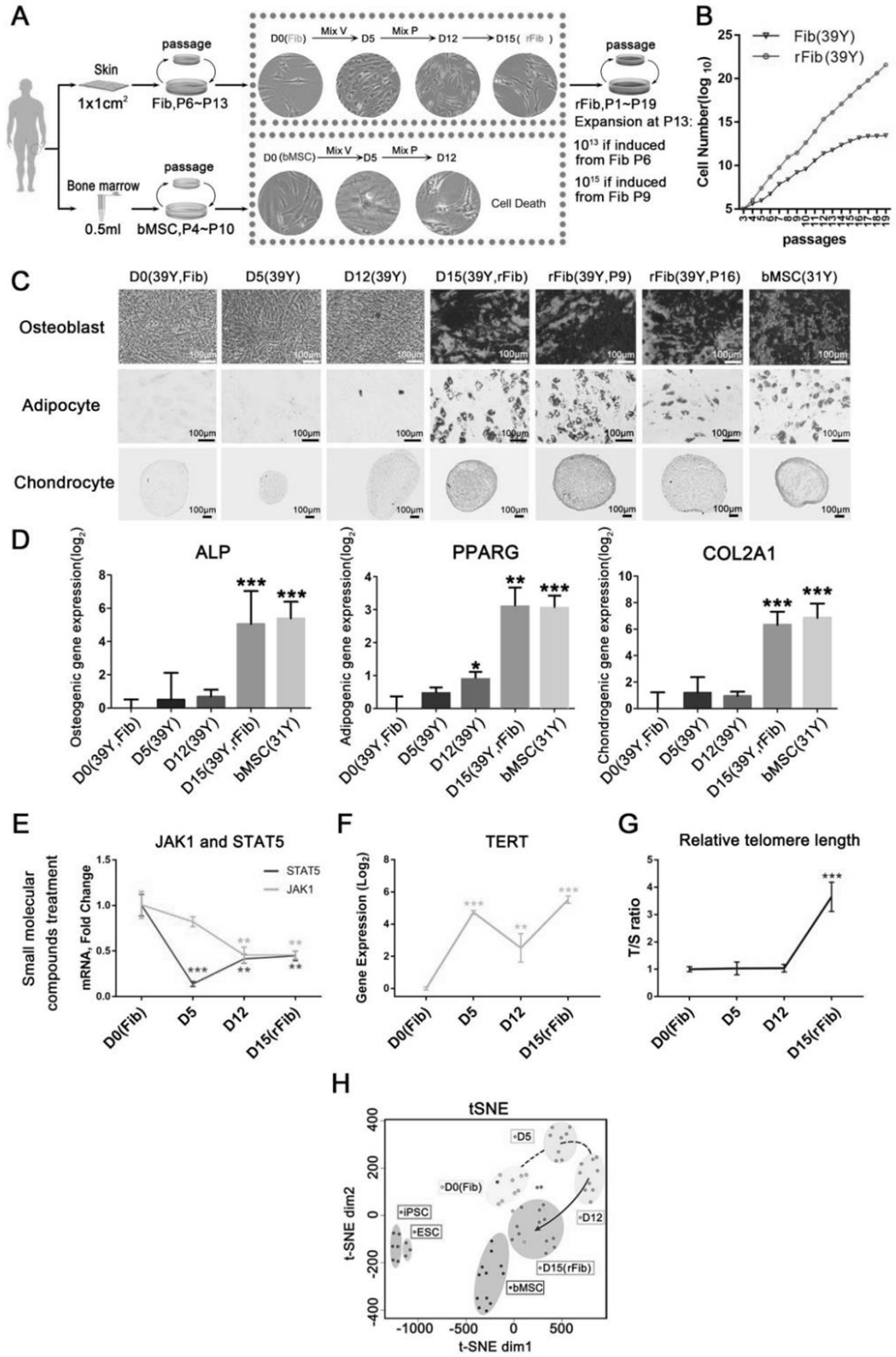

A
Skin
1x1cm²
passage
Fib,P6~P13
Bone marrow
0.5ml
passage
bMSC,P4~P10
D0(Fib)
Mix V
D5
Mix P
D12
D15(rFib)
D0 (bMSC)
Mix V
D5
Mix P
D12
Cell Death
passage
rFib,P1~P19
Expansion at P13:
10¹³ if induced from Fib P6
10¹⁵ if induced from Fib P9
B
Fib(39Y)
rFib(39Y)
Cell Number(log 10)
passages
C
D0(39Y,Fib)
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

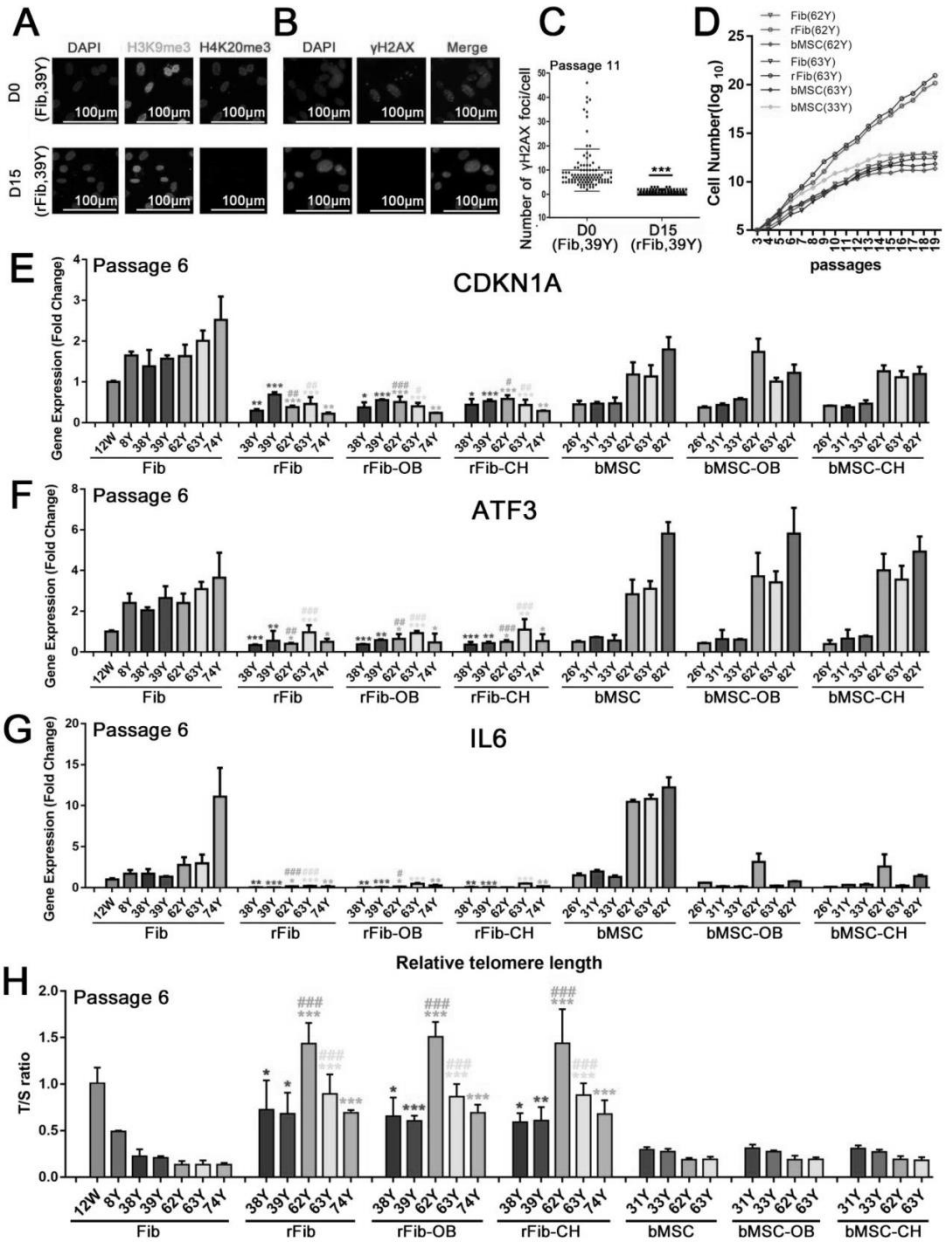

A
DAPI
H3K9me3
H4K20me3
D0
(Fib,39Y)
D15
(rFib,39Y)
100μm
B
DAPI
γH2AX
Merge
C
Passage 11
Number of γH2AX foci/cell
D0
(Fib,39Y)
D15
(rFib,39Y)
***
D
Fib(62Y)
rFib(62Y)
bMSC(62Y)
Fib(63Y)
rFib(63Y)
bMSC(63Y)
bMSC(33Y)
Cell Number(log 10)
passages
E
Passage 6
CDKN1A
Gene Expression (Fold Change)
F
Passage 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

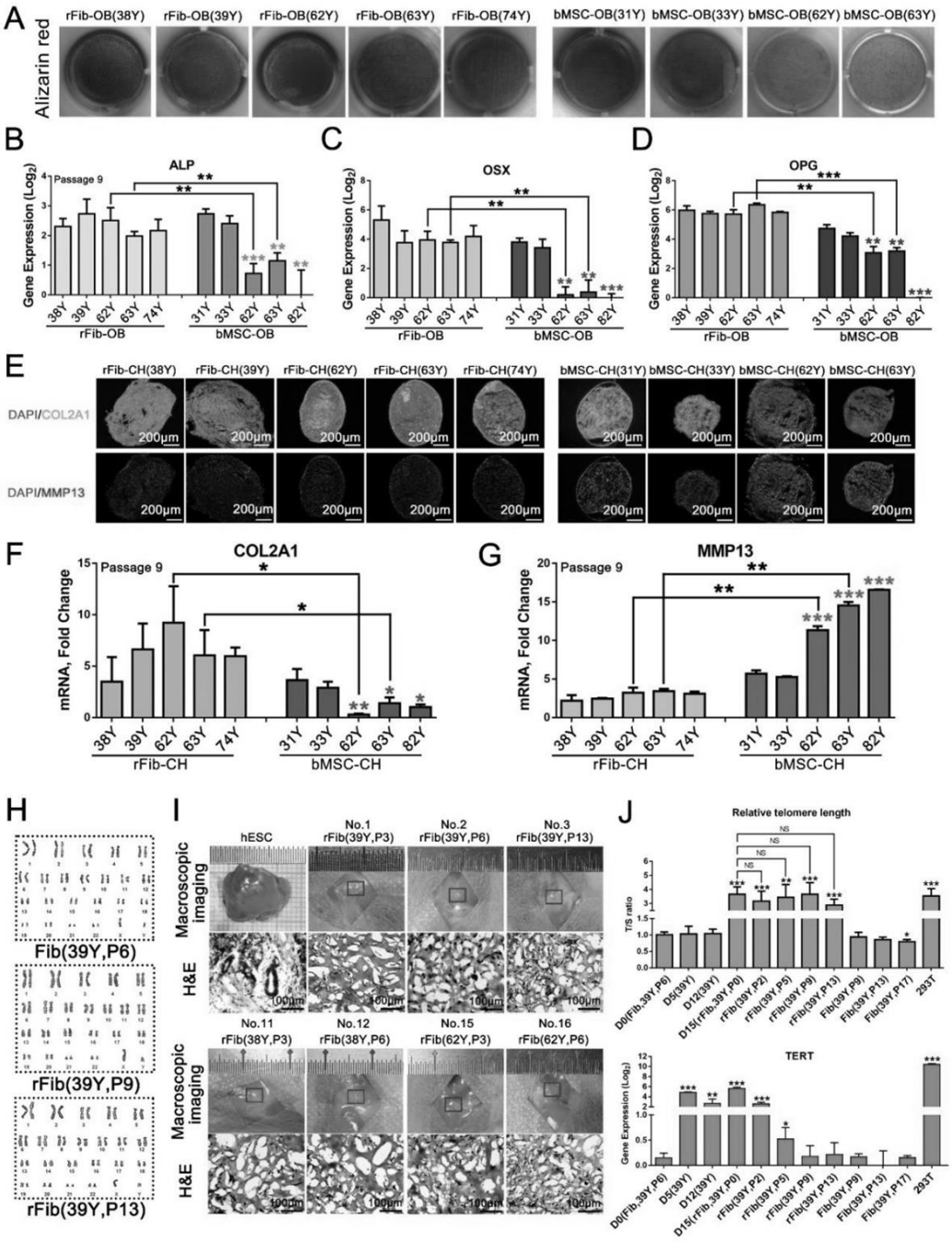

A
Alizarin red
rFib-OB(38Y)
rFib-OB(39Y)
rFib-OB(62Y)
rFib-OB(63Y)
rFib-OB(74Y)
bMSC-OB(31Y)
bMSC-OB(33Y)
bMSC-OB(62Y)
bMSC-OB(63Y)
B
ALP
C
OSX
D
OPG
Gene Expression (Log2)
Passage 9
rFib-OB
bMSC-OB
E
rFib-CH(38Y)
rFib-CH(39Y)
rFib-CH(62Y)
rFib-CH(63Y)
rFib-CH(74Y)
bMSC-CH(31Y)
bMSC-CH(33Y)
bMSC-CH(62Y)
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

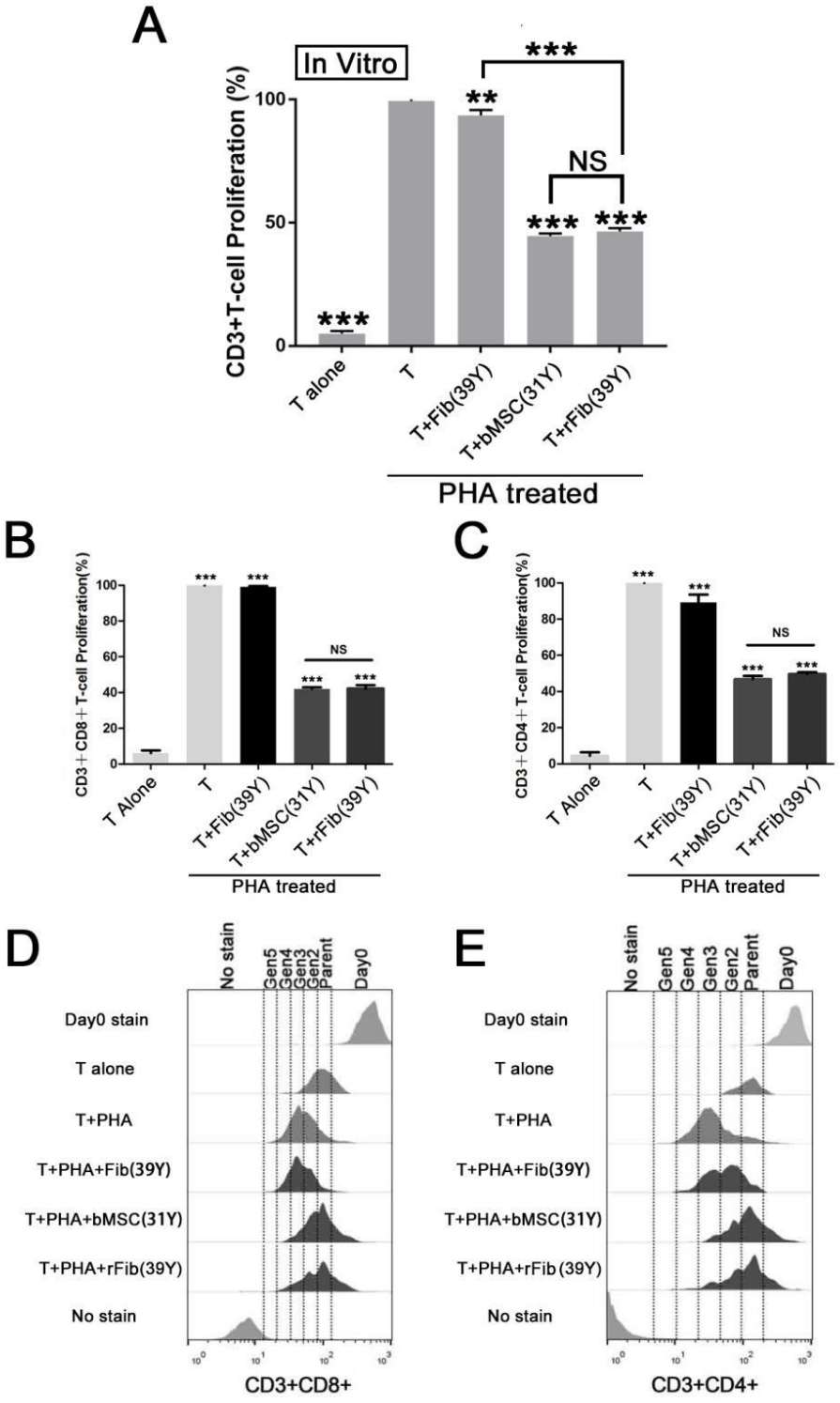

A
In Vitro
CD3+T-cell Proliferation (%)
100
50
0
***
**
***
***
NS
***
T alone
T
T+Fib(39Y)
T+bMSC(31Y)
T+rFib(39Y)
PHA treated
B
CD3+CD8+T-cell Proliferation(%)
T Alone
T
T+Fib(39Y)
T+bMSC(31Y)
T+rFib(39Y)
PHA treated
C
CD3+CD4+T-cell Proliferation(%)
T Alone
T
T+Fib(39Y)
T+bMSC(31Y)
T+rFib(39Y)
PHA 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

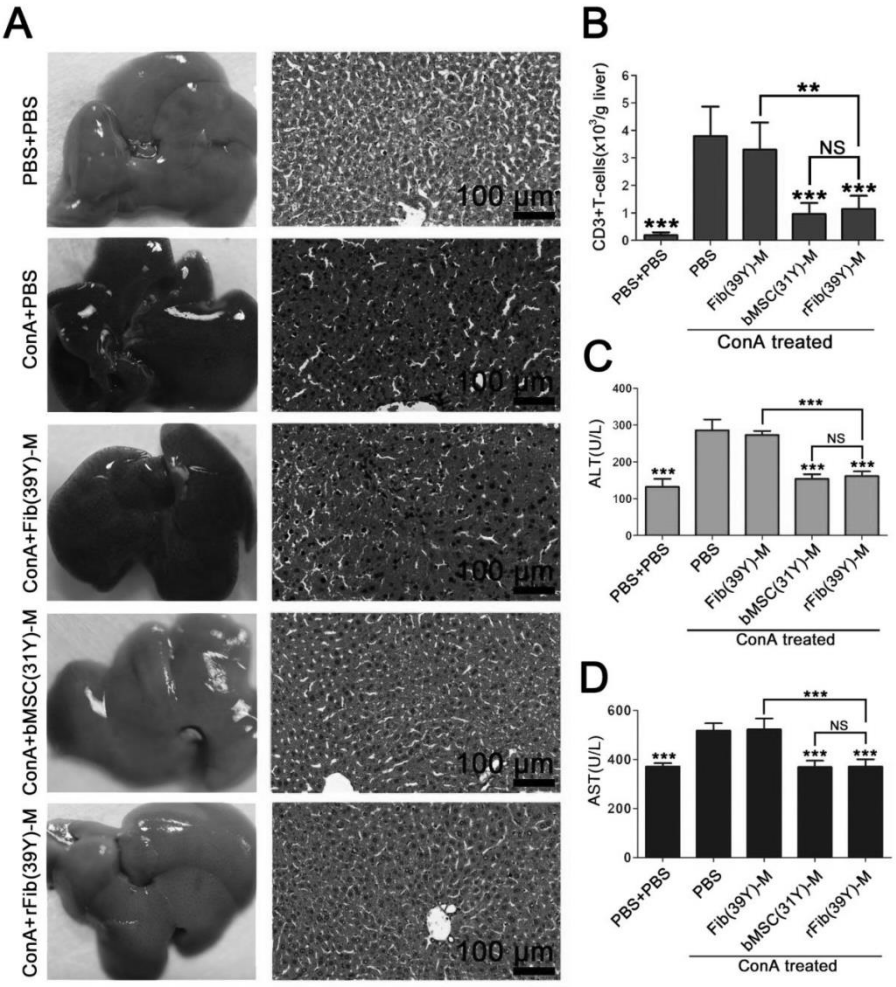

A
PBS+PBS
ConA+PBS
ConA+Fib(39Y)-M
ConA+bMSC(31Y)-M
ConA+rFib(39Y)-M
100 μm
B
CD3+T-cells(x10^3/g liver)
**
NS
***
PBS+PBS
PBS
Fib(39Y)-M
bMSC(31Y)-M
rFib(39Y)-M
ConA treated
C
ALT(U/L)
D
AST(U/L)

FIG. 5

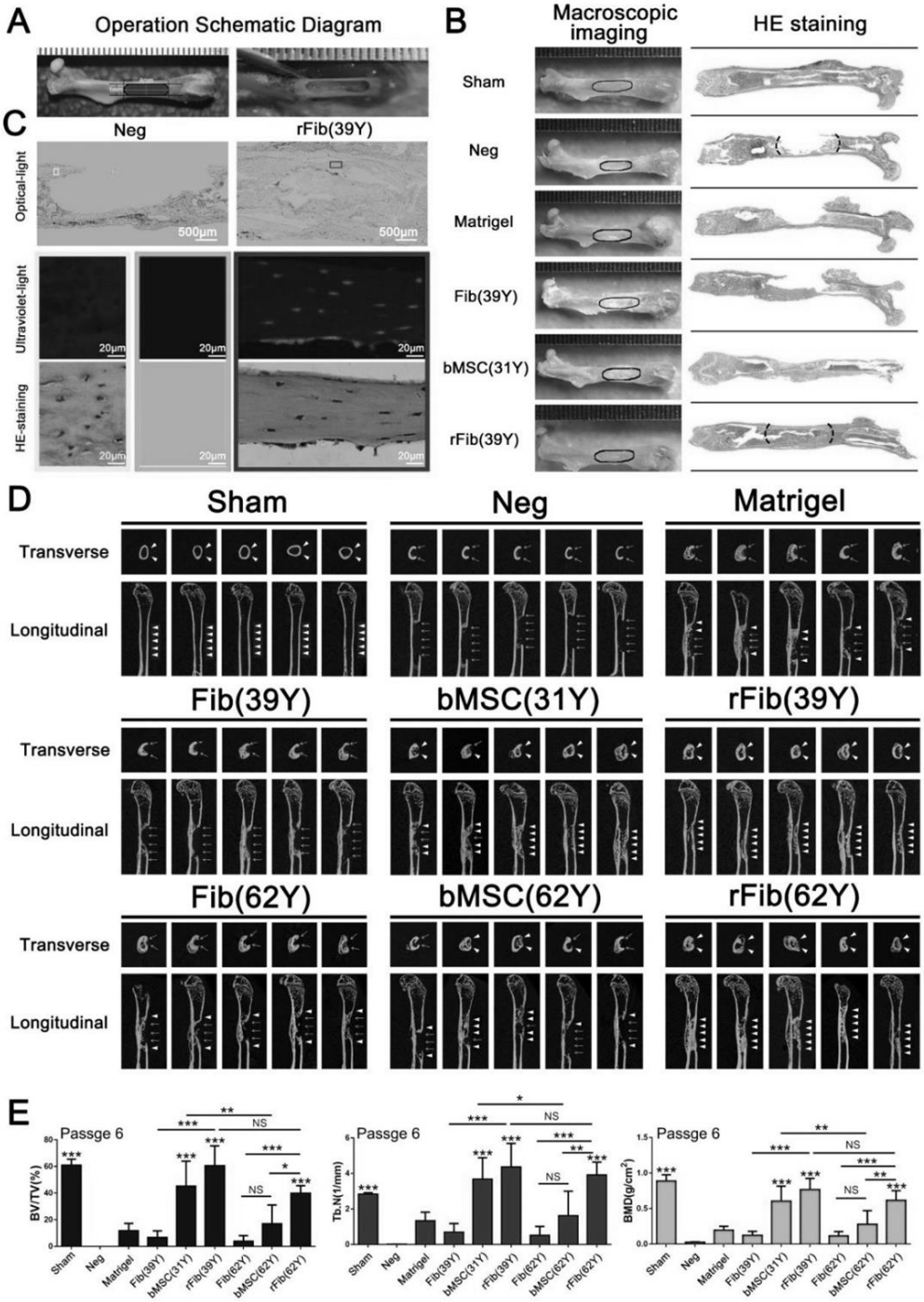

A
Operation Schematic Diagram
B
Macroscopic imaging
HE staining
Sham
Neg
Matrigel
Fib(39Y)
bMSC(31Y)
rFib(39Y)
C
Neg
rFib(39Y)
Optical-light
Ultraviolet-light
HE-staining
500μm
20μm
D
Sham
Neg
Matrigel
Fib(39Y)
bMSC(31Y)
rFib(39Y)
Fib(62Y)
bMSC(62Y)
rFib(62Y)
Transverse
Longitudinal
E
Passge 6
BV/TV(%)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

FIG. 6

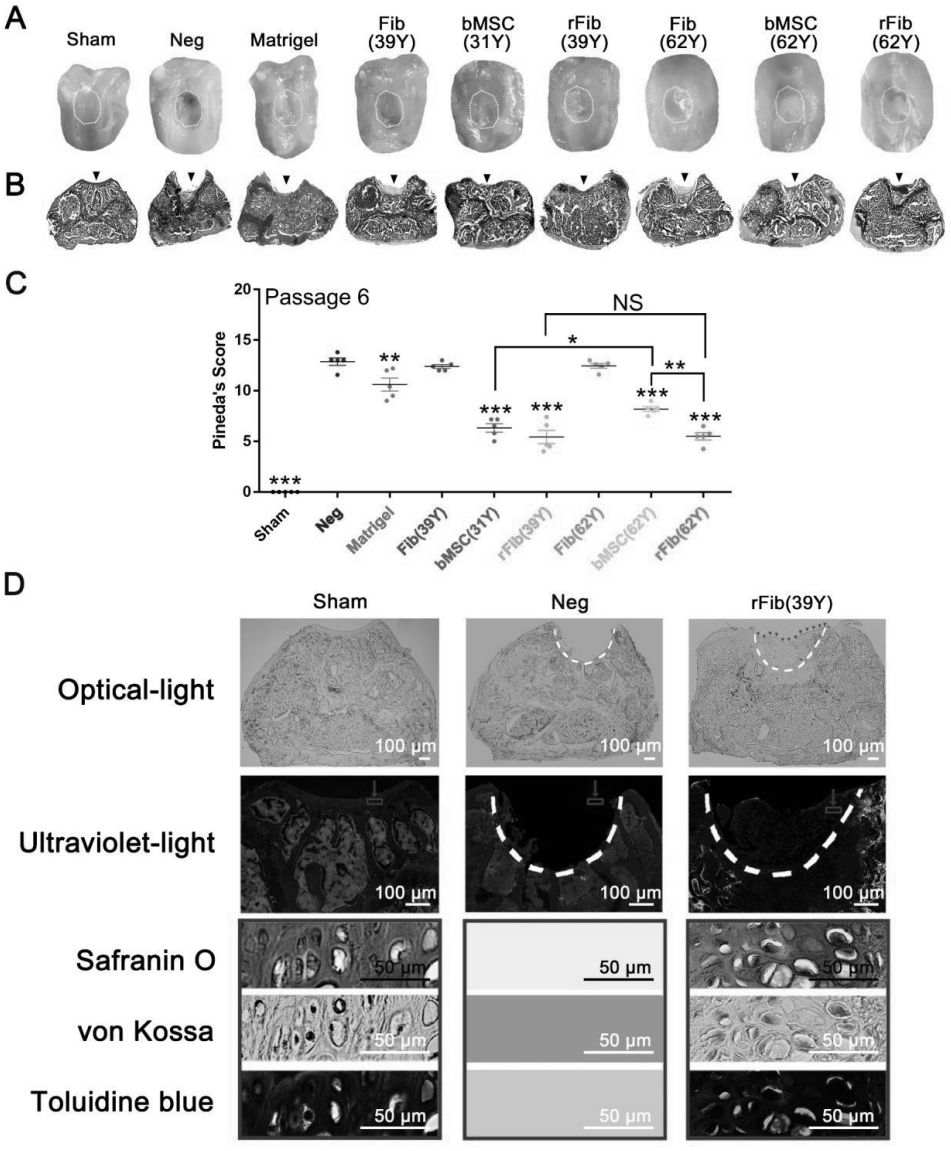

A
Sham
Neg
Matrigel
Fib (39Y)
bMSC (31Y)
rFib (39Y)
Fib (62Y)
bMSC (62Y)
rFib (62Y)
B
C
Passage 6
Pineda's Score
NS
Sham
Neg
Matrigel
Fib(39Y)
bMSC(31Y)
rFib(39Y)
Fib(62Y)
bMSC(62Y)
rFib(62Y)
D
Sham
Neg
rFib(39Y)
Optical-light
Ultraviolet-light
Safranin O
von Kossa
Toluidine blue
100 μm
50 μm

FIG. 7

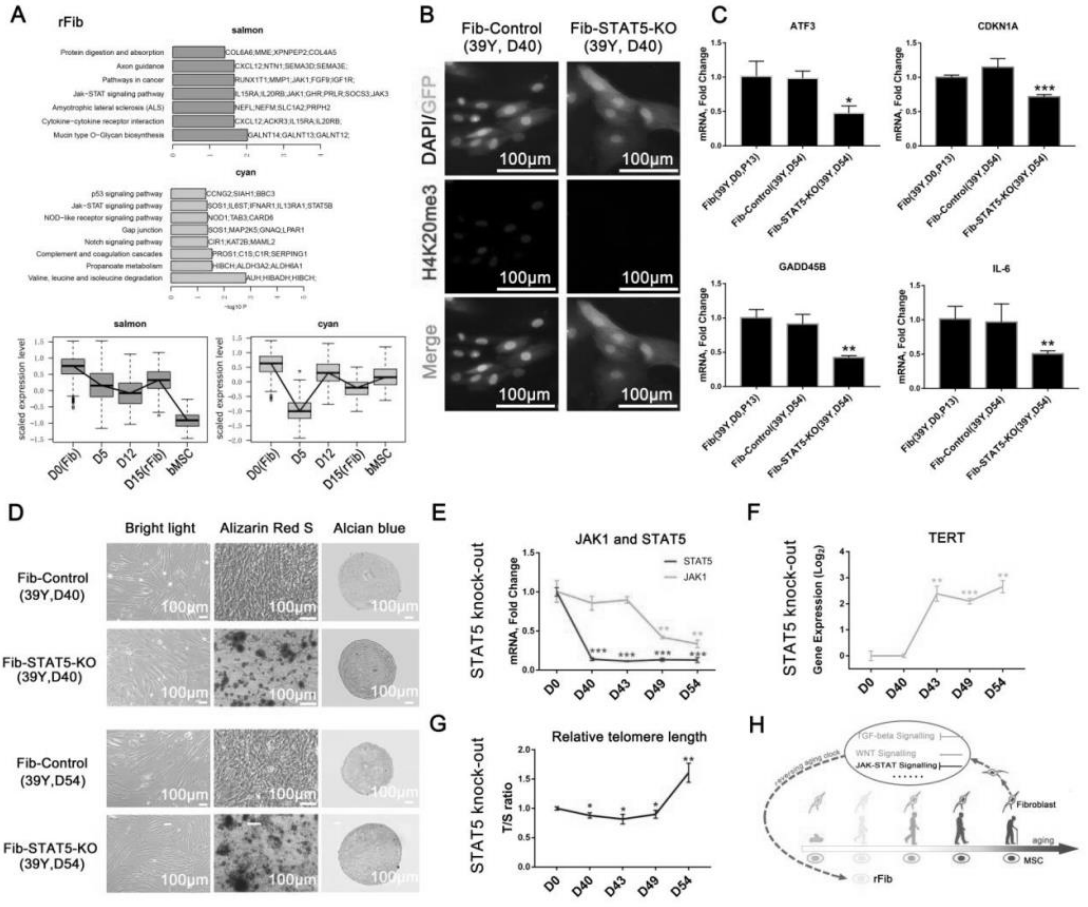

A
rFib
salmon
Protein digestion and absorption
Axon guidance
Pathways in cancer
Jak−STAT signaling pathway
Amyotrophic lateral sclerosis (ALS)
Cytokine−cytokine receptor interaction
Mucin type O−Glycan biosynthesis
cyan
p53 signaling pathway
Jak−STAT signaling pathway
NOD−like receptor signaling pathway
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

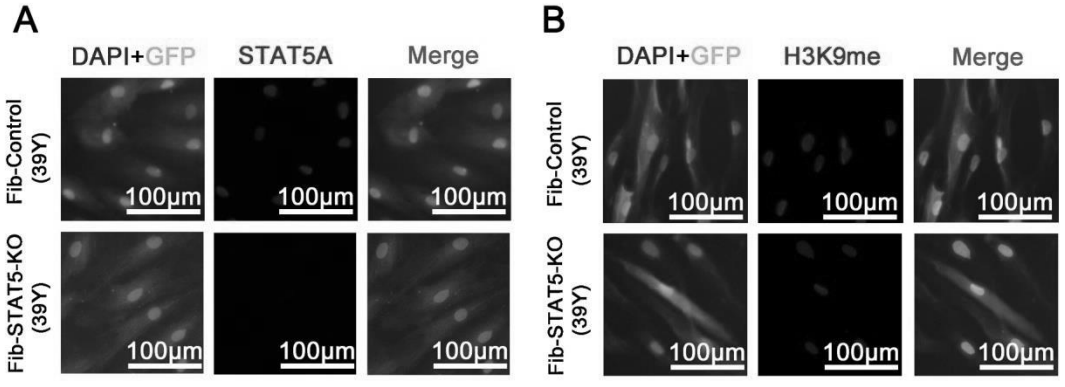

A
DAPI+GFP
STAT5A
Merge
Fib-Control (39Y)
Fib-STAT5-KO (39Y)
100μm
B
DAPI+GFP
H3K9me
Merge
Fib-Control (39Y)
Fib-STAT5-KO (39Y)
100μm

FIG. 9

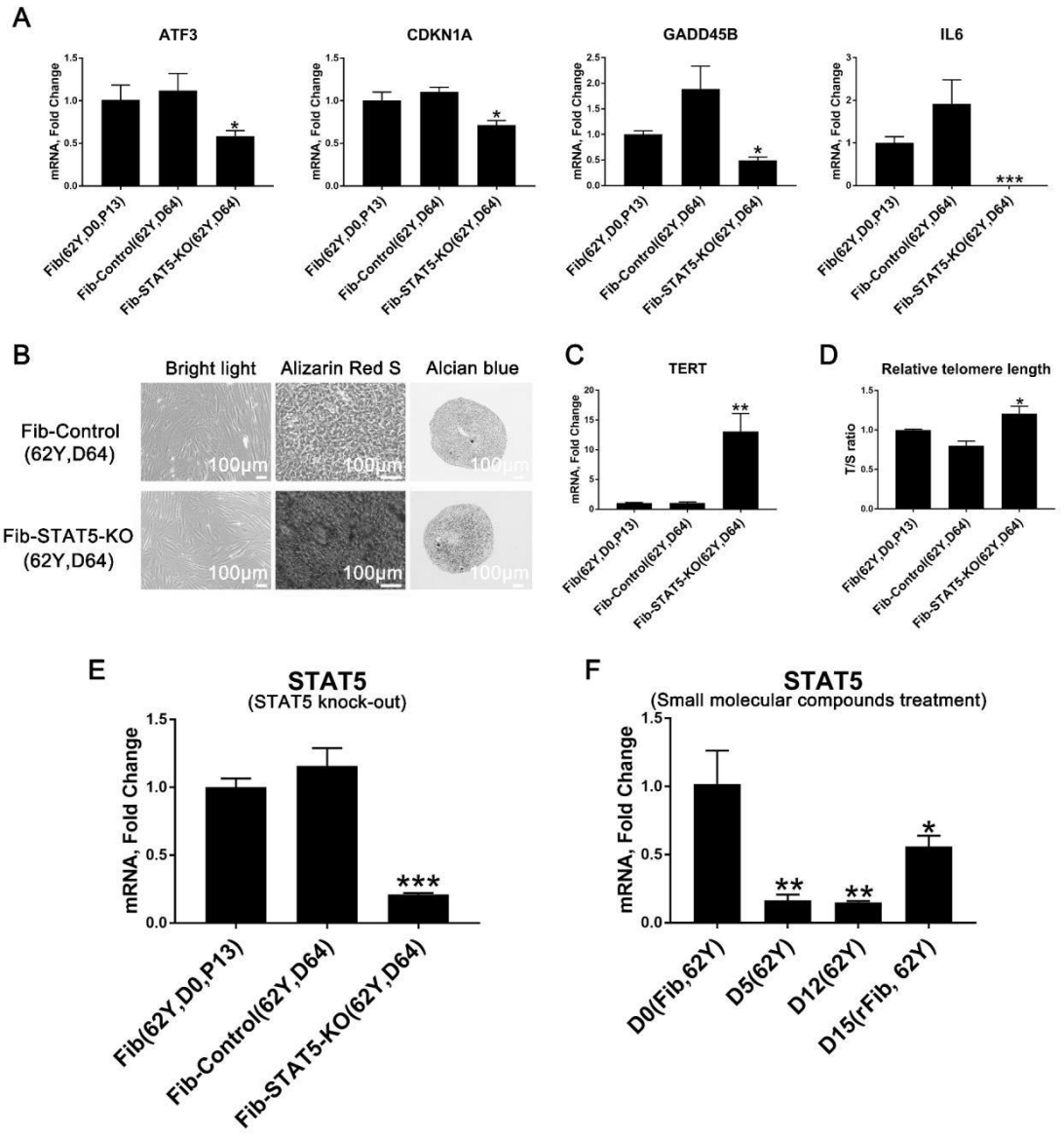

A
ATF3
CDKN1A
GADD45B
IL6
mRNA, Fold Change
Fib(62Y,D0,P13)
Fib-Control(62Y,D64)
Fib-STAT5-KO(62Y,D64)
B
Bright light
Alizarin Red S
Alcian blue
Fib-Control (62Y,D64)
Fib-STAT5-KO (62Y,D64)
100μm
C
TERT
D
Relative telomere length
T/S ratio
E
STAT5
(STAT5 knock-out)
F
STAT5
(Small molecular compounds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

FIG. 10

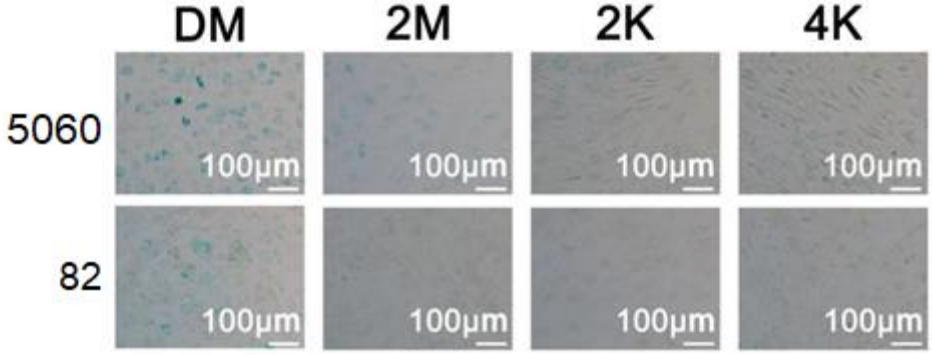

DM
2M
2K
4K
5060
82
100μm

FIG. 11

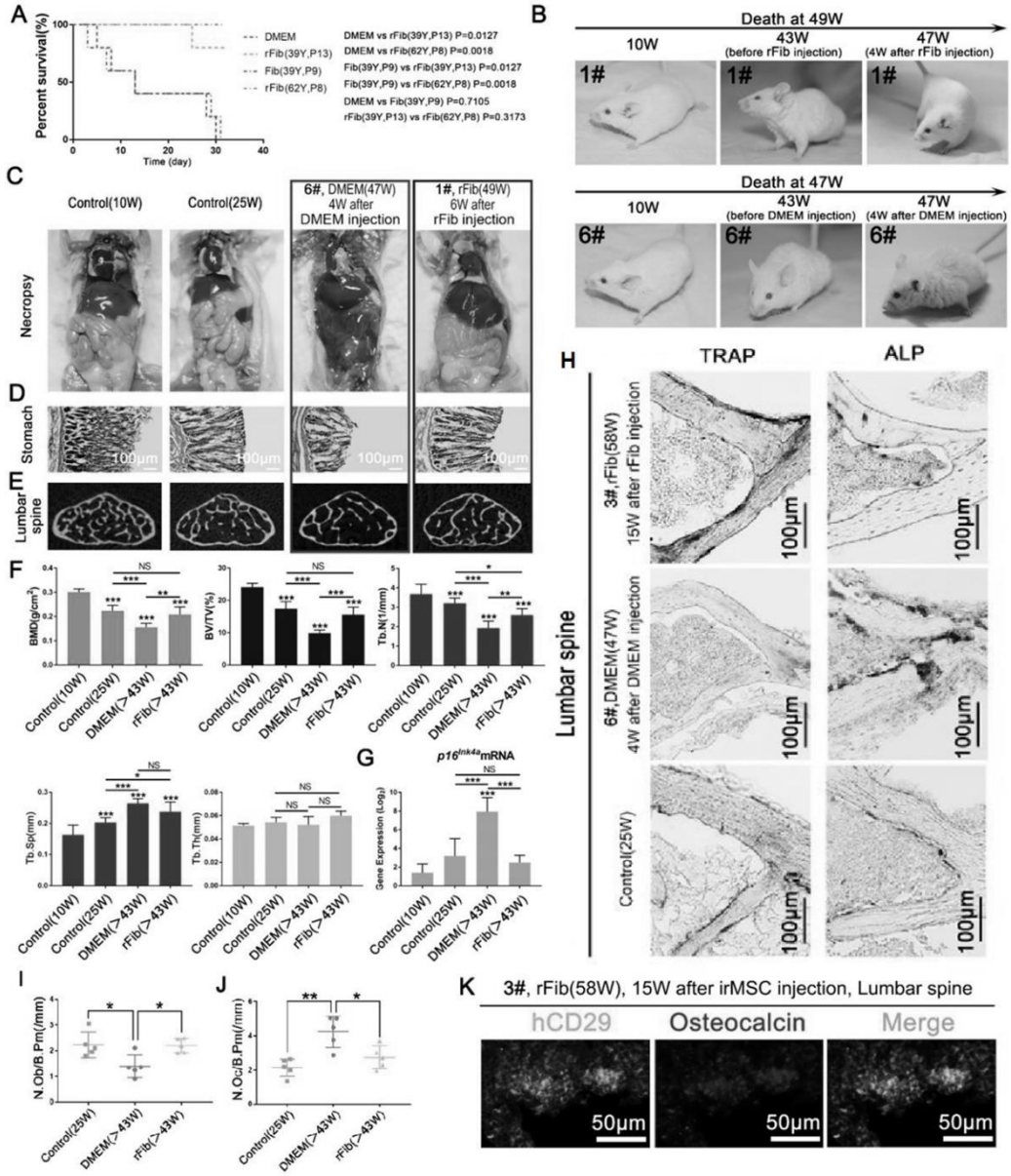

A
Percent survival(%)
Time (day)
DMEM
rFib(39Y,P13)
Fib(39Y,P9)
rFib(62Y,P8)
DMEM vs rFib(39Y,P13) P=0.0127
DMEM vs rFib(62Y,P8) P=0.0018
Fib(39Y,P9) vs rFib(39Y,P13) P=0.0127
Fib(39Y,P9) vs rFib(62Y,P8) P=0.0018
DMEM vs Fib(39Y,P9) P=0.7105
rFib(39Y,P13) vs rFib(62Y,P8) P=0.3173
B
Death at 49W
10W
43W
(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

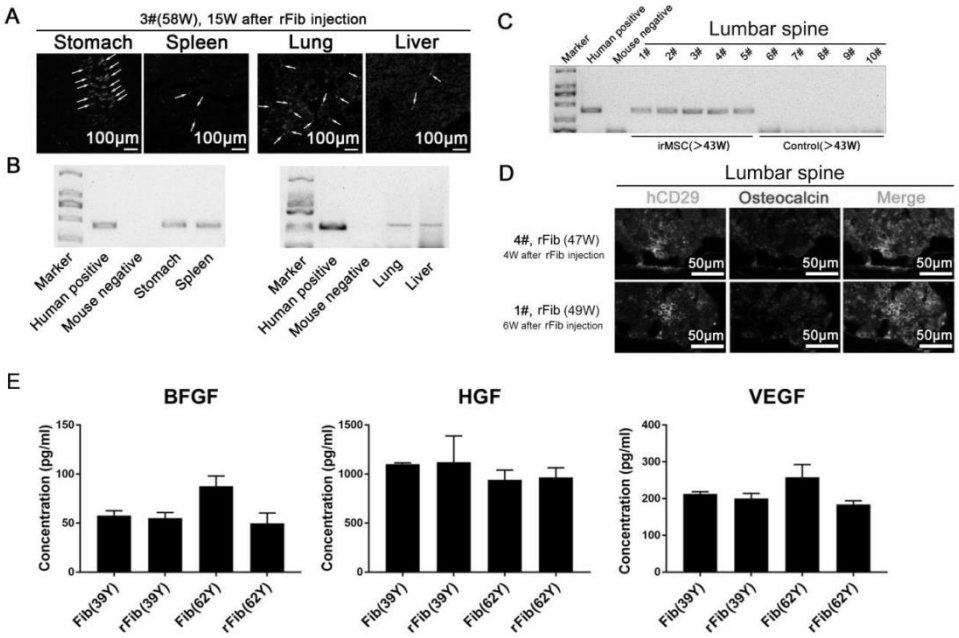

A
3#(58W), 15W after rFib injection
Stomach
Spleen
Lung
Liver
100μm
B
Marker
Human positive
Mouse negative
Stomach
Spleen
Lung
Liver
C
Lumbar spine
Marker
Human positive
Mouse negative
1#
2#
3#
4#
5#
6#
7#
8#
9#
10#
irMSC(>43W)
Control(>43W)
D
Lumbar spine
hCD29
Osteocalcin
Merge
4#, rFib (47W)
4W after 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

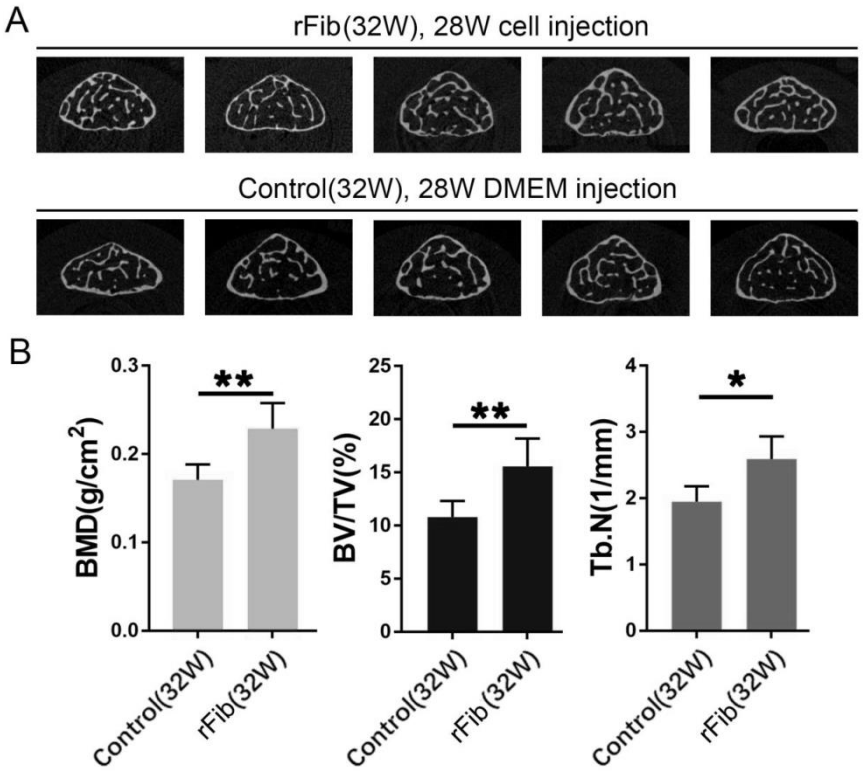

A
rFib(32W), 28W cell injection
Control(32W), 28W DMEM injection
B
BMD(g/cm2)
0.3
0.2
0.1
0.0
**
Control(32W)
rFib(32W)
BV/TV(%)
25
20
15
10
5
0
**
Control(32W)
rFib(32W)
Tb.N(1/mm)
4
3
2
1
0
*
Control(32W)
rFib(32W)

FIG. 14

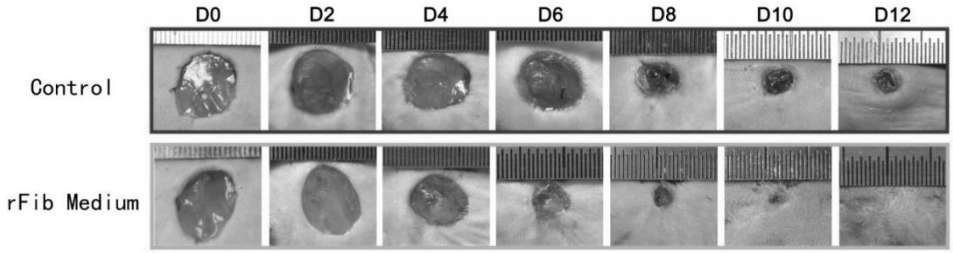

D0
D2
D4
D6
D8
D10
D12
Control
rFib Medium

FIG. 15

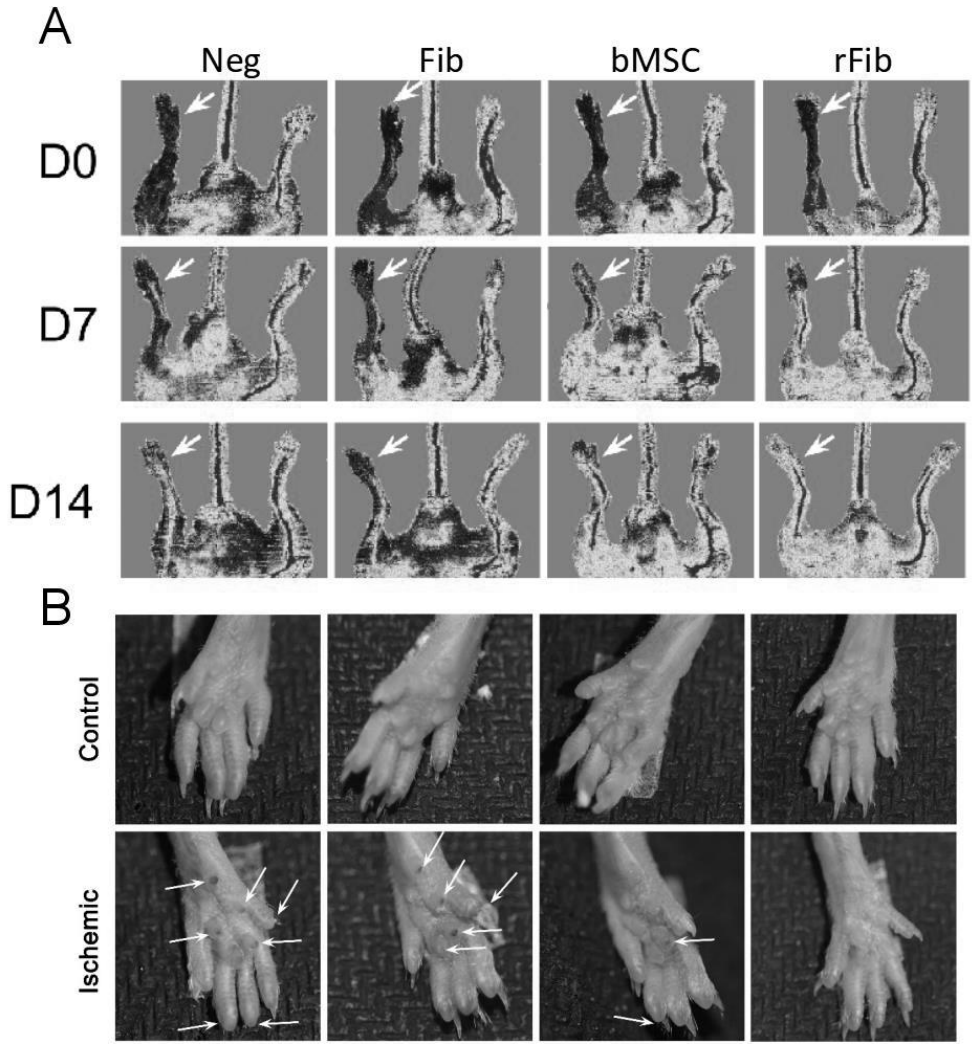

A
Neg
Fib
bMSC
rFib
D0
D7
D14
B
Control
Ischemic

FIG. 16

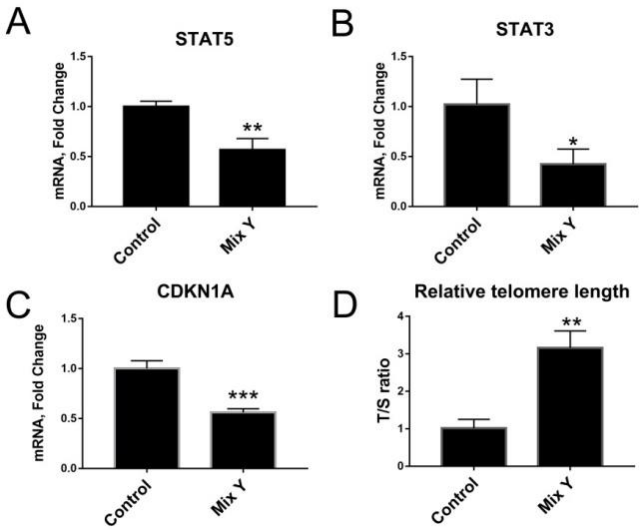

A
STAT5
mRNA, Fold Change
1.5
1.0
0.5
0.0
**
Control
Mix Y
B
STAT3
mRNA, Fold Change
1.5
1.0
0.5
0.0
*
Control
Mix Y
C
CDKN1A
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Y
D
Relative telomere length
T/S ratio
4
3
2
1
0
**
Control
Mix Y

FIG. 17

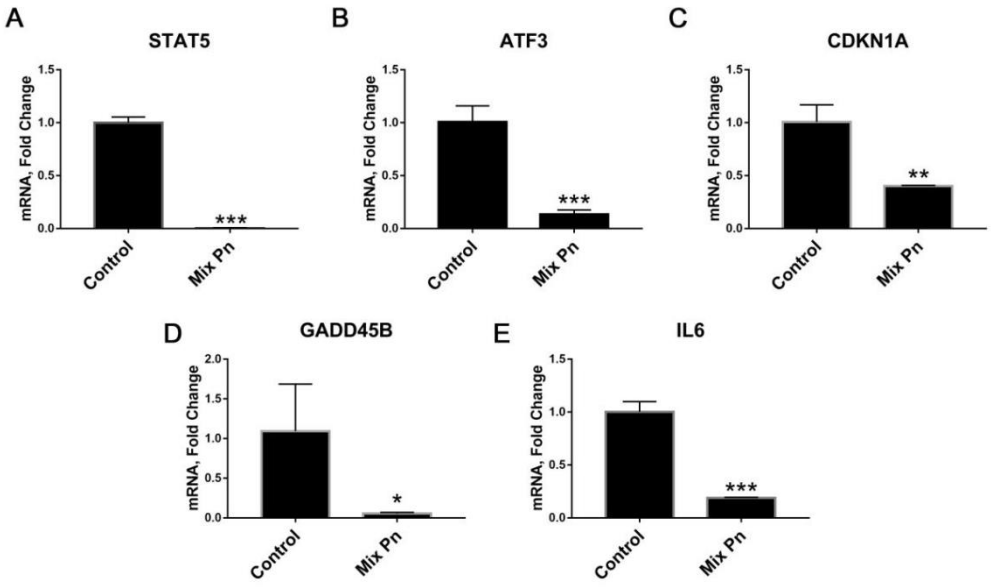

A
STAT5
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Pn
B
ATF3
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix Pn
C
CDKN1A
mRNA, Fold Change
1.5
1.0
0.5
0.0
**
Control
Mix Pn
D
GADD45B
mRNA, Fold Change
2.0
1.5
1.0
0.5
0.0
*
Control
Mix Pn
E
IL6
mRNA, Fold Change
1.5
1.0
0.5
0.0
***
Control
Mix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

FIG. 18

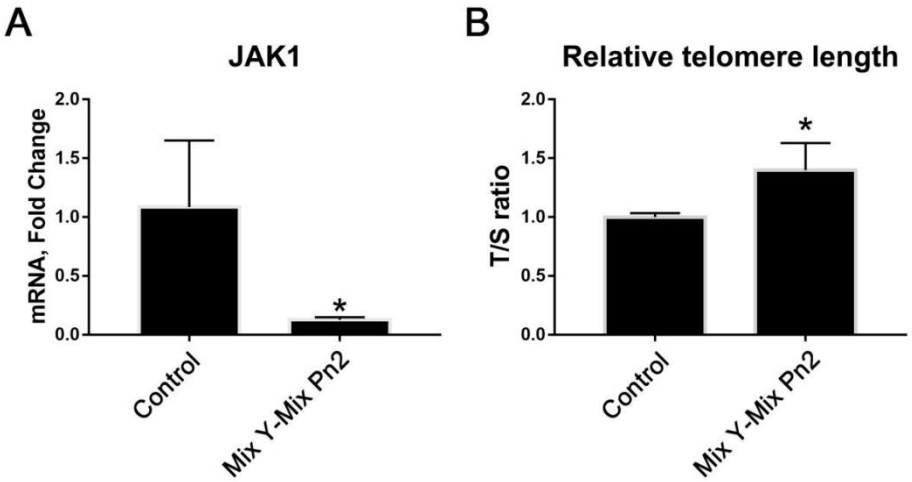

A
JAK1
mRNA, Fold Change
2.0
1.5
1.0
0.5
0.0
*
Control
Mix Y-Mix Pn2
B
Relative telomere length
T/S ratio
2.0
1.5
1.0
0.5
0.0
*
Control
Mix Y-Mix Pn2

FIG. 19

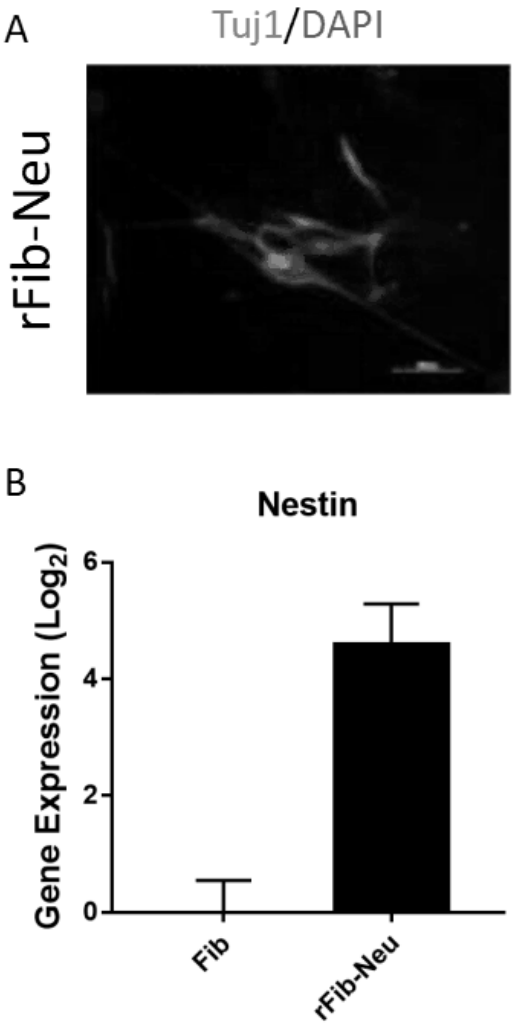

A
Tuj1/DAPI
rFib-Neu
B
Nestin
Gene Expression (Log2)
6
4
2
0
Fib
rFib-Neu

FIG. 20

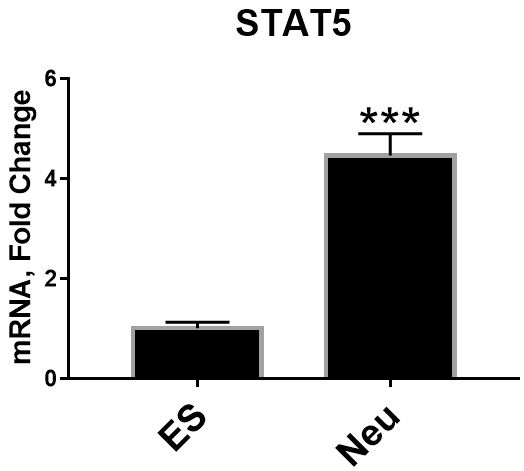

STAT5
mRNA, Fold Change
6
4
2
0
***
ES
Neu

FIG. 21

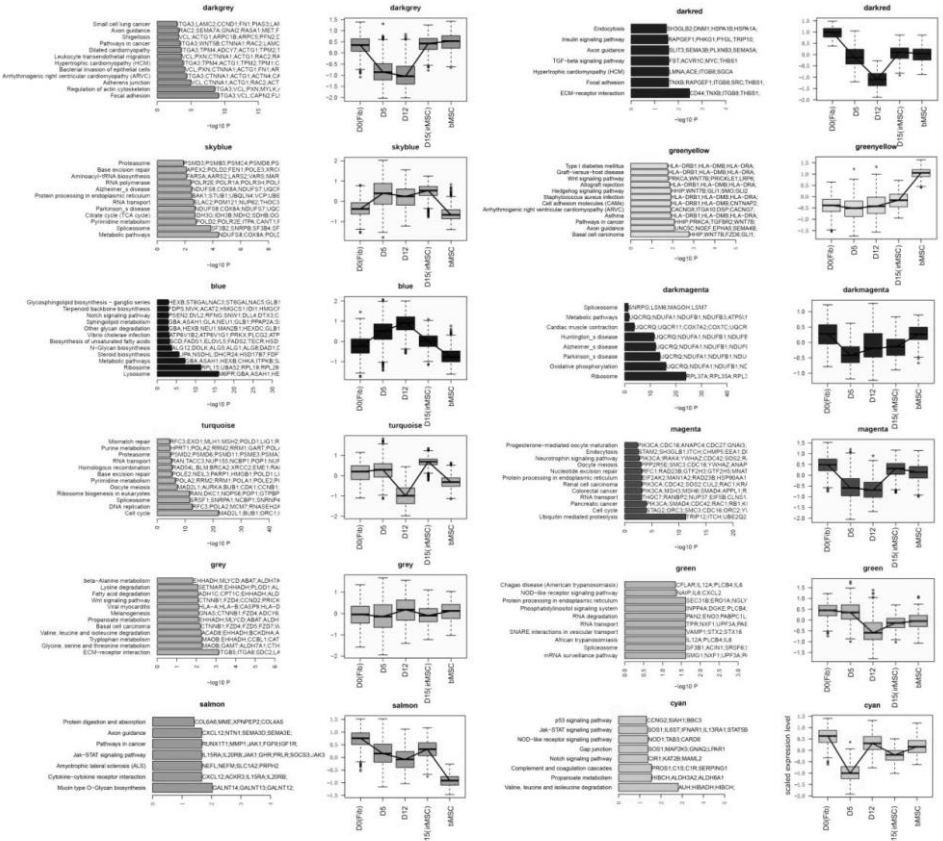

darkgrey
darkgrey
darkred
darkred
skyblue
skyblue
greenyellow
greenyellow
blue
blue
darkmagenta
darkmagenta
turquoise
turquoise
magenta
magenta
grey
grey
green
green
salmon
salmon
cyan
cyan
-log10 P
scaled expression level
D0(Fib)
D5
D12
D15(rMSC)
bMSC

FIG. 22