Supplementary Table 1

Study ID	Group	Age	Sex	Weight (kg)	Height (cm)	BMI	Blood Pressure (mmHg)	Diabetes type	Diabetes duration
STREAM1/003	R	56	M	93	180	28.7	135/80	Type 2	10-15 years
STREAM1/006	R	47	M	94.5	181	28.8	141/62	Type 1	> 15 years
STREAM1/007	R	72	F	63.5	147	29.4	160/70	Type 2	> 15 years
STREAM1/009	NR	63	M	141	164	52.4	125/67	Type 2	> 15 years
STREAM1/011	NR	60	F	99.1	152	42.8	156/61	Type 2	> 15 years
STREAM1/012	NR	89	F	72.2	151	31.6	134/81	Type 2	5-10 years

Supplementary Table 1: Demographics and characteristics of participants of this study.
Legend: R, DME responders; NR, DME non-responders

Supplementary Table 2

PRIMER		SEQUENCE
CD235	Forward	GCCCATCTGATGTAAAACCTCTC
	Reverse	TGGTGAACAGATTCTCATTGATCAC
CD71	Forward	TATCAGGACAGCAACTGGGC
	Reverse	CTGCTCGTGCCACTTTGTTC
POU5F1	Forward	AGAACATGTGTAAGCTGCGG
	Reverse	GTTGCCTCTCACTCGGTTC
LIN28	Forward	GCAGAAGCGCAGATCAAAAG
	Reverse	CGGACATGAGGCTACCATATG
NANOG	Forward	GAAATACCTCAGCCTCCAGC
	Reverse	GCGTCACACCATTGCTATTC
CD144	Forward	AAACACCTCACTTCCCCATC
	Reverse	ACCTTGCCCACATATTCTCC
CD31	Forward	TCAGAAGGACAAGGCGATTG
	Reverse	GTTATGTTGACCACGATGCTG
VEGFR2	Forward	ATAGAAGGTGCCCAGGAAAAG
	Reverse	GTCTTCAGTTCCCCTCCATTG
NPTX2	Forward	CCACTCCGCACAAACTACCT
	Reverse	TAGGAGAAGGGGGTGCCAAT

Supplementary Table 2: PCR primers and their corresponding sequences

Supplementary Table 3

Treatment response	Eyes, n (%)
Full responders	39 (27.9)
Partial responders	92 (65.7)
Non-responders	9 (6.4)

Supplementary Table 3: Anatomical response to anti-VEGF in 100 patients (140 eyes) included in the cohort study.

Supplementary Table 4

	Full responders (n = 39)	Partial responders (n = 91)	Non responders (n= 9)	Overall (n = 140)	p-value*
Age	65 (14.2)	65 (9.6)	66 (14.9)	65 (11.4)	0.959
Gender Male/female	28/11	62/29	4/5	94/45	0.398
Type I/II DM	8/31	15/76	3/6	26/113	0.559
BCVA baseline	59.0 (16.7)	59.7 (14.8)	63.1 (17.5)	59.7 (15.4)	0.868
BCVA 12 months	67.1 (13.9)	67.7 (14.6)	64.2 (15.8)	67.3 (14.4)	0.853
CRST baseline	459 (140)	491 (142)	487 (124)	482 (140)	0.283
CRST 12 months	310 (87)	327 (73)	440 (102)	330 (84)	**0.001**
Anti-VEGF injections received by month 12	6.9 (2.2)	7.8 (2.0)	7.7 (1.2)	7.5 (2.0)	**0.013**

Supplementary Table 4. Demographics and clinical characteristics of "full responders", "partial responders" and "non-responders.
DM = Diabetes Mellitus; BCVA = best corrected visual acuity; CRST = central retinal subfield thickness. In bold, values considered statistically significant.

Supplementary Table 5

	P003	P006	P007	P009	P011	P012
P003		33.33%	26.67%	33.33%	33.33%	33.33%
P006	33.33%		30.00%	30.00%	30.00%	30.00%
P007	26.67%	30.00%		50.00%	36.67%	26.67%
P009	33.33%	30.00%	50.00%		36.67%	16.67%
P011	33.33%	30.00%	36.67%	36.67%		33.33%
P012	33.33%	30.00%	26.67%	16.67%	33.33%	

Supplementary Table 5: The iPS cell lines derived from DME patients are all unique and come from different sources. Short tandem repeat (STR) profiling of these cell lines unveiled that the samples are unique. Comparison between the profiles of each patient shows <57% of similarity, which indicates that they come from different sources and therefore there has been no cross contamination.

ANSI/ATCC ASN-0002-2011. Authentication of Human Cell Lines: Standardization of STR Profiling. ANSI eStandards Store, 2012.

Supplementary Table 6

	P003		P006		Shared
D3S1358	15	16	16	18	1
TH01	9	9	7	9.3	0
D21S11	28	31	29	32	0
D18S51	13	16	16	18	1
Penta E	12	12	7	13	0
D5S818	12	12	9	11	0
D13S317	12	13	9	13	1
D7S820	9	10	8	10	1
D16S539	10	10	12	12	0
CSF1PO	10	12	12	12	1
Penta D	12	13	10	13	1
AMEL	X	Y	X	Y	2
vWA	17	19	15	16	0
D8S1179	13	13	10	14	0
TPOX	8	12	8	9	1
FGA	21	25	23	25	1
Total	30		30		10
Percentage					33.33%

	P007		P009		Shared
D3S1358	14	17	16	17	1
TH01	9.3	9.3	7	7	0
D21S11	27	32.2	30	31	0
D18S51	14	16	11	16	1
Penta E	12	13	13	14	1
D5S818	11	12	10	12	1
D13S317	8	11	9	11	1
D7S820	11	11	11	11	2
D16S539	11	13	11	13	2
CSF1PO	10	11	11	12	1
Penta D	10	12	9	11	0
AMEL	X	X	X	Y	1
vWA	14	16	17	17	0
D8S1179	12	13	12	13	2
TPOX	8	11	8	11	2
FGA	23	26	22	24	0
Total	30		30		15
Percentage					50.00%

	P011		P012		Shared
D3S1358	14	14	15	15	0
TH01	7	8	6	9.3	0
D21S11	28	30	28	31.2	1
D18S51	15	17	12	19	0
Penta E	11	16	11	12	1
D5S818	9	11	9	12	1
D13S317	11	13	10	13	1
D7S820	10	12	11	12	1
D16S539	11	11	12	12	0
CSF1PO	10	12	10	12	0
Penta D	9	12	9	9	1
AMEL	X	X	X	X	2
vWA	16	17	14	19	0
D8S1179	8	15	9	15	1
TPOX	8	11	9	10	0
FGA	20	21	20	25	1
Total	30		30		10
Percentage					33.33%

	P003		P007		Shared
D3S1358	15	16	14	17	0
TH01	9	9	9.3	9.3	0
D21S11	28	31	27	32.2	0
D18S51	13	16	14	16	1
Penta E	12	12	12	13	1
D5S818	12	12	11	12	1
D13S317	12	13	8	11	0
D7S820	9	10	11	11	0
D16S539	10	10	11	13	0
CSF1PO	10	12	10	11	1
Penta D	12	13	10	12	1
AMEL	X	Y	X	X	1
vWA	17	19	14	16	0
D8S1179	13	13	12	13	1
TPOX	8	12	8	11	1
FGA	21	25	23	26	0
Total	30		30		8
Percentage					26.67%

	P003		P009		Shared
D3S1358	15	16	16	17	1
TH01	9	9	7	7	0
D21S11	28	31	30	31	1
D18S51	13	16	11	16	1
Penta E	12	12	13	14	0
D5S818	12	12	10	12	1
D13S317	12	13	9	11	0
D7S820	9	10	11	11	0
D16S539	10	10	11	13	0
CSF1PO	10	12	11	12	1
Penta D	12	13	9	11	0
AMEL	X	Y	X	Y	2
vWA	17	19	17	17	1
D8S1179	13	13	12	13	1
TPOX	8	12	8	11	1
FGA	21	25	22	24	0
Total	30		30		10
Percentage					33.33%

	P003		P011		Shared
D3S1358	15	16	14	14	0
TH01	9	9	7	8	0
D21S11	28	31	28	30	1
D18S51	13	16	15	17	0
Penta E	12	12	11	16	0
D5S818	12	12	9	11	0
D13S317	12	13	11	13	1
D7S820	9	10	10	12	1
D16S539	10	10	11	11	0
CSF1PO	10	12	10	12	2
Penta D	12	13	9	12	1
AMEL	X	Y	X	X	1
vWA	17	19	16	17	1
D8S1179	13	13	8	15	0
TPOX	8	12	8	11	1
FGA	21	25	20	21	1
Total	30		30		10
Percentage					33.33%

	P003		P012		Shared
D3S1358	15	16	15	15	1
TH01	9	9	6	9.3	0
D21S11	28	31	28	31.2	1
D18S51	13	16	12	19	0
Penta E	12	12	11	12	1
D5S818	12	12	9	12	1
D13S317	12	13	10	13	1
D7S820	9	10	11	12	0
D16S539	10	10	12	12	0
CSF1PO	10	12	10	12	2
Penta D	12	13	9	9	0
AMEL	X	Y	X	X	1
vWA	17	19	14	19	1
D8S1179	13	13	9	15	0
TPOX	8	12	9	10	0
FGA	21	25	20	25	1
Total	30		30		10
Percentage					33.33%

	P006		P007		Shared
D3S1358	16	18	14	17	0
TH01	7	9.3	9.3	9.3	1
D21S11	29	32	27	32.2	0
D18S51	16	18	14	16	1
Penta E	7	13	12	13	1
D5S818	9	11	11	12	1
D13S317	9	13	8	11	0
D7S820	8	10	11	11	0
D16S539	12	12	11	13	0
CSF1PO	12	12	10	11	0
Penta D	10	13	10	12	1
AMEL	X	Y	X	X	1
vWA	15	16	14	16	1
D8S1179	10	14	12	13	0
TPOX	8	9	8	11	1
FGA	23	25	23	26	1
Total	30		30		9
Percentage					30.00%

	P006		P009		Shared
D3S1358	16	18	16	17	1
TH01	7	9.3	7	7	1
D21S11	29	32	30	31	0
D18S51	16	18	11	16	1
Penta E	7	13	13	14	1
D5S818	9	11	10	12	0
D13S317	9	13	9	11	1
D7S820	8	10	11	11	0
D16S539	12	12	11	13	0
CSF1PO	12	12	11	12	1
Penta D	10	13	9	11	0
AMEL	X	Y	X	Y	2
vWA	15	16	17	17	0
D8S1179	10	14	12	13	0
TPOX	8	9	8	11	1
FGA	23	25	22	24	0
Total	30		30		9
Percentage					30.00%

	P006		P011		Shared
D3S1358	16	18	14	14	0
TH01	7	9.3	7	8	1
D21S11	29	32	28	30	0
D18S51	16	18	15	17	0
Penta E	7	13	11	16	0
D5S818	9	11	9	11	2
D13S317	9	13	11	13	1
D7S820	8	10	10	12	1
D16S539	12	12	11	11	0
CSF1PO	12	12	10	12	1
Penta D	10	13	9	12	0
AMEL	X	Y	X	X	1
vWA	15	16	16	17	1
D8S1179	10	14	8	15	0
TPOX	8	9	8	11	1
FGA	23	25	20	21	0
Total	30		30		9
Percentage					30.00%

	P006		P012		Shared
D3S1358	16	18	15	15	0
TH01	7	9.3	6	9.3	1
D21S11	29	32	28	31.2	0
D18S51	16	18	12	19	0
Penta E	7	13	11	12	0
D5S818	9	11	9	12	1
D13S317	9	13	10	13	1
D7S820	8	10	11	12	0
D16S539	12	12	12	12	2
CSF1PO	12	12	10	12	1
Penta D	10	13	9	9	0
AMEL	X	Y	X	X	1
vWA	15	16	14	19	0
D8S1179	10	14	9	15	0
TPOX	8	9	9	10	1
FGA	23	25	20	25	1
Total	30		30		9
Percentage					30.00%

	P007		P011		Shared
D3S1358	14	17	14	14	1
TH01	9.3	9.3	7	8	0
D21S11	27	32.2	28	30	0
D18S51	14	16	15	17	0
Penta E	12	13	11	16	0
D5S818	11	12	9	11	1
D13S317	8	11	11	13	1
D7S820	11	11	10	12	0
D16S539	11	13	11	11	1
CSF1PO	10	11	10	12	1
Penta D	10	12	9	12	1
AMEL	X	X	X	X	2
vWA	14	16	16	17	1
D8S1179	12	13	8	15	0
TPOX	8	11	8	11	2
FGA	23	26	20	21	0
Total	30		30		11
Percentage					36.67%

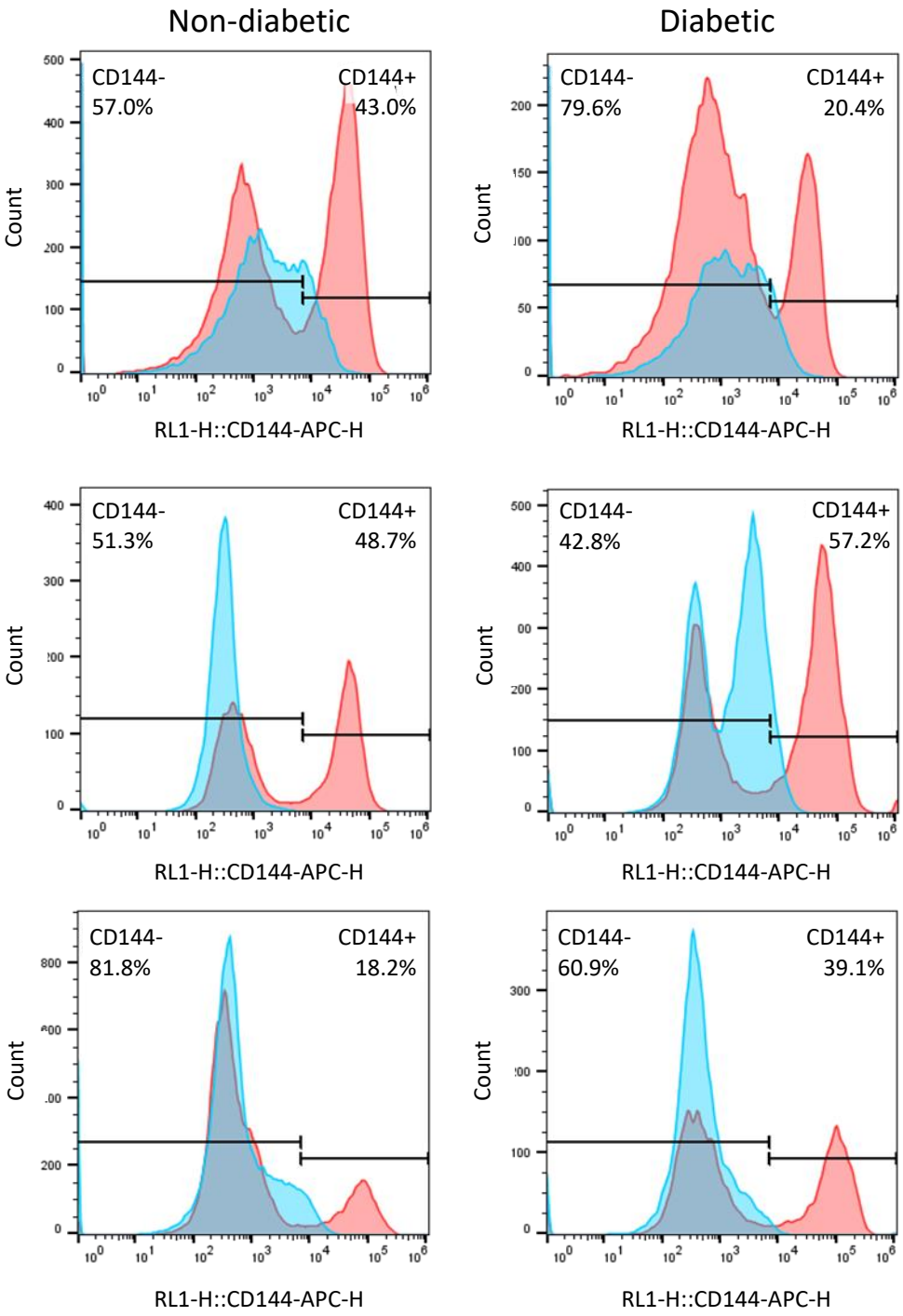
	P007		P012		Shared
D3S1358	14	17	15	15	0
TH01	9.3	9.3	6	9.3	1
D21S11	27	32.2	28	31.2	0
D18S51	14	16	12	19	0
Penta E	12	13	11	12	1
D5S818	11	12	9	12	1
D13S317	8	11	10	13	0
D7S820	11	11	11	12	1
D16S539	11	13	12	12	0
CSF1PO	10	11	10	12	1
Penta D	10	12	9	9	0
AMEL	X	X	X	X	2
vWA	14	16	14	19	1
D8S1179	12	13	9	15	0
TPOX	8	11	9	10	0
FGA	23	26	20	25	0
Total	30		30		8
Percentage					26.67%

	P009		P011		Shared
D3S1358	16	17	14	14	0
TH01	7	7	7	8	1
D21S11	30	31	28	30	1
D18S51	11	16	15	17	0
Penta E	13	14	11	16	0
D5S818	10	12	9	11	0
D13S317	9	11	11	13	1
D7S820	11	11	10	12	0
D16S539	11	13	11	11	1
CSF1PO	11	12	10	12	1
Penta D	9	11	9	12	1
AMEL	X	Y	X	X	2
vWA	17	17	16	17	1
D8S1179	12	13	8	15	0
TPOX	8	11	8	11	2
FGA	22	24	20	21	0
Total	30		30		11
Percentage					36.67%

	P009		P012		Shared
D3S1358	16	17	15	15	0
TH01	7	7	6	9.3	0
D21S11	30	31	28	31.2	0
D18S51	11	16	12	19	0
Penta E	13	14	11	12	0
D5S818	10	12	9	12	1
D13S317	9	11	10	13	0
D7S820	11	11	11	12	1
D16S539	11	13	12	12	0
CSF1PO	11	12	10	12	1
Penta D	9	11	9	9	1
AMEL	X	Y	X	X	1
vWA	17	17	14	19	0
D8S1179	12	13	9	15	0
TPOX	8	11	9	10	0
FGA	22	24	20	25	0
Total	30		30		5
Percentage					16.67%

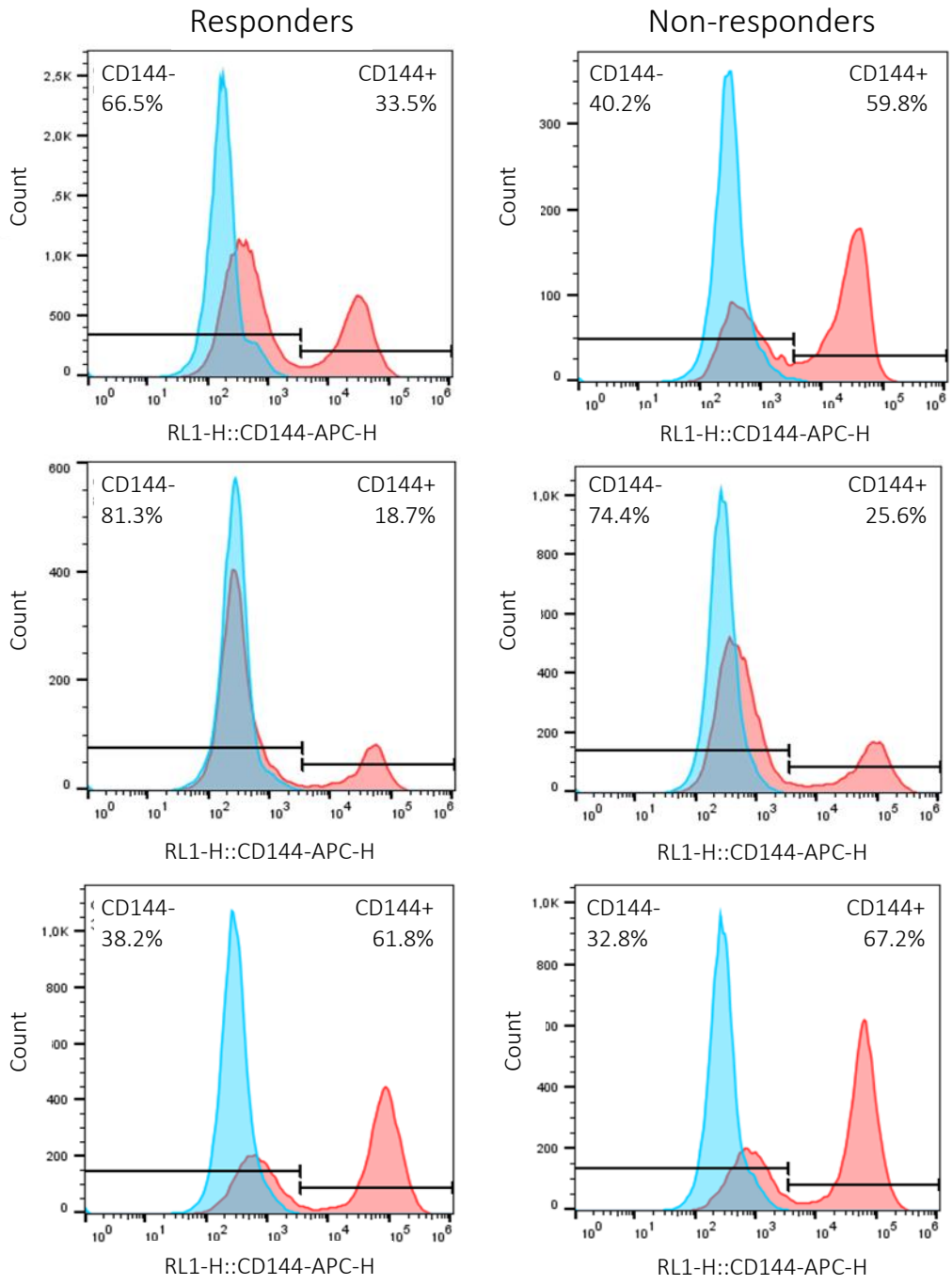
Supplementary Table 6: STR profiling results comparison. The alleles of each cell line were compared side by side with the other lines. The percentage of similarity between lines was always lower or equal to 50%, which means that all cells come from different individuals.

Supplementary Figure S1



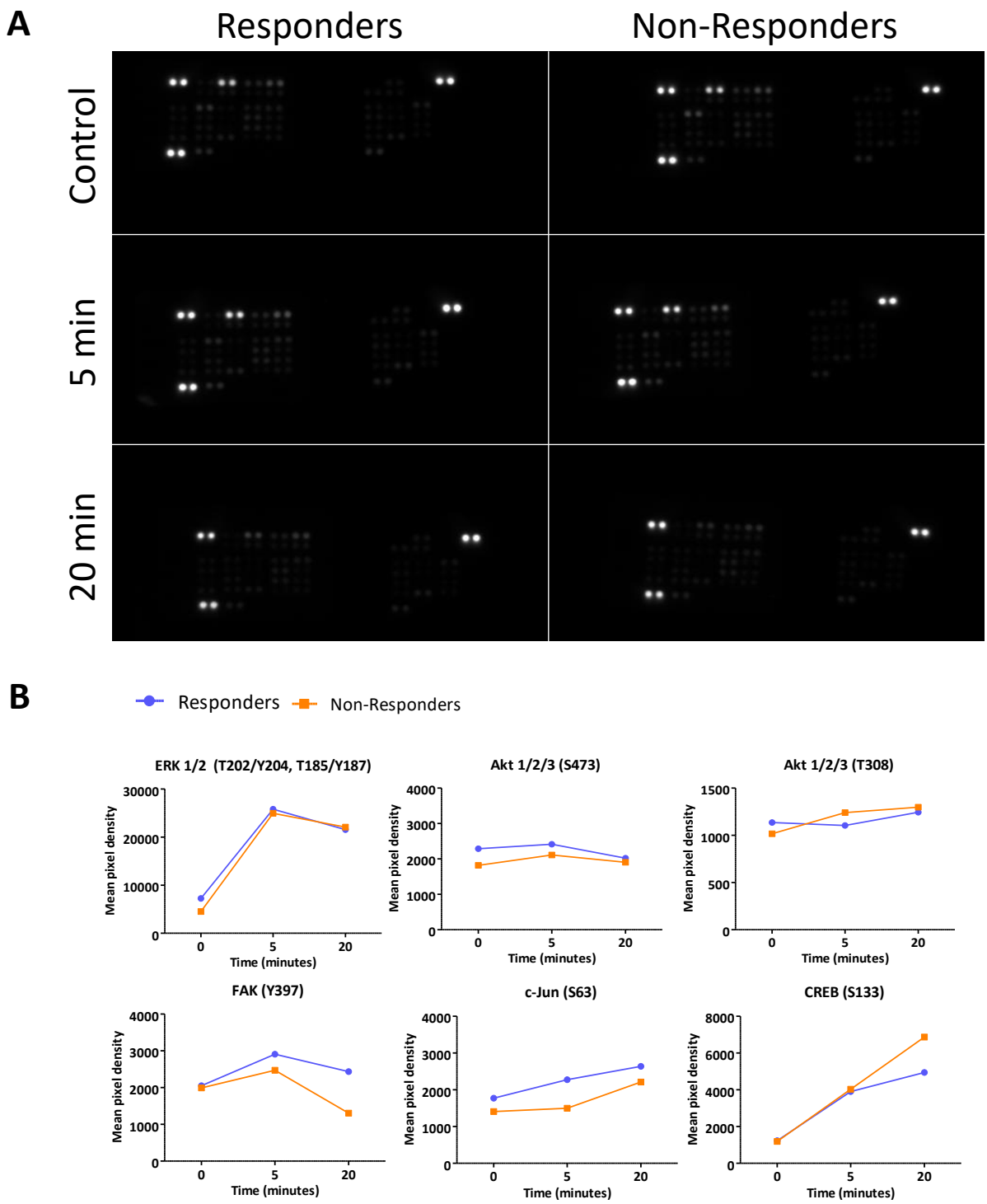
Supplementary Figure S1 : Differentiation efficiency of iPS cells towards endothelial cells. The efficiency is calculated by measuring the percentage of the population that expressed the endothelial marker CD144 on day 6 of differentiation. The levels of CD144+ cells are measured using flow cytometry and compared to an isotype control. The efficiency of the differentiation process in these representative plots of non-diabetic and diabetic cells varies from 18.2% to 57.2%.

Supplementary Figure S2



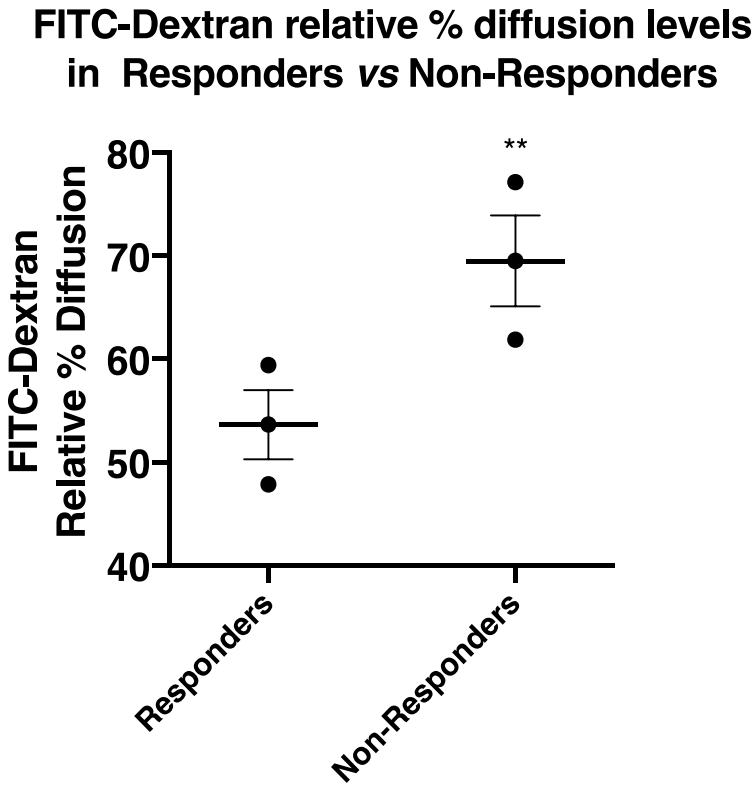
Supplementary Figure S2: Differentiation efficiency of DME iPS cells towards endothelial cells. The efficiency is calculated by measuring the percentage of the population that expressed the endothelial marker CD144 on day 6 of differentiation. The levels of CD144+ cells are measured using flow cytometry and compared to an isotype control. The efficiency of the differentiation process in these representative plots between responders and non-responders varies from 18.7% to 67.2%.

Supplementary Figure S3



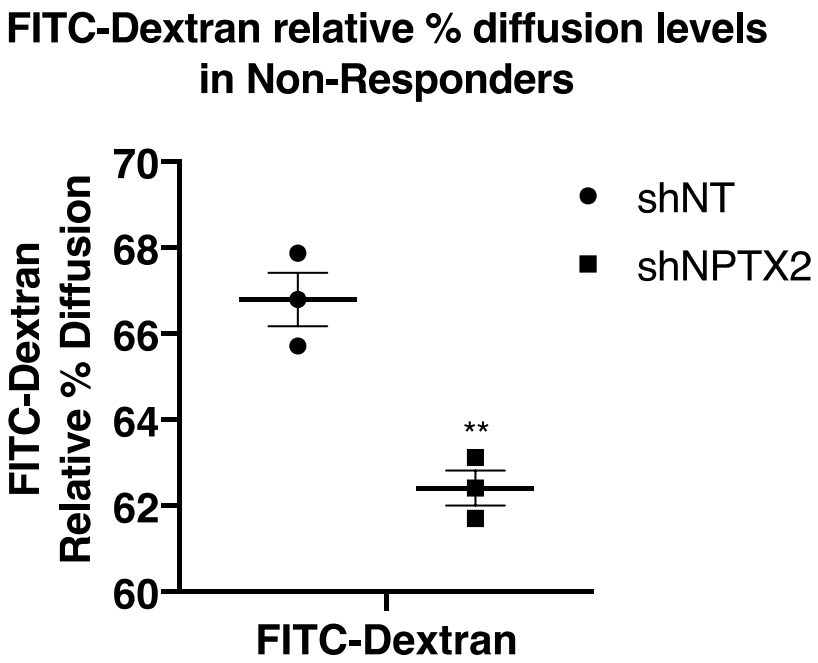
Supplementary Figure S3: Phosphokinase array blotted with protein from iPS-ECs from DME responders or non-responders 5 and 20 minutes after treatment with VEGF. A) In each blot, every dot pair corresponds to a phosphorylated protein or to a pair of reference spots (corners). The signal intensity is directly proportional to the amount of phosphorylation of the protein. **B)** Upon VEGF treatment of iPS-ECs, the phosphorylation state of determined proteins is different in Responders and Non-Responders.

Supplementary Figure S4



Supplementary Figure S4: FITC-Dextran relative % diffusion levels in additional cell lines in Responders vs Non-Responders. (Data are means ±SEM (n=3), **p<0.01).

Supplementary Figure S5



Supplementary Figure S5: FITC-Dextran relative % diffusion levels after NPTX2 knockdown in additional cell lines of Non-Responders. (Data are means ±SEM (n=3), **p<0.01).