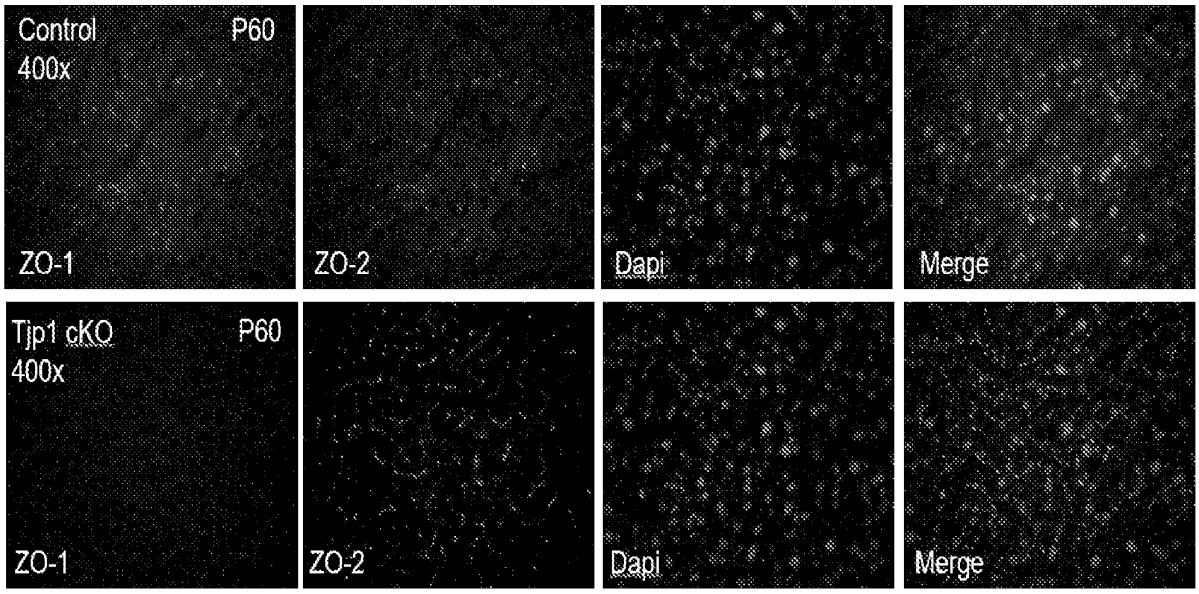
Fig. 1A

Immunofluorescence (IF)



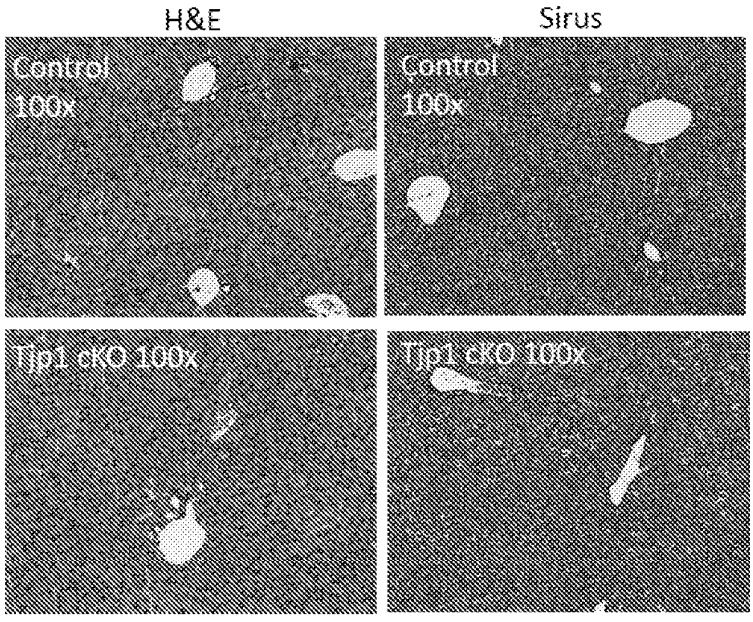


Fig. 1B

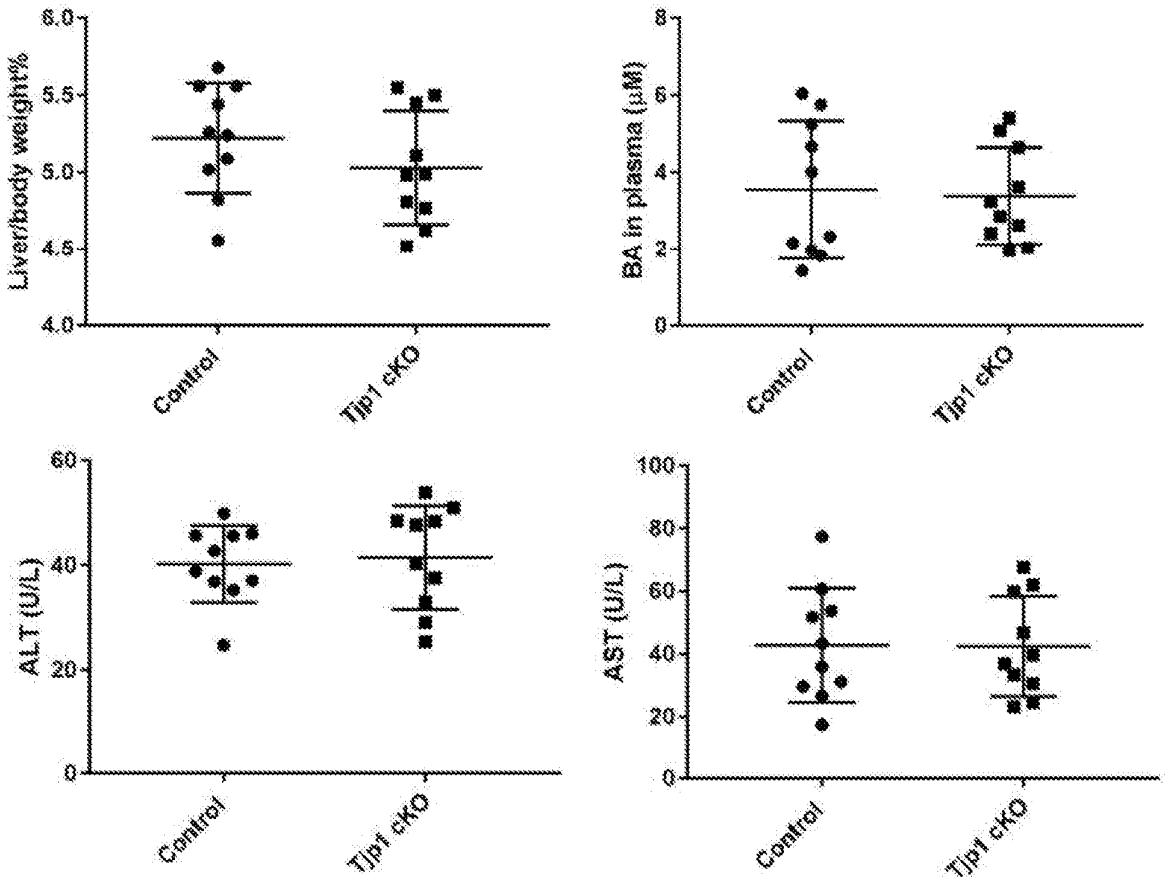

Liver/body weight%
6.0
5.5
5.0
4.5
4.0
Control
Tjp1 cKO
BA in plasma (μM)
8
6
4
2
0
Control
Tjp1 cKO
ALT (U/L)
60
40
20
0
Control
Tjp1 cKO
AST (U/L)
100
80
60
40
20
0
Control
Tjp1 cKO

Fig. 1C

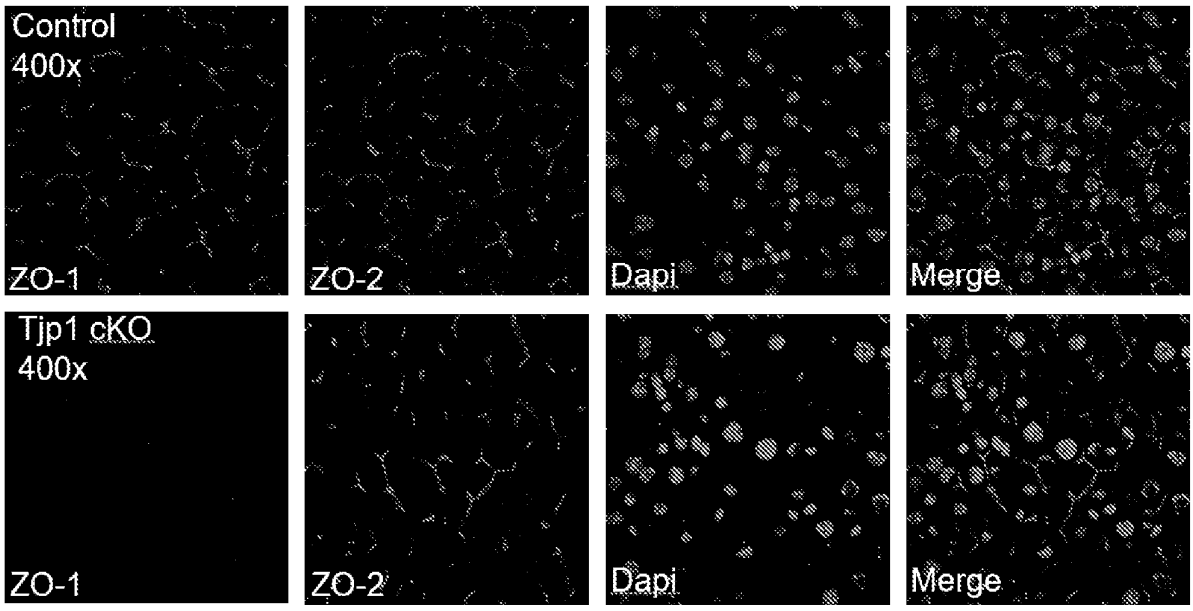

Control
400x
ZO-1
ZO-2
Dapi
Merge
Tjp1 cKO
400x
ZO-1
ZO-2
Dapi
Merge

Fig. 1D

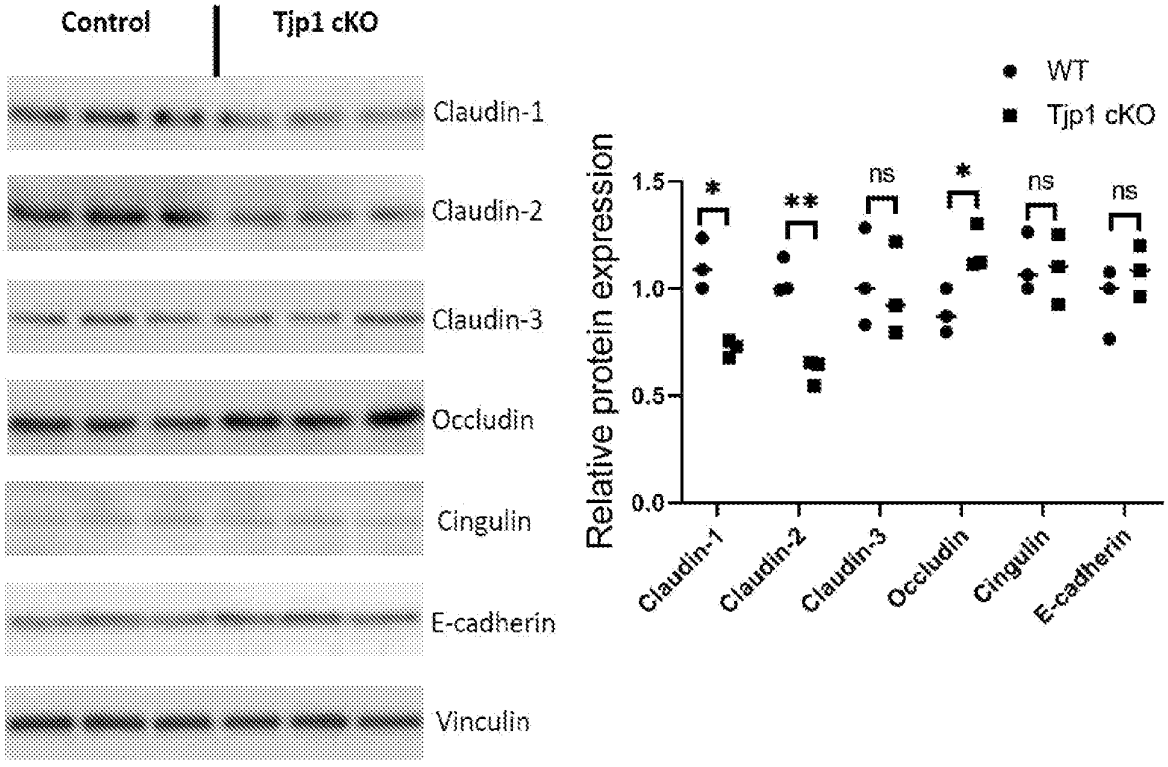

Control
Tjp1 cKO
Claudin-1
Claudin-2
Claudin-3
Occludin
Cingulin
E-cadherin
Vinculin
WT
Tjp1 cKO
Relative protein expression
1.5
1.0
0.5
0.0
*
**
ns
*
ns
ns
Claudin-1
Claudin-2
Claudin-3
Occludin
Cingulin
E-cadherin

Fig. 1E

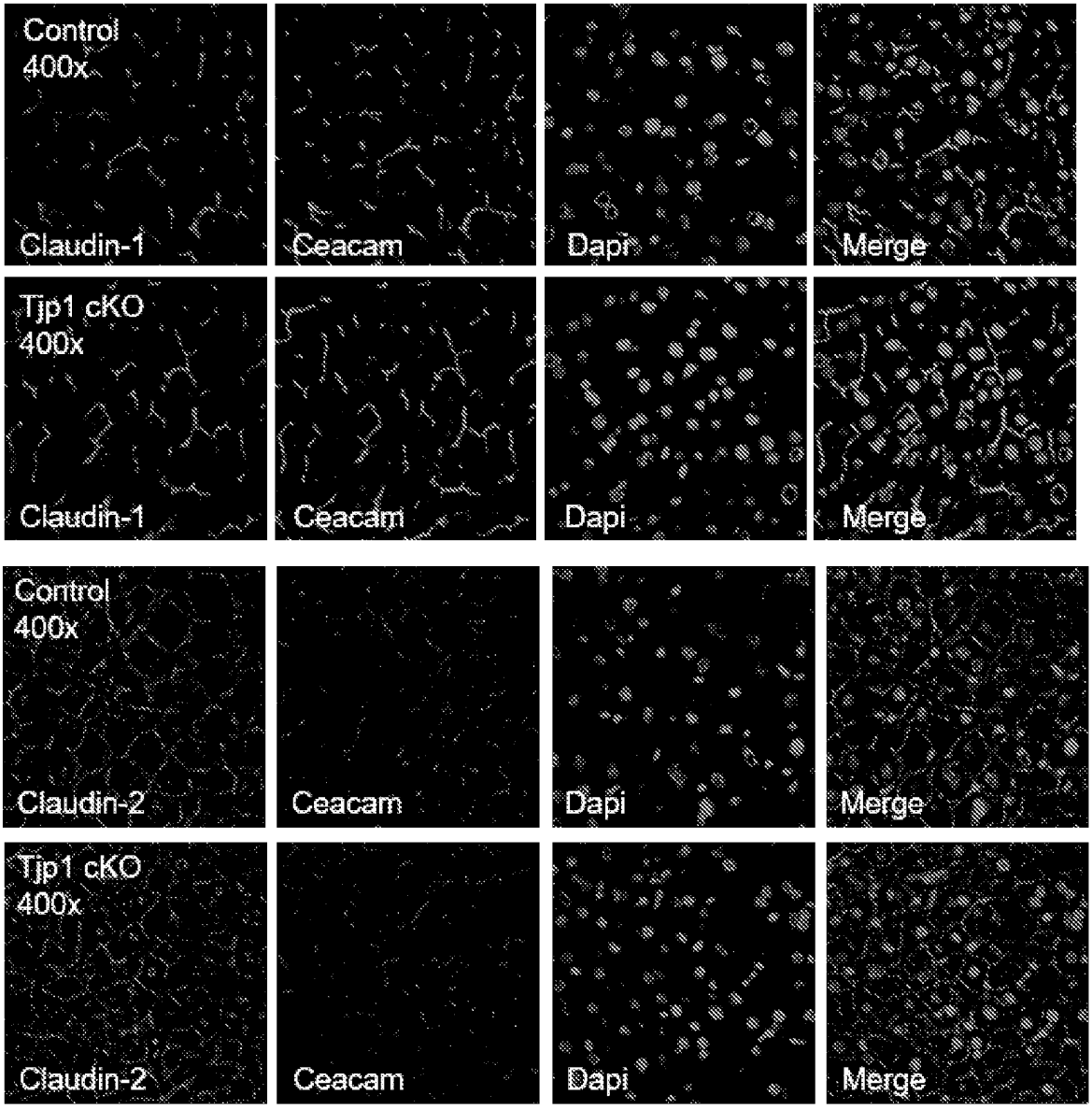

Control
400x
Claudin-1
Ceacam
Dapi
Merge
Tjp1 cKO
400x
Claudin-1
Ceacam
Dapi
Merge
Control
400x
Claudin-2
Ceacam
Dapi
Merge
Tjp1 cKO
400x
Claudin-2
Ceacam
Dapi
Merge

Fig. 1E (cont.)

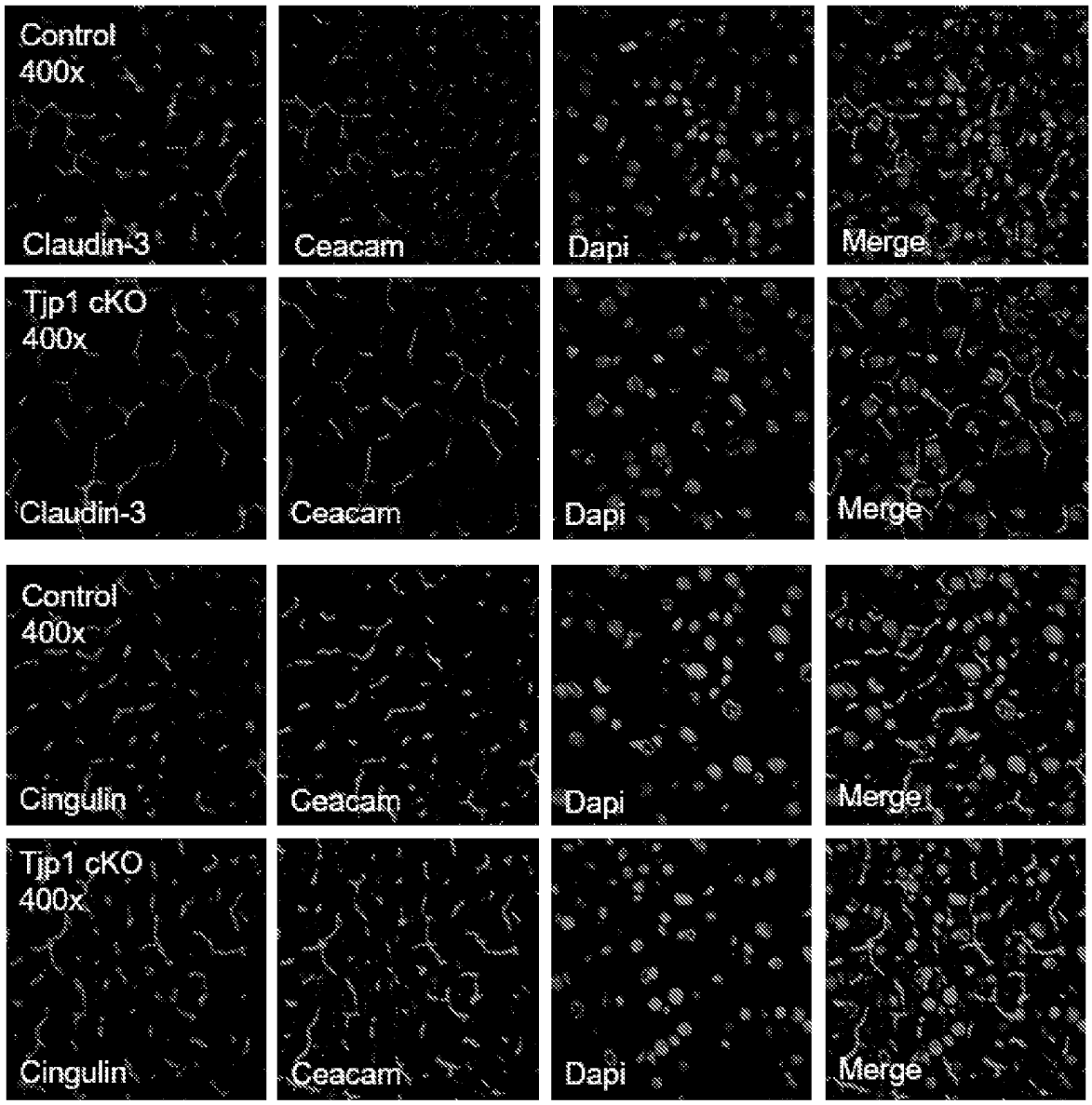

Control
400x
Claudin-3
Ceacam
Dapi
Merge
Tjp1 cKO
400x
Claudin-3
Ceacam
Dapi
Merge
Control
400x
Cingulin
Ceacam
Dapi
Merge
Tjp1 cKO
400x
Cingulin
Ceacam
Dapi
Merge

Fig. 1F

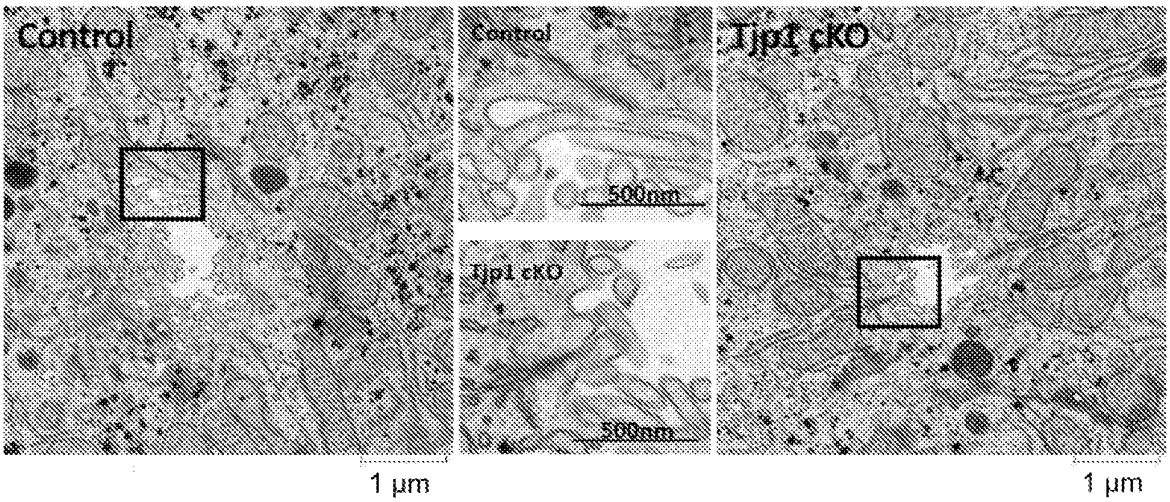


Fig. 1G

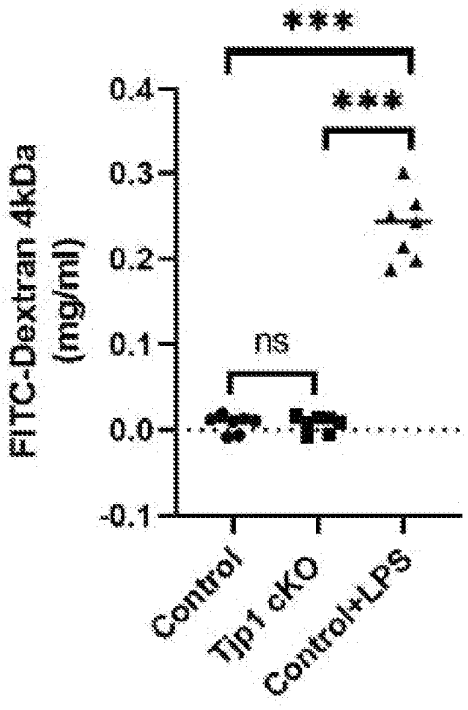


Fig. 2A

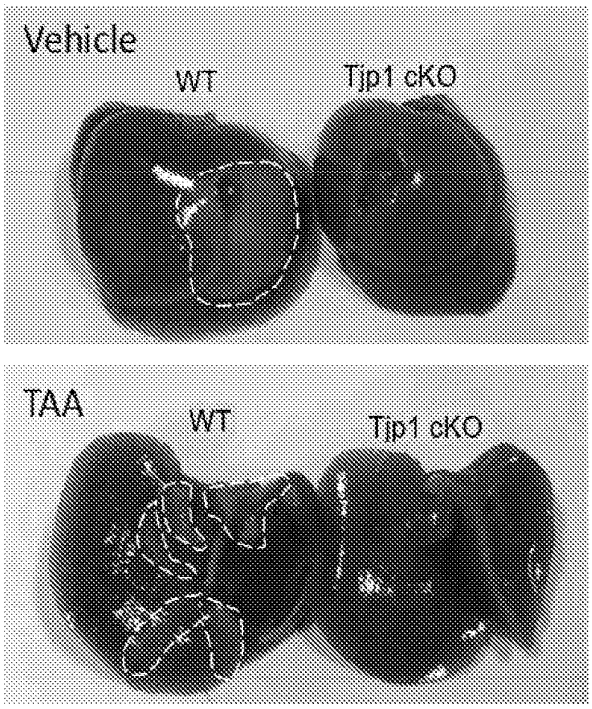


Fig. 2B

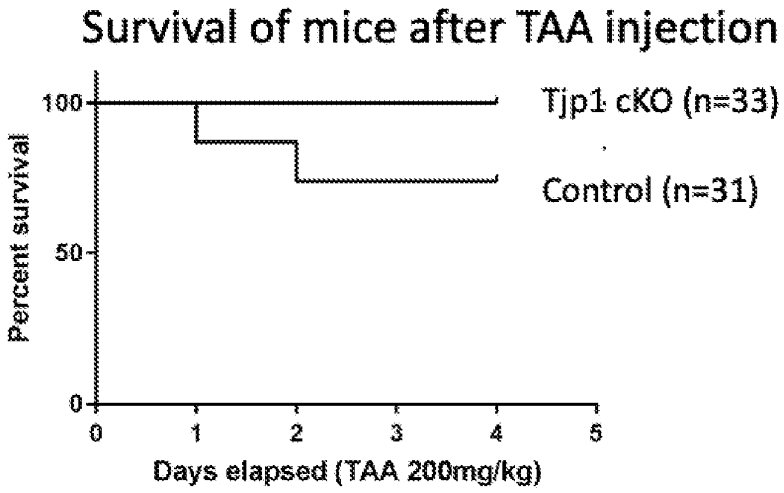

Survival of mice after TAA injection
Tjp1 cKO (n=33)
Control (n=31)
Percent survival
100
50
0
0
1
2
3
4
5
Days elapsed (TAA 200mg/kg)

Fig. 2C

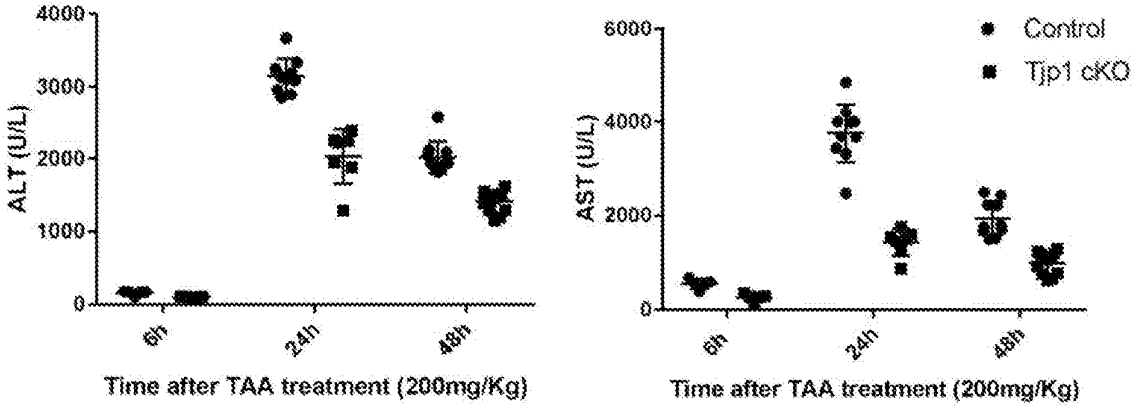
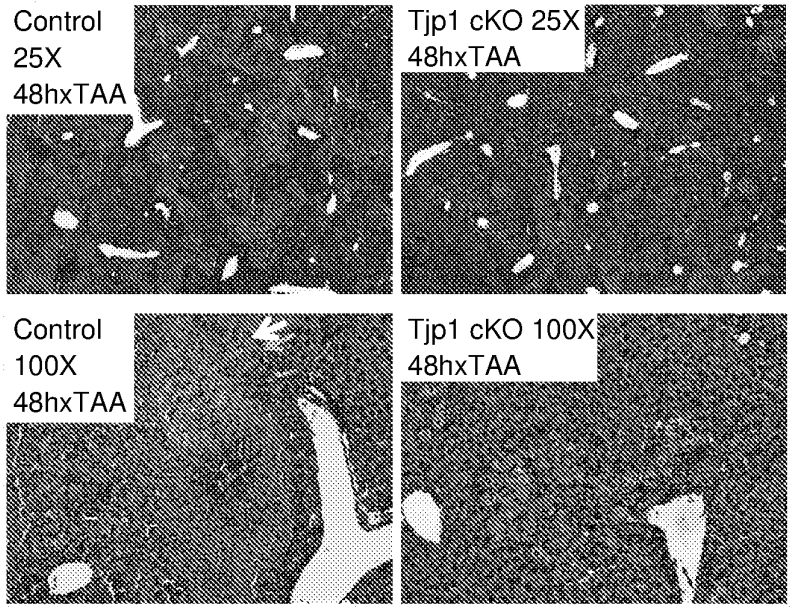

ALT (U/L)
4000
3000
2000
1000
0
6h
24h
48h
Time after TAA treatment (200mg/Kg)
AST (U/L)
6000
4000
2000
0
Control
Tjp1 cKO
6h
24h
48h
Time after TAA treatment (200mg/Kg)

Fig. 2D


Control
25X
48hxTAA
Tjp1 cKO 25X
48hxTAA
Control
100X
48hxTAA
Tjp1 cKO 100X
48hxTAA

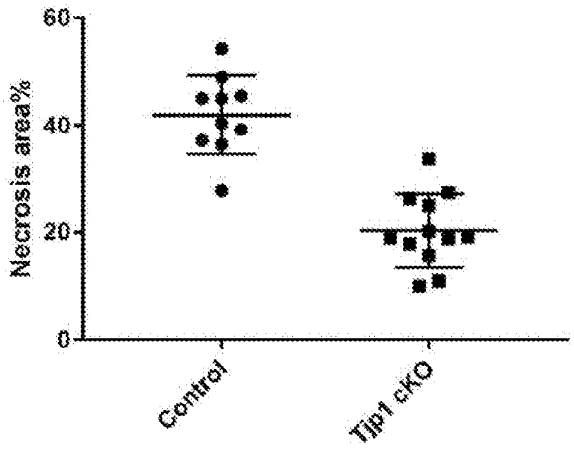

Necrosis area%
60
40
20
0
Control
Tjp1 cKO

Fig. 2E

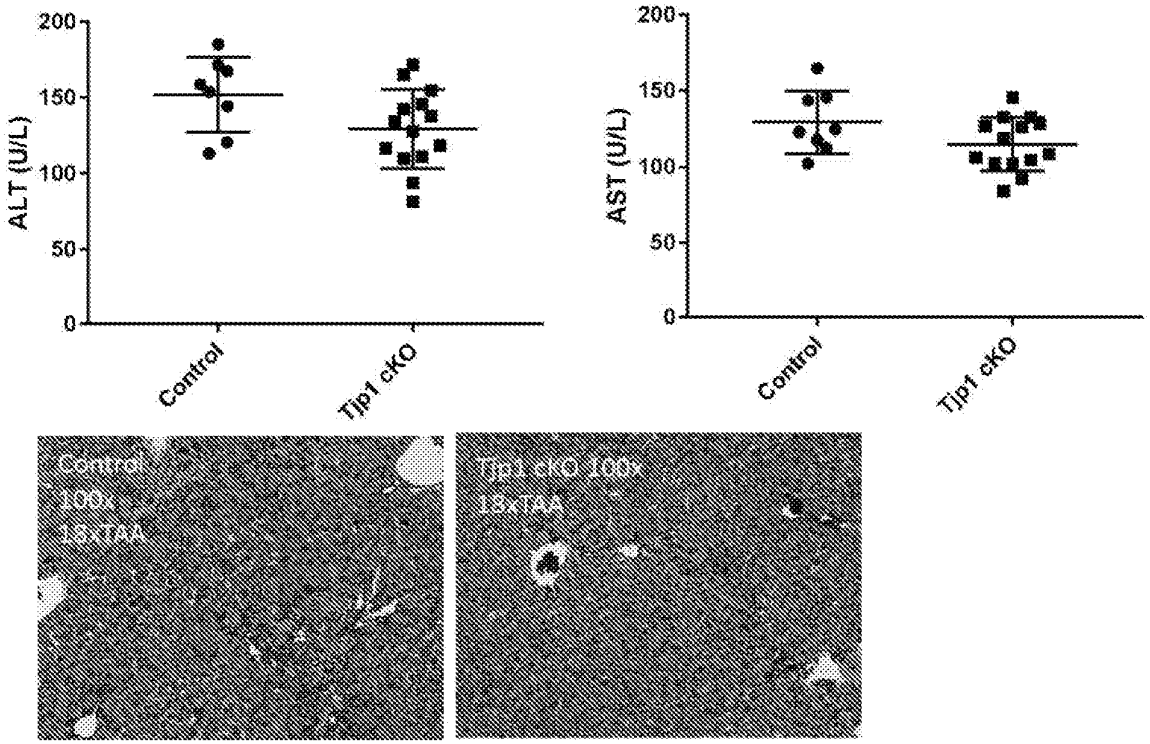

ALT (U/L)
200
150
100
50
0
Control
Tjp1 cKO
AST (U/L)
200
150
100
50
0
Control
Tjp1 cKO
Control 100x 18xTAA
Tjp1 cKO 100x 18xTAA

Fig. 2F

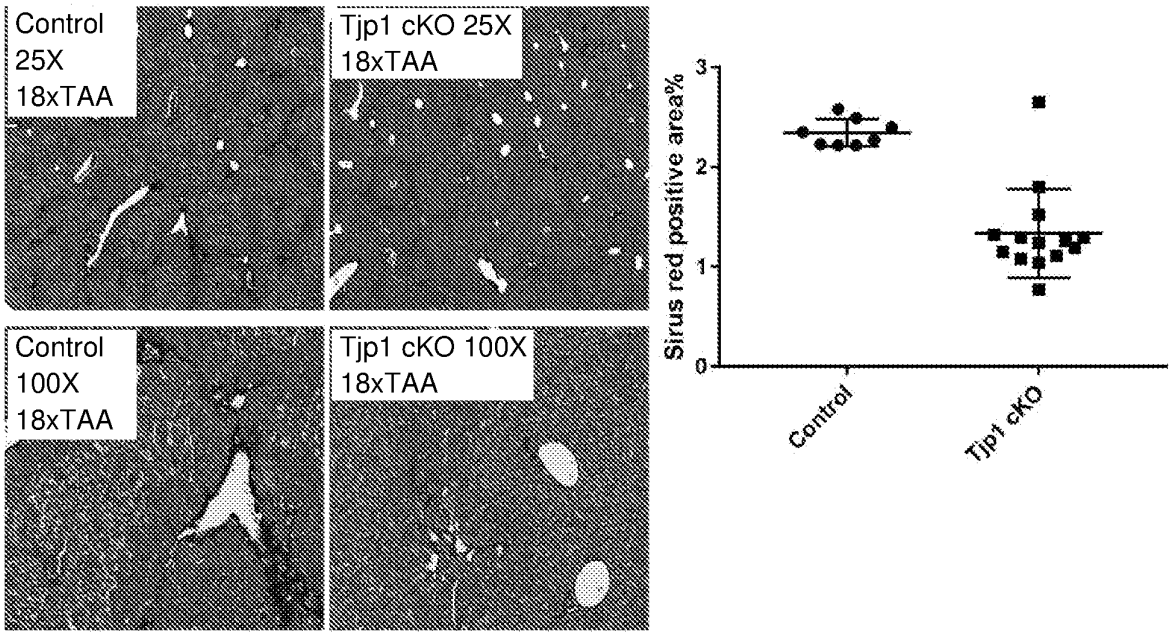

Control 25X 18xTAA
Tjp1 cKO 25X 18xTAA
Control 100X 18xTAA
Tjp1 cKO 100X 18xTAA
Sirus red positive area%
3
2
1
0
Control
Tjp1 cKO

Fig. 2G

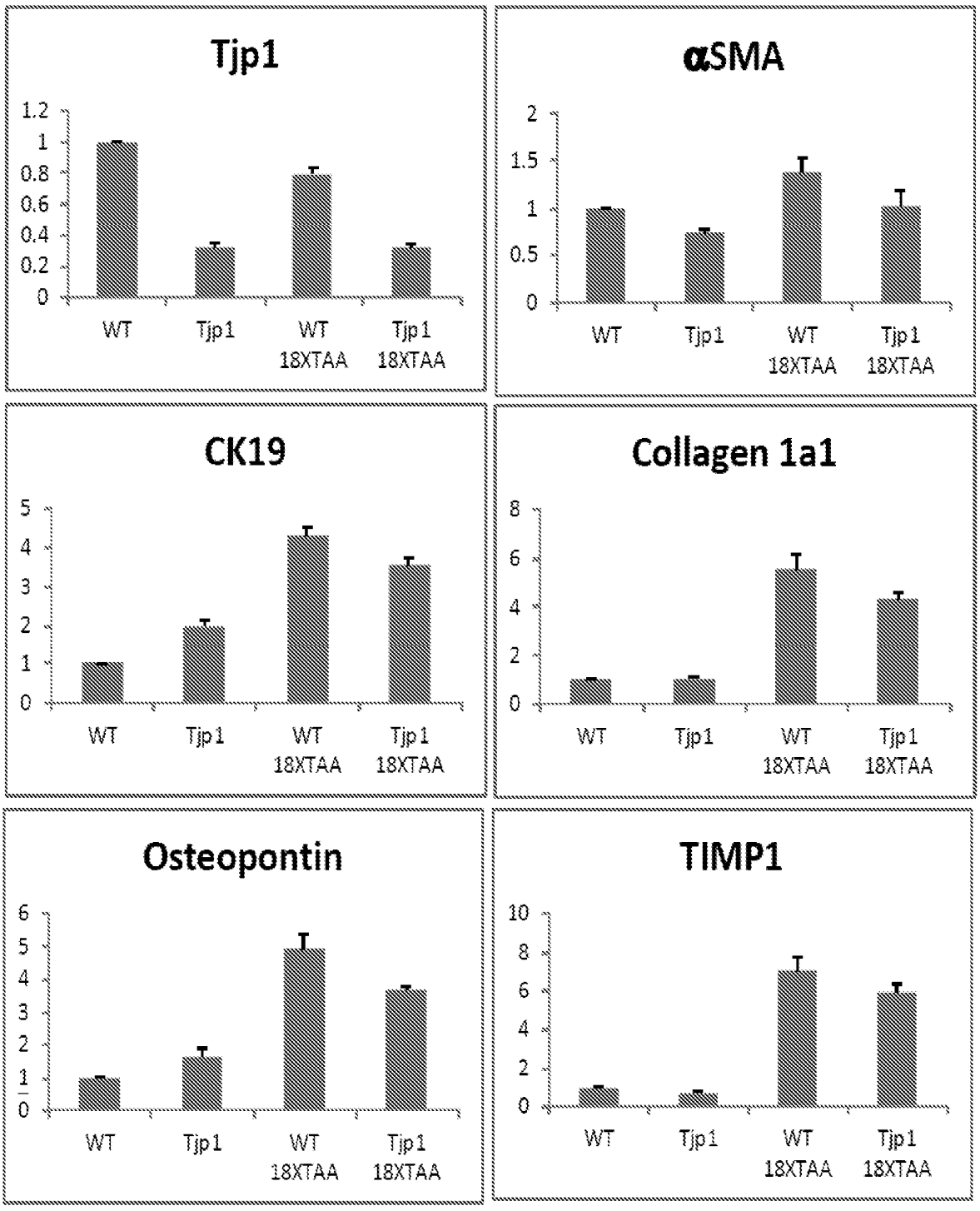

Tjp1
1.2
1
0.8
0.6
0.4
0.2
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
αSMA
2
1.5
1
0.5
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
CK19
5
4
3
2
1
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
Collagen 1a1
8
6
4
2
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
Osteopontin
6
5
4
3
2
1
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
TIMP1
10
8
6
4
2
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA

Fig. 2G (cont.)

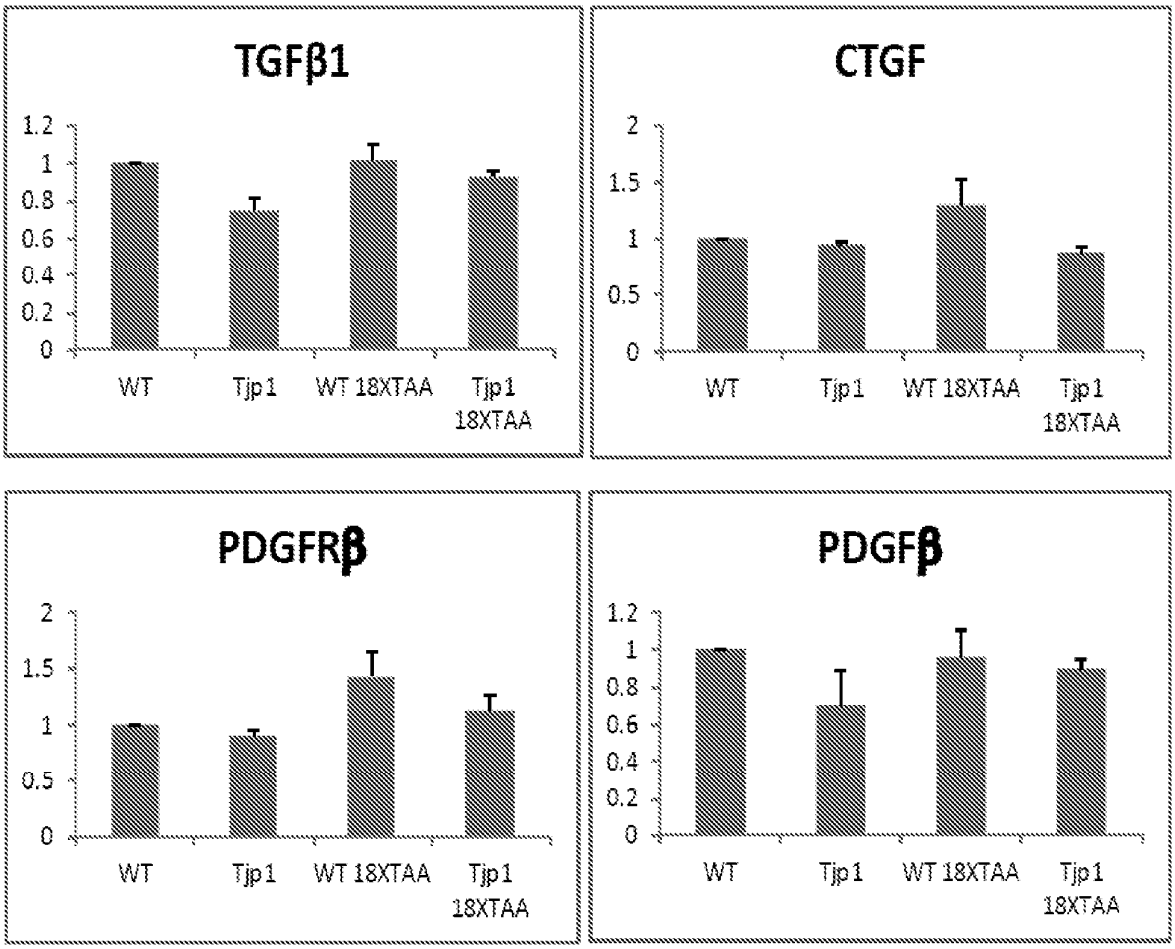
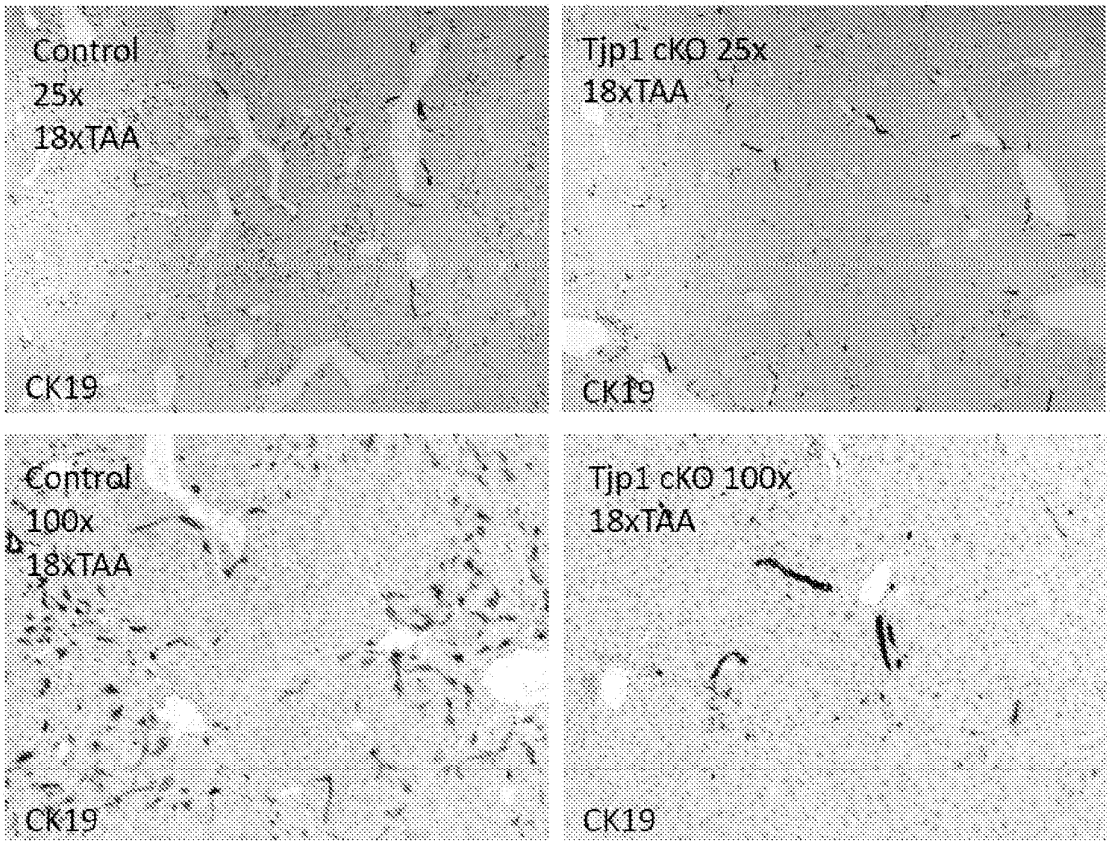

TGFβ1
1.2
1
0.8
0.6
0.4
0.2
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
CTGF
2
1.5
1
0.5
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
PDGFRβ
2
1.5
1
0.5
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA
PDGFβ
1.2
1
0.8
0.6
0.4
0.2
0
WT
Tjp1
WT 18XTAA
Tjp1 18XTAA

Fig. 2H


Control
25x
18xTAA
CK19
Tjp1 cKO 25x
18xTAA
CK19
Control
100x
18xTAA
CK19
Tjp1 cKO 100x
18xTAA
CK19

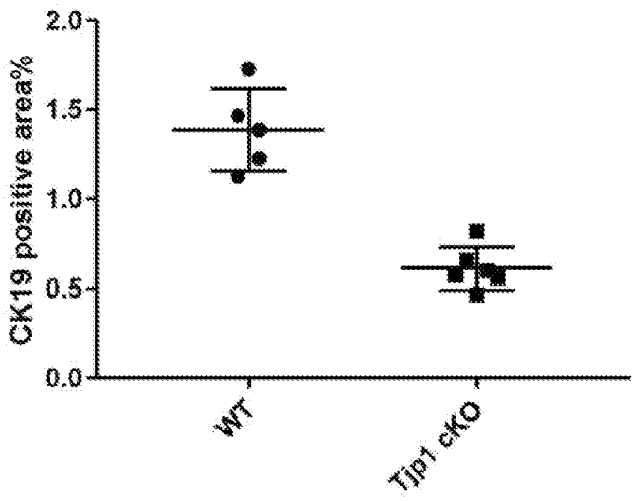
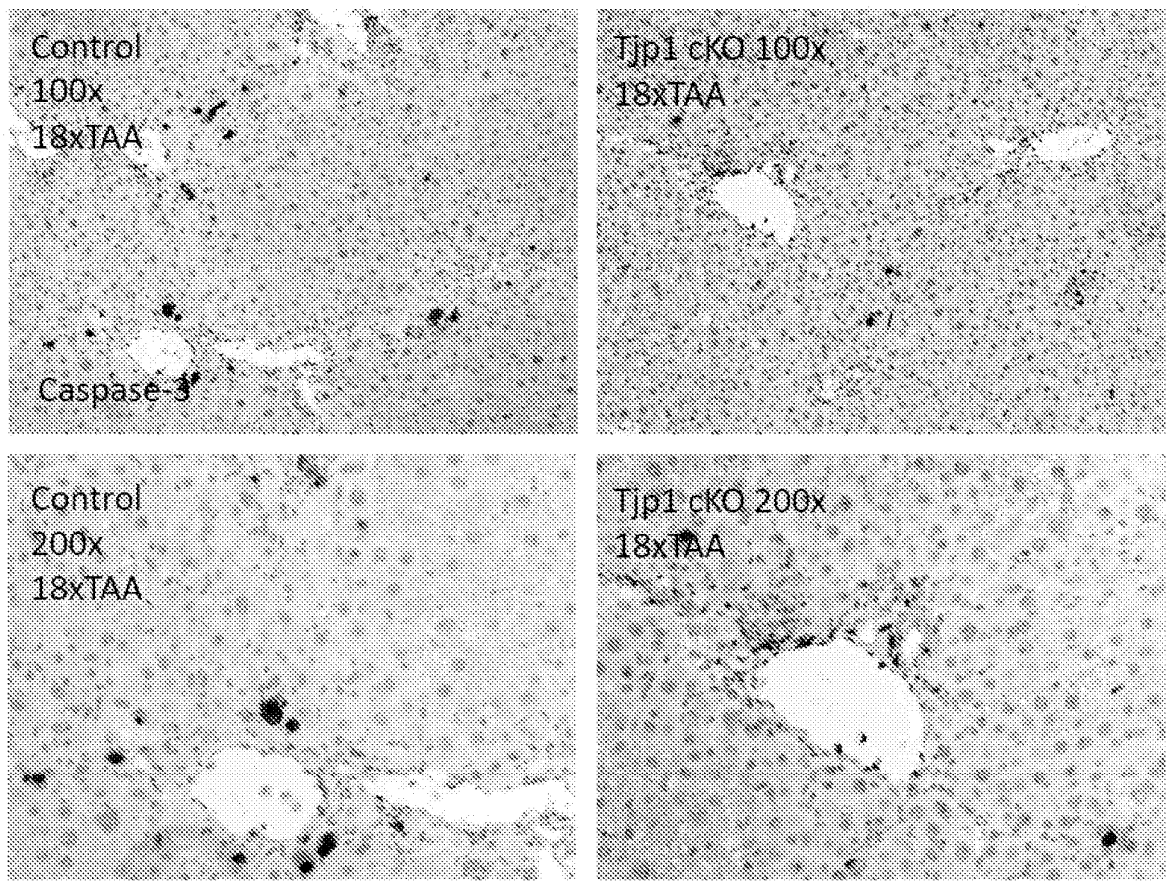

CK19 positive area%
2.0
1.5
1.0
0.5
0.0
WT
Tjp1 cKO

Fig. 2I


Control
100x
18xTAA
Caspase-3
Tjp1 cKO 100x
18xTAA
Control
200x
18xTAA
Tjp1 cKO 200x
18xTAA

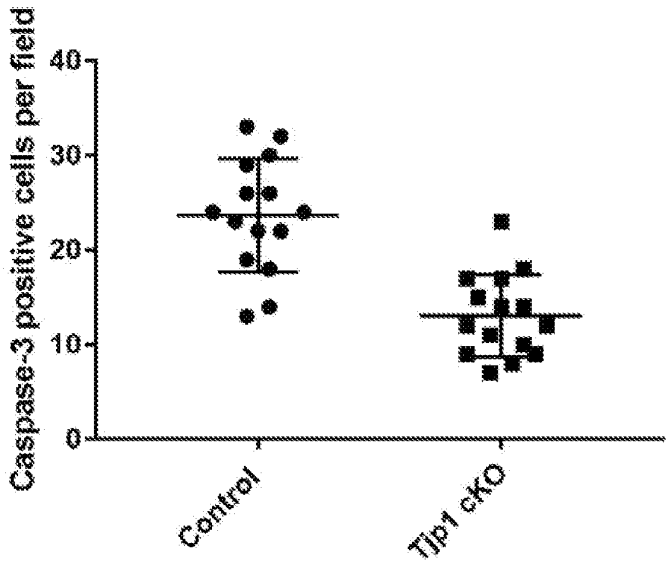

Caspase-3 positive cells per field
40
30
20
10
0
Control
Tjp1 cKO

Fig. 3A

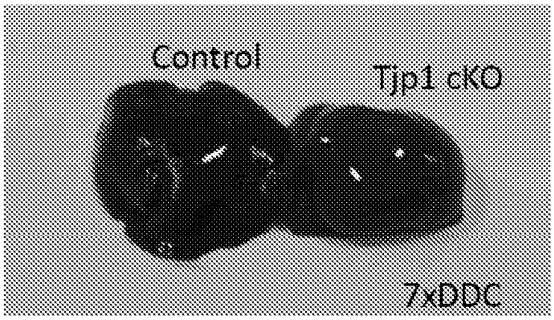


Fig. 3B

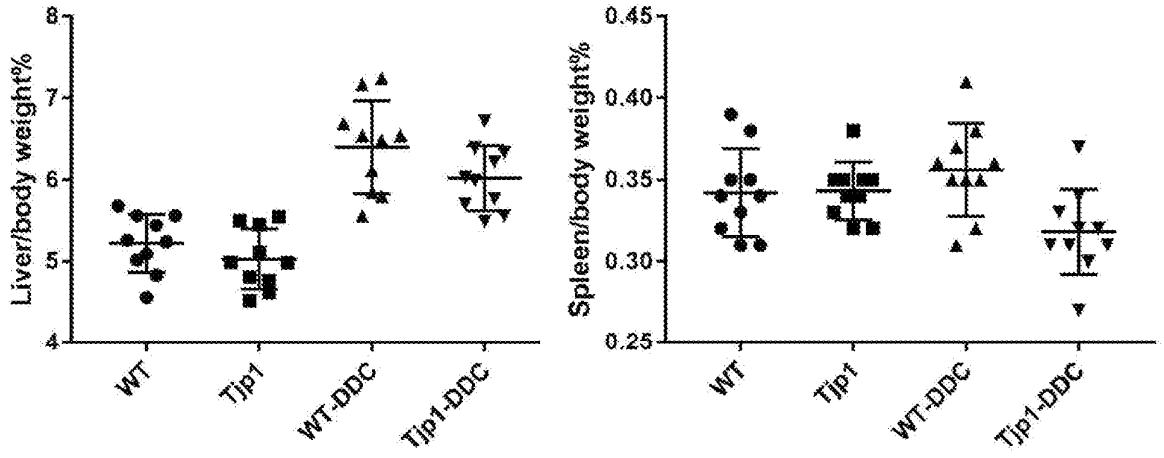


Fig. 3C

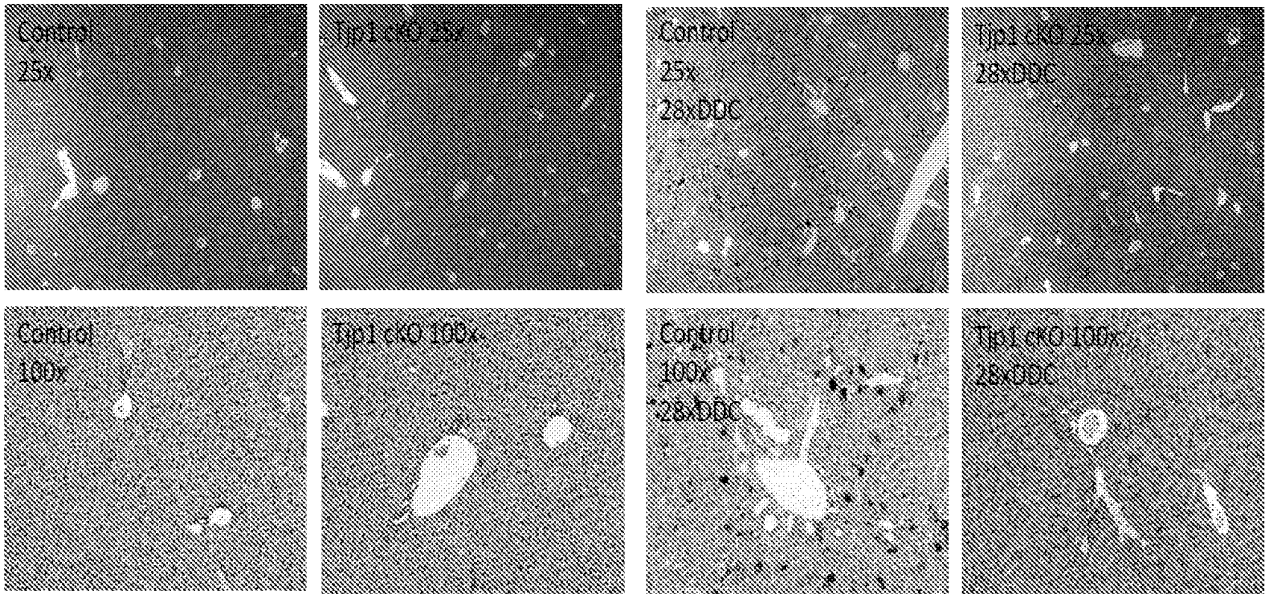


Fig. 3D

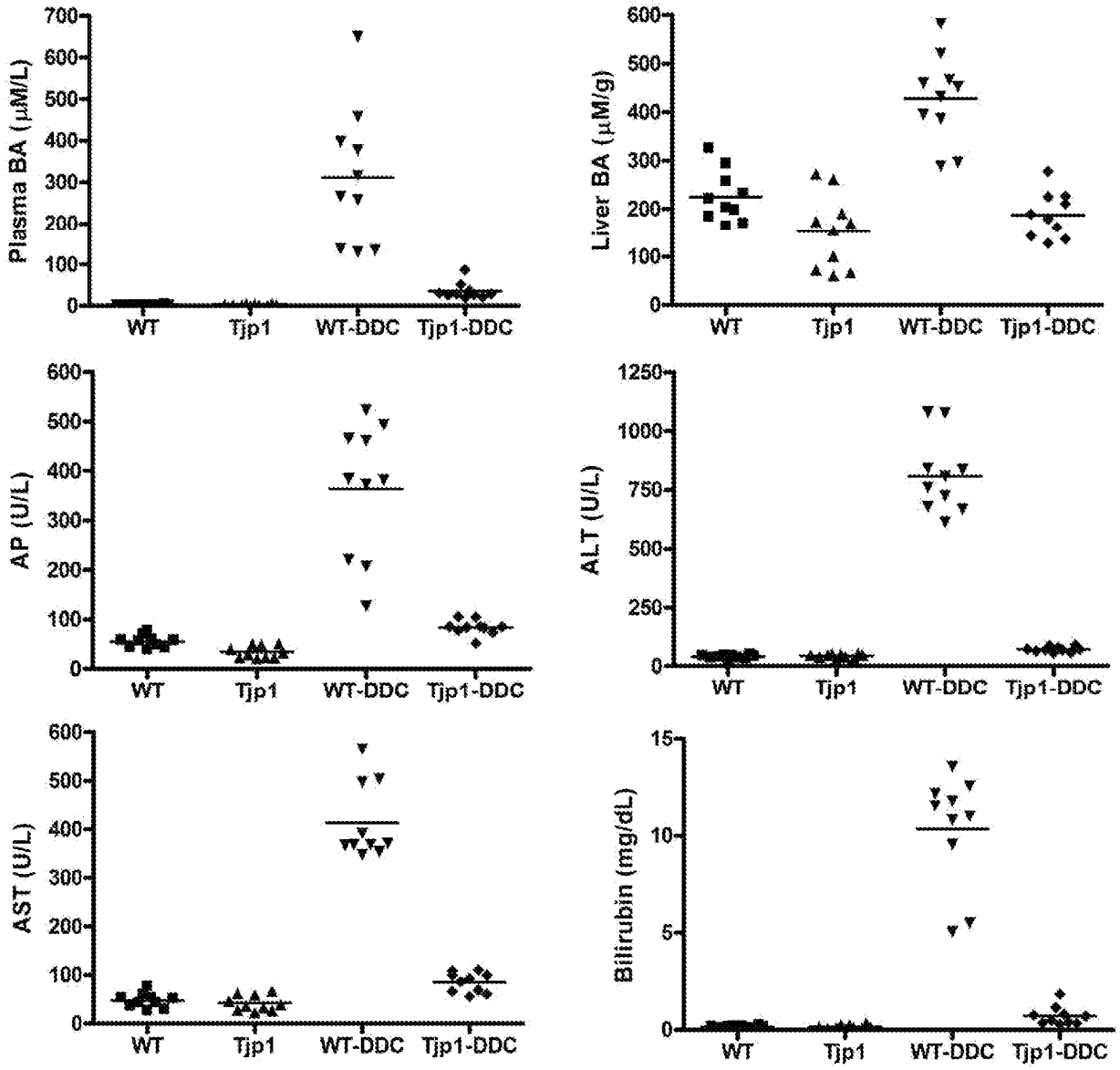

Plasma BA (μM/L)
Liver BA (μM/g)
AP (U/L)
ALT (U/L)
AST (U/L)
Bilirubin (mg/dL)
WT
Tjp1
WT-DDC
Tjp1-DDC

Fig. 3E

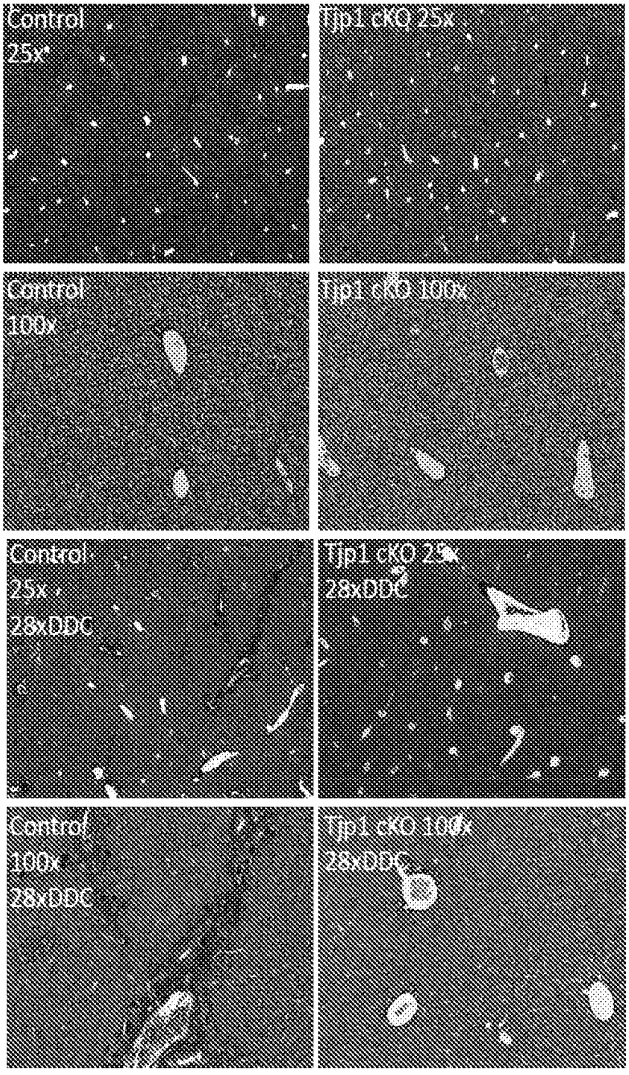
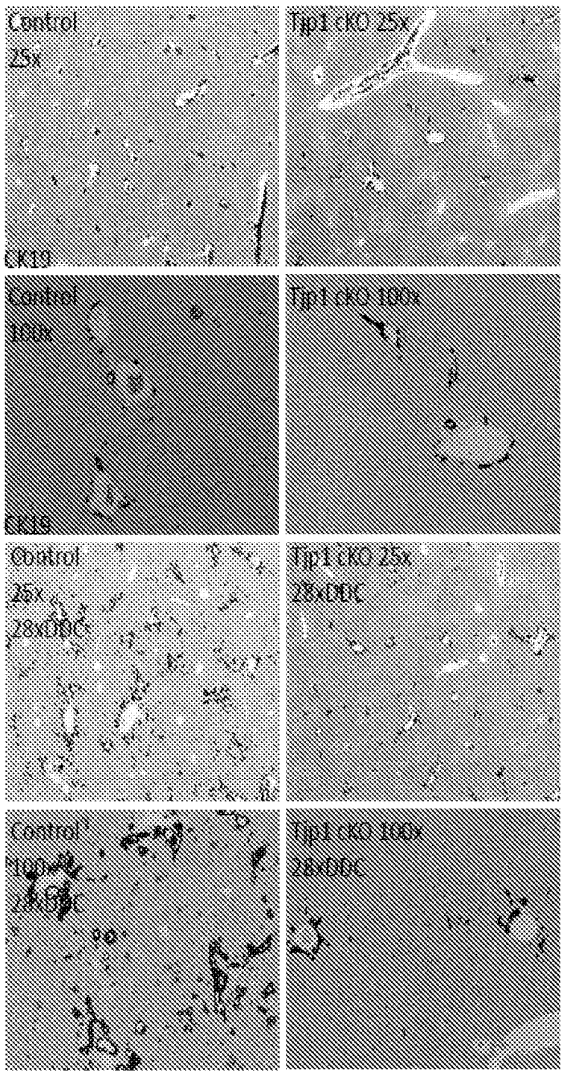
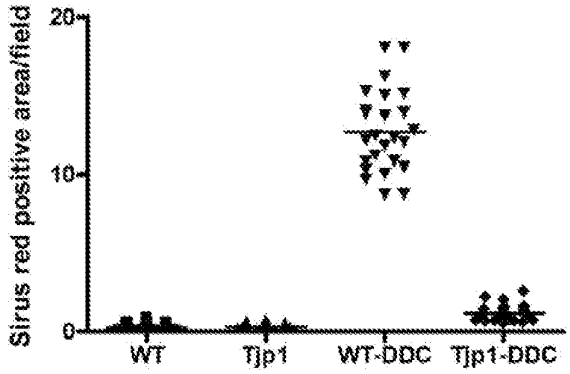

Control
25x
Tjp1 cKO 25x
Control
100x
Tjp1 cKO 100x
Control
25x
28xDDC
Tjp1 cKO 25x
28xDDC
Control
100x
28xDDC
Tjp1 cKO 100x
28xDDC

Fig. 3F


Control
25x
Tjp1 cKO 25x
CK19
Control
100x
Tjp1 cKO 100x
Control
25x
28xDDC
Tjp1 cKO 25x
28xDDC
Control
100x
28xDDC
Tjp1 cKO 100x
28xDDC


Sirus red positive area/field
20
10
0
WT
Tjp1
WT-DDC
Tjp1-DDC

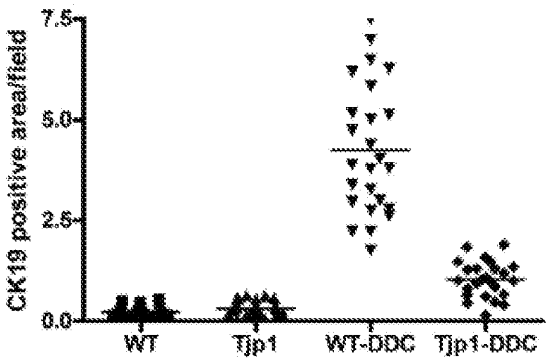

CK19 positive area/field
7.5
5.0
2.5
0.0
WT
Tjp1
WT-DDC
Tjp1-DDC

Fig. 3G

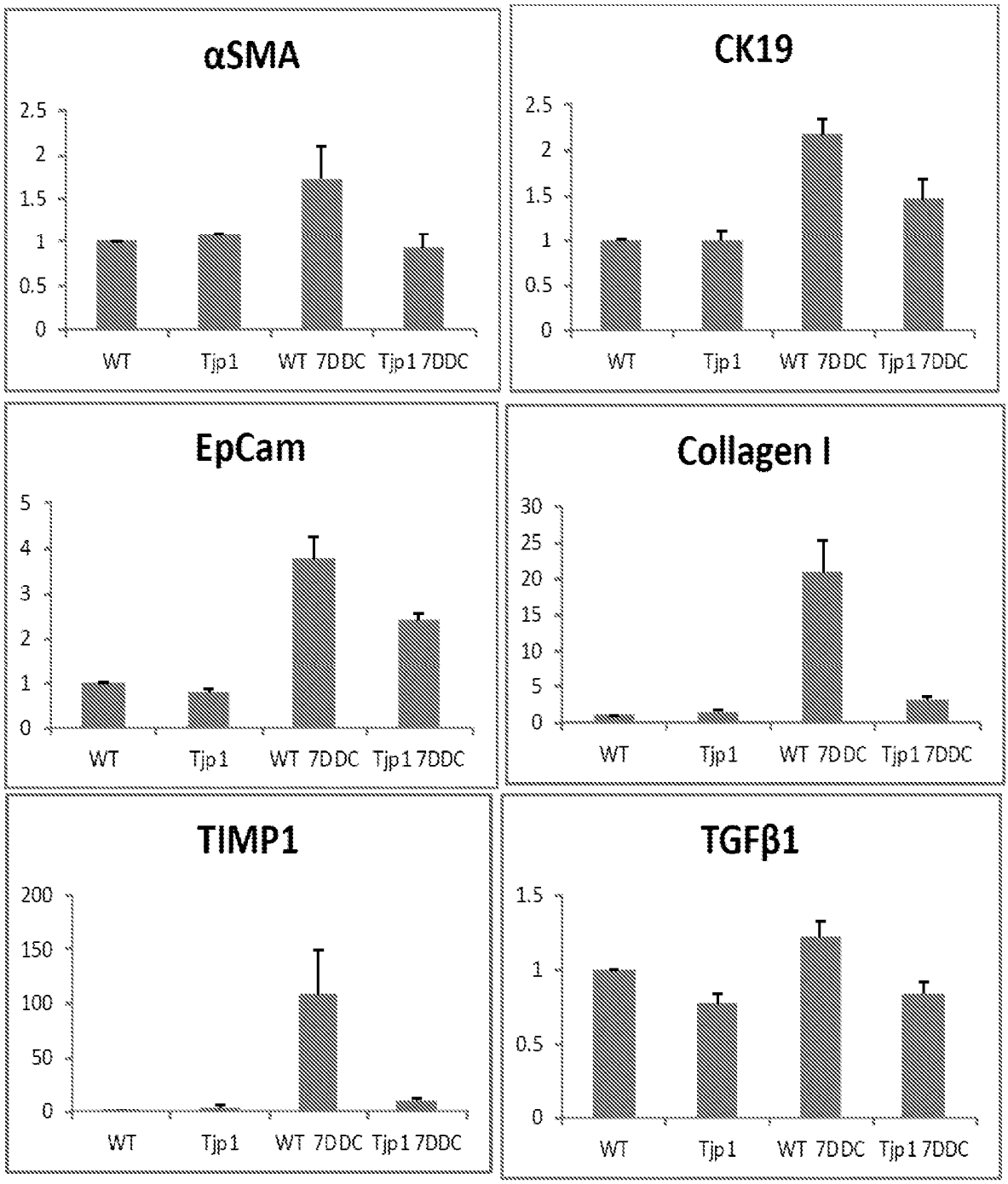

αSMA
2.5
2
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
CK19
2.5
2
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
EpCam
5
4
3
2
1
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
Collagen I
30
25
20
15
10
5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
TIMP1
200
150
100
50
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
TGFβ1
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC

Fig. 3G (cont.)

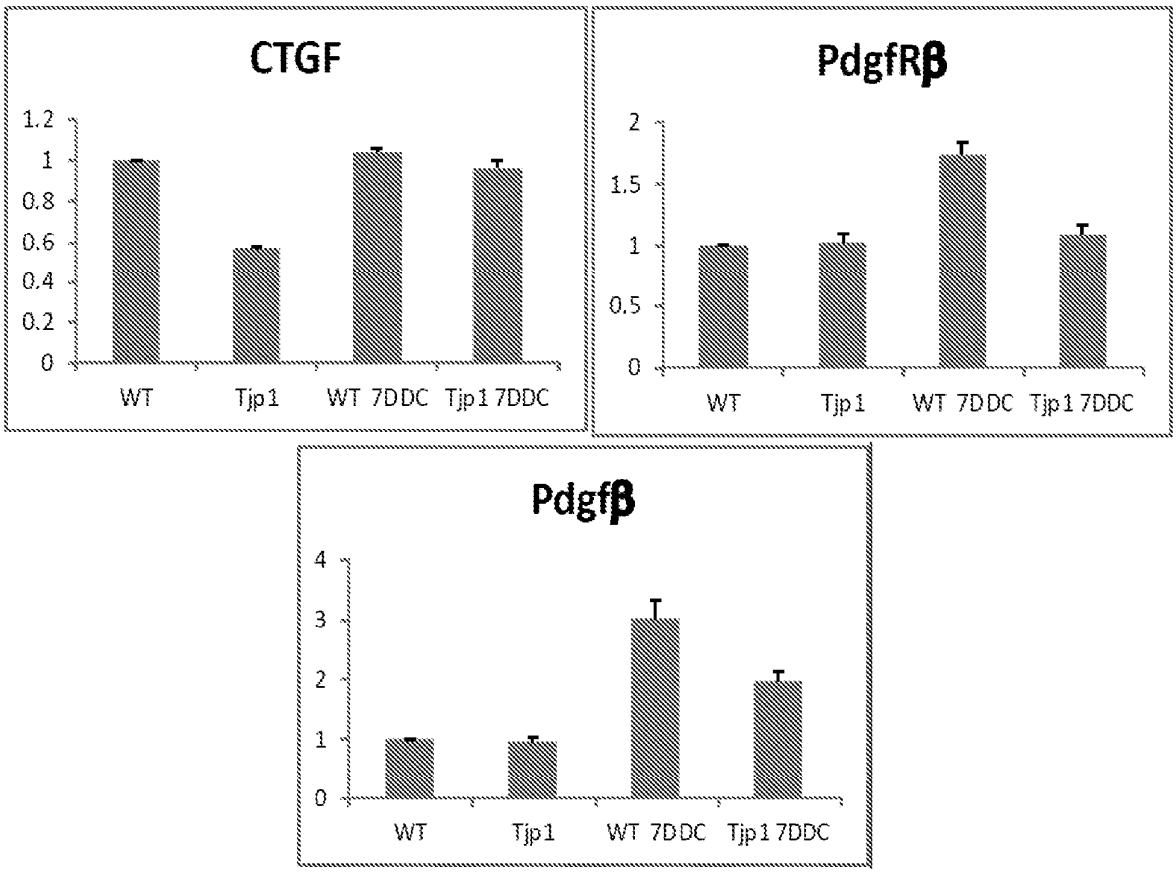


Fig. 3H

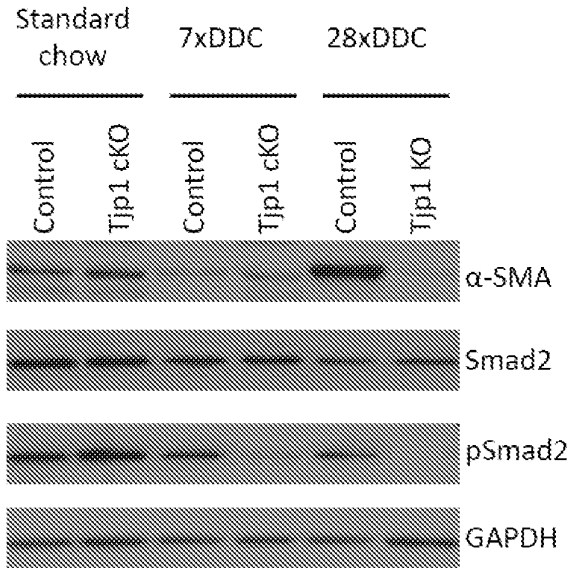


Fig. 3 (cont.)

Fig. 3I

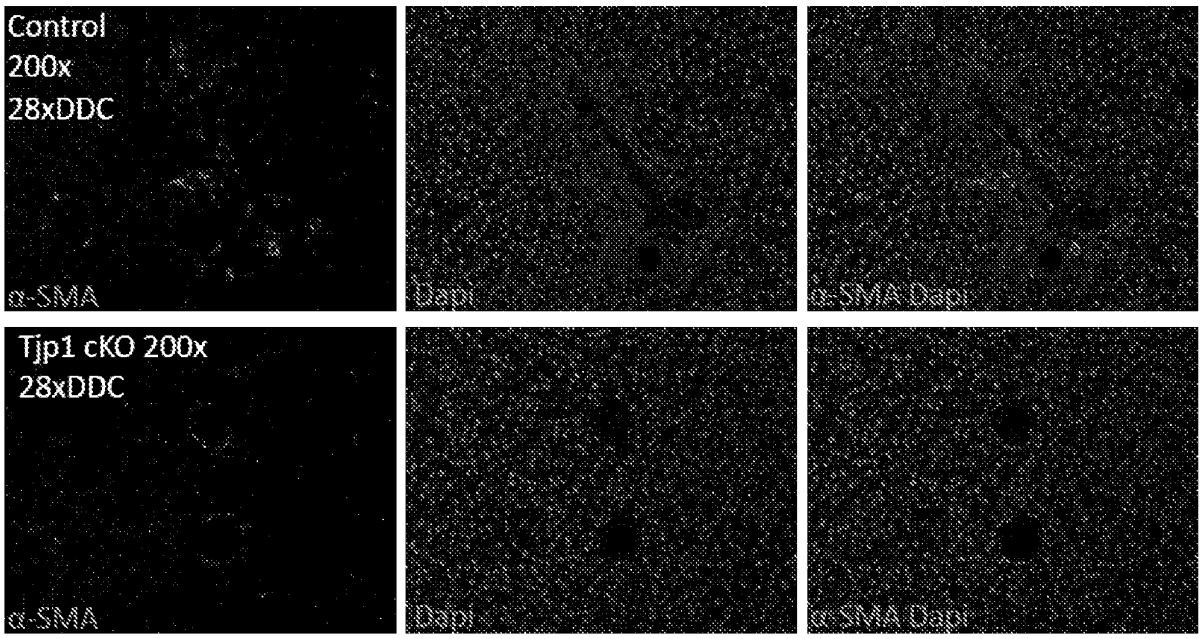

Control
200x
28xDDC
α-SMA
Dapi
α-SMA Dapi
Tjp1 cKO 200x
28xDDC
α-SMA
Dapi
α-SMA Dapi

Fig. 3J

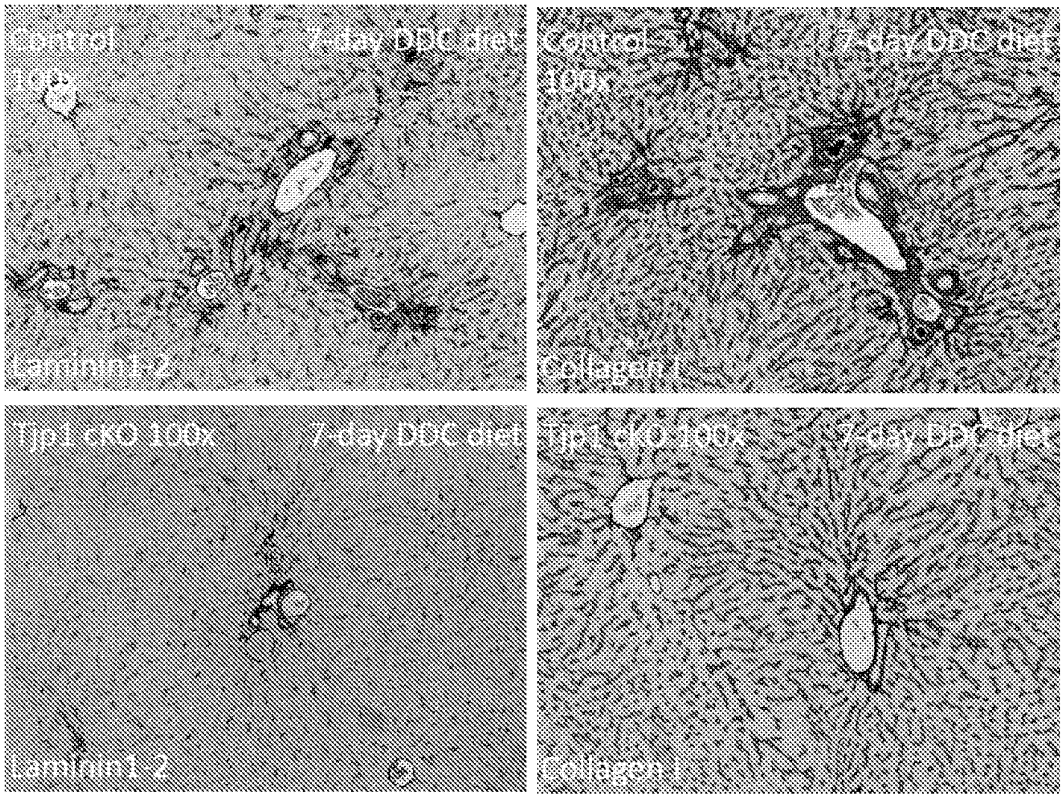

Control
7-day DDC diet
100x
Laminin1-2
Control
7-day DDC diet
100x
Collagen I
Tjp1 cKO 100x
7-day DDC diet
Laminin1-2
Tjp1 cKO 100x
7-day DDC diet
Collagen I

Fig. 3K

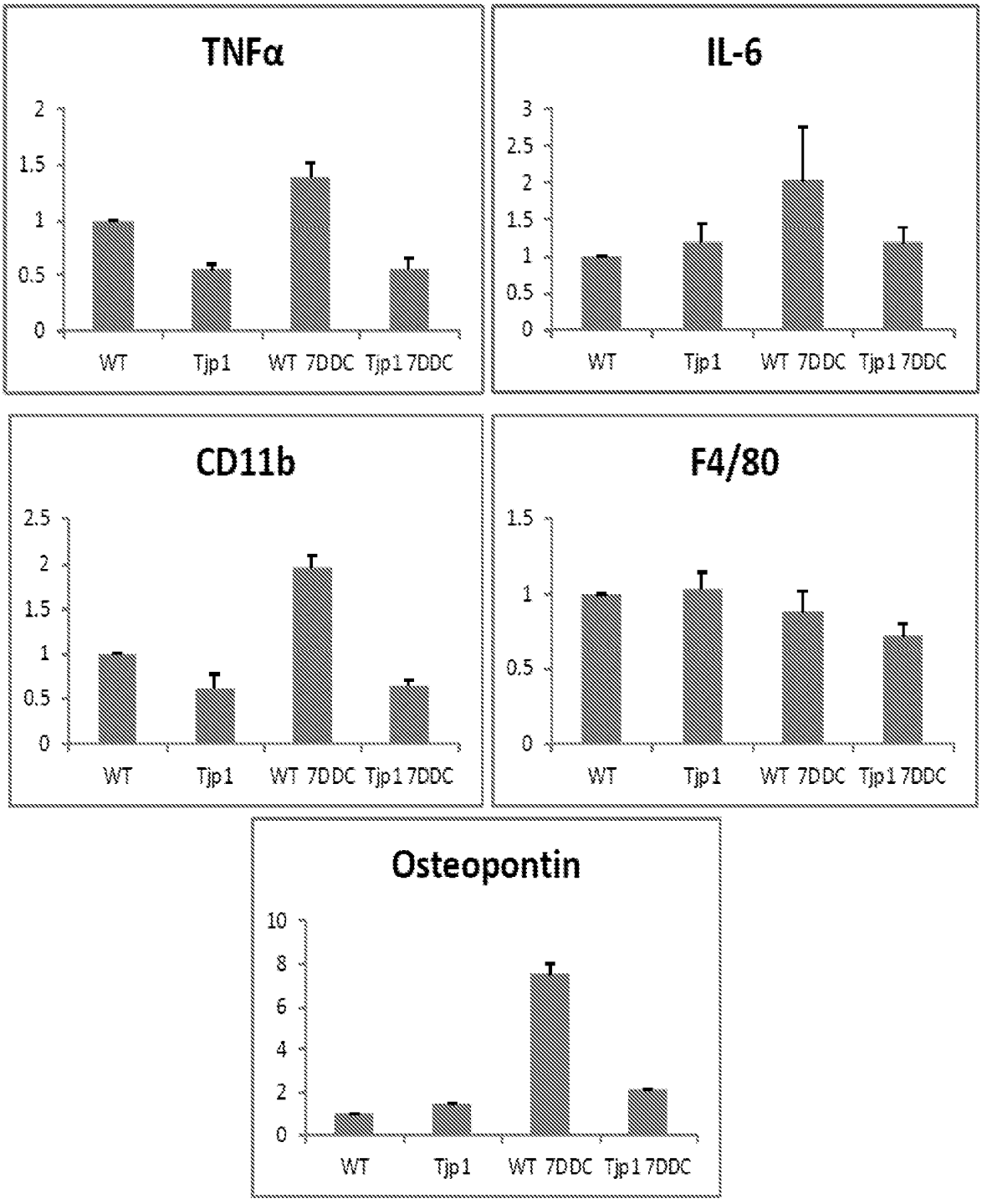

TNFα
2
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
IL-6
3
2.5
2
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
CD11b
2.5
2
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
F4/80
1.5
1
0.5
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC
Osteopontin
10
8
6
4
2
0
WT
Tjp1
WT 7DDC
Tjp1 7DDC

Fig. 4A

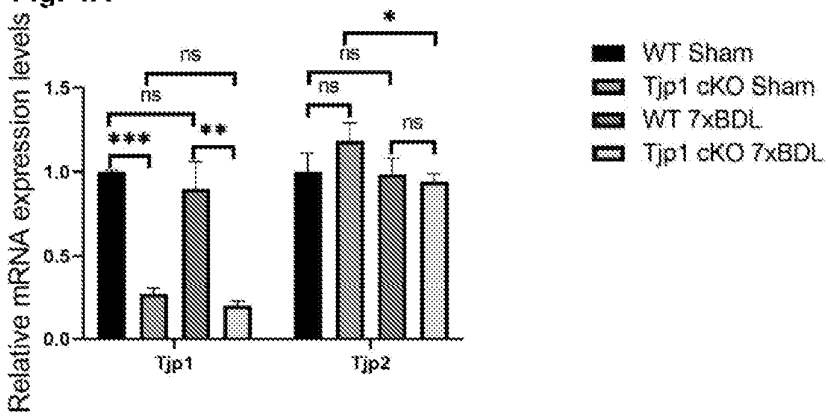

Relative mRNA expression levels
1.5
1.0
0.5
0.0
ns
ns
ns
ns
ns
*
***
**
Tjp1
Tjp2
WT Sham
Tjp1 cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL

Fig. 4B

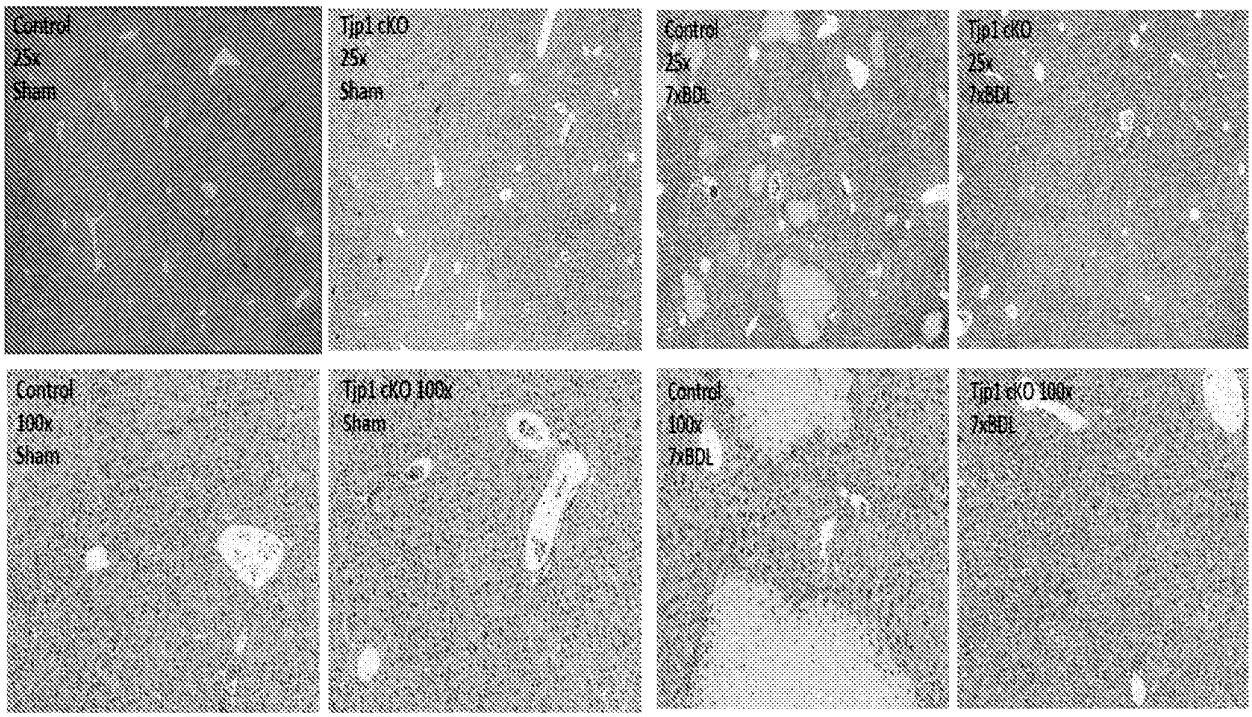

Control
25x
Sham
Tjp1 cKO
25x
Sham
Control
25x
7xBDL
Tjp1 cKO
25x
7xBDL
Control
100x
Sham
Tjp1 cKO 100x
Sham
Control
100x
7xBDL
Tjp1 cKO 100x
7xBDL

Fig. 4B (cont.)

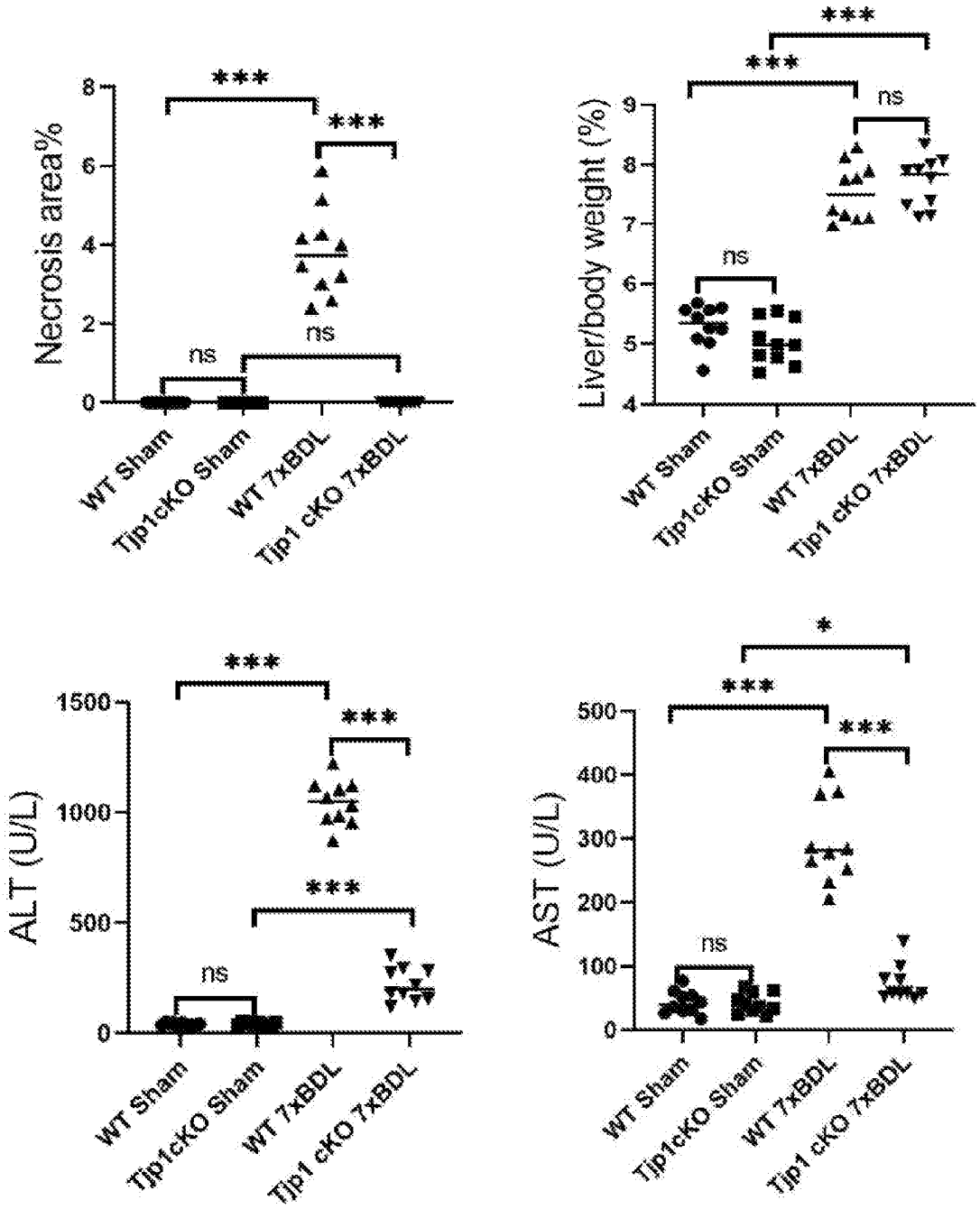

Necrosis area%
***
***
ns
ns
WT Sham
Tjp1cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL
Liver/body weight (%)
***
***
ns
ns
ALT (U/L)
***
***
***
ns
AST (U/L)
*
***
***
ns

Fig. 4C

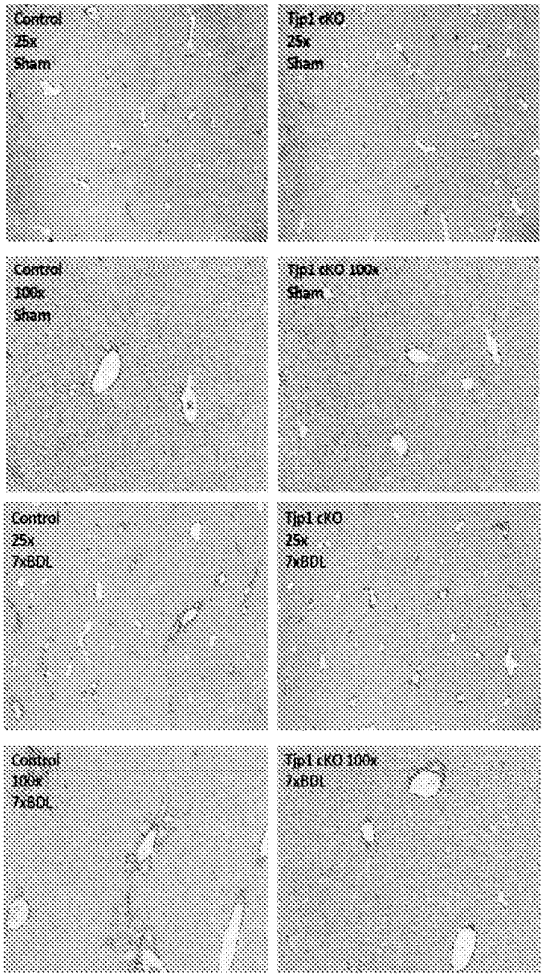
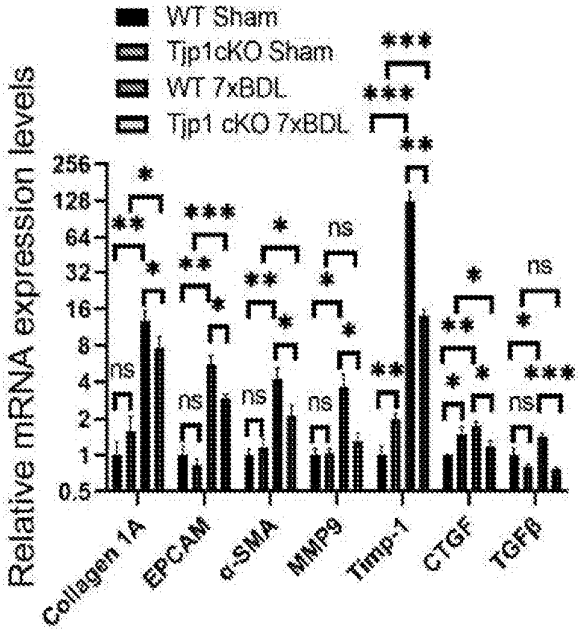
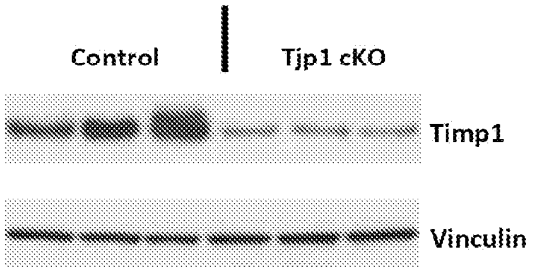
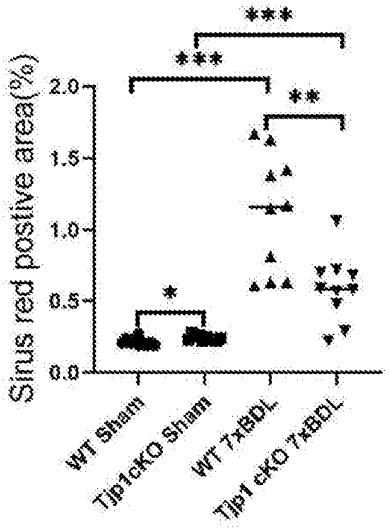

Control
25x
Sham
Tjp1 cKO
25x
Sham
Control
100x
Sham
Tjp1 cKO 100x
Sham
Control
25x
7xBDL
Tjp1 cKO
25x
7xBDL
Control
100x
7xBDL
Tjp1 cKO 100x
7xBDL

Fig. 4D


WT Sham
Tjp1cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL
Relative mRNA expression levels
256
128
64
32
16
8
4
2
1
0.5
ns
Collagen 1A
EPCAM
α-SMA
MMP9
Timp-1
CTGF
TGFβ


Control
Tjp1 cKO
Timp1
Vinculin


Sirus red postive area(%)
2.0
1.5
1.0
0.5
0.0
WT Sham
Tjp1cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL

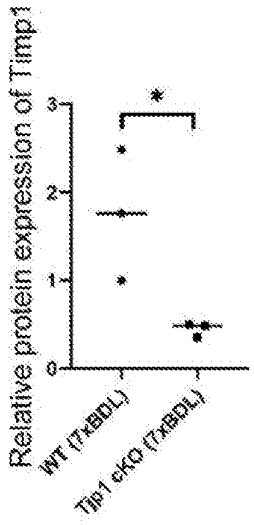

Relative protein expression of Timp1
3
2
1
0
WT (7xBDL)
Tjp1 cKO (7xBDL)

Fig. 4E

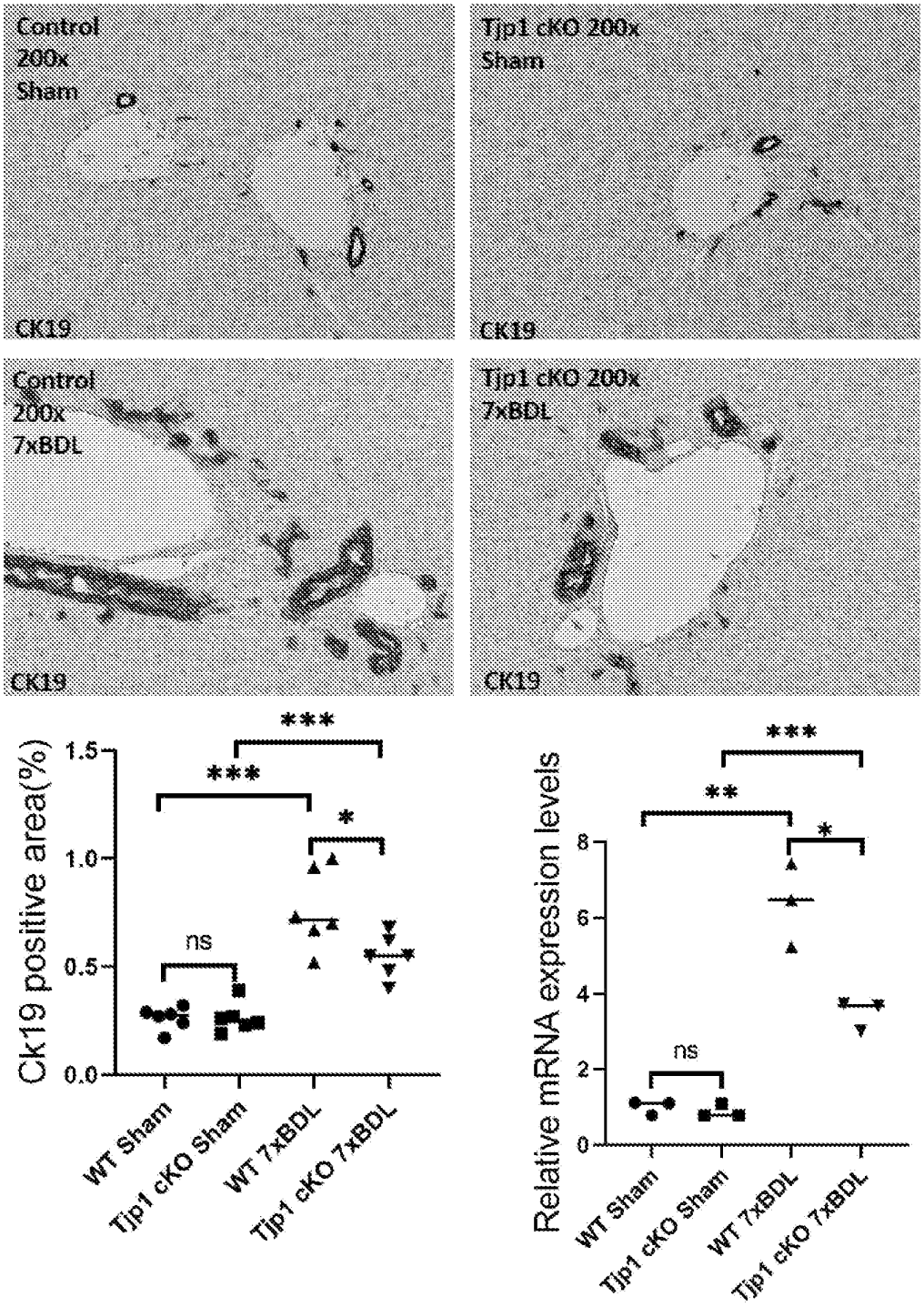

Control
200x
Sham
CK19
Tjp1 cKO 200x
Sham
CK19
Control
200x
7xBDL
CK19
Tjp1 cKO 200x
7xBDL
CK19
Ck19 positive area(%)
1.5
1.0
0.5
0.0
***
***
*
ns
WT Sham
Tjp1 cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL
Relative mRNA expression levels
8
6
4
2
0
***
**
*
ns
WT Sham
Tjp1 cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL

Fig. 4F

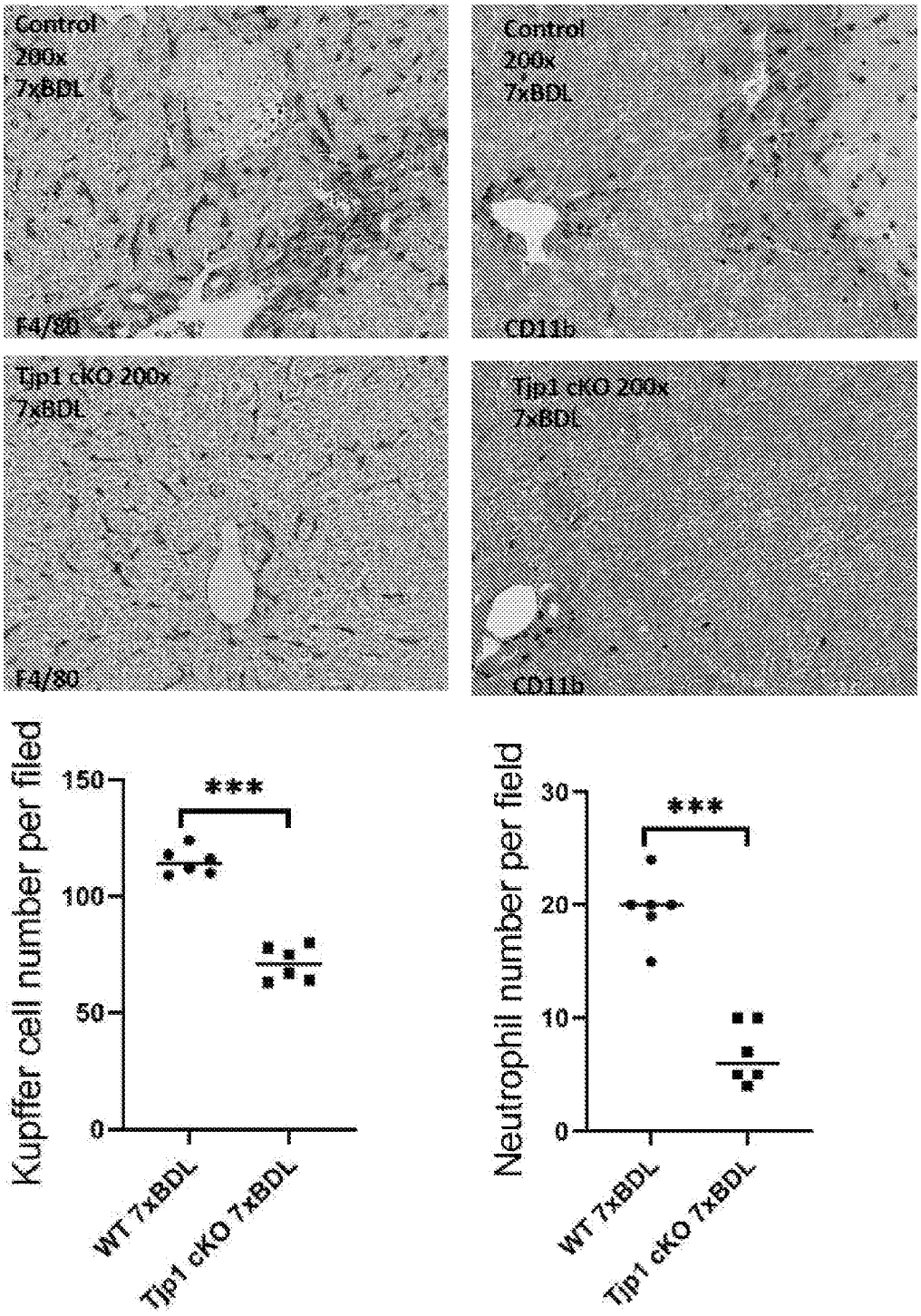

Control
200x
7xBDL
F4/80
Control
200x
7xBDL
CD11b
Tjp1 cKO 200x
7xBDL
F4/80
Tjp1 cKO 200x
7xBDL
CD11b
Kupffer cell number per filed
150
100
50
0
***
WT 7xBDL
Tjp1 cKO 7xBDL
Neutrophil number per field
30
20
10
0
***
WT 7xBDL
Tjp1 cKO 7xBDL

Fig. 4F (cont.)

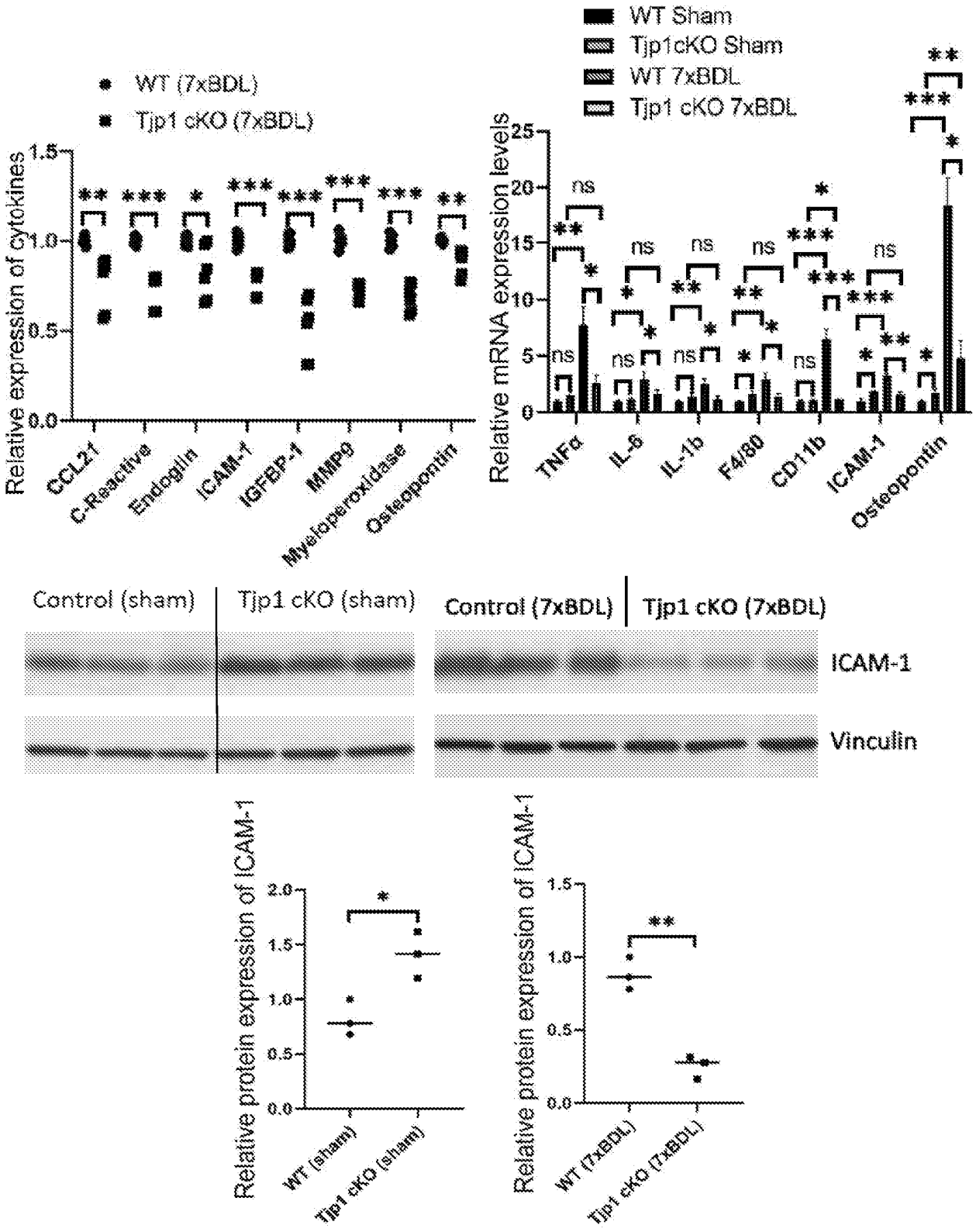

WT (7xBDL)
Tjp1 cKO (7xBDL)
Relative expression of cytokines
CCL21
C-Reactive
Endoglin
ICAM-1
IGFBP-1
MMP9
Myeloperoxidase
Osteopontin
WT Sham
Tjp1cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL
Relative mRNA expression levels
TNFα
IL-6
IL-1b
F4/80
CD11b
ICAM-1
Osteopontin
Control (sham)
Tjp1 cKO (sham)
Control (7xBDL)
Tjp1 cKO (7xBDL)
ICAM-1
Vinculin
Relative protein expression of ICAM-1
WT (sham)
Tjp1 cKO (sham)
Relative protein expression of ICAM-1
WT (7xBDL)
Tjp1 cKO (7xBDL)

Fig. 4G

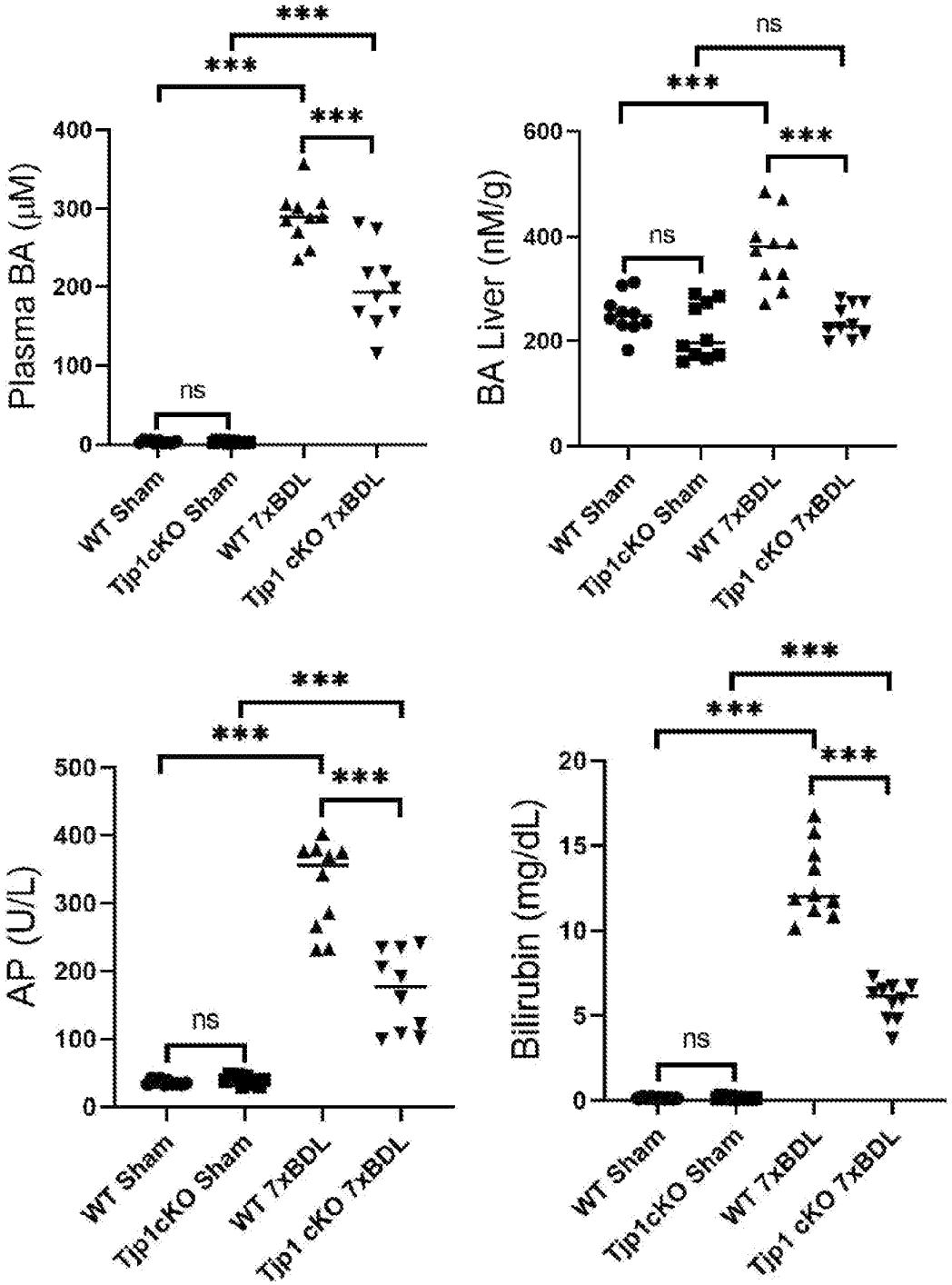

Plasma BA (μM)
BA Liver (nM/g)
AP (U/L)
Bilirubin (mg/dL)
ns
***
WT Sham
Tjp1cKO Sham
WT 7xBDL
Tjp1 cKO 7xBDL

Fig. 4H

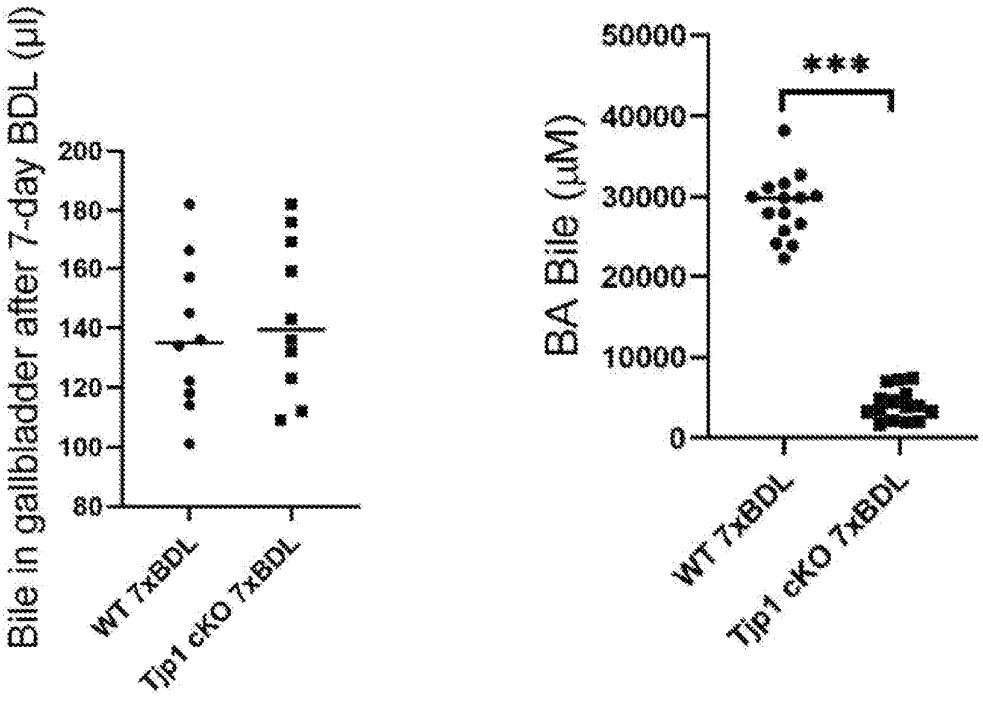

Bile in gallbladder after 7-day BDL (μl)
200
180
160
140
120
100
80
WT 7xBDL
Tjp1 cKO 7xBDL
BA Bile (μM)
50000
40000
30000
20000
10000
0
***
WT 7xBDL
Tjp1 cKO 7xBDL

Fig. 4I

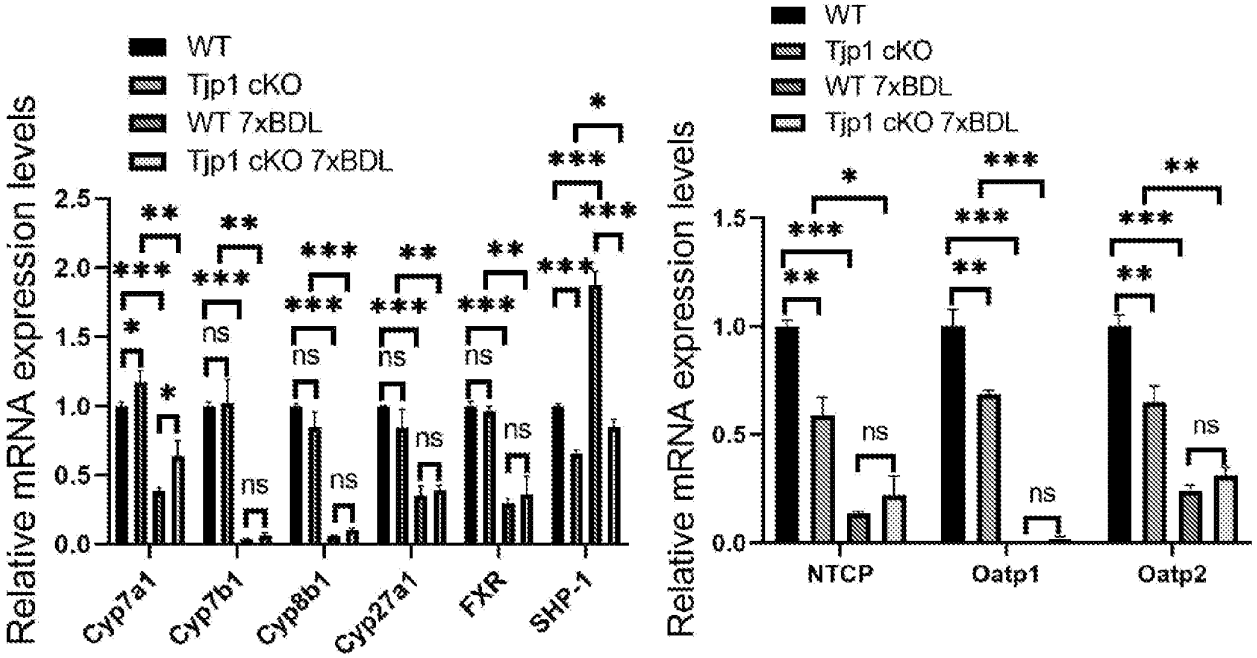

WT
Tjp1 cKO
WT 7xBDL
Tjp1 cKO 7xBDL
Relative mRNA expression levels
2.5
2.0
1.5
1.0
0.5
0.0
Cyp7a1
Cyp7b1
Cyp8b1
Cyp27a1
FXR
SHP-1
ns
NTCP
Oatp1
Oatp2

Fig. 4I (cont.)

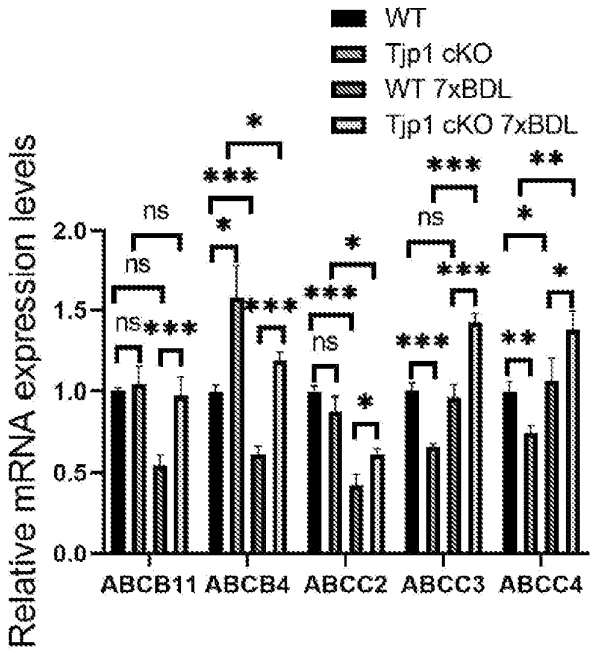


Fig. 4J

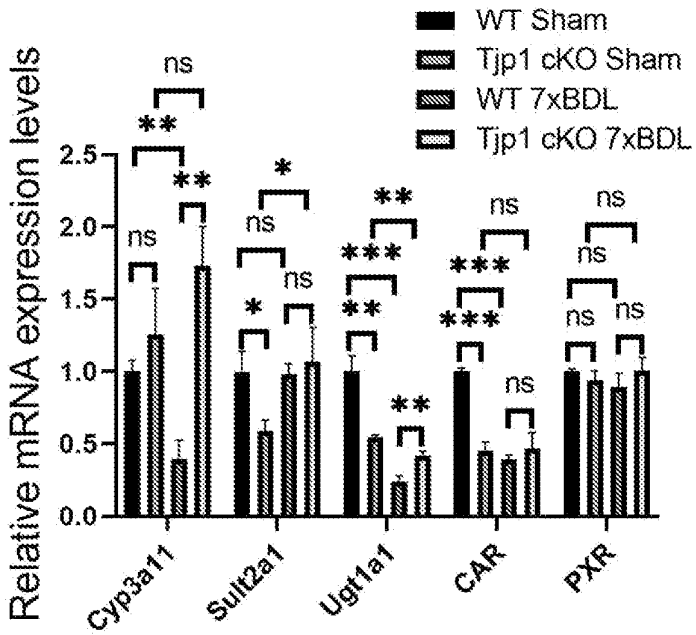


Fig. 4K

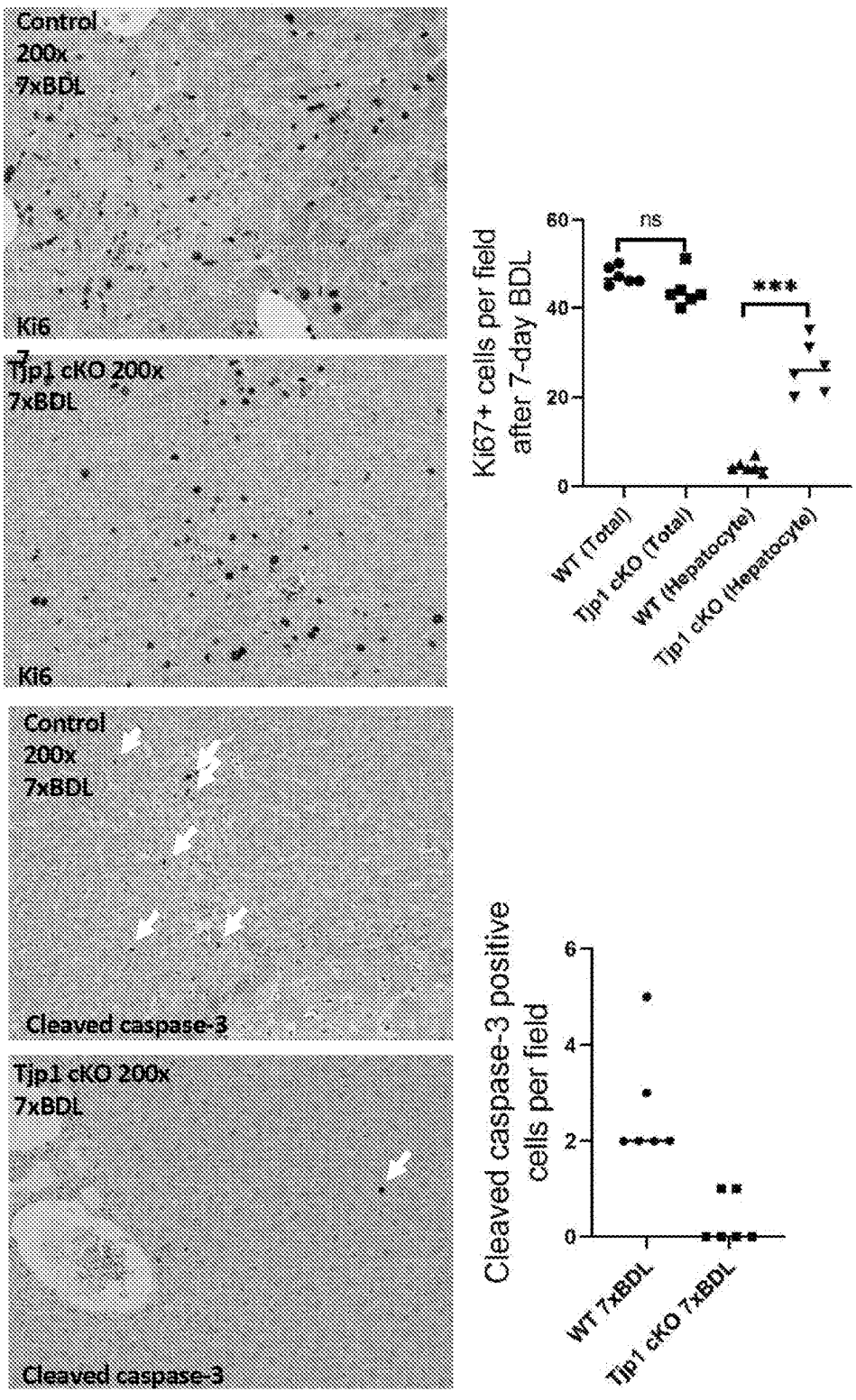

Control
200x
7xBDL
Ki6
7
Tjp1 cKO 200x
7xBDL
Ki6
Control
200x
7xBDL
Cleaved caspase-3
Tjp1 cKO 200x
7xBDL
Cleaved caspase-3
Ki67+ cells per field after 7-day BDL
ns
***
60
40
20
0
WT (Total)
Tjp1 cKO (Total)
WT (Hepatocyte)
Tjp1 cKO (Hepatocyte)
Cleaved caspase-3 positive cells per field
6
4
2
0
WT 7xBDL
Tjp1 cKO 7xBDL

Fig. 5A

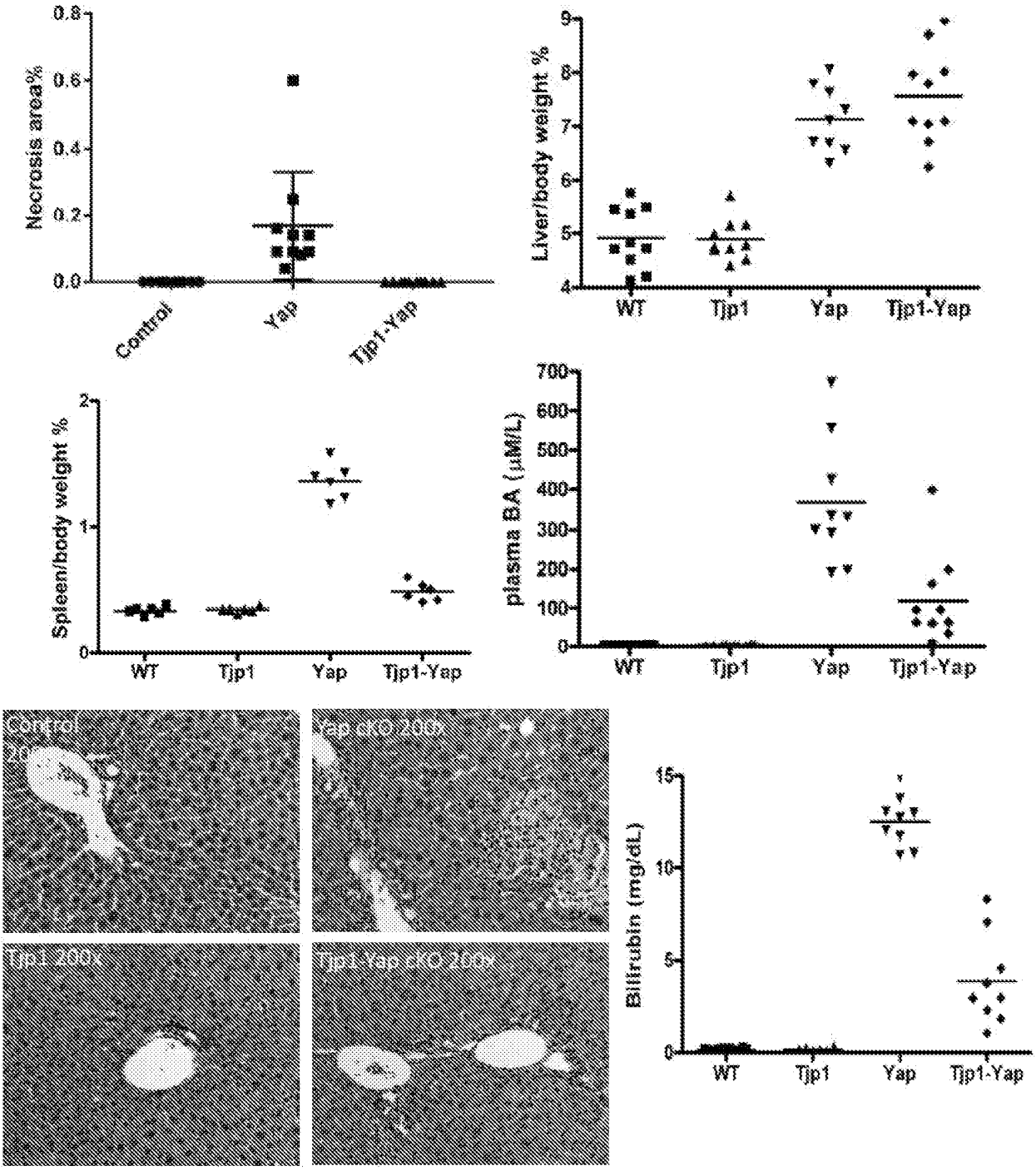
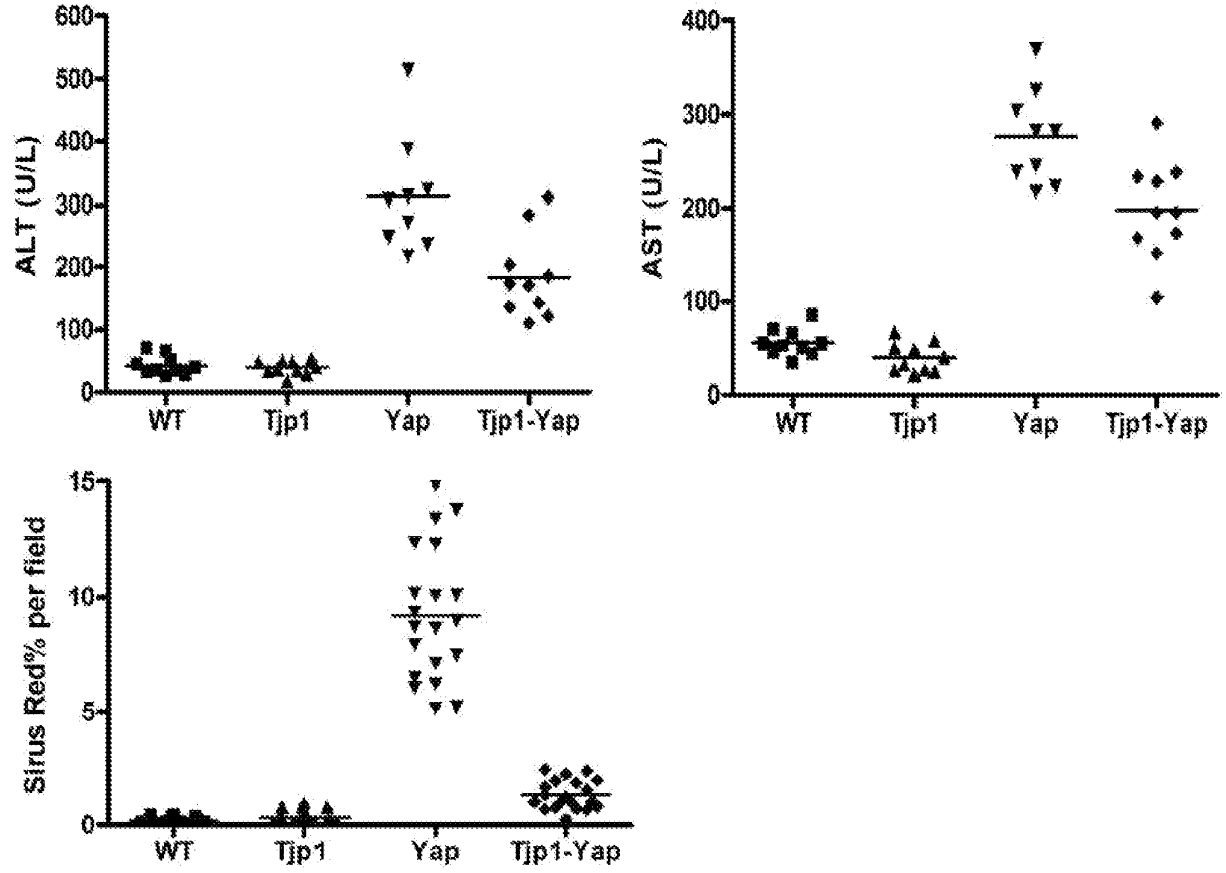

Necrosis area%
0.8
0.6
0.4
0.2
0.0
Control
Yap
Tjp1-Yap
Liver/body weight %
9
8
7
6
5
4
WT
Tjp1
Yap
Tjp1-Yap
Spleen/body weight %
2
1
0
WT
Tjp1
Yap
Tjp1-Yap
plasma BA (μM/L)
700
600
500
400
300
200
100
0
WT
Tjp1
Yap
Tjp1-Yap
Control 200x
Yap cKO 200x
Tjp1 200x
Tjp1-Yap cKO 200x
Bilirubin (mg/dL)
15
10
5
0
WT
Tjp1
Yap
Tjp1-Yap

Fig. 5B


ALT (U/L)
600
500
400
300
200
100
0
WT
Tjp1
Yap
Tjp1-Yap
AST (U/L)
400
300
200
100
0
WT
Tjp1
Yap
Tjp1-Yap
Sirus Red% per field
15
10
5
0
WT
Tjp1
Yap
Tjp1-Yap

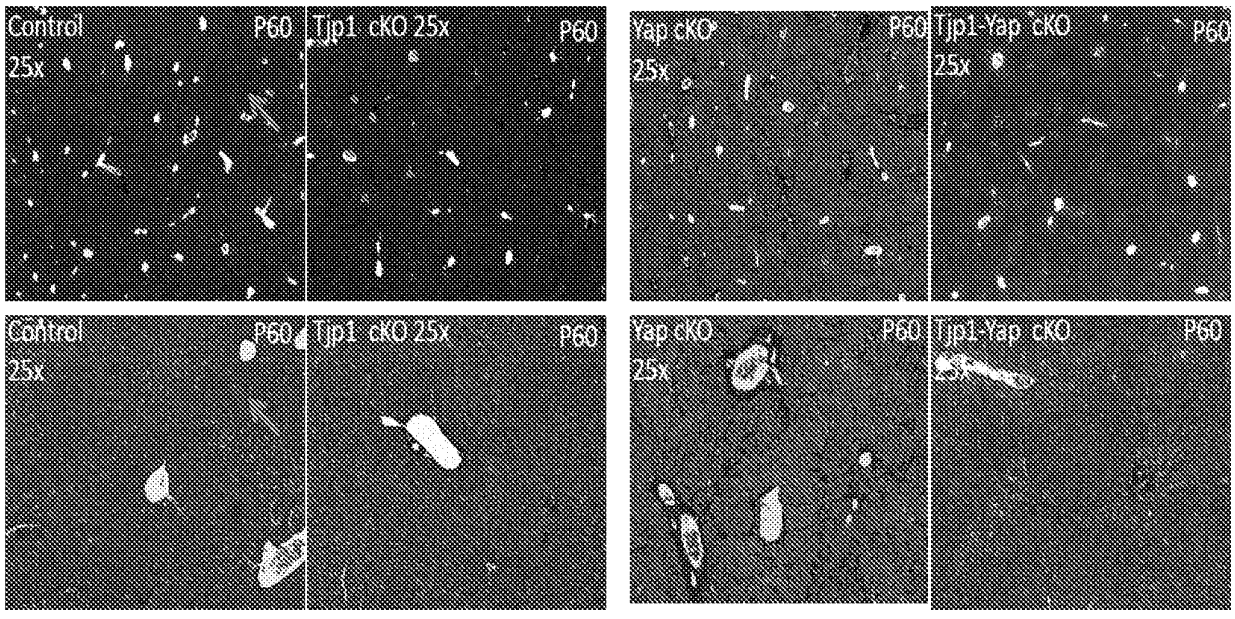

Control
P60
25x
Tjp1 cKO 25x
P60
Yap cKO
P60
25x
Tjp1-Yap cKO
P60
25x
Control
P60
25x
Tjp1 cKO 25x
P60
Yap cKO
P60
25x
Tjp1-Yap cKO
P60

Fig. 5C

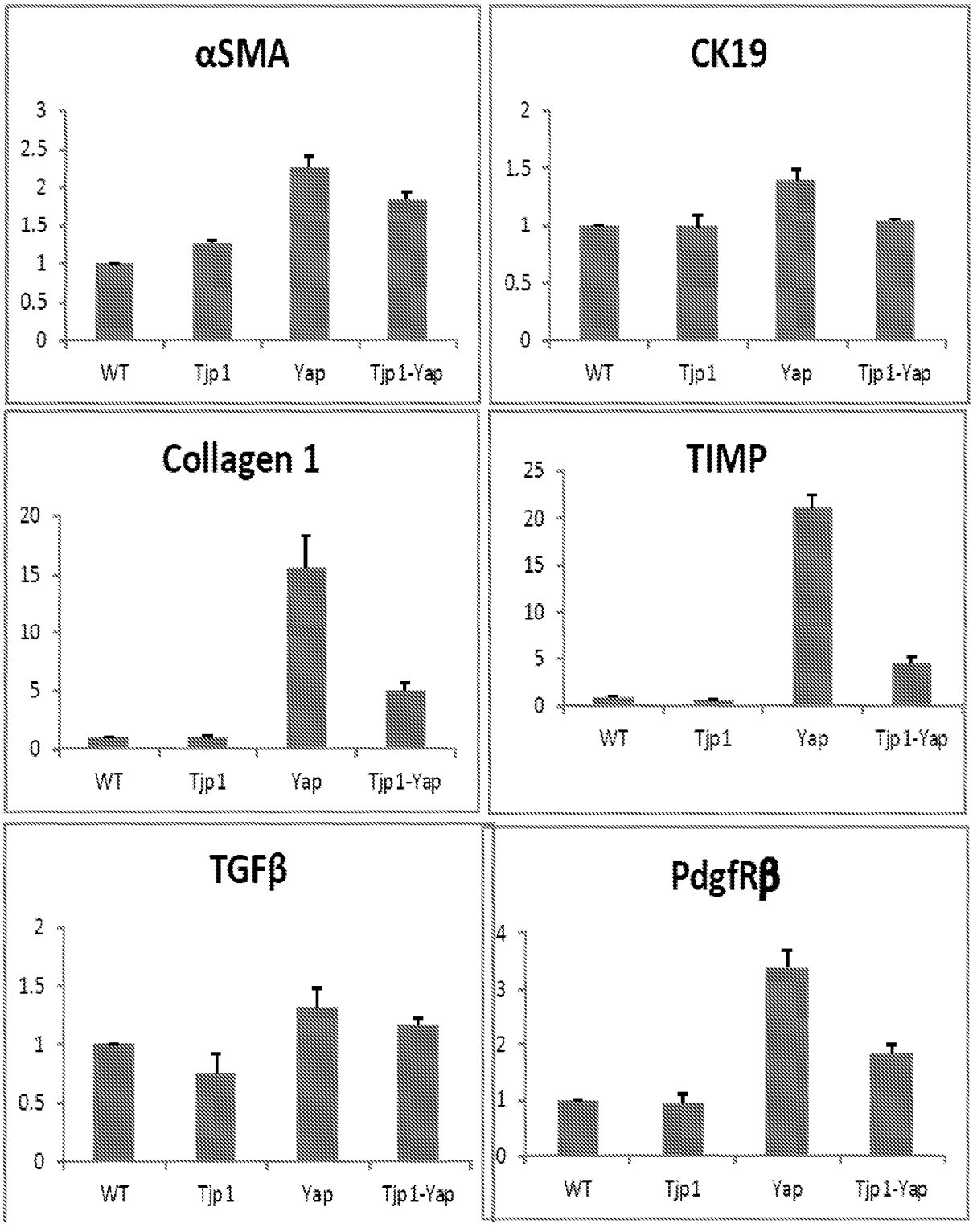

αSMA
3
2.5
2
1.5
1
0.5
0
WT
Tjp1
Yap
Tjp1-Yap
CK19
2
1.5
1
0.5
0
WT
Tjp1
Yap
Tjp1-Yap
Collagen 1
20
15
10
5
0
WT
Tjp1
Yap
Tjp1-Yap
TIMP
25
20
15
10
5
0
WT
Tjp1
Yap
Tjp1-Yap
TGFβ
2
1.5
1
0.5
0
WT
Tjp1
Yap
Tjp1-Yap
PdgfRβ
4
3
2
1
0
WT
Tjp1
Yap
Tjp1-Yap

Fig. 5C (cont.)

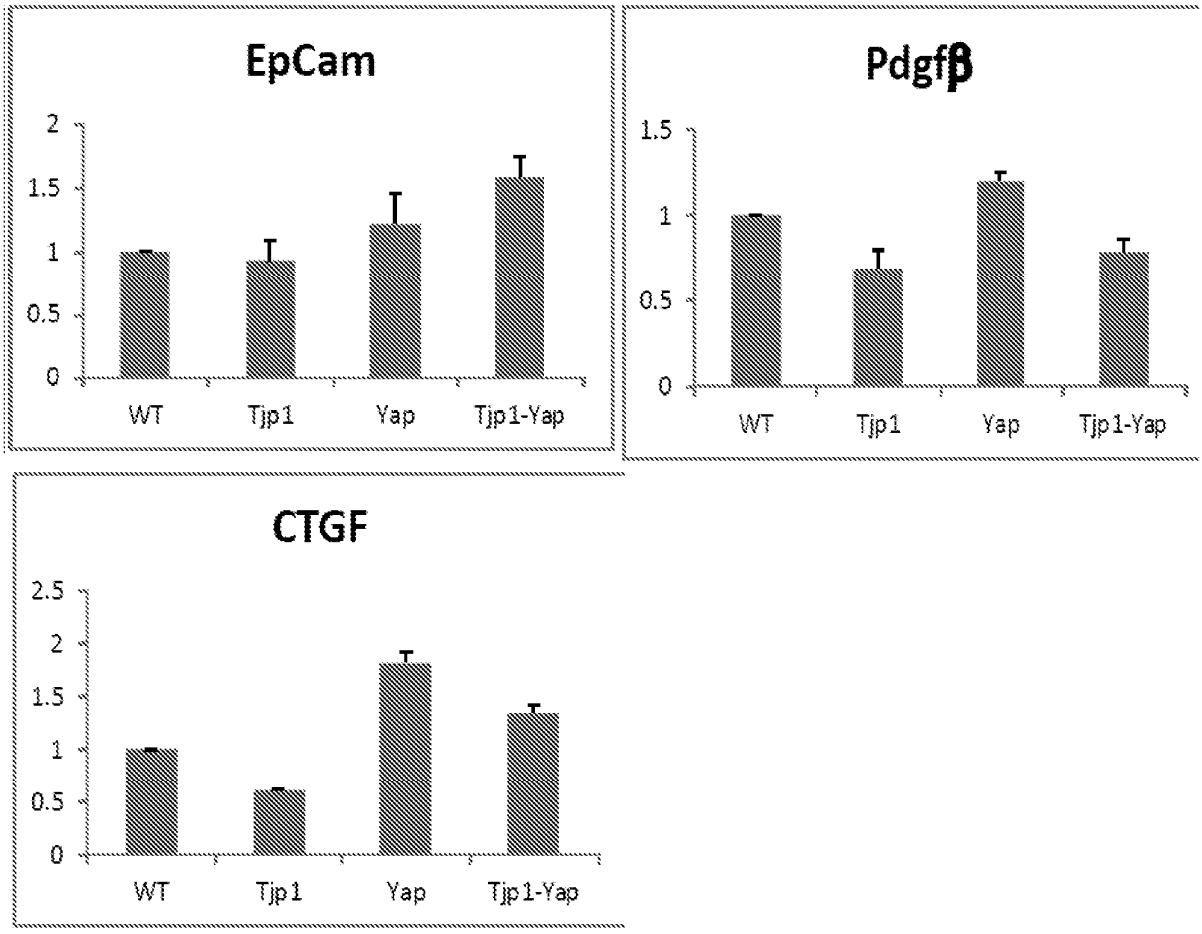


Fig. 5D

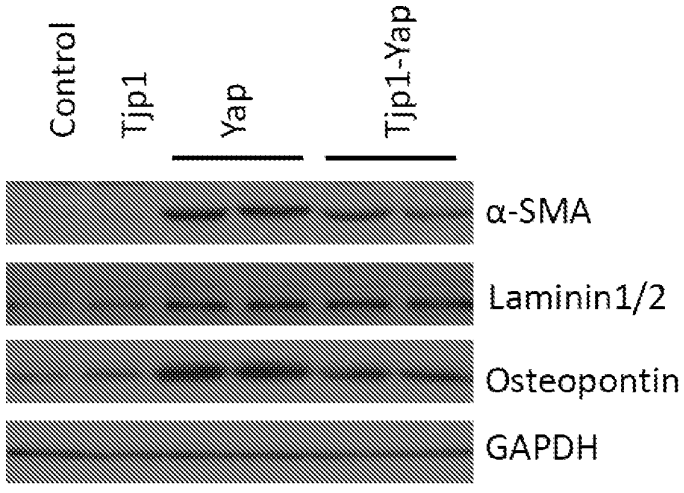


Fig. 5E

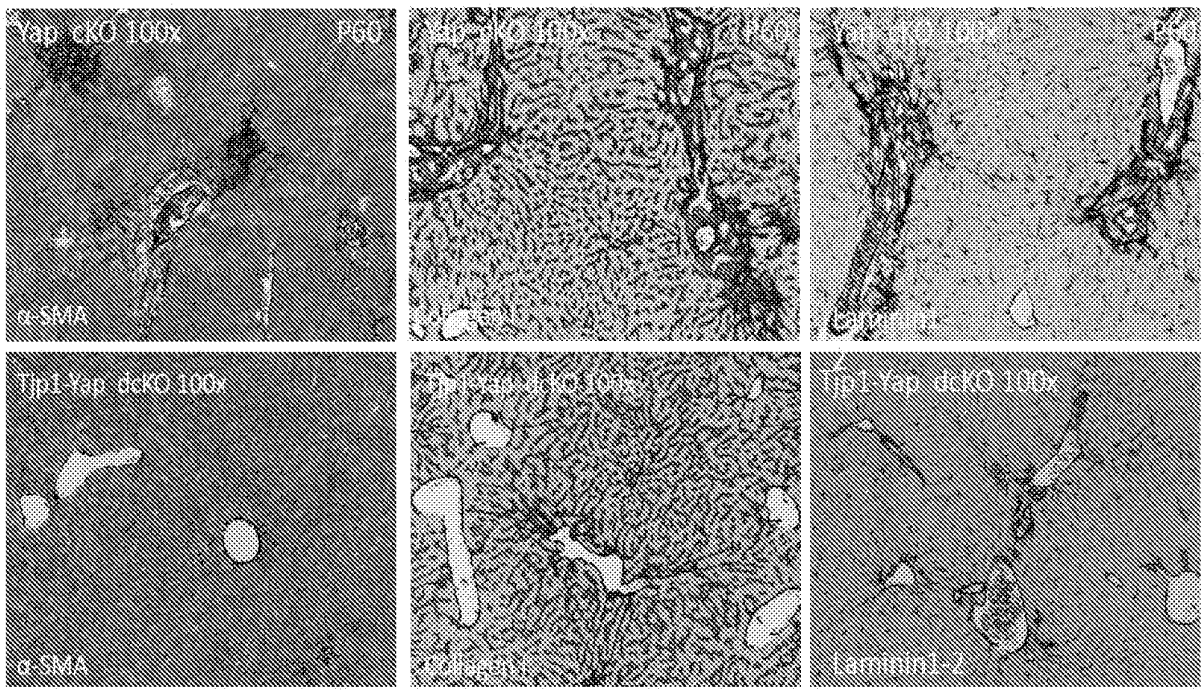

Yap dcKO 100x
P60
α-SMA
Tjp1 Yap dcKO 100x
α-SMA
Tjp1-Yap dcKO 100x
Laminin1-2

Fig. 5F

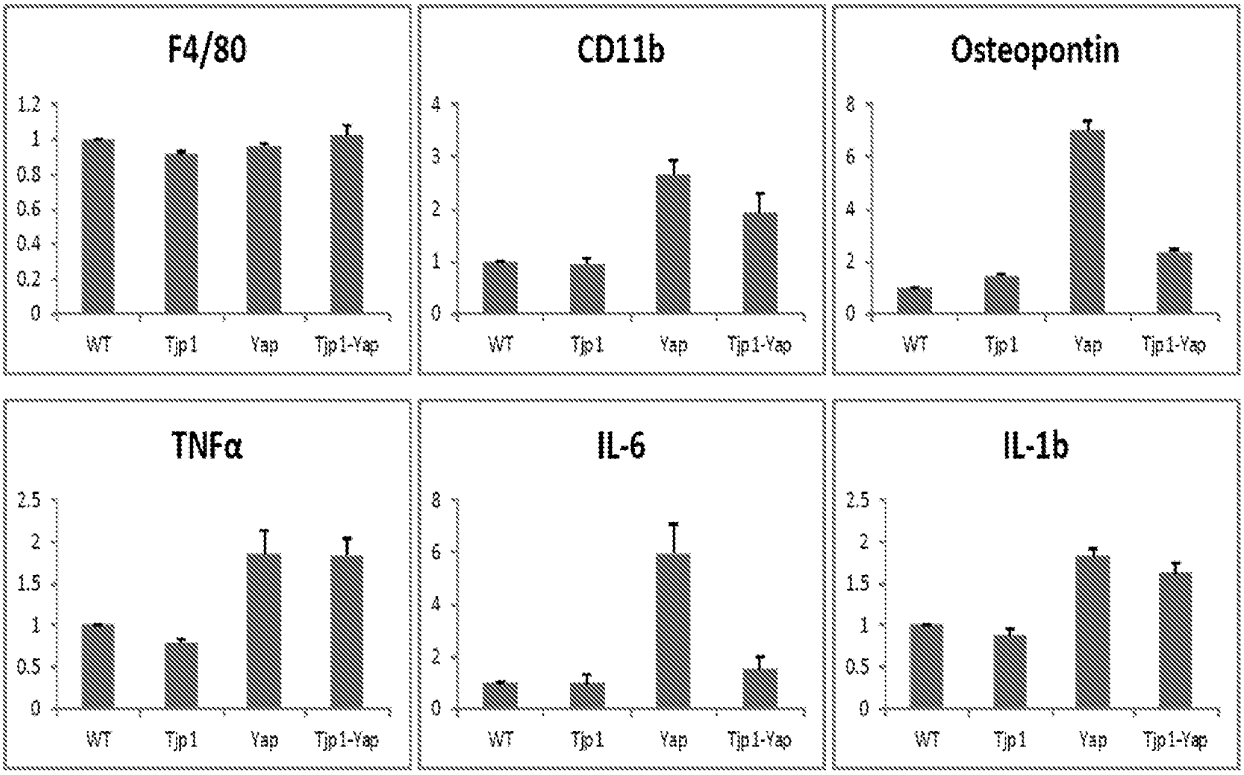

F4/80
CD11b
Osteopontin
TNFα
IL-6
IL-1b
WT
Tjp1
Yap
Tjp1-Yap

Fig. 5G

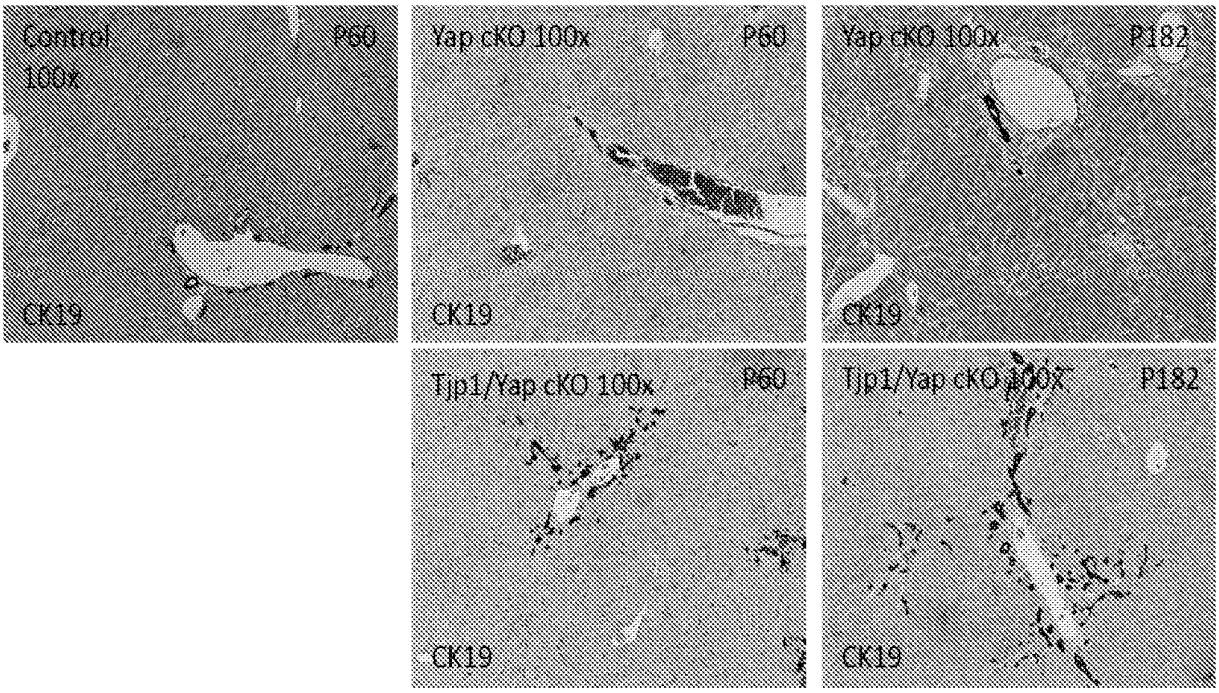

Control
100x
P60
CK19
Yap cKO 100x
P60
CK19
Yap cKO 100x
P182
CK19
Tjp1/Yap cKO 100x
P60
CK19
Tjp1/Yap cKO 100x
P182
CK19

Fig. 5H

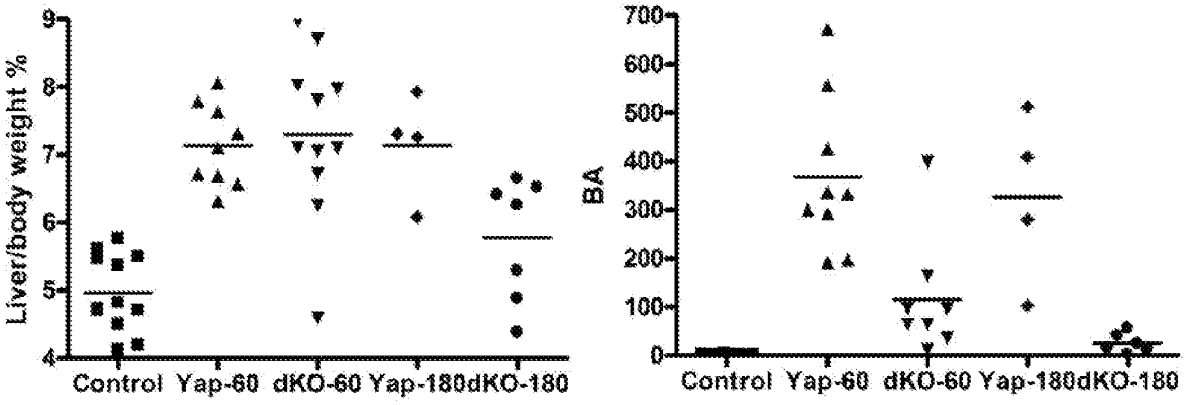

Liver/body weight %
9
8
7
6
5
4
Control
Yap-60
dKO-60
Yap-180
dKO-180
BA
700
600
500
400
300
200
100
0
Control
Yap-60
dKO-60
Yap-180
dKO-180

Fig. 5H (cont.)

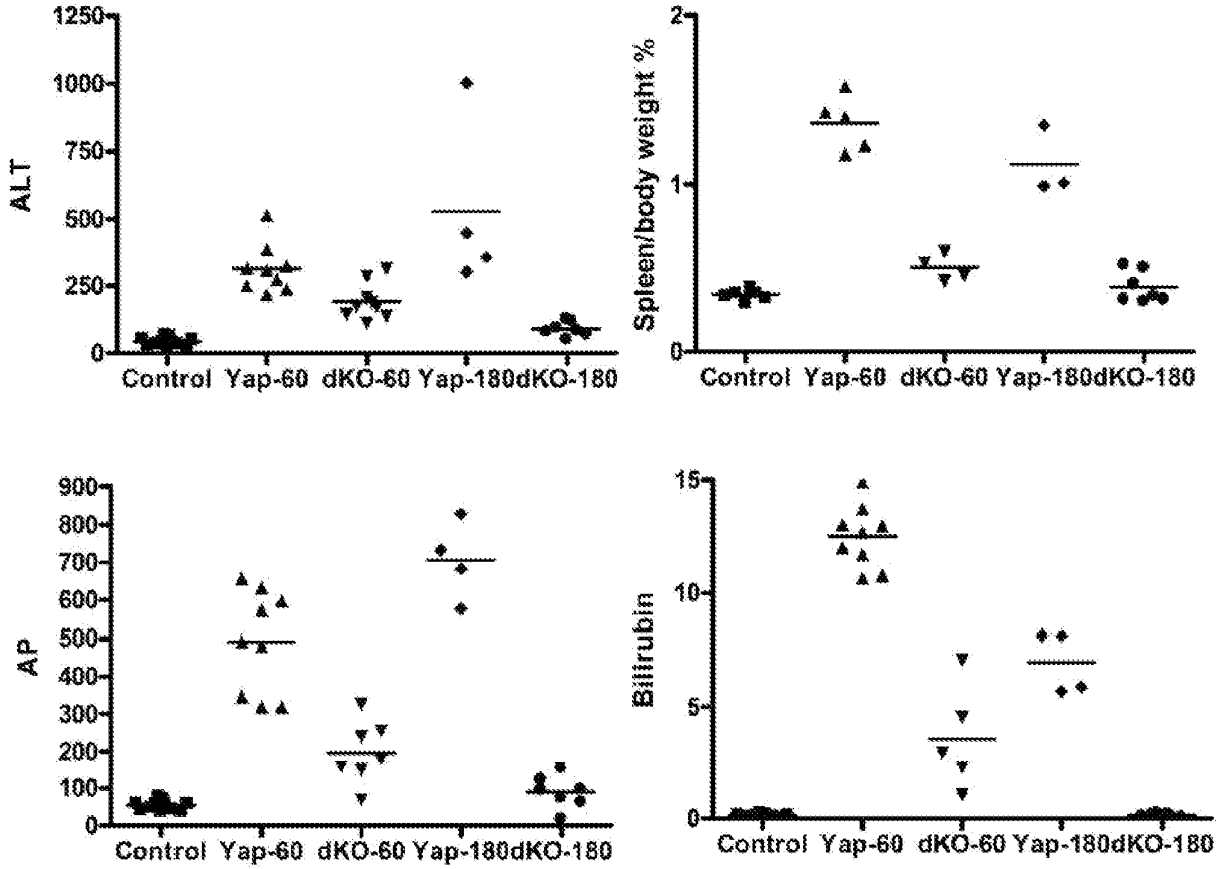


Fig. 6A

TJP1# 18: (SEQ ID NO: 1)
CCGG**CGTGGATTGAACTTACTAAAT**CTCGAGAT
TTAGTAAGTTCAATCCACGTTTTTG

TJP1#21:(SEQ ID NO: 2)
CCGG**CCGCGAAGTTATGAGCAAGTT**CTCGAGA
ACTTGCTCATAACTTCGCGGTTTTTG

TJP1 shRNA#22 (SEQ ID NO: 3)
CCGG**CGGCCATTTGAACGCAAATTT**CTCGAGA
AATTTGCGTTCAAATGGCCGTTTTTG

Fig. 6B

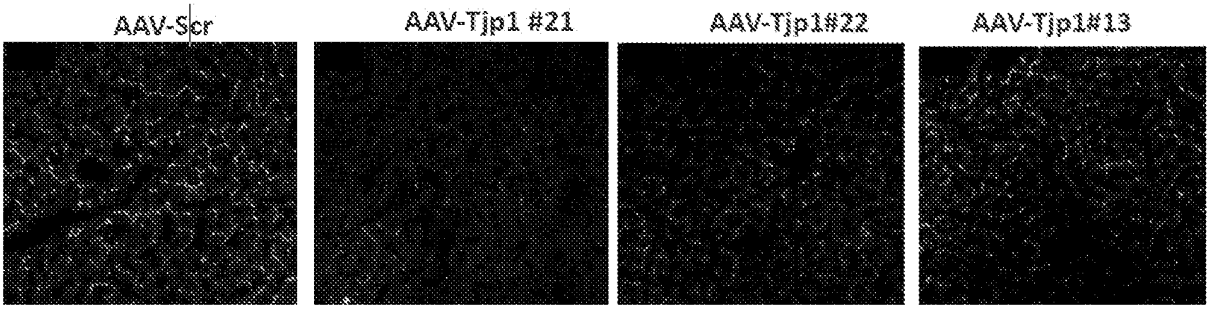
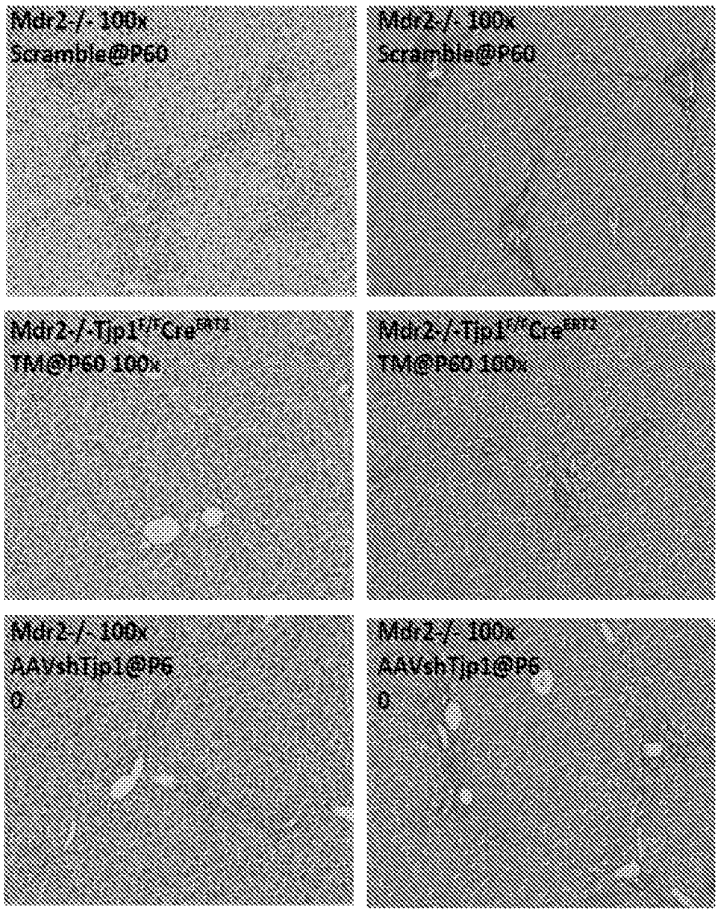
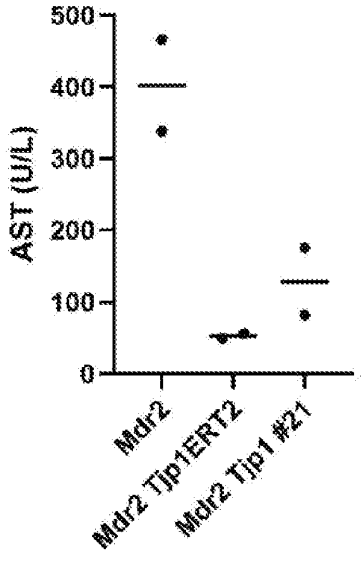

AAV-Scr
AAV-Tjp1 #21
AAV-Tjp1#22
AAV-Tjp1#13

Fig. 6C


Mdr2-/- 100x
Scramble@P60
Mdr2-/- 100x
Scramble@P60
Mdr2-/-Tjp1f/fCreERT2
TM@P60 100x
Mdr2-/-Tjp1f/fCreERT2
TM@P60 100x
Mdr2-/- 100x
AAVshTjp1@P6
0
Mdr2-/- 100x
AAVshTjp1@P6
0


AST (U/L)
500
400
300
200
100
0
Mdr2
Mdr2 Tjp1ERT2
Mdr2 Tjp1 #21

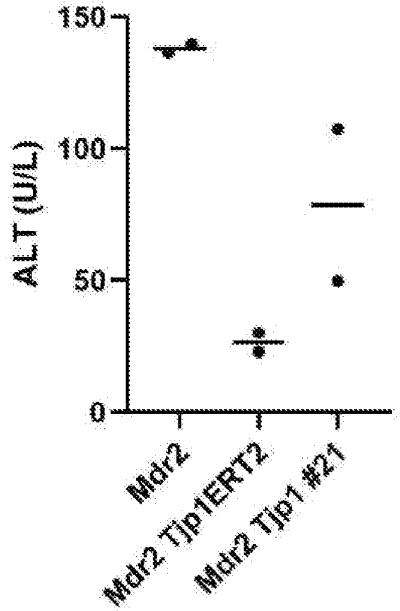
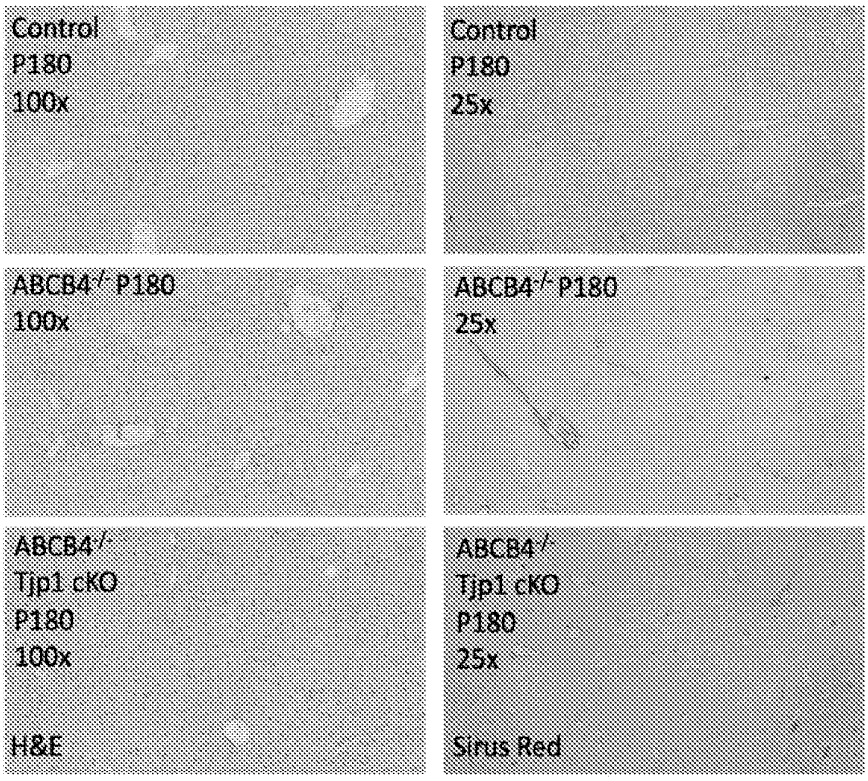

ALT (U/L)
150
100
50
0
Mdr2
Mdr2 Tjp1ERT2
Mdr2 Tjp1 #21

Fig. 7


Control
P180
100x
Control
P180
25x
ABCB4-/- P180
100x
ABCB4-/- P180
25x
ABCB4-/-
Tjp1 cKO
P180
100x
H&E
ABCB4-/-
Tjp1 cKO
P180
25x
Sirus Red

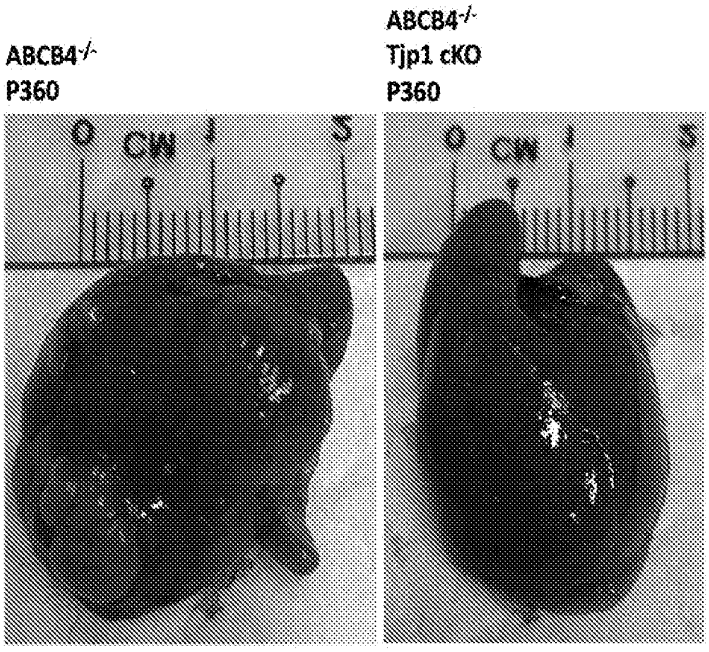
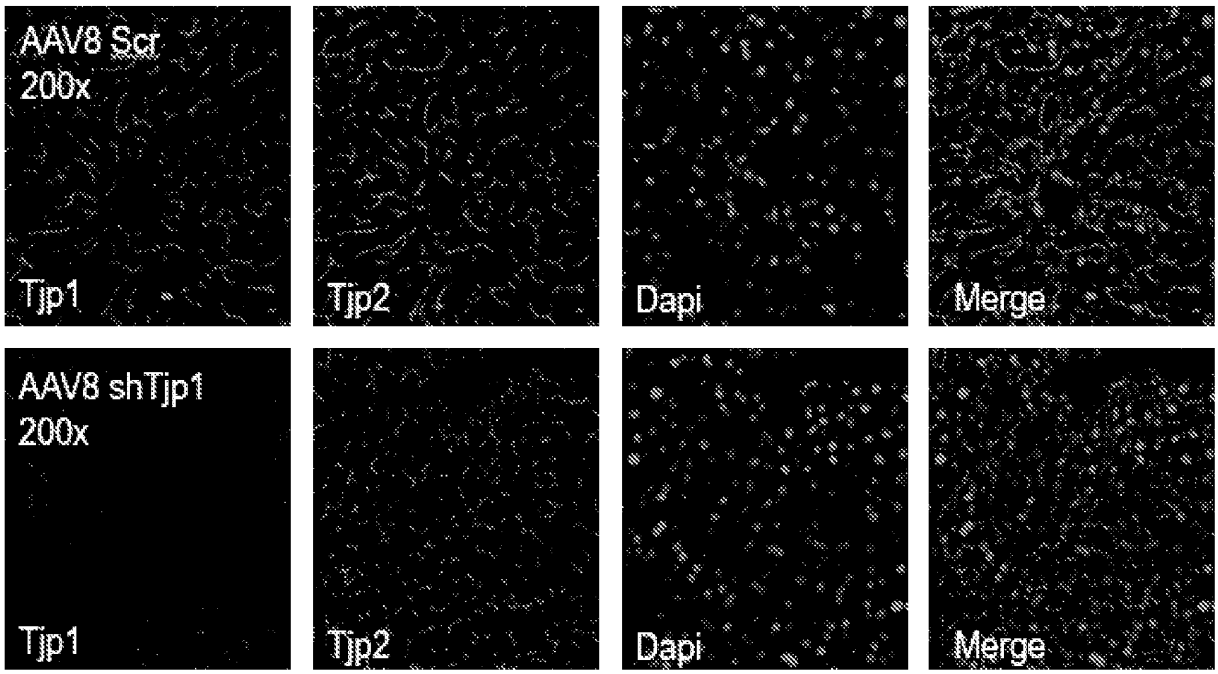

ABCB4-/-
P360
ABCB4-/-
Tjp1 cKO
P360
O
CW
J
S
O
CW
J
S

Fig. 8A


AAV8 Scr
200x
Tjp1
Tjp2
Dapi
Merge
AAV8 shTjp1
200x
Tjp1
Tjp2
Dapi
Merge

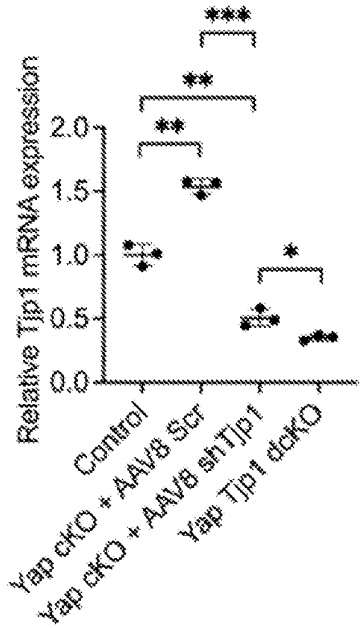

Relative Tjp1 mRNA expression
2.0
1.5
1.0
0.5
0.0
***
**
**
*
Control
Yap cKO + AAV8 Scr
Yap cKO + AAV8 shTjp1
Yap Tjp1 dcKO

Fig. 8B

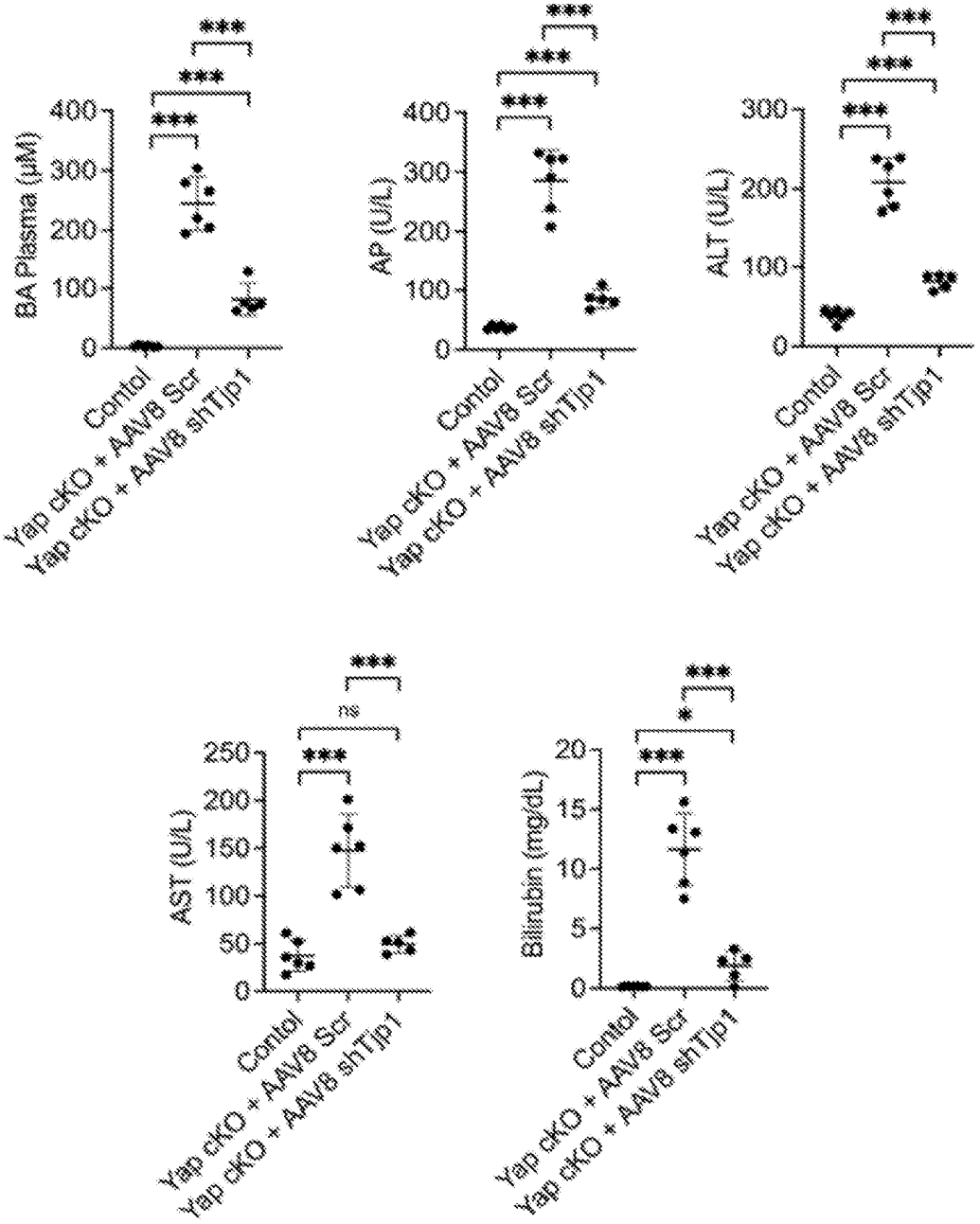
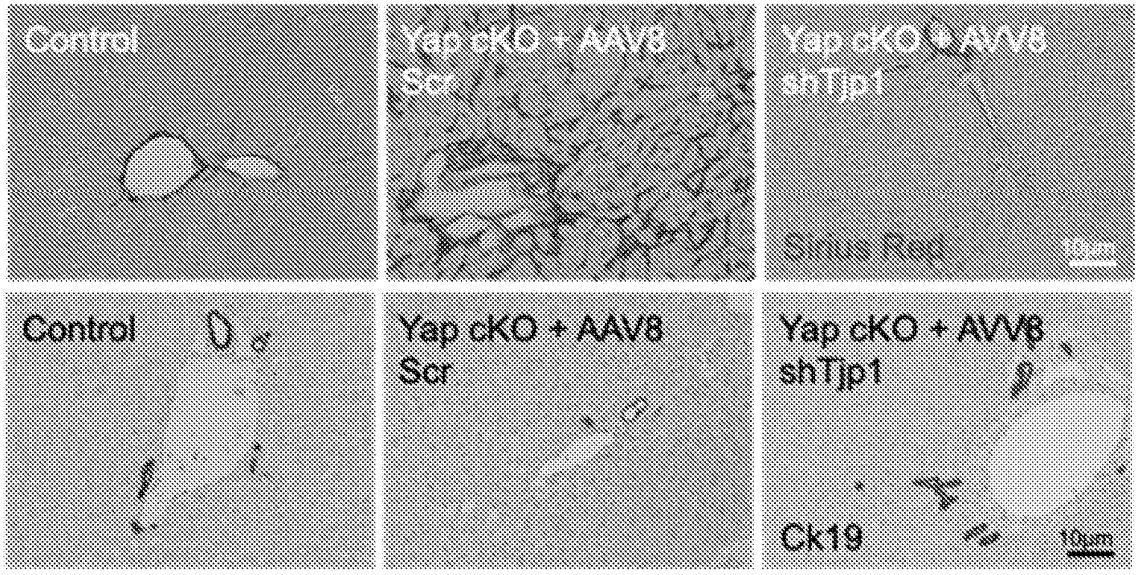

BA Plasma (μM)
AP (U/L)
ALT (U/L)
AST (U/L)
Bilirubin (mg/dL)
Contol
Yap cKO + AAV8 Scr
Yap cKO + AAV8 shTjp1
***
ns
*

Fig. 8C


Control
Yap cKO + AAV8 Scr
Yap cKO + AAV8 shTjp1
Sirius Red
Control
Yap cKO + AAV8 Scr
Yap cKO + AAV8 shTjp1
Ck19

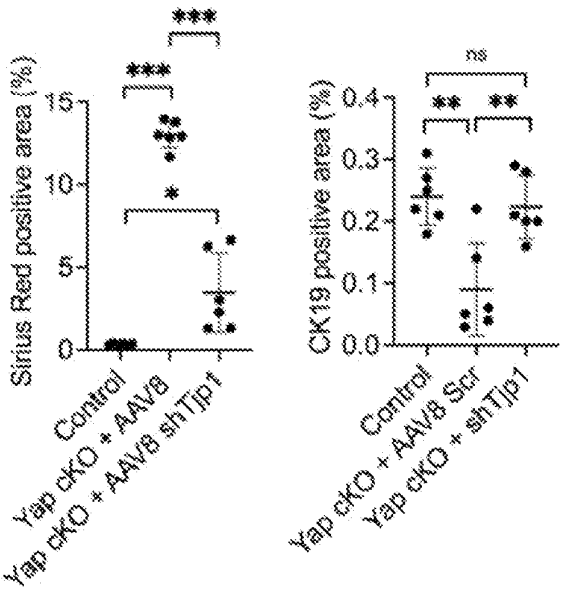
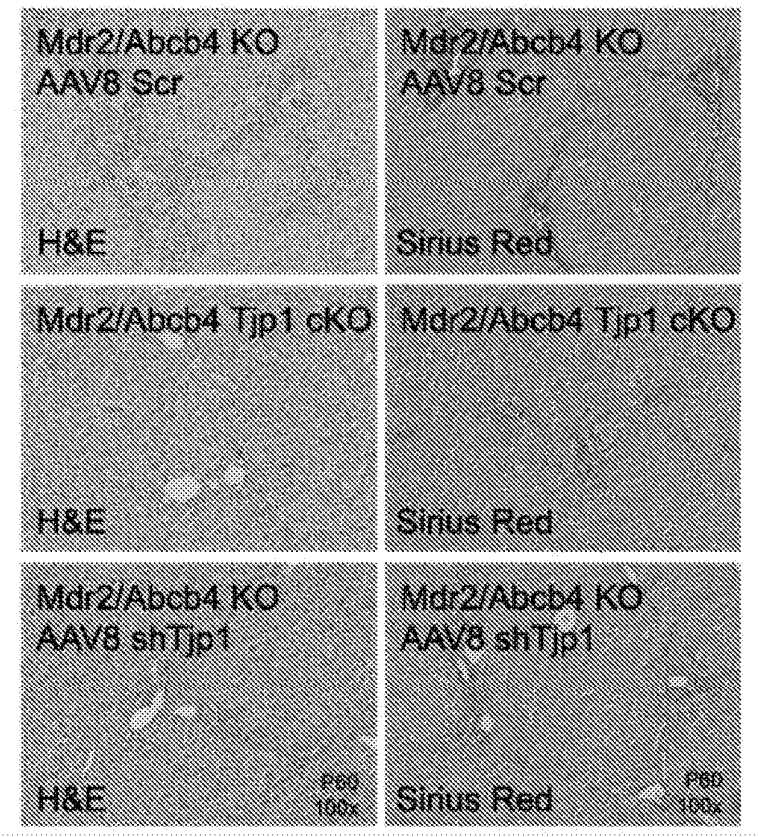
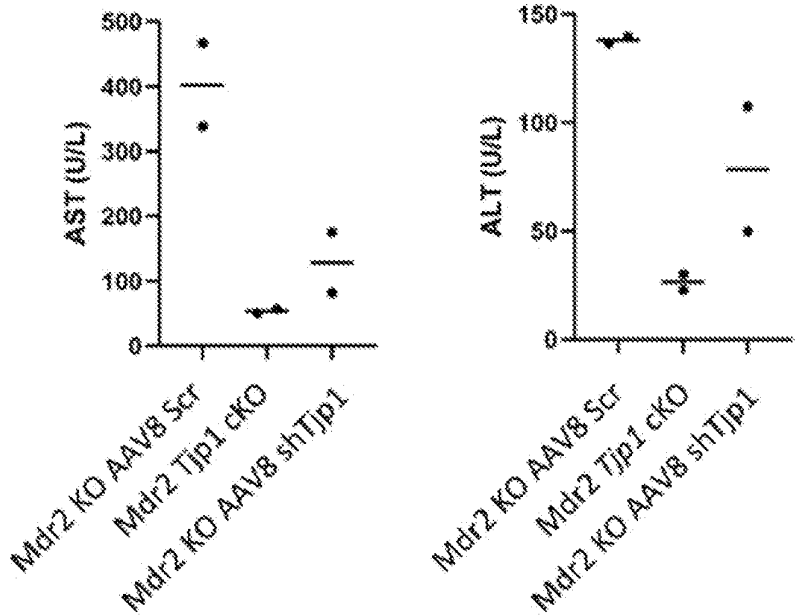

Sirius Red positive area (%)
CK19 positive area (%)
Control
Yap cKO + AAV8
Yap cKO + AAV8 shTjp1
Yap cKO + AAV8 Scr
Yap cKO + shTjp1
ns

Fig. 8D


Mdr2/Abcb4 KO
AAV8 Scr
H&E
Mdr2/Abcb4 KO
AAV8 Scr
Sirius Red
Mdr2/Abcb4 Tjp1 cKO
H&E
Mdr2/Abcb4 Tjp1 cKO
Sirius Red
Mdr2/Abcb4 KO
AAV8 shTjp1
H&E
P60
100x
Mdr2/Abcb4 KO
AAV8 shTjp1
Sirius Red
P60
100x


AST (U/L)
500
400
300
200
100
0
Mdr2 KO AAV8 Scr
Mdr2 Tjp1 cKO
Mdr2 KO AAV8 shTjp1
ALT (U/L)
150
100
50
0
Mdr2 KO AAV8 Scr
Mdr2 Tjp1 cKO
Mdr2 KO AAV8 shTjp1