ELECTRONIC SUPPLEMENTARY MATERIALS

ESM Table 1. Expression of HIF1α genes by RNA Seq analysis

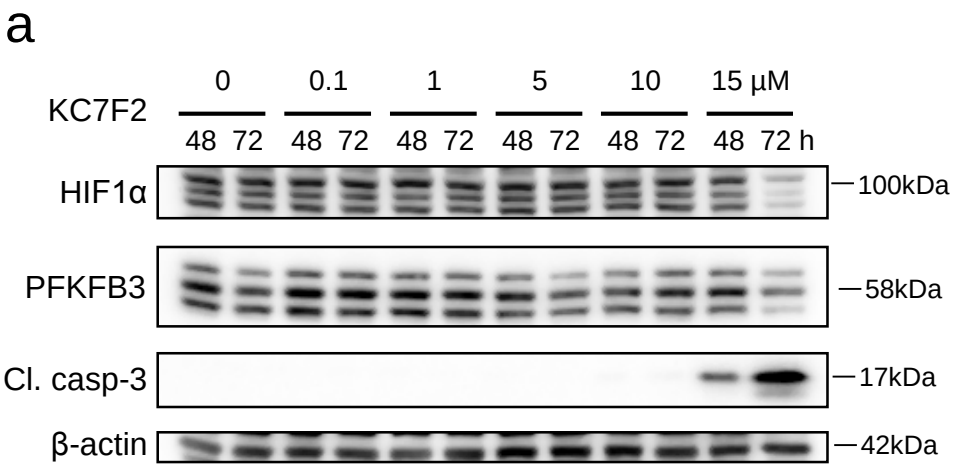
Ratio of relative expression of known HIF1α target genes evaluated by RNA Seq analyses of human islets (columns 1 and 2) or isolated beta-cells (column 3) from individuals with T1D versus non diabetic controls (columns 1 and 3), and human islets from non diabetic individual exposed to cytokines versus untreated controls (2). * indicates increased expression of HIF1α targets in type-1 diabetes.

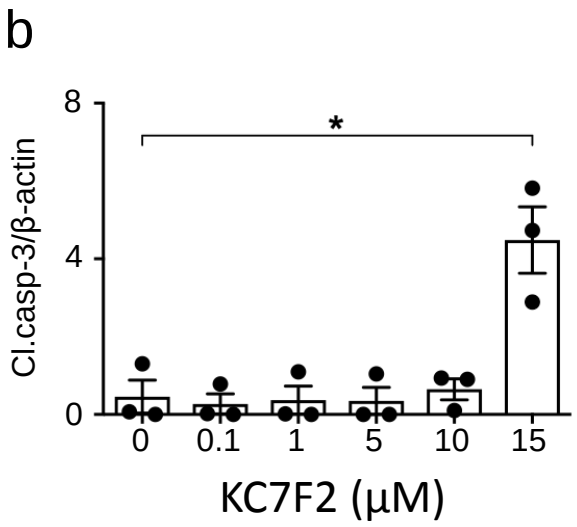
Eizirik et al. [11] column 1; Mastracci et al [10] Column 2, and Wang et al. [12] Column 3

Gene	1	2	3
ADM	2.33	0.81	0.25
AHNAK	0.85	2.12	1.83*
ALDOA	2.1	1.85	0.955
ALDOC	1.44	0.9	9.51
ATF4	0.93	1.12	0.84
BBC3	2.78	2.83	n.d
BMP2	2.66	2.58	2.63*
BNIP3	1.3	2.12	0.14
BNIP3L	1.57	1.16	1.03
BTG1	1.05	1.57	4.16
CA9	3.89	17.84	n.d
CDKN1B	1.23	0.75	1.23
COX4I2	1.01	n.d.	n.d
CXCR4	0.68	0.71	0.45*
DDIT4	1.92	3.03	0.11
DLL4	1.41	0.54	0.43*
DUSP1	3	1.05	4.2
EDN1	1.87	1.86	0.44
EGFR	1.29	2.14	2.21*
EGLN1	1.1	1.37	0.14
EGLN3	2.97	7.32	2.19*
ENO1	1.66	2.15	0.41
ERO1A	2.76	3.99	6.45

FOXO3	1.07	1.3	3.83
GAPDH	1.77	1.33	0.31
GBE1	1.55	2.9	0.01
GCK	1.78	0.01	10.63
GK	6.5	1.73	4.86*
GPI	1.25	1.21	4.45
HK1	1.53	1.9	n.d
HK2	3.79	6.34	n.d
ID2	2.9	0.83	0.75
IGF1R	0.65	0.42	1.35
IGFBP3	4.88	1.01	0.46*
IGFBP5	1.49	0.12	0.64
IRF1	10.24	1.49	9.08
JMY	0.72	0.54	2.17
LDHA	1.76	4.22	22.84
LONP1	1.49	0.88	0.02
LOX	1.98	1.49	n.d
MAFF	1.85	0.85	0.37*
MIF	1.4	0.51	1.44
MXI1	0.57	1.51	1.83
NRN1	3.02	0.82	0.31*
P4HA1	1.64	2.15	2.91
P4HA2	1.11	1.75	0.85
PDGFB	0.85	1.65	0.67*
PDK1	1.55	1.73	14.39
PDK3	0.98	0.32	0.95
PFKFB3	2.84	3.6	37.57*
PFKL	2.09	1.23	4.22
PFKP	1.7	1.04	0.37
PGAM1	1.83	1.16	0.37
PGK1	2.38	2.34	0.43
PGM1	1.2	1.84	0.28
PIM1	0.76	1.69	1.22*
PKM	1.82	1.35	1.98
PLOD1	1.34	1.04	2.18*
PLOD2	1.6	3.94	1.68
RORA	1.27	0.53	1.25
SERPINE1	1.14	1.11	3.91
SLC16A1	1.04	0.88	3.9*
SLC16A3	5.5	2.76	n.d
SLC2A1	2.28	1.68	0.01
SLC2A3	0.98	0.54	227.45*
STC1	4.11	0.68	1.23

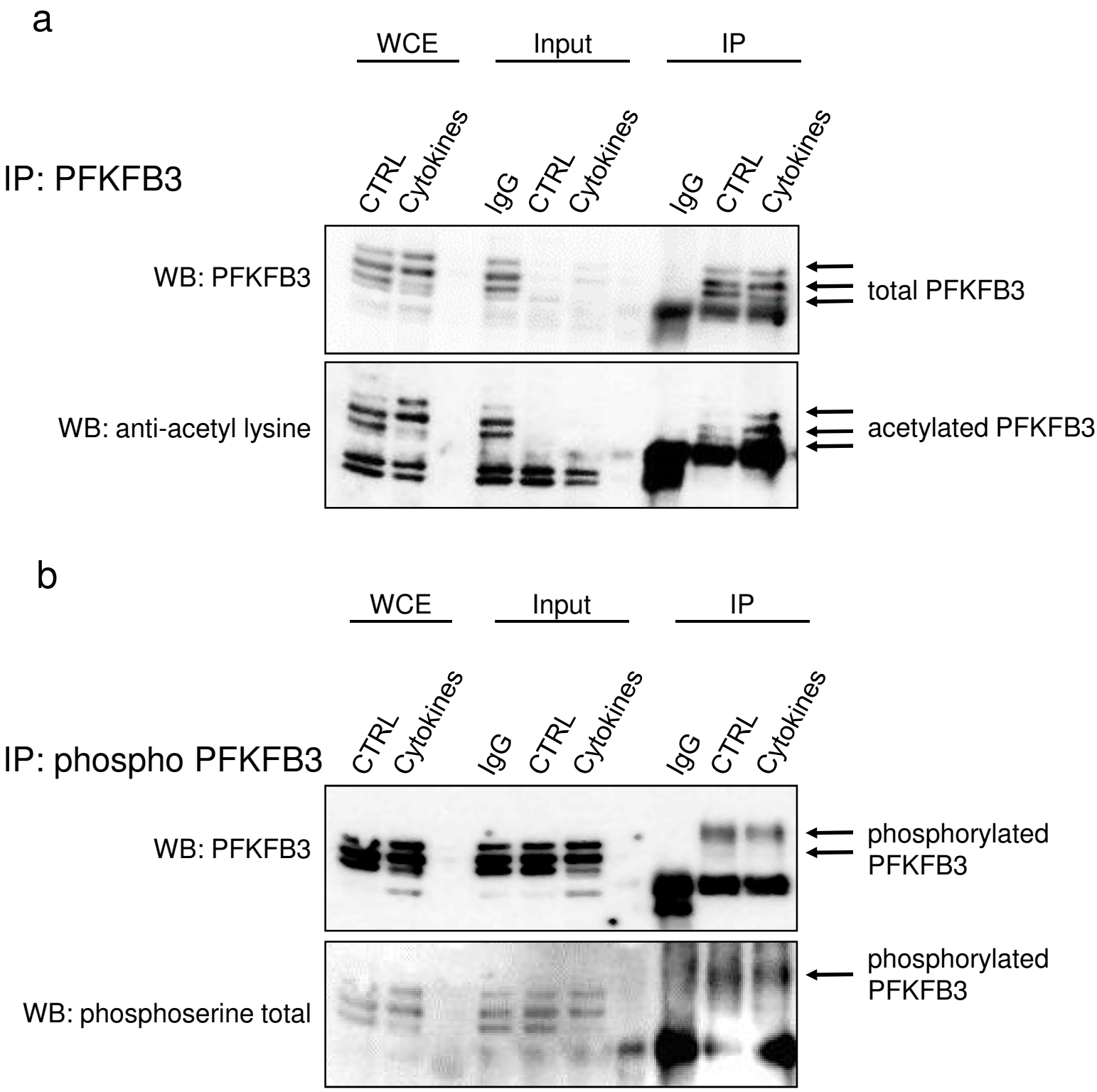
STC2	3.39	0.75	0.22*
TBK1	1.02	0.64	1.67
TEF	0.71	0.48	29
TKT	1.25	n.d.	0.27
TMEM45A	1.47	0.64	3.3
TNFAIP3	2.92	2.57	20.85
TPI1	1.65	1.51	0.59
TRPC1	0.94	0.19	1.23*
VEGFA	1.01	0.7	0.54
VEGFB	0.84	0.39	0.91





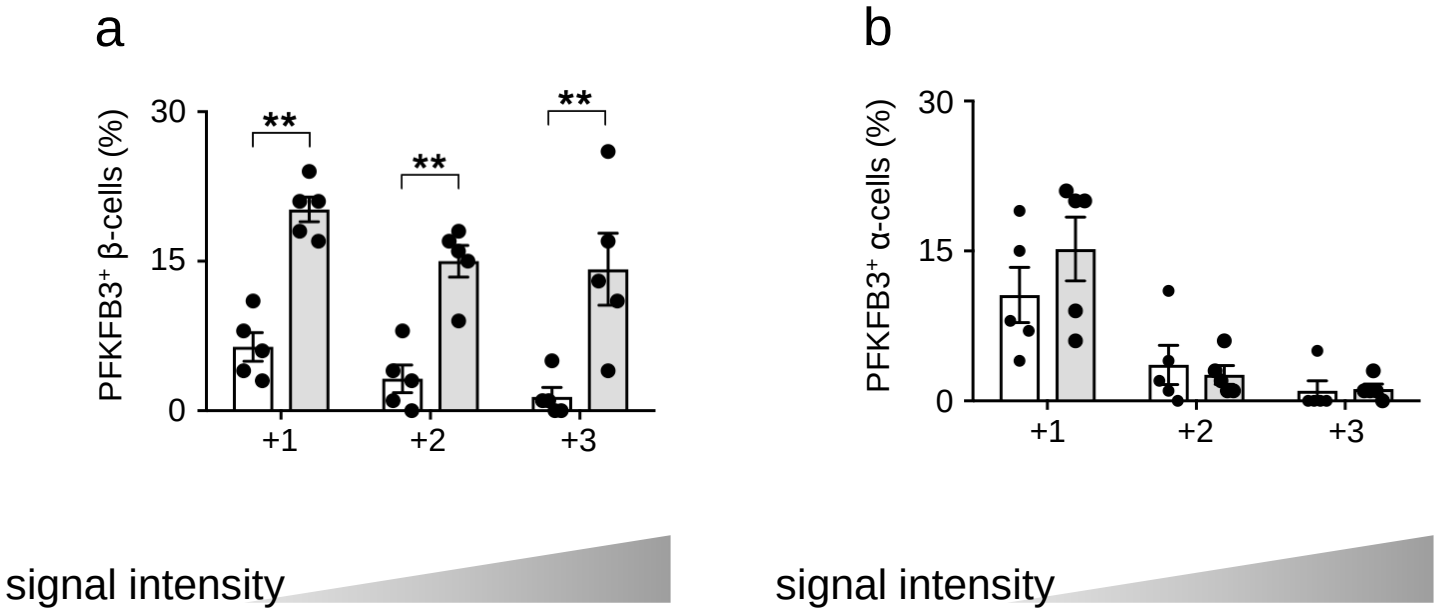
a. Representative immunoblotting of whole cell extracts from INS-1 832/13 cells treated with KC7F2 inhibitor (0-15 µM) for either 48 or 72 hours. Time- and concentration dependent toxicity was confirmed using detection of cleaved caspase 3 (Cl. casp-3) and concomitant decrease in PFKFB3 levels with specific antibodies. **b**. Quantification of the cleaved caspase-3 band intensity after Western blot analysis of cell lysates from 48h treatment with KC7F2; Data are expressed as mean ± SEM. n=3, * $p<0.05$, two-tailed unpaired Student's *t* test.

ESM Fig.1



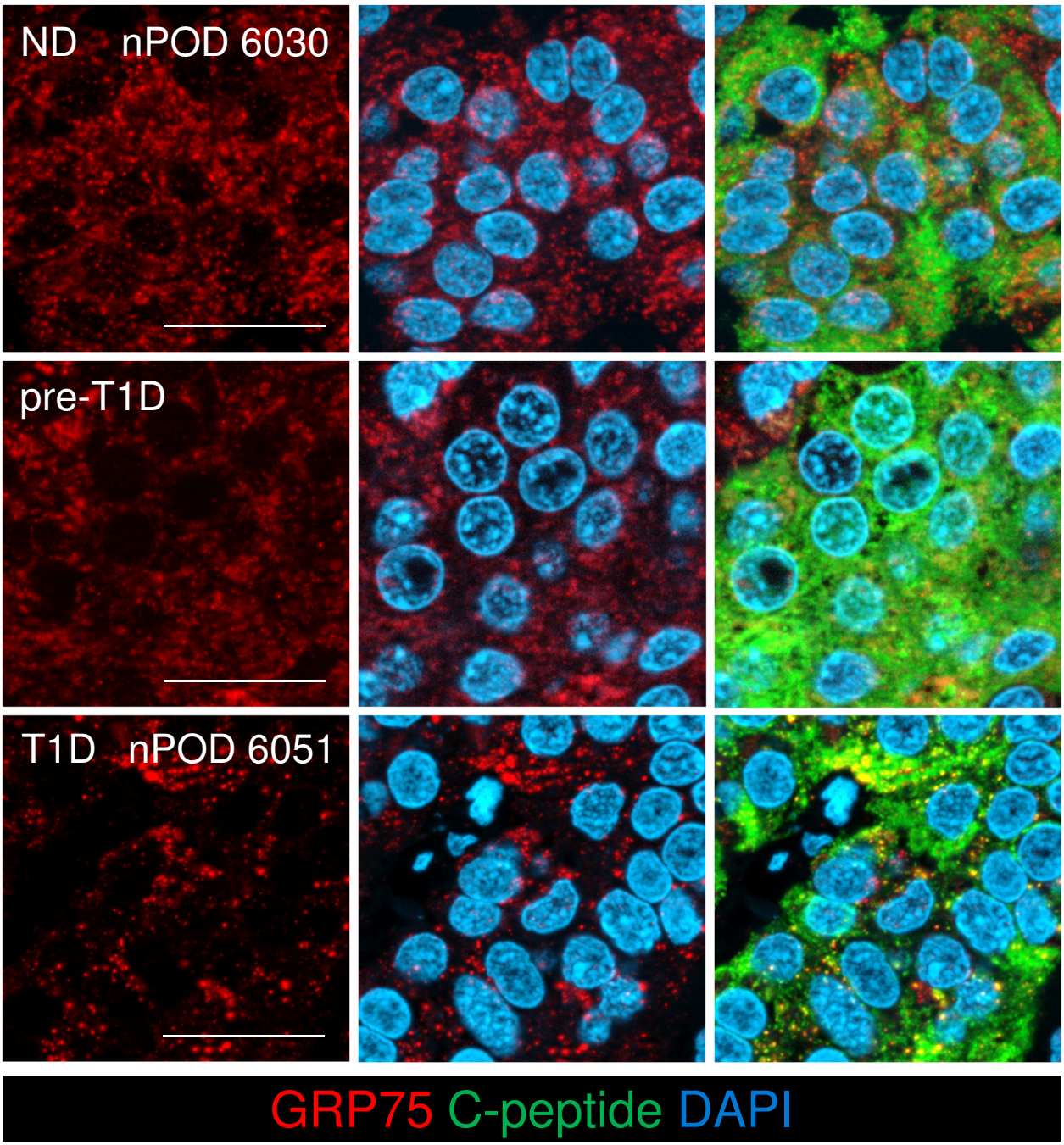
Whole cell extracts from control- and cytokines treated INS-1 832/13 cells were used to pull down PFKFB3 using either **a**. anti-PFKFB3 or **b.** anti-phospho PFKFB3 antibodies isolated on the Protein A-magnetic beads. Immunoblotting of purified immunocomplexes using anti-acetyl lysine and anti-phospho serine antibodies revealed that each of the 3 PFKFB3 detected bands are partly acetylated and phosphorylated.

ESM Fig.2



Mean of percentage of **a**. beta-cells and **b.** alpha-cells positive for PFKFB3 in non-diabetics (white bar) and type 1 diabetes (gray bar) scored for intensity of immunoreactivity for PFKFB3; +1 weakly positive, +2 moderately positive and +3 strongly positive. Beta-cells in T1D were not only more often immunoreactive for PFKFB3 in T1D than in non-diabetic controls, but were also more intensively positive. In contrast there was no difference in intensity in alpha-cells immunoreactive for PFKFB3 in T1D and ND, n=5, ** p <0.01, two-tailed unpaired Student's *t* test.

ESM Fig.3



Images of pancreatic islets from non-diabetic (ND) control, donor with pre-type 1 diabetes (pre-T1D) and type 1 diabetes (T1D) stained for GRP75 (to visualize mitochondria, red), C-peptide (green) and nuclei DAPI (blue). GRP75 immunostaining reveals perinuclear fragmented mitochondrial networks with reduced density in beta-cells from a pre-T1D individual an appearance more pronounced in T1D, thus corroborating the findings with Tom20 immunostaining (Fig 5). Size bars correspond to 20 µm.

ESM Fig.4

Diabetologia

Checklist for reporting human islet preparations used in research

Adapted from Hart NJ, Powers AC (2018) Progress, challenges, and suggestions for using human islets to understand islet biology and human diabetes. Diabetologia https://doi.org/10.1007/s00125-018-4772-2

Islet preparation	1	2	3	4	5	6	7	8[a]
MANDATORY INFORMATION								
Unique identifier	SAMN09370567	SAMN10439569	HP-19017-01	HP-19102-01				
Donor age (years)	32	53	62	67				
Donor sex (M/F)	M	F	F	F				
Donor BMI (kg/m^2)	28.5	30.0	36.1	31.8				
Donor HbA_{1c} or other measure of blood glucose control	Average blood glucose: 146.80 mg/dl	Average blood glucose: 117.60 mg/dl	HbA1c: 5.7%	HbA1c: 4.8%				
Origin/source of islets[b]	IIDP	IIDP	Prodo Laboratories, Inc.	Prodo Laboratories, Inc.				
Islet isolation centre	University of Wisconsin	Southern California Islet Cell Resources Center	Prodo Laboratories, Inc.	Prodo Laboratories, Inc.				
Donor history of diabetes? Please select yes/no from drop down list	No	No	No	No				
If Yes, complete the next two lines if this information is available								
Diabetes duration (years)								
Glucose-lowering therapy at time of death[c]								
RECOMMENDED INFORMATION								
Donor cause of death	Head trauma	Cardiovascular/stroke	Stroke	Stroke				

Warm ischaemia time (h)	0.1	0.5	0	0				
Cold ischaemia time (h)	12.5	6.3	11.8	6.6				
Estimated purity (%)	95	85	90	95				
Estimated viability (%)	91	97	95	95				
Total culture time (h)[d]	46	48	100	84				
Glucose-stimulated insulin secretion or other functional measurement[e]								
Handpicked to purity? Please select yes/no from drop down list	Yes	Yes	Yes	Yes				
Additional notes								

[a]If you have used more than eight islet preparations, please complete additional forms as necessary
[b]For example, IIDP, ECIT, Alberta IsletCore
[c]Please specify the therapy/therapies
[d]Time of islet culture at the isolation centre, during shipment and at the receiving laboratory
[e]Please specify the test and the results