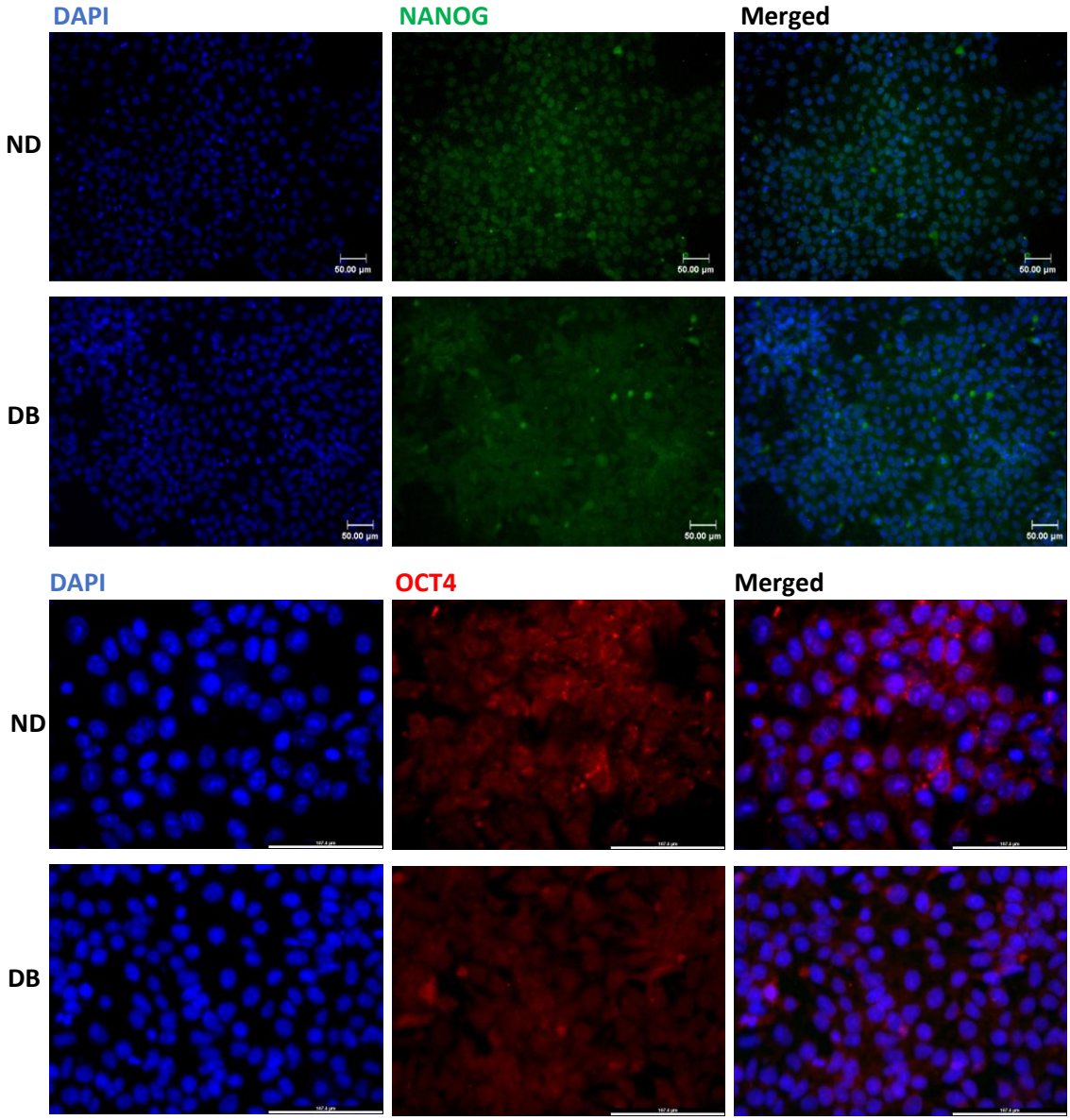
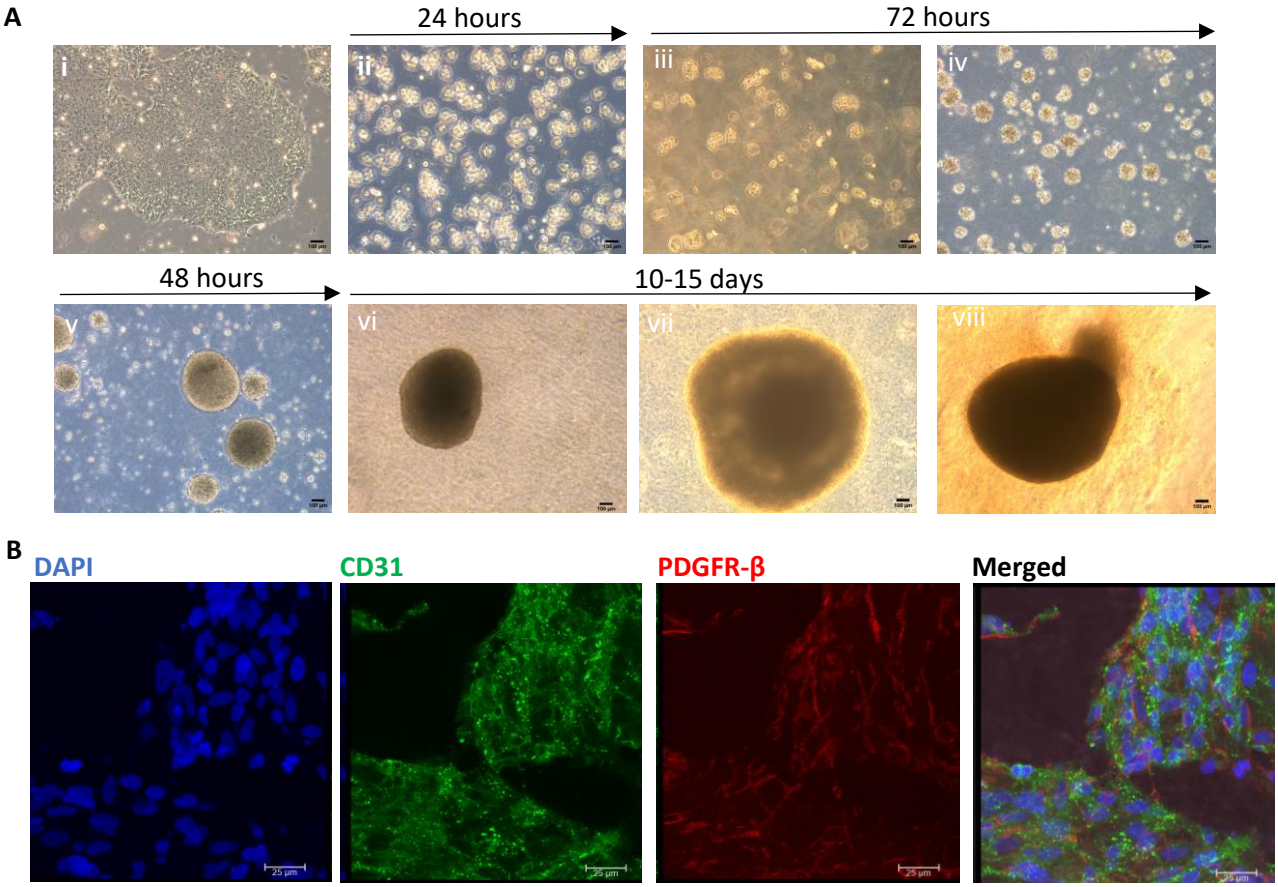
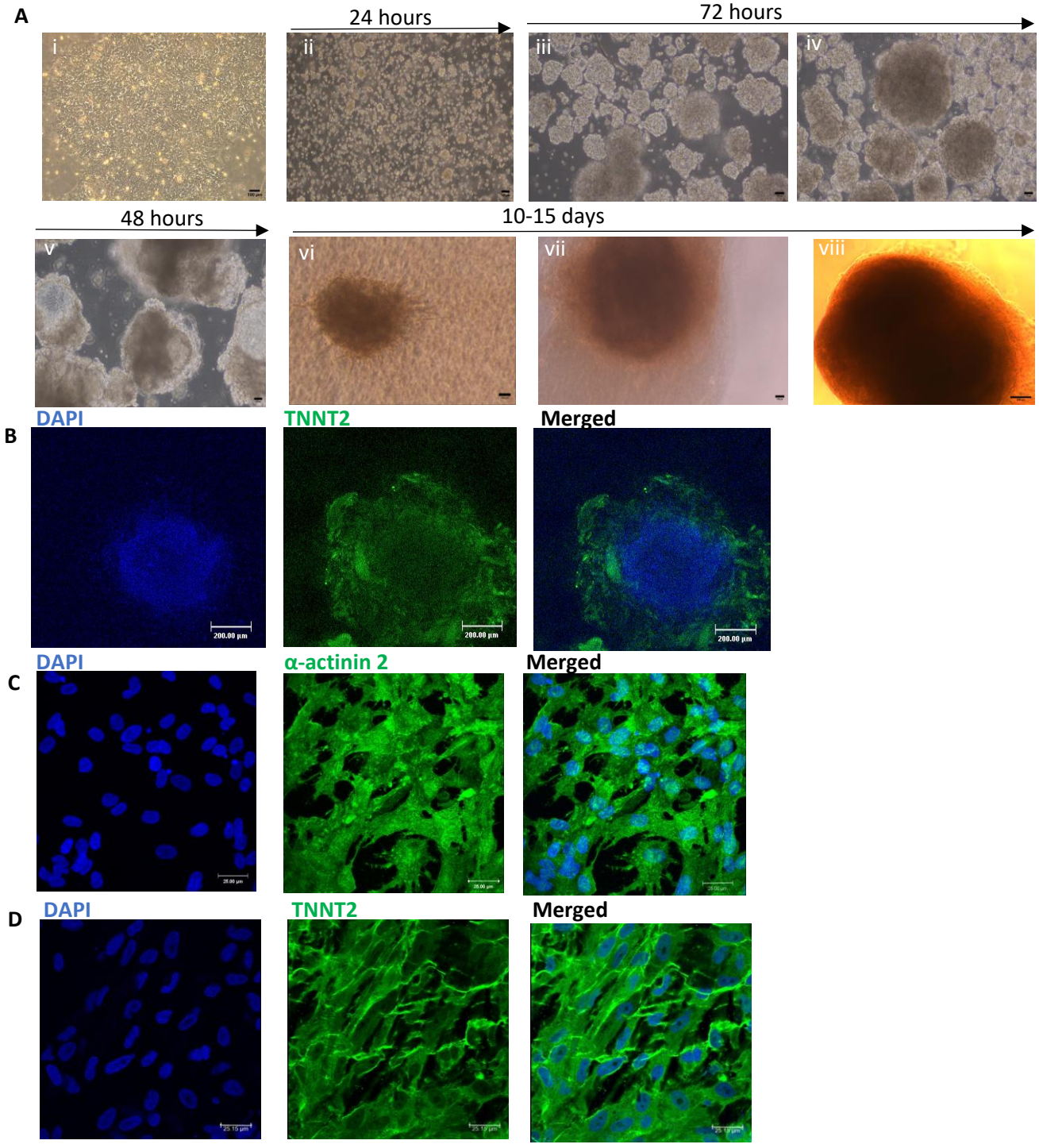


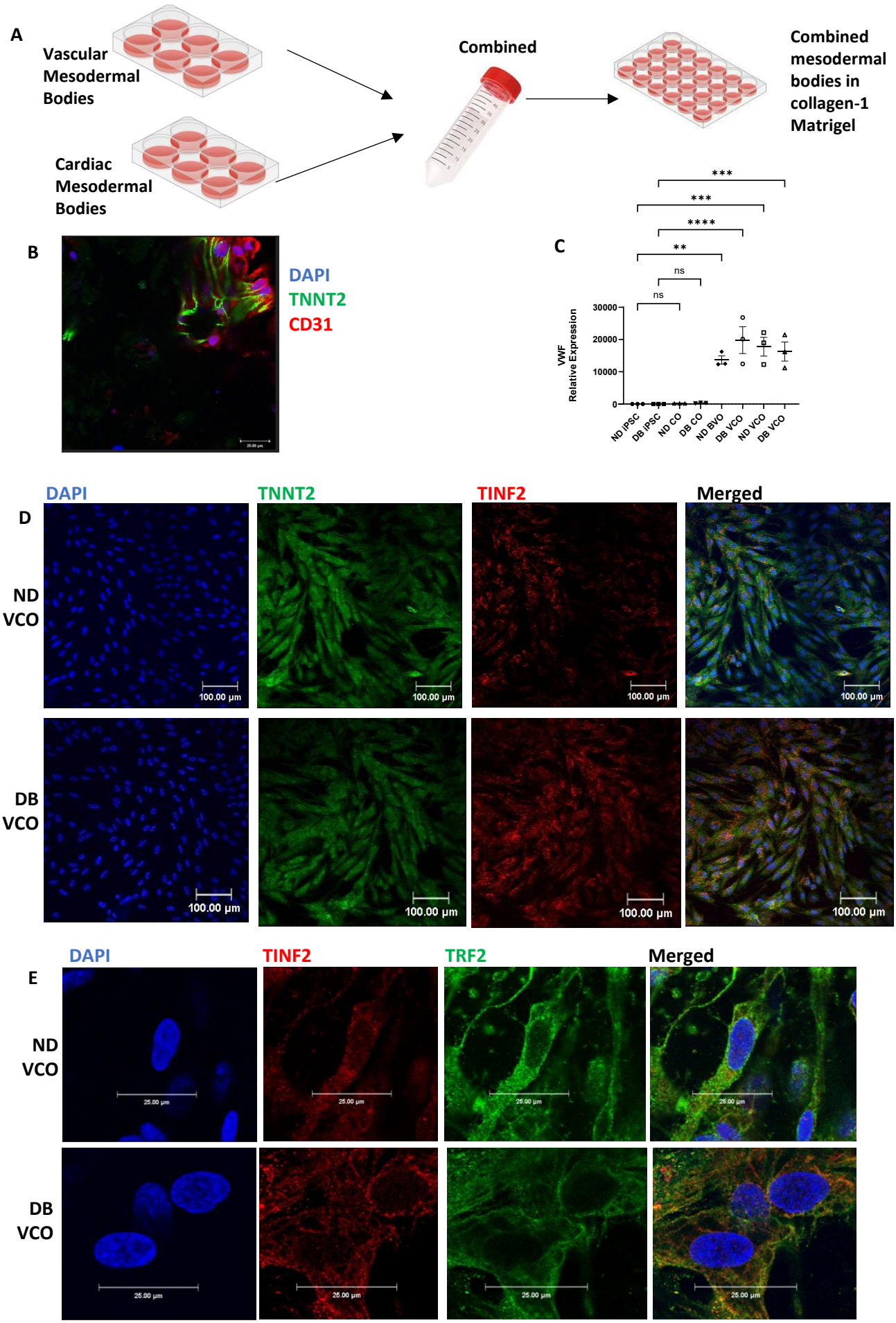
Supplementary Fig. 1. Determination of pluripotency markers using ICC imaging of ND and DB-donor iPSCs. iPSCs at 95% confluency were handled and sub-cultured accordingly as previously established and were investigated for pluripotency and characterisation markers. **A-B** ICC confocal imaging of ND and DB iPSCs for pluripotency marker NANOG and OCT 4 with corresponding secondary antibody AF 488 or 594 and DAPI stain. Images taken on Leica DMi8 SP1 microscope at 10x or 20x mgfi. Scale bar 100-200 µm.



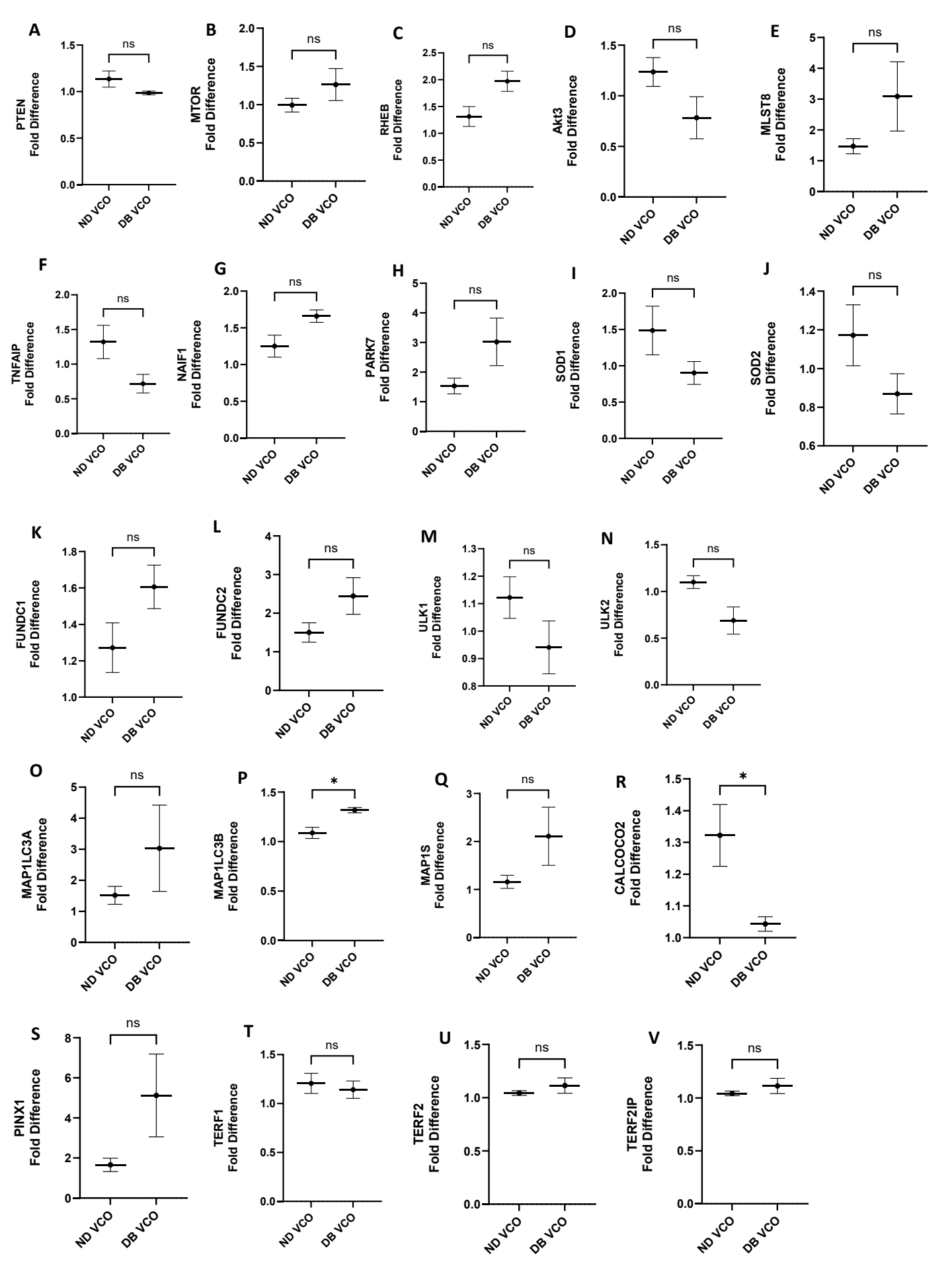
Supplementary Fig. 2. The establishment of ND and DB-donor iPSC-derived blood vessel organoid.
A ND and DB donor-derived iPSCs at 95% confluency were differentiated into following the 15-day protocol (scale bar 100 µm). **Ai** Confluent IPSCs were differentiated into aggregates (**Aii**) via resuspension with Y-27632 Rho-Kinase inhibitor in aggregation media (knock-out DMEM/F12, knock-out serum replacement, Glutamax, non-essential amino acids, PEN-STREP & β-mercaptoethanol) for 24 hours prior to transformation to embryonic bodies (**Aiii-Aiv**) for 72-hour incubation with CHIRR99021 & BMP-4 in N2B27 media (DMEM/F12, neurobasal media, B27 supplement, N2 supplement minus insulin, Glutamax, PEN-STREP & β-mercaptoethanol) using low-suspension plates. **Av-Avi** Embryonic bodies were then transformed for vascular-specific mesodermal bodies via 48-hour incubation with VEGF-A & Forskolin in N2B27 media. **Aviii** Mesodermal bodies were seeded onto regular suspension plates pre-coated with collagen-1-Matrigel matrix solution with SFM Complete Media (StemPro34, StemPro nutrient supplement, Glutamax, PEN-STREP) for days 10-15 for maturation. **B** ICC Leica SP8 confocal imaging of mature blood vessel organoids for CD31, PDGFR-β and DAPI at 63x magnification. Laser intensity at 1% PMT and 2% HYD, scale bar 25-200µm.



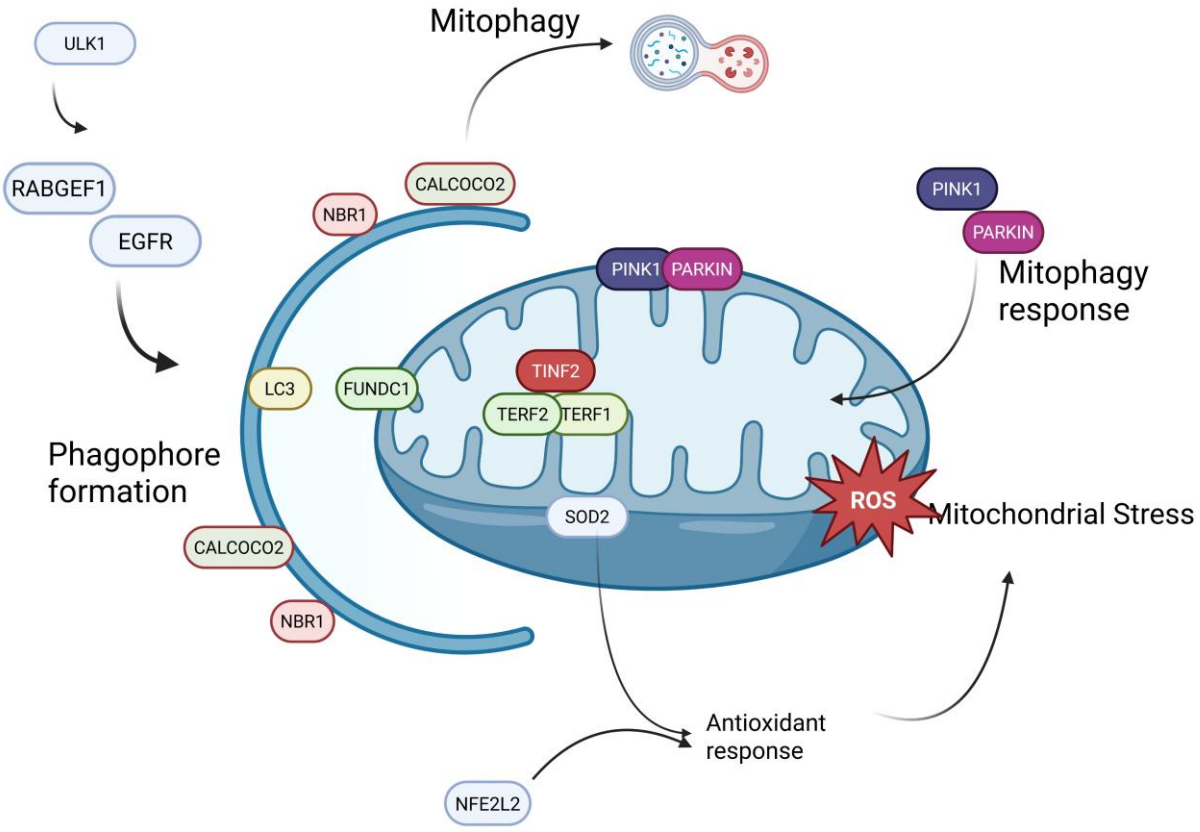
Supplementary Fig. 3. The establishment of ND and DB-donor iPSC-derived cardiac organoid. A ND and DB donor-derived iPSCs at 95% confluency were differentiated into following the 15-day protocol (scale bar 100 µm). **Ai** Confluent IPSCs were differentiated into aggregates (**Aii**) via resuspension with Y-27632 Rho-Kinase inhibitor in aggregation media (knock-out DMEM/F12, knock-out serum replacement, Glutamax, non-essential amino acids, PEN-STREP & β-mercaptoethanol) for 24 hours prior to transformation to embryonic bodies (**Aiii-Aiv**) for 72-hour incubation with CHIRR99021 & BMP-4 in N2B27 media (DMEM/F12, neurobasal media, B27 supplement, N2 supplement minus insulin, Glutamax, PEN-STREP & β-mercaptoethanol) using low-suspension plates. **Av-Avi** Embryonic bodies were then transformed for cardiac-specific mesodermal bodies via 48-hour incubation with C59 (Selleckchem) in N2B27 media. **Avii-viii** Mesodermal bodies were seeded onto regular suspension plates pre-coated with collagen-1-Matrigel matrix solution with SFM Complete Media (StemPro34, StemPro nutrient supplement, Glutamax, PEN-STREP) for days 10-15 for maturation. Contraction was recorded at day 10 (**supplementary video**). **B-C** ICC Leica SP8 confocal imaging of mature cardiac organoids for cardiac troponin (TNNT2) or α-actinin 2 and DAPI at 10x mgfi with higher-magnification at 63x imaging for α-actinin, TNNT2 and DAPI. Laser intensity at 1% PMT and 2% HYD, scale bar 25-200µm.


A
Vascular Mesodermal Bodies
Cardiac Mesodermal Bodies
Combined
Combined mesodermal bodies in collagen-1 Matrigel
B
DAPI
TNNT2
CD31
C
***
***
****
**
ns
ns
VWF Relative Expression
30000
20000
10000
0
ND iPSC
DB iPSC
ND CO
DB CO
ND BVO
DB VCO
ND VCO
DB VCO
D
DAPI
TNNT2
TINF2
Merged
ND VCO
DB VCO
100.00 µm
E
DAPI
TINF2
TRF2
Merged
ND VCO
DB VCO
25.00 µm

Supplementary Fig 4. The generation of the vascularised cardiac organoid from ND & DB donor iPSCs continued. **A** schematic summarised diagram of the combined mesodermal bodies approach, combining both mesodermal bodies programmed for either vascular or cardiac lineages. **B** ICC z stack image scan recording of VCO for CD31, TNNT2 and DAPI for z stack position transition from +10 to -10, scale bar 25 µm **C** RT-PCR analysis for von Willebrand Factor (VWF) for vascular cell marker for VCO compared to blood vessel organoid, cardiac organoid and iPSC donor line. **D** ICC confocal imaging of mature (day 15-20) ND and DB-derived VCOs for TINF2 with cardiac troponin and DAPI for ND and DB VCOs. Images taken on Leica SP8 confocal microscope at 10x mgfi (scale bar 100 µm). **E** ICC confocal imaging of mature (day 15-20) ND and DB-derived VCOs for TINF2, TERF2 and DAPI for ND and DB VCOs. Images taken on Leica SP8 confocal microscope at 63x mgfi (scale bar 25 µm). RT-PCR data presented as mean±SEM of n=3 using one-way ANOVA statistical analysis and standardised to ND group, $p<0.001$***, $p<0.0001$****. Scale bars 25-100um, images taken using Leica SP1 confocal microscope at 10-20x mgfi.


A
PTEN
Fold Difference
ns
ND VCO
DB VCO
B
MTOR
Fold Difference
ns
ND VCO
DB VCO
C
RHEB
Fold Difference
ns
ND VCO
DB VCO
D
Akt3
Fold Difference
ns
ND VCO
DB VCO
E
MLST8
Fold Difference
ns
ND VCO
DB VCO
F
TNFAIP
Fold Difference
ns
ND VCO
DB VCO
G
NAIF1
Fold Difference
ns
ND VCO
DB VCO
H
PARK7
Fold Difference
ns
ND VCO
DB VCO
I
SOD1
Fold Difference
ns
ND VCO
DB VCO
J
SOD2
Fold Difference
ns
ND VCO
DB VCO
K
FUNDC1
Fold Difference
ns
ND VCO
DB VCO
L
FUNDC2
Fold Difference
ns
ND VCO
DB VCO
M
ULK1
Fold Difference
ns
ND VCO
DB VCO
N
ULK2
Fold Difference
ns
ND VCO
DB VCO
O
MAP1LC3A
Fold Difference
ns
ND VCO
DB VCO
P
MAP1LC3B
Fold Difference
*
ND VCO
DB VCO
Q
MAP1S
Fold Difference
ns
ND VCO
DB VCO
R
CALCOCO2
Fold Difference
*
ND VCO
DB VCO
S
PINX1
Fold Difference
ns
ND VCO
DB VCO
T
TERF1
Fold Difference
ns
ND VCO
DB VCO
U
TERF2
Fold Difference
ns
ND VCO
DB VCO
V
TERF2IP
Fold Difference
ns
ND VCO
DB VCO

Supplementary Fig. 5. RNA Seq Analysis of VCO revels T2DM-associated changes in Mitophagy Markers
A-H RT-PCR for PTEN, mTOR, RHEB, Akt3, MLST8, TNFAIP, NAIF1 and PARK7 were measured for signalling pathways associated with loss of mitochondria redox, apoptosis, ROS and cardiac toxicity in DB & ND VCOs. **I-J** RT-PCR for SOD1 and SOD2 were measured for ROS & stress response in DB & ND VCOs. **K-N** RT-PCR for FUNDC1, FUNDC2, ULK1 and ULK2 for mitophagy initiating and stress response. **O-R** RT-PCR for MAP1LC3A, MAP1LC3B, MAP1S and CALCOCO2 were measured for phagophore formation. **S-V** RT-PCR for PINX1, TERF1, TERF2 and TERF2IP for telomeric and shelterin complex formation markers. All data represented as mean±SEM of n=3 of VCOs derived from 3 different ND and 3 different DB donor iPSC lines. All values were standardised to the ND-VCO group value $p<0.05$*, $p<0.01$**, $p<0.001$***, $p<0.0001$****.



Supplementary Fig. 6. Schematic diagram for mitophagy-associated markers and shelterin complex in ND environment for mitochondrial targeting for mitophagy.
Image generated using Bio Render.

Supplementary Table 1				
No	Gene	Accession RRID Number	Forward	Reverse
1	β Actin	NM_001101.5	GCACAGAGCCTCGCCTTT	CGCGGCGATATCATCATCCA
2	AMPK	NM_206907.4	AGGAAGAATCCTGTGACAAGCAC	CCGATCTCTGTGGAGTAGCAGT
3	mTOR	NM_001386500	CAAGAACTCGCTGATCCAAATG	GCTGTACGTTCCTTCTCCTTC
4	PINK1	NM_032409.3	GTGGACCATCTGGTTCAACAGG	GCAGCCAAAATCTGCGATCACC
5	PARKIN	NM_004562.3	CCAGAGGAAAGTCACCTGCGAA	CTGAGGCTTCAAATACGGCACTG
6	TRF1	NM_017489.3	CATGGAACCCAGCAACAAGACC	CTGCTTTCAGTGGCTCTTCTGC
7	TRF2	NM_005652.5	GTGGAAAAGCCACCCAGAGAAC	TGCAAAGGCTGCCTCAGAATCC
8	TNNT2	NM_001406727	AGACAGAGCGGAAAAGTGGG	ACCTTCCTCCTCTCAGCCAG
9	α ACTININ-2	NM_001103	GCTGAGAAGCACCTGGATATT	TGGCTCTTTCATCGGGTTTAG
10	MYL7	XM_017012478	CCAACGTGGTTCTTCCAACG	GCTGAAGGCTTCTTTGAACTCC
11	OCT4 POU5F1	NM_001285986	AGAACATGTGTAAGCTGCGG	GTTGCCTCTCACTCGGTTC
12	NANOG	NM_024865	GAAATACCTCAGCCTCCAGC	GCGTCACACCATTGCTATTC
13	CD31	XM_017024741	TGAGGTCAAAGGATCAGACGAC	TGGTGGCAAGGGACTAAGGA
14	C144	XM_047433471	AAACACCTCACTTCCCCATC	ACCTTGCCCACATATTCTCC
15	VWF	NM_001445507	ATGAGTATGAGTGTGCCTGC	GTAGATGGTGCTTCGGTGG
16	TINF2	XM_011536642	CCACTAGGGGAGGCCATAAG	CAGGCAAGTCAACTGGGTTC
17	FOXO1	XM_054374285	GCTGCATCCATGGACAACAACA	CGAGGGCGAAATGTACTCCAGTT
18	ULK1	XM_054373405	GGCAAGTTCGAGTTCTCCCG	TAATGCACTTGACGGCGACC
19	RABGEF1	NM_001367731	GCCTTGGGAACTCCAAGACA	GGGTTGCCGTAGTAACCACA
20	EGFR	XM_047419953	ATGCTCTACAACCCCACCAC	GCCCTTCGCACTTCTTACAC
21	NBR1	XM_047436061	GGAAGCAGAAGAAGACCTGAGTG	CCAGAGTCTGTGAGGTCGTGAG
22	CALCOCO2	NM_001261390	ACCATGGAGGAGACCATCAA	TTCTGGACGGAATTGGAAAG
23	LC3	NM_181509	ACACTGTCTCAGTTTTGCAGATG	TTACAGCGGTCGGCTGGG
24	SOD2	NM_001322816	CGTGAACAACCTGAACGTCA	GTGCCTGGAAAACTCGGAAC
25	NFE2L2	NM_001313901	ATGCCCTCACCTGCTACTTT	AGGCCAAGTAGTGTGTCTCC
26	FUNDC1	NM_173794	ATGGGTGGCGTTACTGGC	TGCTTTGTTCGCTCGTTT
27	PINX1	NM_001284356	TCCAGAGGAGAACGAAACCACG	TACGTTCCACCTGCGTCTCAGA
28	FAK1	NM_001352709	ATCCCACACATCTTGCTGACTT	GCATTCCTTTTCTGTCCTTGTC
29	PTEN	NM_000314.8	TGAGTTCCCTCAGCCGTTACCT	GAGGTTTCCTCTGGTCCTGGTA
30	MTERF1	XM_005250593	TATCCACGAGCAATAACACG	TTACGGGTCAATCCAACTGAG

Supplementary Table 1.
List of RT-PCR primers with Accession numbers

Supplementary Table 2. PCR Condition			
Cycles	**Time**	**Temperature**	**Function**
1	5 minutes	95°C	**Initial DNA denaturation**
40	15 seconds	95°C	**DNA denaturation**
	30 seconds	60°C	**Annealing, extension and fluorescence reading**
1	15 seconds	95°C	**Melting curve measurement**
	15 seconds	60°C	
	15 seconds	95°C	

Supplementary Table 2.
PCR conditions performed for all RNA samples.

Supplementary Table 3. List of antibodies

No	Primary antibodies	Dilution	Company	Catalogue number
1	β-ACTIN	1:5000 (WB)	R&D Biotechne	MAB-8929
2	OCT(4)	1:500 (ICC)	Thermofisher Scientific	MA1-104
3	Lin28	1:100 (ICC)	Thermofisher Scientific	MA1-106
4	Nanog	1:100 (ICC)	Thermofisher Scientific	MA1-017
5	TOM20	1.:500 (ICC)	ProteinTech	11802-1-AP
6	CD144	1:500 (ICC)	Abcam	ab33168
7	CD31	1:500 (ICC) 1:1000 (WB)	Abcam	ab28364
8	CD31	1:500 (ICC)	ProteinTech	66065-2-IG
9	TNNT2	1:500 (ICC) 1:1000 (WB)	ProteinTech	15513-1-AP
10	TNNT2	1:500 (ICC)	ProteinTech	66376-1-IG
11	α-Actinin	1:500 (ICC)	ProteinTech	11313-2-AP
12	Vimentin	1:500 (ICC)	Thermofisher Scientific	MA5-16409
13	PDGFR-β	1:500 (ICC)	R&D Biotechne	AF385
14	COL-IV	1:500 (ICC)	Abcam	ab6311
15	TINF2	1:500 (ICC)	ProteinTech	11368-1-AP
16	TRF1	1:500 (ICC)	ProteinTech	11899-1-AP
17	TRF2	1:500 (ICC)	ProteinTech	66893-1-Ig
18	DAPI	1:10000 (ICC)	Thermofisher Scientific	66248
	Secondary antibodies			
1	Goat Anti-Rabbit IgG HRP Conjugate	1:3000 (WB)	Bio-Rad	1706515
2	Goat Anti-Mouse IgG HRP Conjugate	1:3000 (WB)	Bio-Rad	1706516
3	Goat Anti-Rabbit IgG Alexa Flour™ 488	1:250 (ICC)	Thermofisher Scientific	A11034
4	Goat Anti-Mouse IgG Alexa Fluor™ 568	1:250 (ICC)	Thermofisher Scientific	A21202
6	Donkey Anti-Rabbit IgG Alexa Fluor™ 594	1:250 (ICC)	Thermofisher Scientific	A21207
7	Donkey Anti-Mouse IgG Alexa Fluor™ 488	1:250 (ICC)	Thermofisher Scientific	A21202
7	Donkey Anti-Goat IgG Alexa Fluor™ 647	1:250 (ICC)	Thermofisher Scientific	A21447

Supplementary Table 3.
List of primary and secondary antibodies

Supplementary Table 4 IPSC Donor Profile									
Study ID	**Age**	**Sex**	**Weight (kg)**	**Height (cm)**	**BMI**	**Blood Pressure (mmHg)**	**Diabetes State**	**Diabetes duration**	**RNA-Seq Code**
DB07	72	**F**	63.5	147	29.4	160/70	Type 2	> 15 years	DB1
DB13	70	M	85.4	165	31.3	148/76	Type 2	> 15 years	DB2
DB14	56	**F**	81.2	156	33.3	140/85	Type 2	10-15 years	DB3
ND05	59	M	88	185	25.7	115/80	Not Diabetic	N/A	ND6
ND19	58	M	92.9	181	28.3	136/83	Not Diabetic	N/A	ND5
ND22	58	M	65.4	163	24.6	131/74	Not Diabetic	N/A	ND4

Supplementary Table 4.
IPSC donor profile