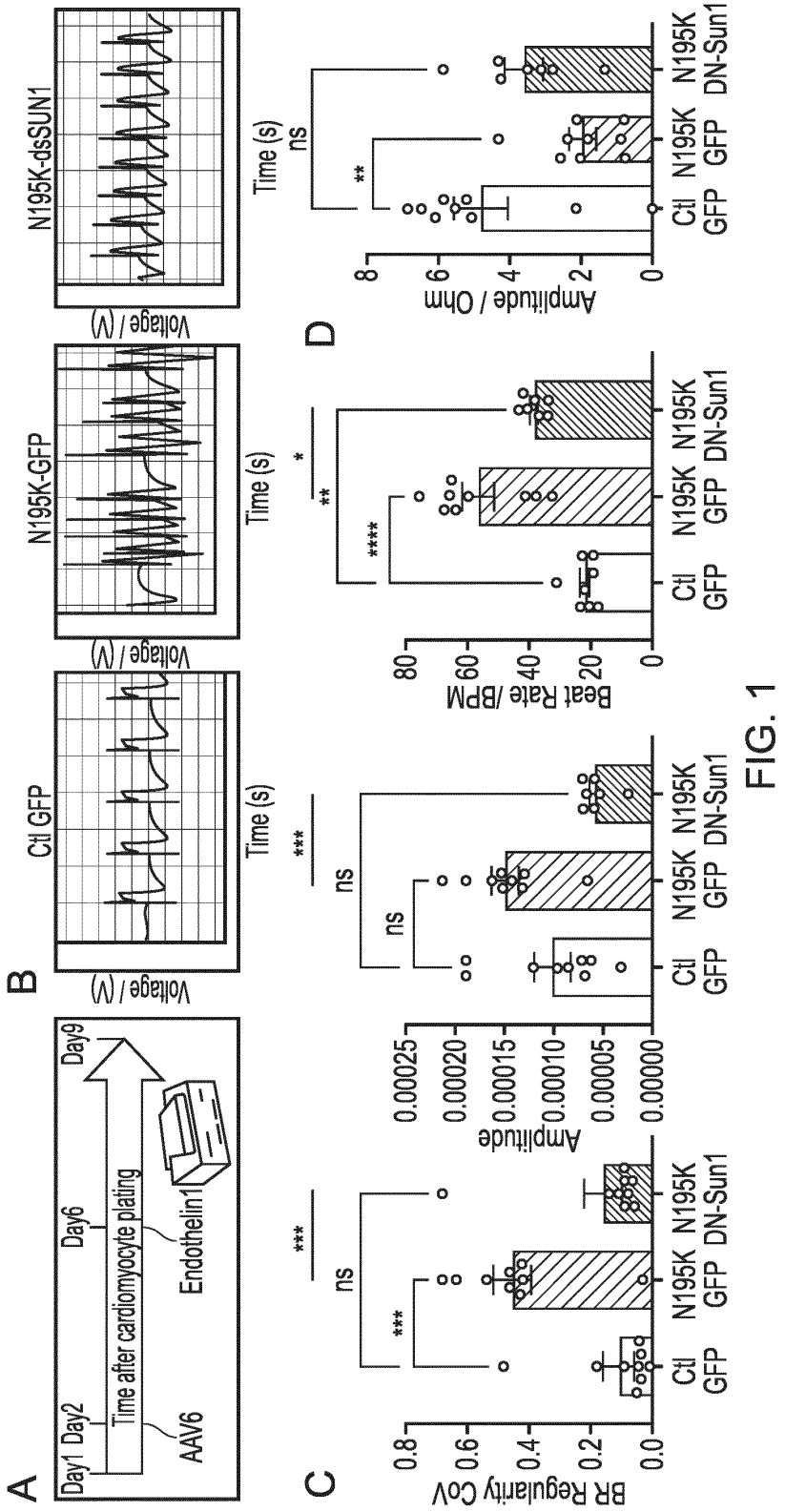

A
Day1 Day2
Time after cardiomyocyte plating
Day6
Day9
AAV6
Endothelin1
B
Ctl GFP
N195K-GFP
N195K-dsSUN1
Voltage / (V)
Time (s)
C
BR Regularity CoV
Amplitude
ns
***
Ctl GFP
N195K GFP
N195K DN-Sun1
D
Beat Rate /BPM
Amplitude / Ohm
****
**
*

FIG. 1

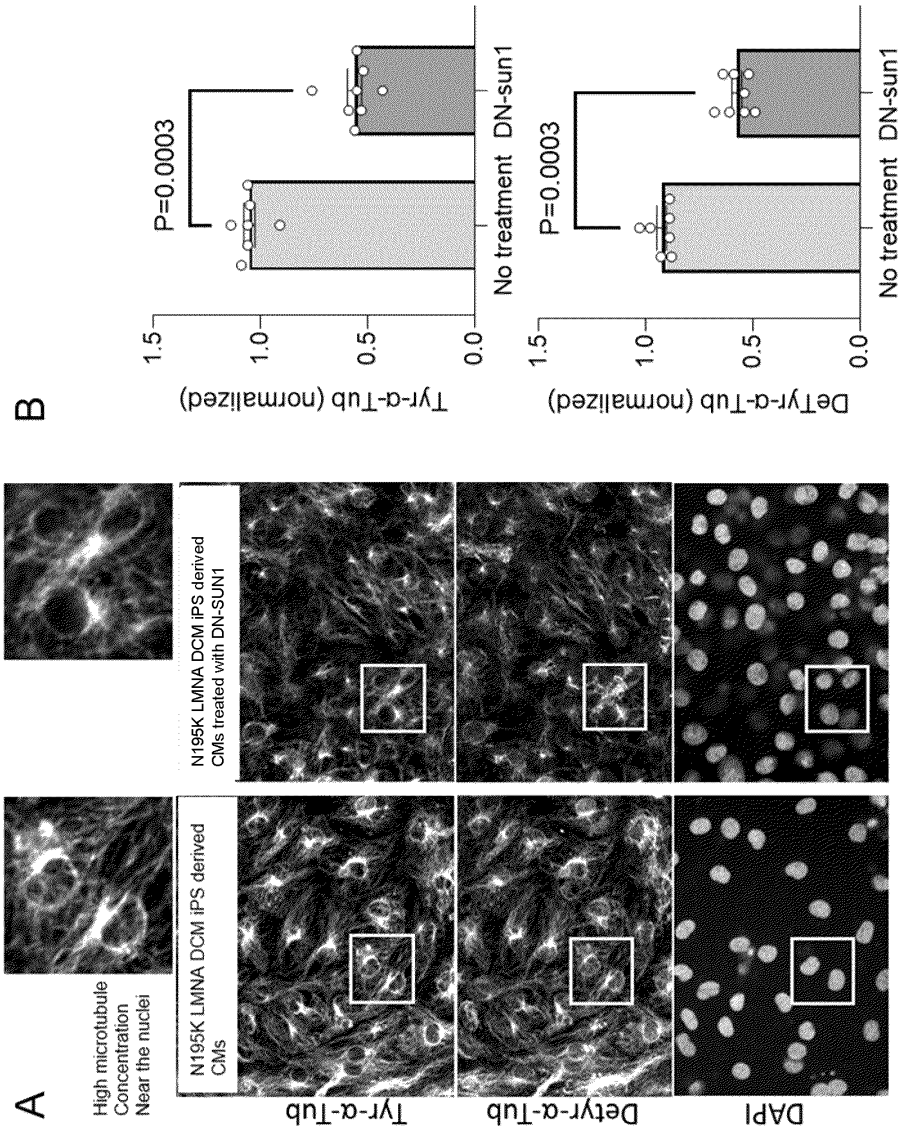

A
High microtubule Concentration Near the nuclei
N195K LMNA DCM iPS derived CMs
N195K LMNA DCM iPS derived CMs treated with DN-SUN1
Tyr-α-Tub
DeTyr-α-Tub
DAPI
B
Tyr-α-Tub (normalized)
DeTyr-α-Tub (normalized)
P=0.0003
P=0.0003
1.5
1.0
0.5
0.0
No treatment
DN-sun1

Figure 2

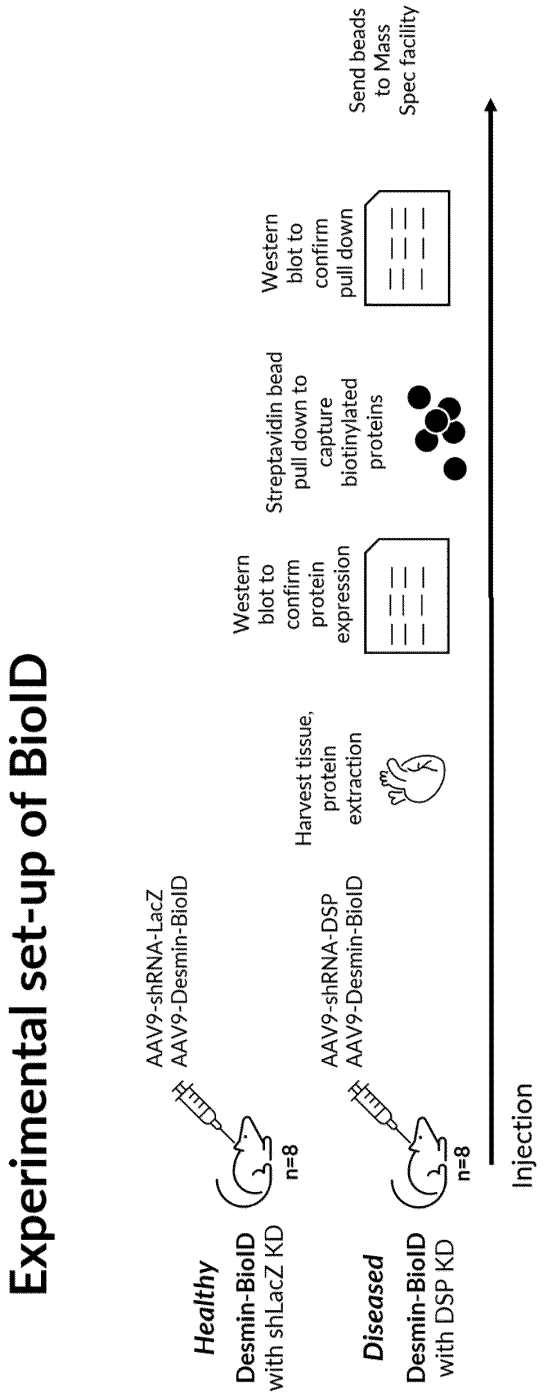

Experimental set-up of BioID
Healthy
Desmin-BioID
with shLacZ KD
AAV9-shRNA-LacZ
AAV9-Desmin-BioID
n=8
Diseased
Desmin-BioID
with DSP KD
AAV9-shRNA-DSP
AAV9-Desmin-BioID
n=8
Injection
Harvest tissue, protein extraction
Western blot to confirm protein expression
Streptavidin bead pull down to capture biotinylated proteins
Western blot to confirm pull down
Send beads to Mass Spec facility

Figure 3

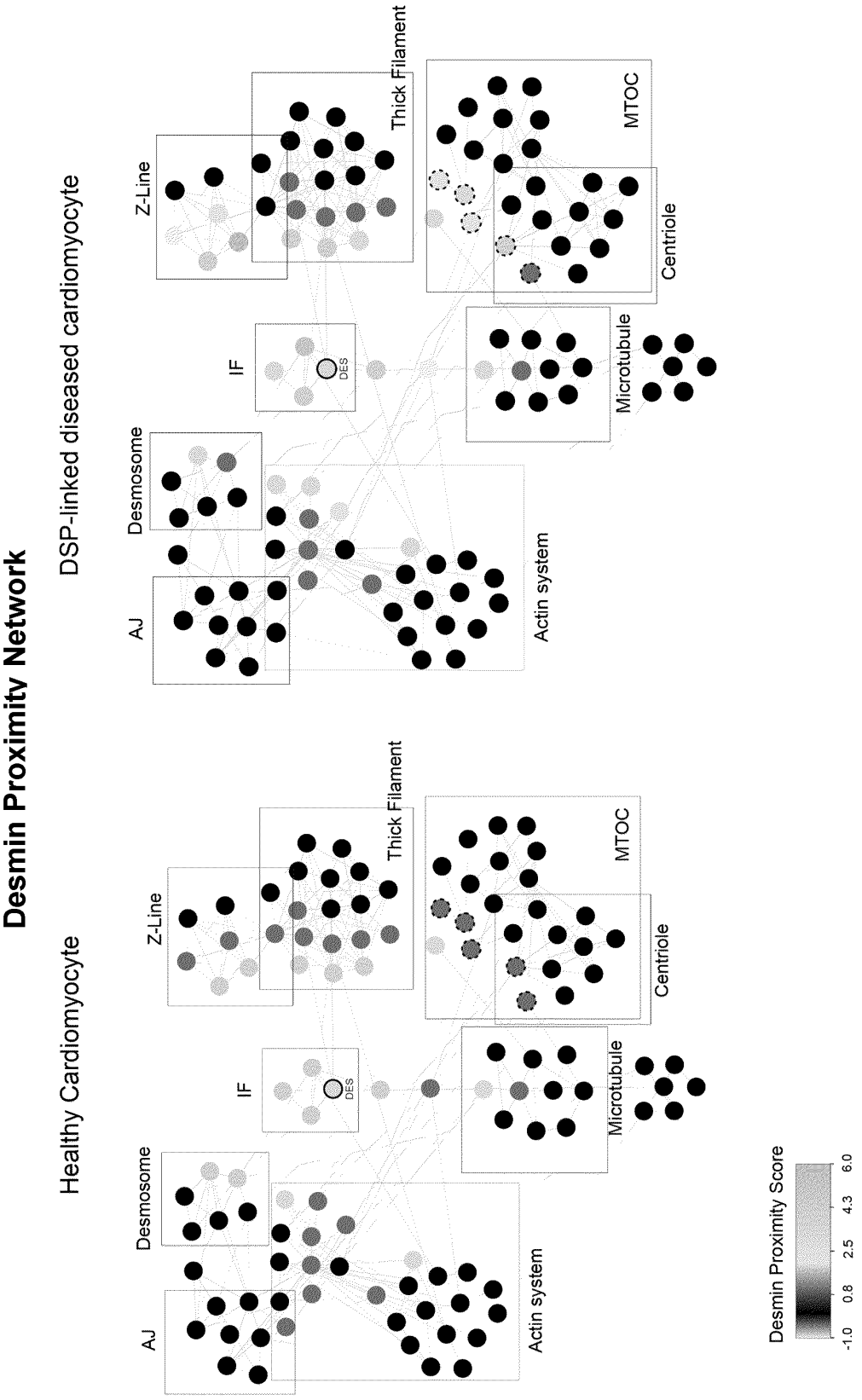

Desmin Proximity Network
Healthy Cardiomyocyte
DSP-linked diseased cardiomyocyte
AJ
Desmosome
IF
DES
Z-Line
Thick Filament
Actin system
Microtubule
MTOC
Centriole
Desmin Proximity Score
-1.0
0.8
2.5
4.3
6.0

Figure 4

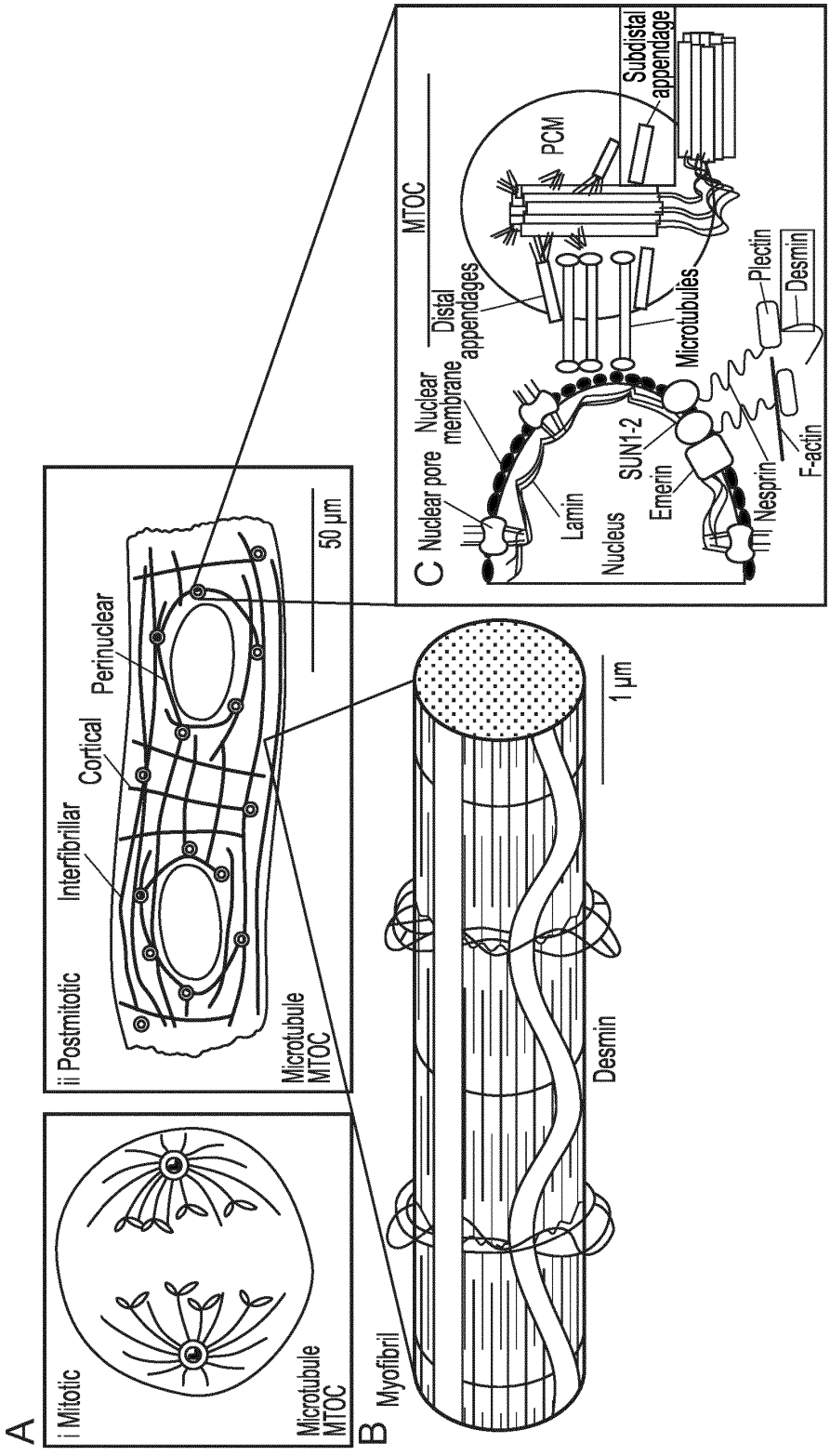
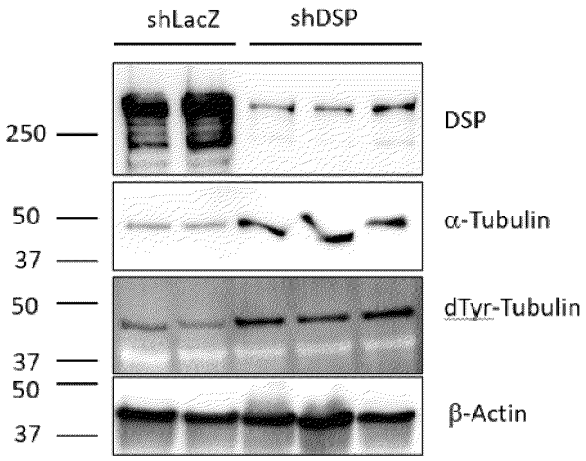

A
i Mitotic
Microtubule MTOC
ii Postmitotic
Interfibrillar
Cortical
Perinuclear
Microtubule MTOC
50 µm
B
Myofibril
Desmin
1 µm
C
MTOC
Distal appendages
PCM
Subdistal appendage
Microtubules
Nuclear membrane
Nuclear pore
Lamin
Nucleus
SUN1-2
Emerin
Nesprin
Plectin
Desmin
F-actin

FIG. 5

A


shLacZ
shDSP
250
DSP
50
α-Tubulin
37
50
dTyr-Tubulin
37
50
β-Actin
37

B

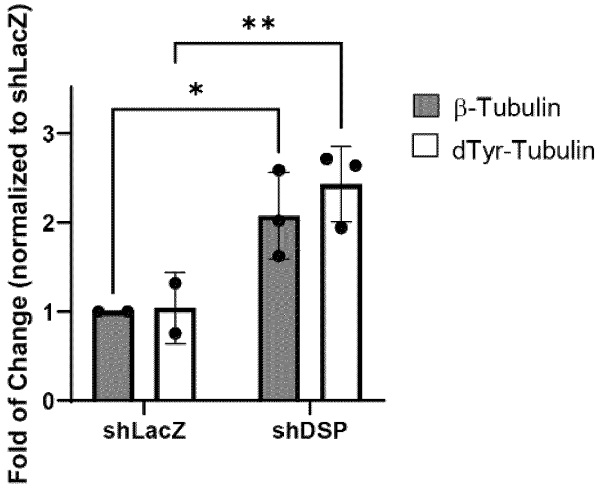

**
*
β-Tubulin
dTyr-Tubulin
Fold of Change (normalized to shLacZ)
3
2
1
0
shLacZ
shDSP

Figure 6

Group 1 (Control): Ctrl shLacZ + Ctrl cTnT-eGFP, N = 5
Group 2 (Control): Ctrl shLacZ + cTnT-DNSUN1, N = 5
Group 3 (DSP KD): shDSP + Ctrl cTnT-eGFP, N = 5
Group 4 (Rescue): shDSP + cTnT-DNSUN1, N = 4

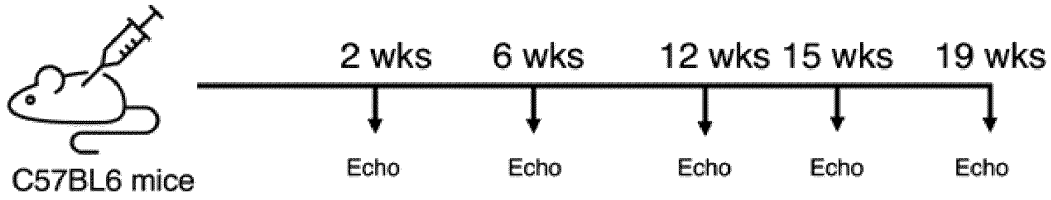


Figure 7A

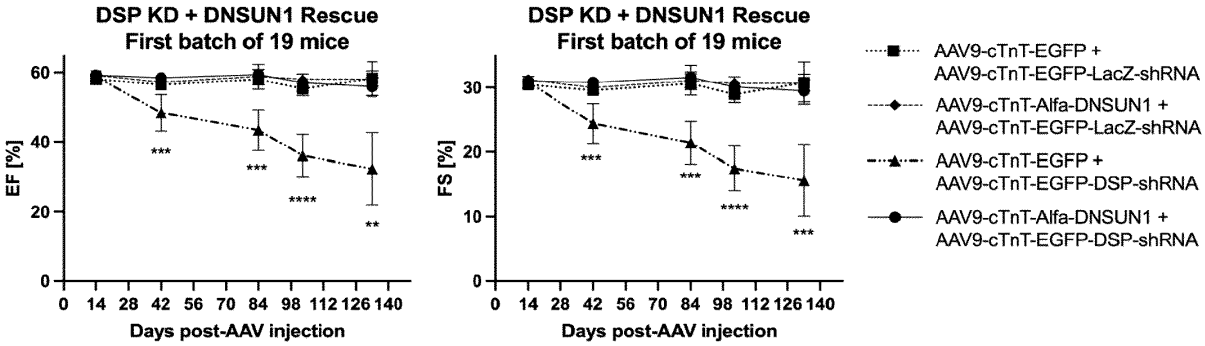


Figure 7B

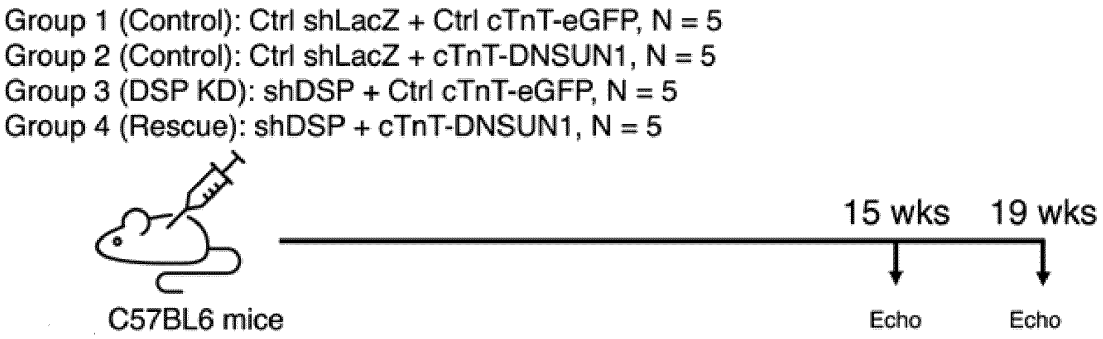


Figure 8A

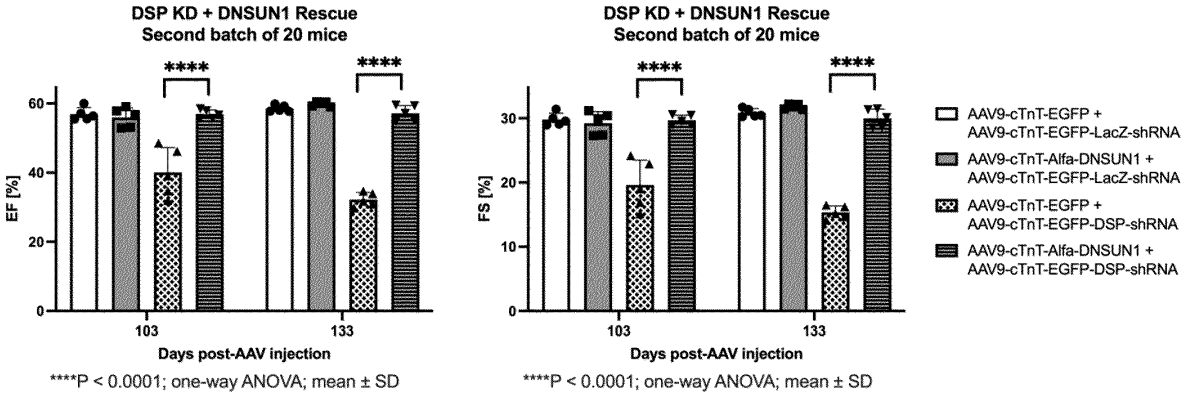


Figure 8B

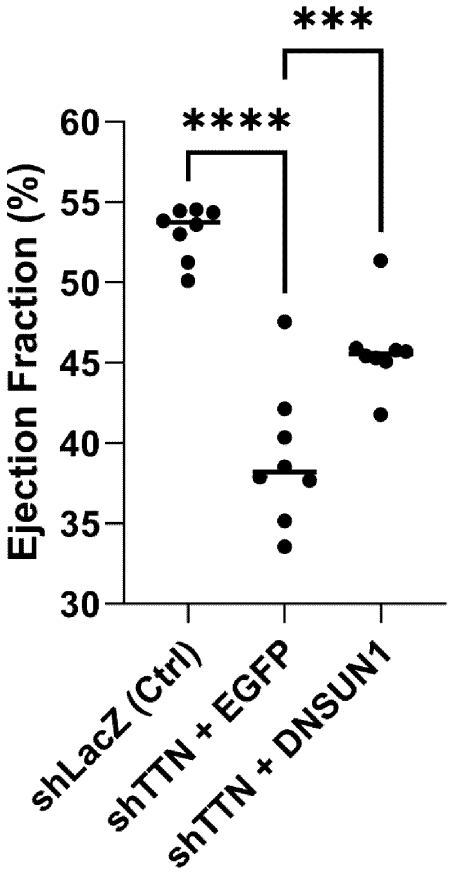


Figure 9A

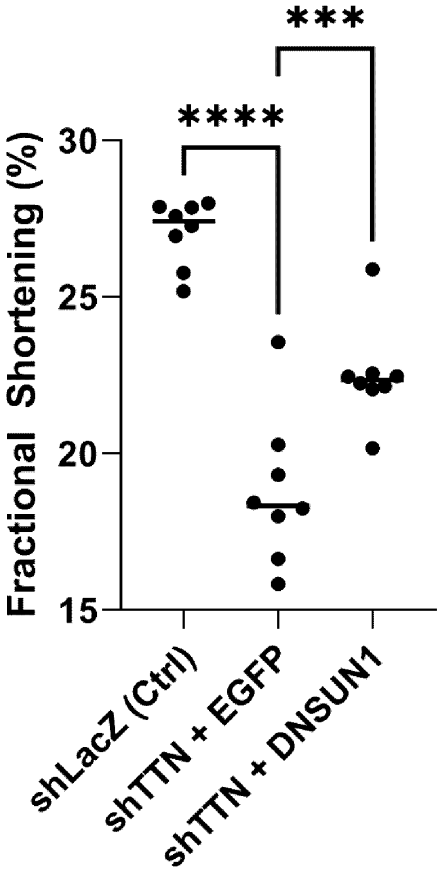


Figure 9B

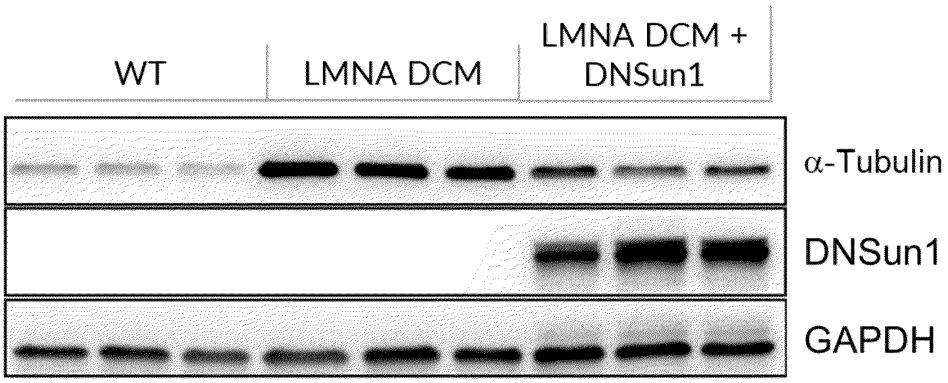


Figure 10A

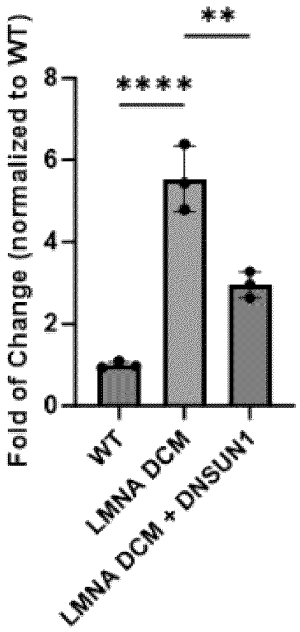


Figure 10B

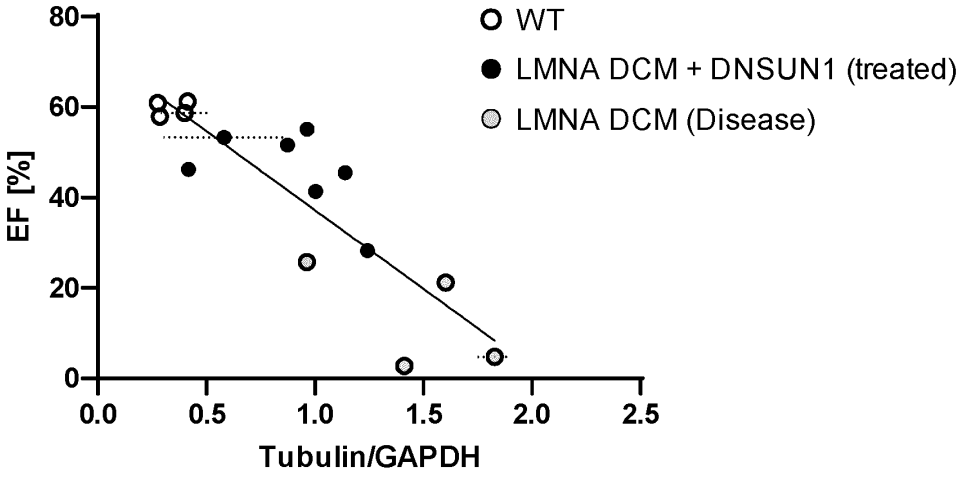


Figure 10C

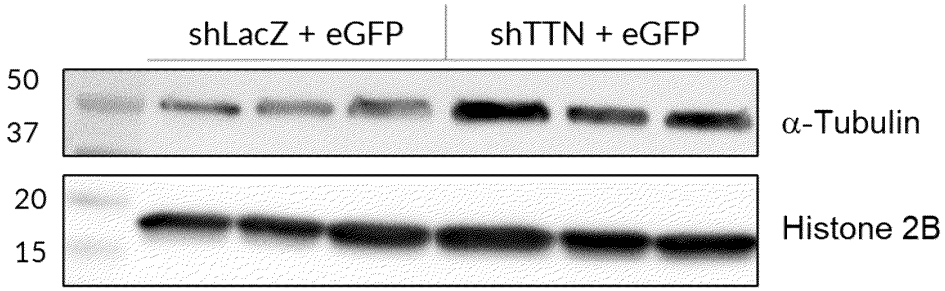


Figure 11A

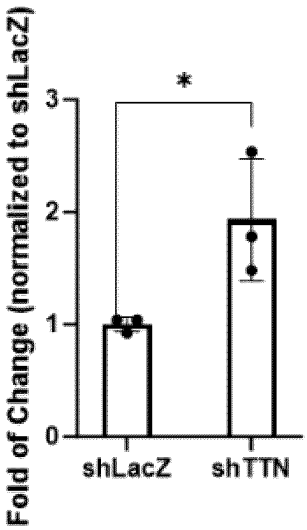


Figure 11B