
bMSC(31Y)
rFib(39Y)
Fib(62Y)
bMSC(62Y)
rFib(62Y)
D
Sham
Neg
rFib(39Y)
Optical-light
Ultraviolet-light
Safranin O
von Kossa
Toluidine blue
100 μm
50 μm

FIG. 7

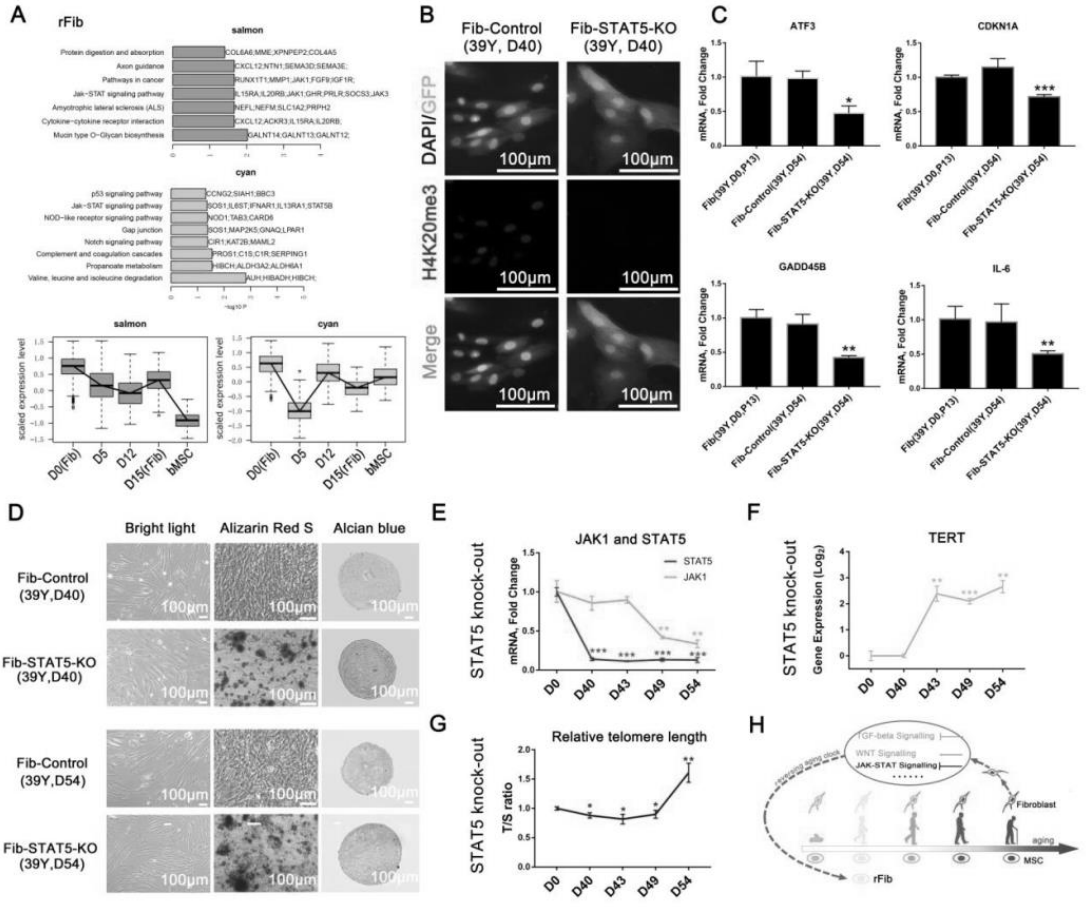

A
rFib
salmon
Protein digestion and absorption
Axon guidance
Pathways in cancer
Jak−STAT signaling pathway
Amyotrophic lateral sclerosis (ALS)
Cytokine−cytokine receptor interaction
Mucin type O−Glycan biosynthesis
cyan
p53 signaling pathway
Jak−STAT signaling pathway
NOD−like receptor signaling pathway
Gap junction
Notch signaling pathway
Complement and coagulation cascades
Propanoate metabolism
Valine, leucine and isoleucine degradation
salmon
cyan
scaled expression level
D0(Fib)
D5
D12
D15(rFib)
bMSC
B
Fib-Control (39Y, D40)
Fib-STAT5-KO (39Y, D40)
DAPI/GFP
H4K20me3
Merge
100μm
C
ATF3
CDKN1A
GADD45B
IL-6
mRNA, Fold Change
Fib(39Y,D0,P13)
Fib-Control(39Y,D54)
Fib-STAT5-KO(39Y,D54)
D
Bright light
Alizarin Red S
Alcian blue
Fib-Control (39Y,D40)
Fib-STAT5-KO (39Y,D40)
Fib-Control (39Y,D54)
Fib-STAT5-KO (39Y,D54)
E
JAK1 and STAT5
STAT5 knock-out
STAT5
JAK1
mRNA, Fold Change
D0
D40
D43
D49
D54
F
TERT
STAT5 knock-out
Gene Expression (Log2)
G
Relative telomere length
STAT5 knock-out
T/S ratio
H
TGF-beta Signalling
WNT Signalling
JAK-STAT Signalling
Fibroblast
aging
MSC
rFib

FIG. 8

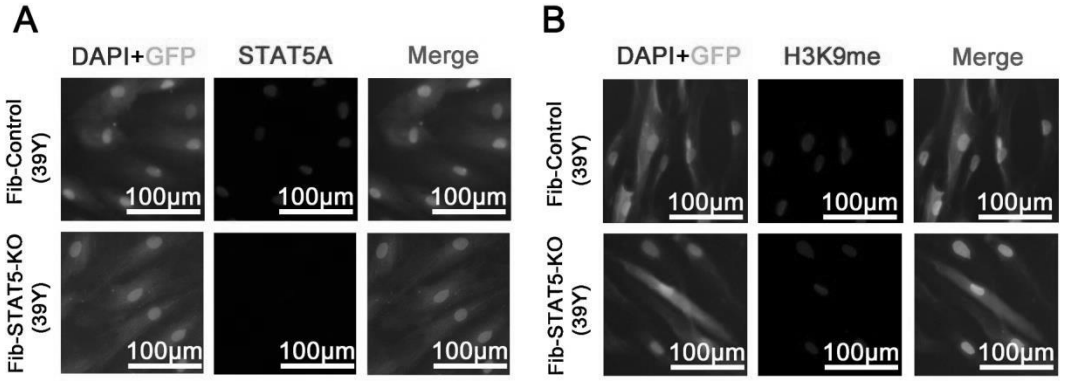

A
DAPI+GFP
STAT5A
Merge
Fib-Control (39Y)
Fib-STAT5-KO (39Y)
100μm
B
DAPI+GFP
H3K9me
Merge
Fib-Control (39Y)
Fib-STAT5-KO (39Y)
100μm

FIG. 9

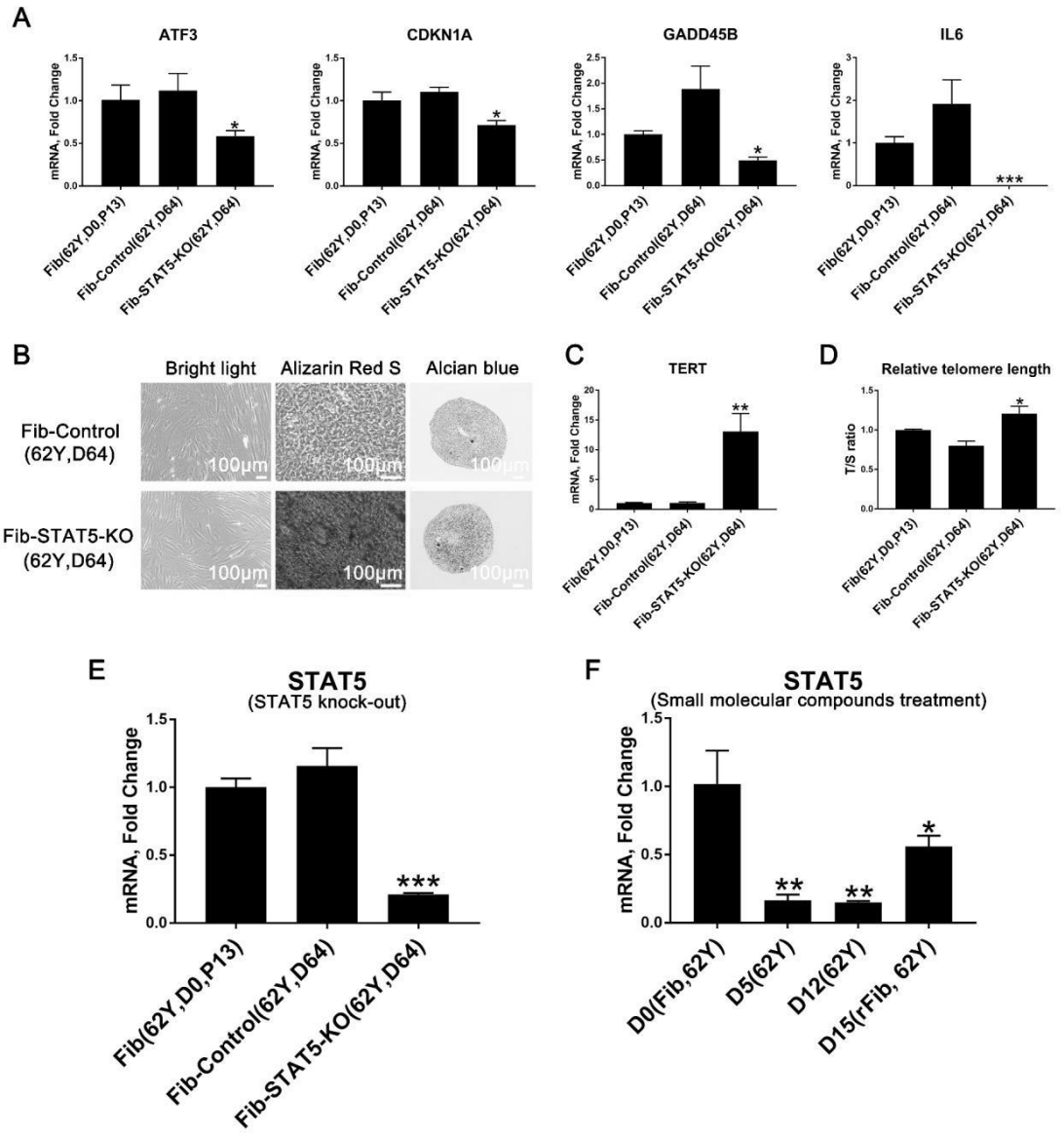

A
ATF3
CDKN1A
GADD45B
IL6
mRNA, Fold Change
Fib(62Y,D0,P13)
Fib-Control(62Y,D64)
Fib-STAT5-KO(62Y,D64)
B
Bright light
Alizarin Red S
Alcian blue
Fib-Control (62Y,D64)
Fib-STAT5-KO (62Y,D64)
100μm
C
TERT
D
Relative telomere length
T/S ratio
E
STAT5
(STAT5 knock-out)
F
STAT5
(Small molecular compounds treatment)
D0(Fib,62Y)
D5(62Y)
D12(62Y)
D15(rFib, 62Y)

FIG. 10

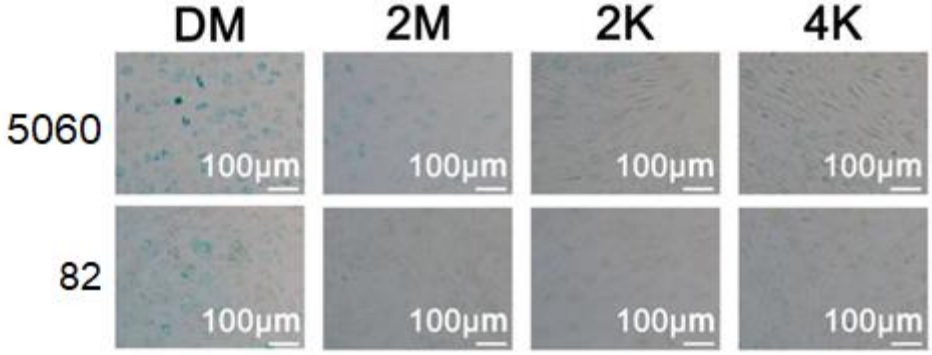

DM
2M
2K
4K
5060
82
100μm

FIG. 11

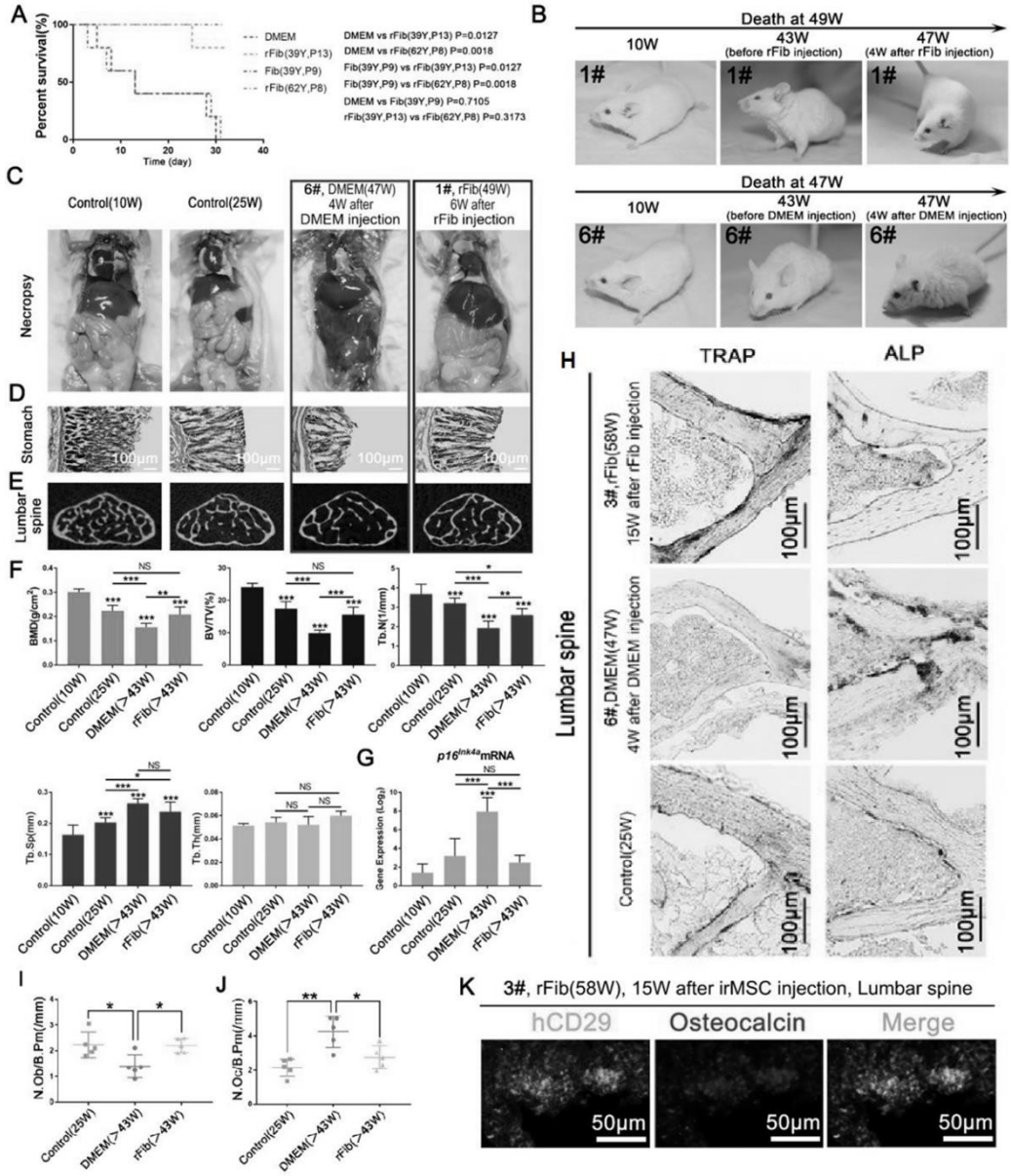

A
Percent survival(%)
Time (day)
DMEM
rFib(39Y,P13)
Fib(39Y,P9)
rFib(62Y,P8)
DMEM vs rFib(39Y,P13) P=0.0127
DMEM vs rFib(62Y,P8) P=0.0018
Fib(39Y,P9) vs rFib(39Y,P13) P=0.0127
Fib(39Y,P9) vs rFib(62Y,P8) P=0.0018
DMEM vs Fib(39Y,P9) P=0.7105
rFib(39Y,P13) vs rFib(62Y,P8) P=0.3173
B
Death at 49W
10W
43W
(before rFib injection)
47W
(4W after rFib injection)
1#
Death at 47W
10W
43W
(before DMEM injection)
47W
(4W after DMEM injection)
6#
C
Control(10W)
Control(25W)
6#, DMEM(47W) 4W after DMEM injection
1#, rFib(49W) 6W after rFib injection
Necropsy
D
Stomach
100μm
E
Lumbar spine
F
BMD(g/cm²)
BV/TV(%)
Tb.N(1/mm)
Control(10W)
Control(25W)
DMEM(>43W)
rFib(>43W)
G
p16Ink4a mRNA
Gene Expression (Log2)
Tb.Sp(mm)
Tb.Th(mm)
H
TRAP
ALP
Lumbar spine
3#,rFib(58W) 15W after rFib injection
6#,DMEM(47W) 4W after DMEM injection
Control(25W)
100μm
I
N.Ob/B.Pm(/mm)
J
N.Oc/B.Pm(/mm)
K
3#, rFib(58W), 15W after irMSC injection, Lumbar spine
hCD29
Osteocalcin
Merge
50μm

FIG. 12

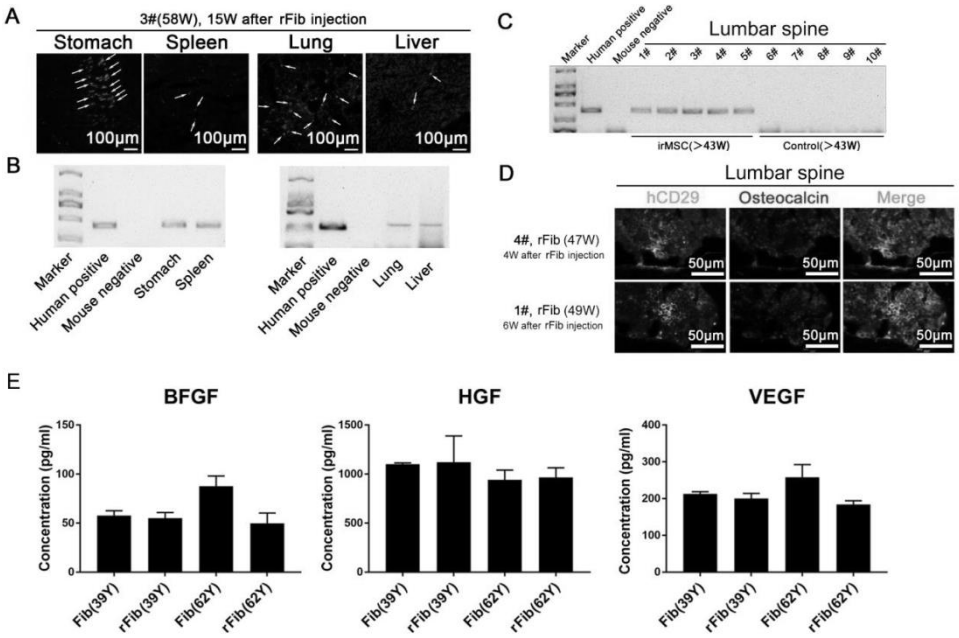

A
3#(58W), 15W after rFib injection
Stomach
Spleen
Lung
Liver
100μm
B
Marker
Human positive
Mouse negative
Stomach
Spleen
Lung
Liver
C
Lumbar spine
Marker
Human positive
Mouse negative
1#
2#
3#
4#
5#
6#
7#
8#
9#
10#
irMSC(>43W)
Control(>43W)
D
Lumbar spine
hCD29
Osteocalcin
Merge
4#, rFib (47W)
4W after rFib injection
1#, rFib (49W)
6W after rFib injection
50μm
E
BFGF
HGF
VEGF
Concentration (pg/ml)
Fib(39Y)
rFib(39Y)
Fib(62Y)
rFib(62Y)

FIG. 13

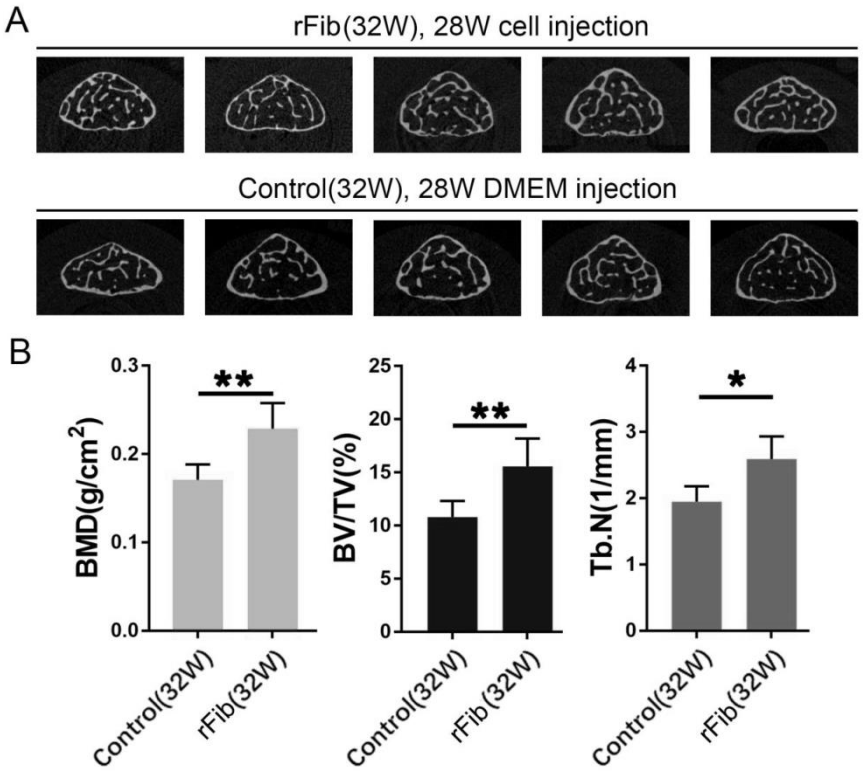

A
rFib(32W), 28W cell injection
Control(32W), 28W DMEM injection
B
BMD(g/cm2)
0.3
0.2
0.1
0.0
**
Control(32W)
rFib(32W)
BV/TV(%)
25
20
15
10
5
0
**
Control(32W)
rFib(32W)
Tb.N(1/mm)
4
3
2
1
0
*
Control(32W)
rFib(32W)

FIG. 14

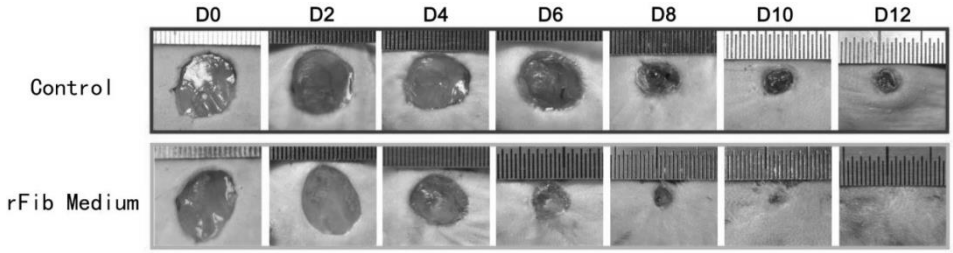

D0
D2
D4
D6
D8
D10
D12
Control
rFib Medium

FIG. 15

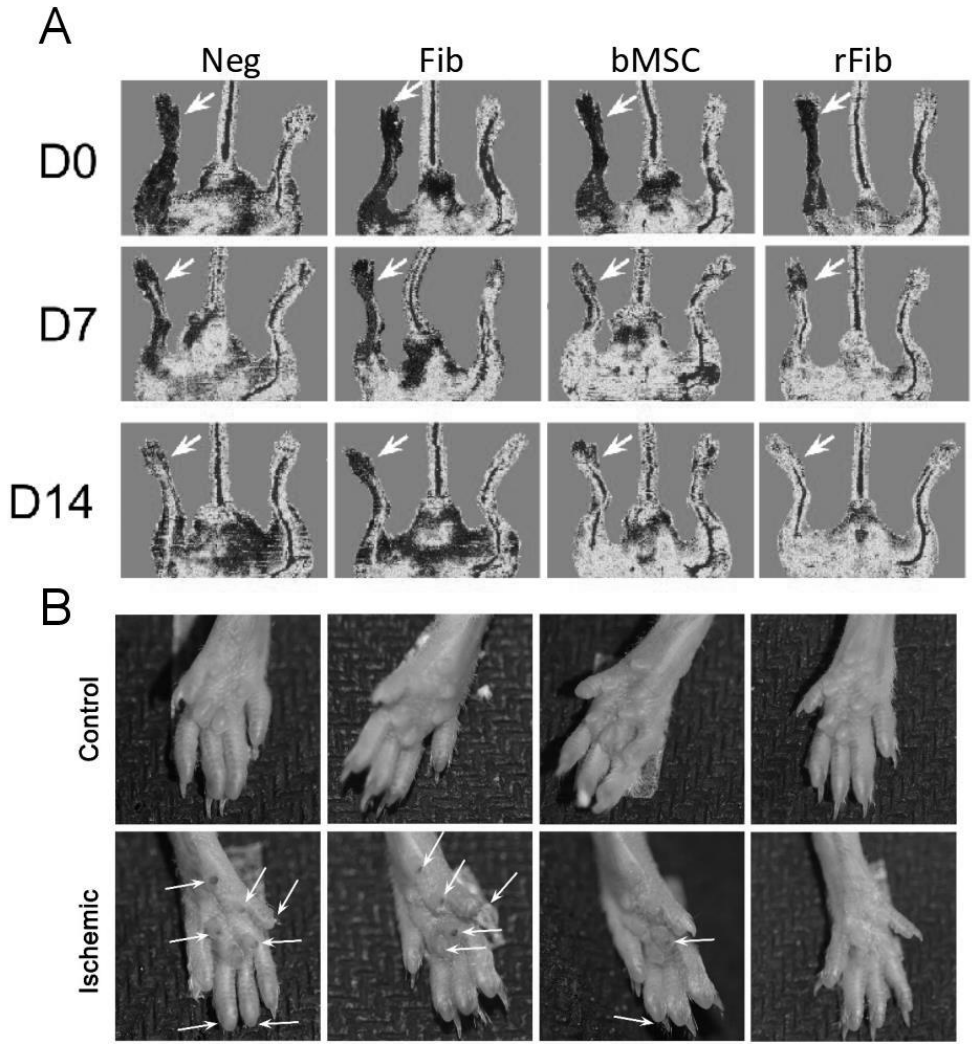

A
Neg
Fib
bMSC
rFib
D0
D7
D14
B
Control
Ischemic

FIG. 16

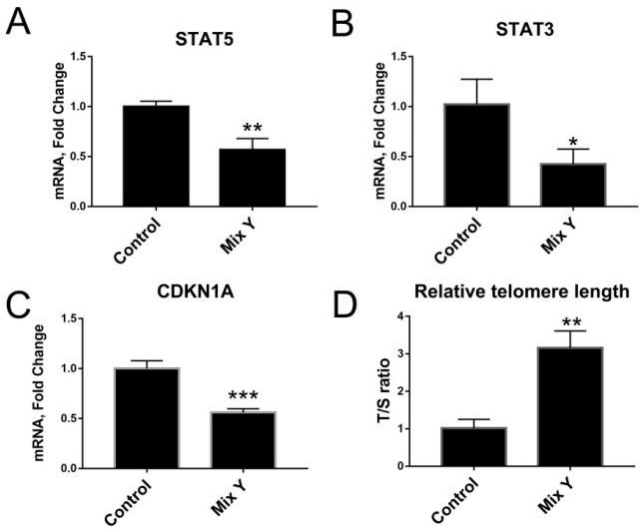

A
STAT5
mRNA, Fold Change
1.5
1.0
0.5
0.0
**
Control
Mix Y
B
STAT3
mRNA, Fold Change
1.5
1.0
0.5
0.0
*
Control
Mix Y
C
CDKN1A
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Y
D
Relative telomere length
T/S ratio
4
3
2
1
0
**
Control
Mix Y

FIG. 17

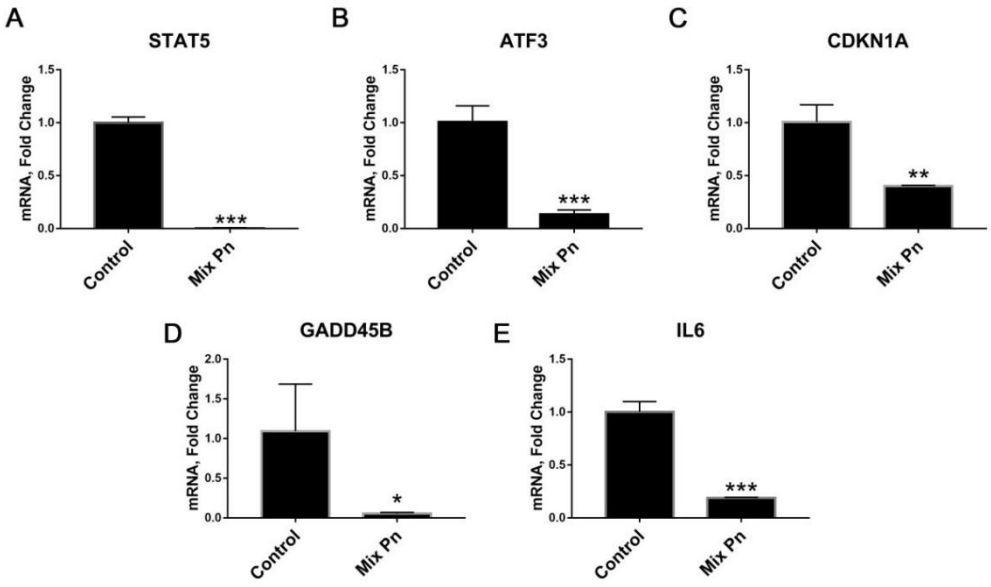

A
STAT5
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Pn
B
ATF3
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Pn
C
CDKN1A
mRNA, Fold Change
1.5
1.0
0.5
0.0
**
Control
Mix Pn
D
GADD45B
mRNA, Fold Change
2.0
1.5
1.0
0.5
0.0
*
Control
Mix Pn
E
IL6
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Pn

FIG. 18

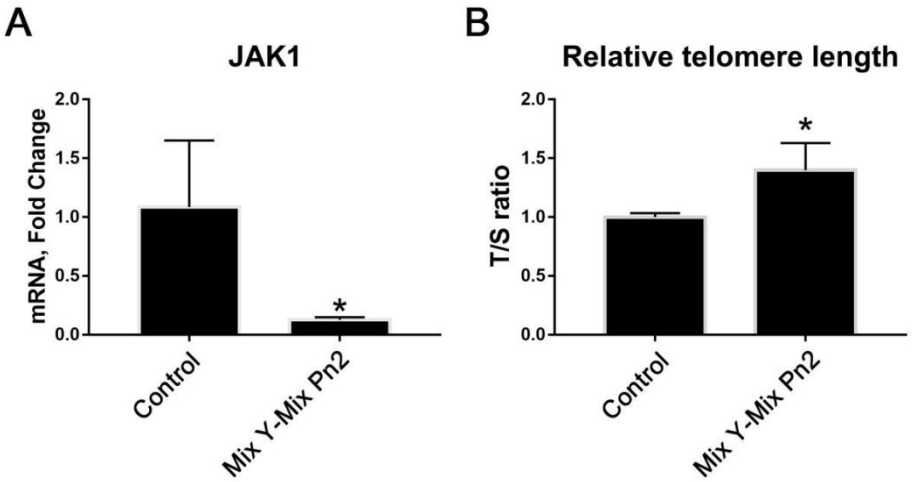

A
JAK1
mRNA, Fold Change
2.0
1.5
1.0
0.5
0.0
*
Control
Mix Y-Mix Pn2
B
Relative telomere length
T/S ratio
2.0
1.5
1.0
0.5
0.0
*
Control
Mix Y-Mix Pn2

FIG. 19

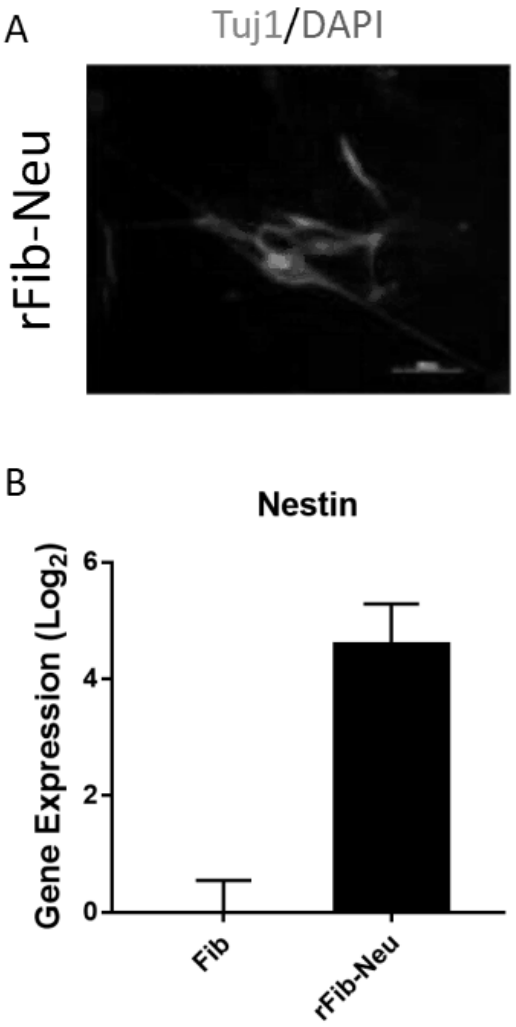

A
Tuj1/DAPI
rFib-Neu
B
Nestin
Gene Expression (Log2)
6
4
2
0
Fib
rFib-Neu

FIG. 20

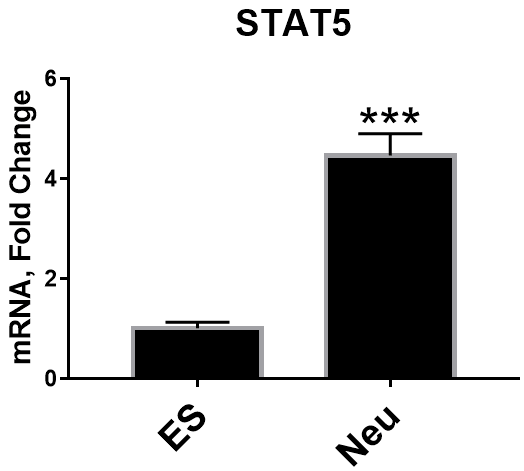

STAT5
mRNA, Fold Change
6
4
2
0
***
ES
Neu

FIG. 21

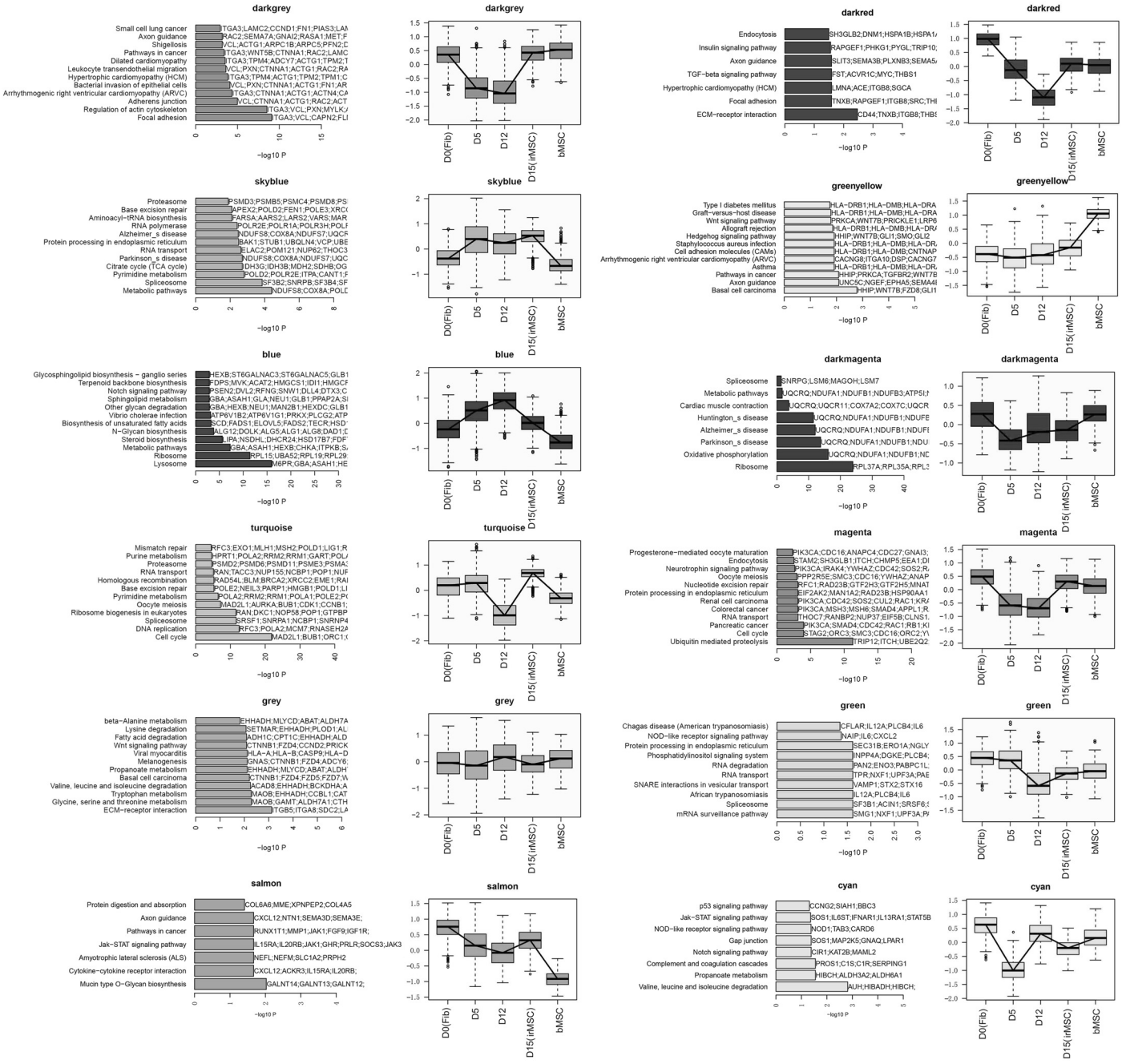

darkgrey
Small cell lung cancer
Axon guidance
Shigellosis
Pathways in cancer
Dilated cardiomyopathy
Leukocyte transendothelial migration
Hypertrophic cardiomyopathy (HCM)
Bacterial invasion of epithelial cells
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Adherens junction
Regulation of actin cytoskeleton
Focal adhesion
−log10 P
darkgrey
D0(Fib)
D5
D12
D15(irMSC)
bMSC
darkred
Endocytosis
Insulin signaling pathway
Axon guidance
TGF−beta signaling pathway
Hypertrophic cardiomyopathy (HCM)
Focal adhesion
ECM−receptor interaction
−log10 P
darkred
skyblue
Proteasome
Base excision repair
Aminoacyl−tRNA biosynthesis
RNA polymerase
Alzheimer_s disease
Protein processing in endoplasmic reticulum
RNA transport
Parkinson_s disease
Citrate cycle (TCA cycle)
Pyrimidine metabolism
Spliceosome
Metabolic pathways
−log10 P
skyblue
greenyellow
Type I diabetes mellitus
Graft−versus−host disease
Wnt signaling pathway
Allograft rejection
Hedgehog signaling pathway
Staphylococcus aureus infection
Cell adhesion molecules (CAMs)
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Asthma
Pathways in cancer
Axon guidance
Basal cell carcinoma
−log10 P
greenyellow
blue
Glycosphingolipid biosynthesis − ganglio series
Terpenoid backbone biosynthesis
Notch signaling pathway
Sphingolipid metabolism
Other glycan degradation
Vibrio cholerae infection
Biosynthesis of unsaturated fatty acids
N−Glycan biosynthesis
Steroid biosynthesis
Metabolic pathways
Ribosome
Lysosome
−log10 P
blue
darkmagenta
Spliceosome
Metabolic pathways
Cardiac muscle contraction
Huntington_s disease
Alzheimer_s disease
Parkinson_s disease
Oxidative phosphorylation
Ribosome
−log10 P
darkmagenta
turquoise
Mismatch repair
Purine metabolism
Proteasome
RNA transport
Homologous recombination
Base excision repair
Pyrimidine metabolism
Oocyte meiosis
Ribosome biogenesis in eukaryotes
Spliceosome
DNA replication
Cell cycle
−log10 P
turquoise
magenta
Progesterone−mediated oocyte maturation
Endocytosis
Neurotrophin signaling pathway
Oocyte meiosis
Nucleotide excision repair
Protein processing in endoplasmic reticulum
Renal cell carcinoma
Colorectal cancer
RNA transport
Pancreatic cancer
Cell cycle
Ubiquitin mediated proteolysis
−log10 P
magenta
grey
beta−Alanine metabolism
Lysine degradation
Fatty acid degradation
Wnt signaling pathway
Viral myocarditis
Melanogenesis
Propanoate metabolism
Basal cell carcinoma
Valine, leucine and isoleucine degradation
Tryptophan metabolism
Glycine, serine and threonine metabolism
ECM−receptor interaction
−log10 P
grey
green
Chagas disease (American trypanosomiasis)
NOD−like receptor signaling pathway
Protein processing in endoplasmic reticulum
Phosphatidylinositol signaling system
RNA degradation
RNA transport
SNARE interactions in vesicular transport
African trypanosomiasis
Spliceosome
mRNA surveillance pathway
−log10 P
green
salmon
Protein digestion and absorption
Axon guidance
Pathways in cancer
Jak−STAT signaling pathway
Amyotrophic lateral sclerosis (ALS)
Cytokine−cytokine receptor interaction
Mucin type O−Glycan biosynthesis
−log10 P
salmon
cyan
p53 signaling pathway
Jak−STAT signaling pathway
NOD−like receptor signaling pathway
Gap junction
Notch signaling pathway
Complement and coagulation cascades
Propanoate metabolism
Valine, leucine and isoleucine degradation
−log10 P
cyan
D0(Fib)
D5
D12
D15(irMSC)
bMSC

FIG. 22