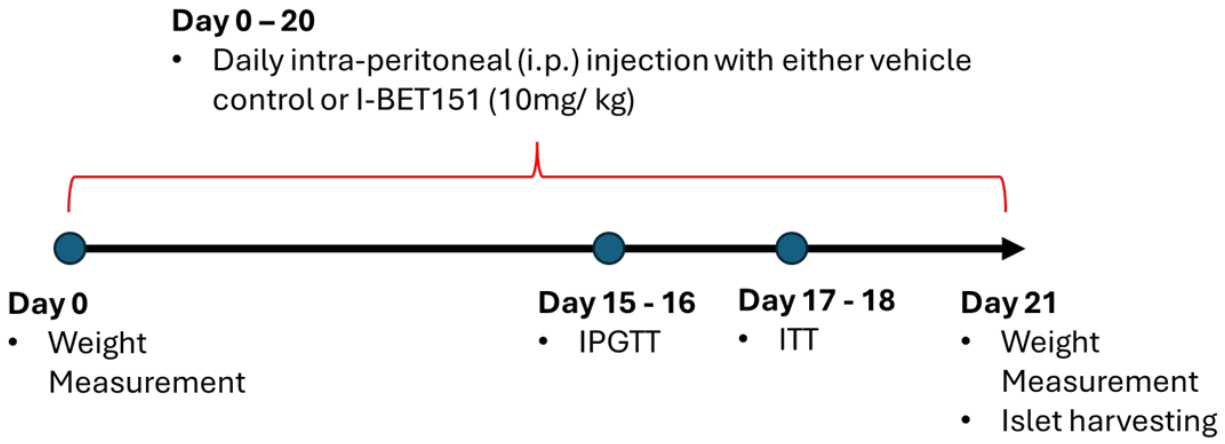
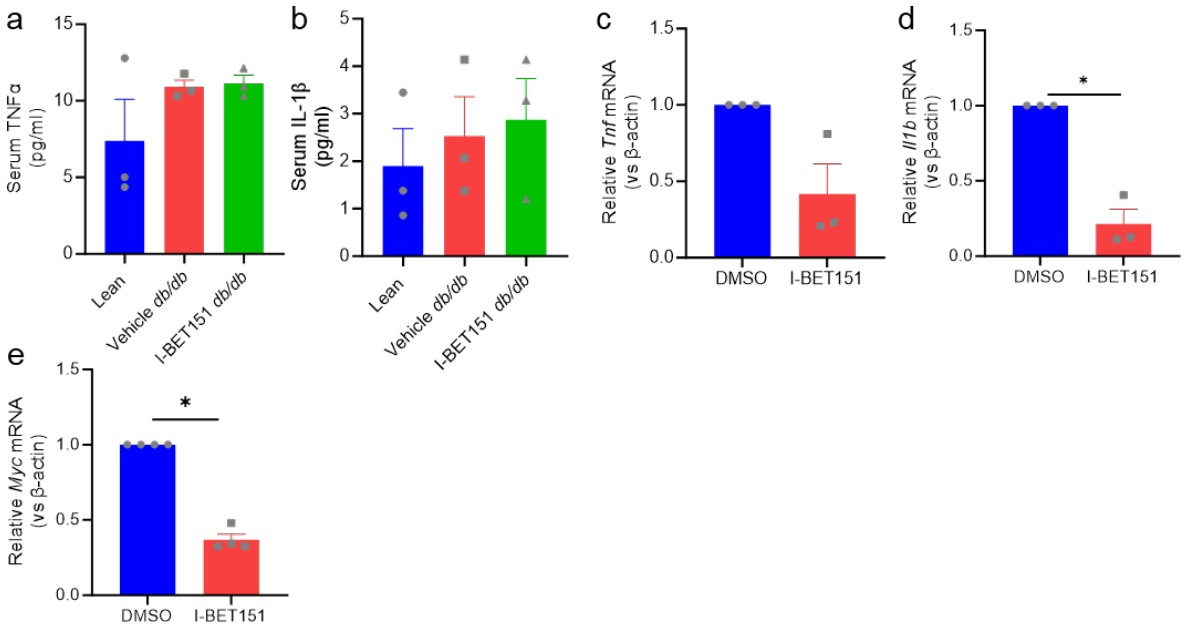
Antibodies	SOURCE	IDENTIFIER	Lot	Dilution
Rabbit GCK Polyclonal Antibody	Invitrogen	Cat#PA5-90199 (1)	XB3493806A	1:1000
Anti-HNF-4-alpha antibody [EPR16885] - ChIP Grade	Abcam	Cat# ab181604	1026268-5	1:1000
Anti-HNF1 alpha antibody	Abcam	Cat#Ab96777	GR3398787-3	1:1000
Anti-beta Actin antibody [AC-15]	Abcam	Cat# Ab6276	GR3324554-1	1:3000
FoxO1 (C29H4) Rabbit mAb	Cell Signaling Technology	Cat#2880S	14	1:1000 (Western blot) or 1:200 (Immunofluoroscnece)
Phospho-FoxO1 (Ser256) Antibody	Cell Signaling Technology	Cat#9461S	8	1:1000
Horse anti-mouse IgG (HRP-linked)	Cell Signaling Technology	Cat#7076	Lot# 38	1:1000
Goat anti-rabbit IgG (HRP-linked)	Cell Signaling Technology	Cat#7074	Lot# 28	1:1000
Goat anti-rabbit IgG, Alexa Fluor 488	Thermo Fisher Scientific	Cat#A32731	Lot# 1622775	1:200

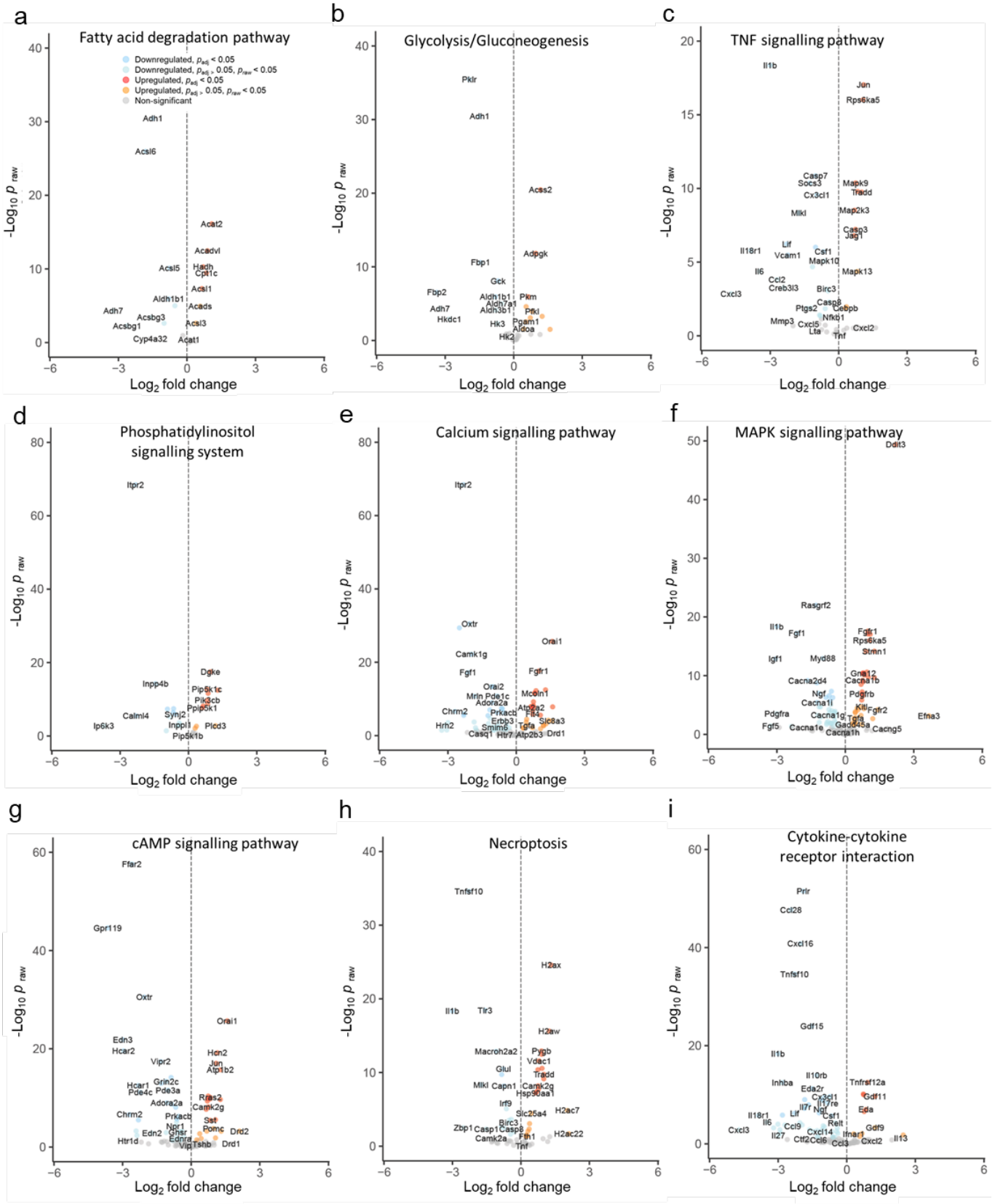
ESM Table 1. Antibody source and dilution factors used for western immunoblotting and immunofluorescence experiments.



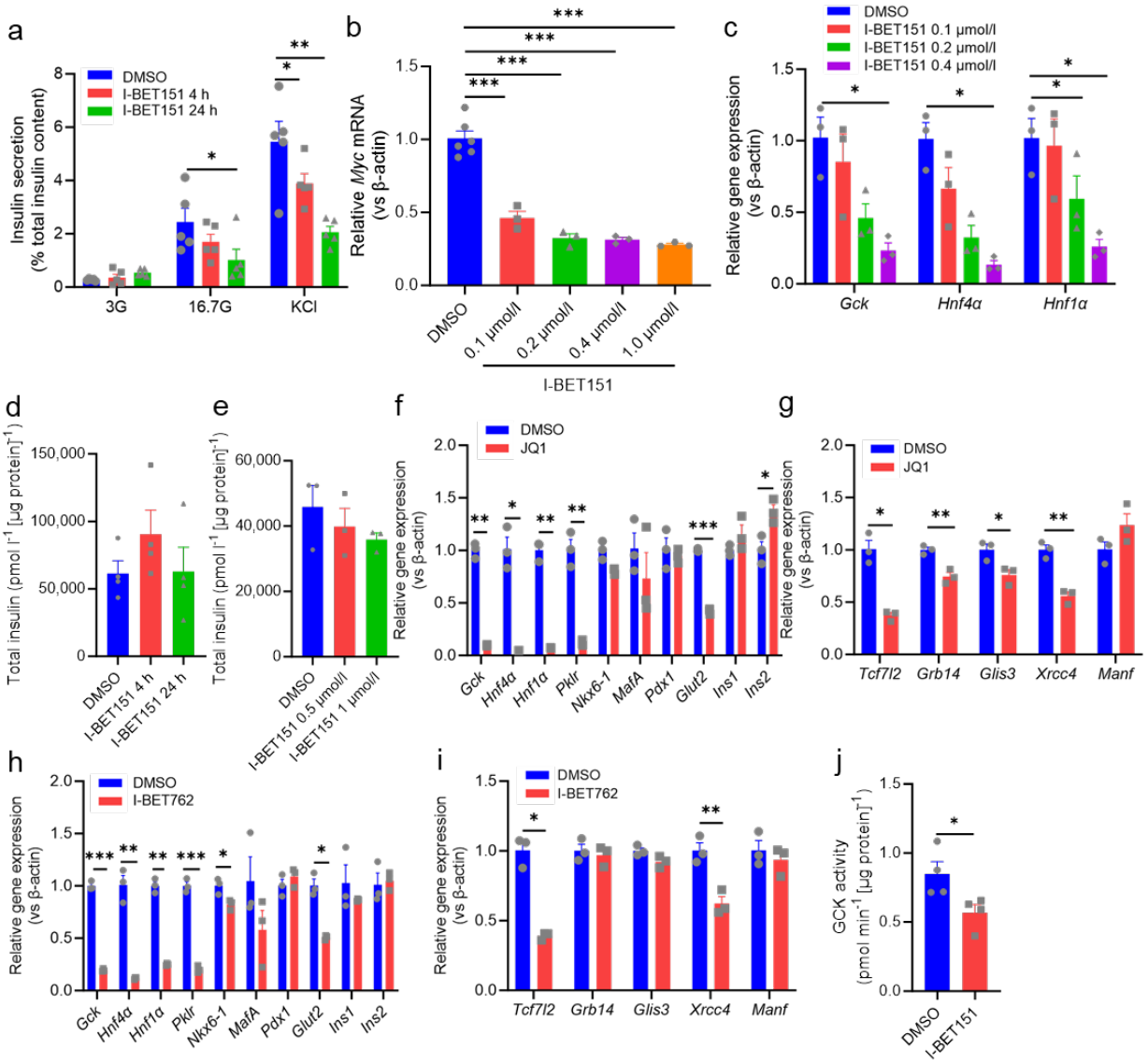
ESM Figure 1. Schematic depiction of I-BET151 administration to either healthy C57BL6/J or BKS db/db mice.



ESM Figure 2. BET inhibitors dysregulate MODY and T2D GWAS genes (a) Serum concentration of TNFα cytokine in lean, Vehicle db/db and I-BET151 db/db mice, *n*=3. (b) Serum concentration of IL-1β cytokine in lean, Vehicle db/db and I-BET151db/db mice, *n*=3. (c) qPCR of *Tnf* mRNA in mouse islets treated with either DMSO or 1 µmol/l I-BET151 for 24 h, *n*=3. (d) qPCR of *Il1b* mRNA in mouse islets treated with either DMSO or 1 µmol/l I-BET151 for 24 h, *n*=3. (e) qPCR of *Myc* mRNA in mouse islets treated with either DMSO or 1 µmol/l I-BET151 for 24 h, *n*=4. Data represents means ± SEM. c,d: For comparison of 2 groups, p-values were determined using unpaired t-test with Welch's correction; e: For comparison of 2 groups with non-normal data, p-value was determined using Mann Whitney U test; a,b: For comparison of >2 groups, p-values were calculated with One-way ANOVA test with post-hoc Dunnett's T3 test; *p<0.05,**p<0.01 and ***p<0.001.

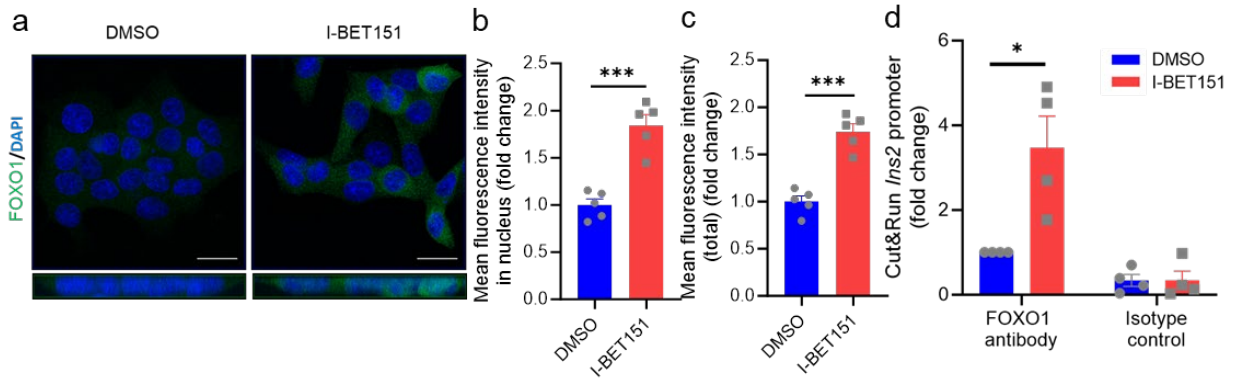

a
Fatty acid degradation pathway
Downregulated, p_{adj} < 0.05
Downregulated, p_{adj} > 0.05, p_{raw} < 0.05
Upregulated, p_{adj} < 0.05
Upregulated, p_{adj} > 0.05, p_{raw} < 0.05
Non-significant
Adh1
Acsl6
Acat2
Acadvl
Acsl5
Hadh
Cpt1c
Acsl1
Aldh1b1
Acads
Adh7
Acsbg3
Acsbg1
Acsl3
Cyp4a32
Acat1
-Log10 p raw
Log2 fold change
b
Glycolysis/Gluconeogenesis
Pklr
Adh1
Acss2
Adpgk
Fbp1
Gck
Fbp2
Aldh1b1
Aldh7a1
Aldh3b1
Pkm
Pfkl
Adh7
Hkdc1
Hk3
Pgam1
Aldoa
Hk2
-Log10 p raw
Log2 fold change
c
TNF signalling pathway
Il1b
Jun
Rps6ka5
Casp7
Socs3
Mapk9
Cx3cl1
Tradd
Mlkl
Map2k3
Casp3
Jag1
Il18r1
Lif
Vcam1
Csf1
Mapk10
Il6
Mapk13
Ccl2
Creb3l3
Cxcl3
Birc3
Casp8
Ptgs2
Cebpb
Nfkbi1
Mmp3
Cxcl5
Lta
Tnf
Cxcl2
-Log10 p raw
Log2 fold change
d
Phosphatidylinositol signalling system
Itpr2
Dgke
Inpp4b
Pip5k1c
Pik3cb
Pip5k1
Calml4
Synj2
Ip6k3
Inpp1
Plcd3
Pip5k1b
-Log10 p raw
Log2 fold change
e
Calcium signalling pathway
Itpr2
Oxtr
Orai1
Camk1g
Fgf1
Fgfr1
Orai2
Mcoln1
Mrln
Pde1c
Adora2a
Atp2a2
Chrm2
Prkacb
Erbb3
Slc8a3
Hrh2
Snim6
Tgfa
Casq1
Htr7
Atp2b3
Drd1
-Log10 p raw
Log2 fold change
f
MAPK signalling pathway
Ddit3
Rasgrf2
Il1b
Fgf1
Fgfr1
Rps6ka5
Stmn1
Igf1
Myd88
Gna12
Cacna2d4
Cacna1b
Ngf
Pdgfrb
Cacna1l
Kitl
Pdgfra
Cacna1g
Tgfa
Fgfr2
Efna3
Fgf5
Cacna1e
Gadd45a
Cacna1h
Cacng5
-Log10 p raw
Log2 fold change
g
cAMP signalling pathway
Ffar2
Gpr119
Oxtr
Orai1
Edn3
Hcar2
Hcn2
Vipr2
Jun
Atp1b2
Hcar1
Grin2c
Pde4c
Pde3a
Rras2
Adora2a
Camk2g
Chrm2
Prkacb
Sst
Npr1
Pomc
Drd2
Edn2
Ghsr
Htr1d
Ednra
Vipr1
Tshb
Drd1
-Log10 p raw
Log2 fold change
h
Necroptosis
Tnfsf10
H2ax
Il1b
Tlr3
H2aw
Macroh2a2
Pygb
Vdac1
Glul
Tradd
Mlkl
Capn1
Camk2g
Hsp90aa1
Irf9
Slc25a4
H2ac7
Birc3
Zbp1
Casp1
Casp8
Fth1
H2ac22
Camk2a
Tnf
-Log10 p raw
Log2 fold change
i
Cytokine-cytokine receptor interaction
Prlr
Ccl28
Cxcl16
Tnfsf10
Gdf15
Il1b
Il10rb
Inhba
Tnfrsf12a
Eda2r
Cx3cl1
Gdf11
Il17re
Il7r
Ngf
Eda
Il18r1
Lif
Csf1
Il6
Ccl9
Relt
Gdf9
Cxcl3
Cxcl14
Ifnar1
Il27
Ctf2
Ccl6
Ccl3
Cxcl2
Il13
-Log10 p raw
Log2 fold change

ESM Figure 3. Dysregulated KEGG pathways in healthy islets treated with I-BET151. Volcano plot of dysregulated genes of indicated KEGG terms in healthy islets treated with either vehicle control (DMSO) or 1 μmol/l I-BET151 for 24 h, N=6. (a) Fatty acid degradation pathway, (b) Glycolysis/Gluconeogenesis, (c) TNF signaling pathway, (d) Phosphotidylinositol signaling system, (e) Calcium signaling pathway, (f) MAPK signaling pathway, (g) cAMP signaling pathway, (h) Necroptosis, (i) Cytokine-cytokine interaction, Upregulated genes (Red) and downregulated genes (Blue) in I-BET151-treated islets compared to DMSO-treated islets, *n*=6.



ESM Figure 4. (a) Glucose stimulated Insulin Secretion (GSIS) assay on INS-1E cells treated with either vehicle control (DMSO) or 1 µmol/l I-BET151 for 4 h and 24 h, *n*=5. (b) qPCR of Myc mRNA in INS-1E treated with either DMSO or 0.1 - 1 µmol/l I-BET151 for 24 h, *n*= 3-6. (c) qPCR analysis of Gck, Hnf4α and Hnf1α mRNA expression on INS-1E cells treated with either vehicle control (DMSO), 0.1, 0.2, or 0.4 µmol/l I-BET151 for 24 h, *n*=3. (d) Total insulin in INS-1E cells treated with either vehicle control (DMSO) or 1 µmol/l I-BET151 for 4 h and 24 h, *n*=4. (e) Total insulin in human islets treated with either DMSO (Vehicle control), 0.5 µM I-BET151 or 1 µmol/l I-BET151 for 24 h, *n*=3. (f) qPCR analysis

of MODY mRNA expression on INS-1E cells treated with either vehicle control (DMSO) or 0.5 µmol/l JQ1 for 24 h, *n*=3. (g) qPCR analysis of T2D GWAS genes including Tcf7l2, Grb14, Glis3, Xrcc4, Manf on INS-1E cells treated with either vehicle control (DMSO) or 0.5 µmol/l JQ1 for 24 h, *n*=3. (h) qPCR analysis of MODY mRNA expression on INS-1E cells treated with either vehicle control (DMSO) or 1 µmol/l I-BET762 for 24 h, *n*=3. (i) qPCR analysis of T2D GWAS genes including Tcf7l2, Grb14, Glis3, Xrcc4, Manf on INS-1E cells treated with either vehicle control (DMSO) or 1 µmol/l I-BET762 for 24 h, *n*=3. (j) GCK activity assay of INS-1E cells treated with either DMSO or 1 µM I-BET151 for 24 h, *n*=4. Data represents means ± SEM. f,g,h,i,j: For comparison of 2 groups, *p*-values were determined using unpaired t-test with Welch's correction; b,c,d,e: For comparison of >2 groups, *p*-values were calculated with One-way ANOVA test with post-hoc Dunnett's T3 test; a: For comparison of groups with 2 variables, *p*-values were calculated with Two-way ANOA test with post-hoc Sidak's test; **p*<0.05,***p*<0.01 and ****p*<0.001.



ESM Figure 5. (a) Representative image of FOXO1 immunostaining in INS-1E cells treated with either vehicle control (DMSO); or 1 μmol/l I-BET151 for 24 h; FOXO1 (green) and DAPI (blue), bottom panel: X-Z plane; Scale bar = 20 μm. (b) Mean Fluorescence intensity of FOXO1 within the nucleus in INS-1E cells treated with either vehicle control (DMSO) or 1 μmol/l I-BET151 for 24 h, *n*=5. (c) Mean Fluorescence intensity of FOXO1 within the whole cell in INS1E cells treated with either vehicle control (DMSO) or 1 μmol/l I-BET151 for 24 h, *n*=5. (d) Cut&Run qPCR for FOXO1 binding on *Ins2* promoter region (130 bp upstream of transcription start site) in INS-1E cells treated with DMSO or 1 μmol/l I-BET151 for 24 h, *n*=4. Data represents means ± SEM. b,c,d: For comparison of 2 groups, *p*-values were determined using unpaired t-test with Welch's correction; **p*<0.05, ***p*<0.01 and ****p*<0.001.

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	HP-23199-01	HP-23293-01	HP-23342-01	HP-24086-01				
Donor age (years)	63	44	34	32				
Donor sex (M/F)	Caucasian Male	Hispanic Female	White Male	White Male				
Donor BMI (kg/m^2)	21.3	24.1	24.6	23.67				
Donor HbA_{1c} or other measure of blood glucose control	5.5%	5.4%	5.4%	5.7%				
Origin/source of islets[b]	Prodolabs/ CA	Prodolabs/ CA	Prodolabs/ CA	Prodolabs/ CA				
Islet isolation centre	Prodo Laboratories Inc.	Prodo Laboratories Inc.	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)	NA	NA	NA	NA				
Glucose-lowering therapy at time of death[c]	NA	NA	NA	NA				
RECOMMENDED INFORMATION								
Donor cause of death	Cerebrovascular/Stroke	Cerebrovascular/Stroke	Anoxia	Anoxia				
Warm ischaemia time (h)	NIL	NIL	NIL	NIL				
Cold ischaemia time (h)	NIL	NIL	NIL	NIL				

Estimated purity (%)	95	90	95	90				
Estimated viability (%)	95	95	95	95				
Total culture time (h)[d]	168	168	168	168				
Glucose-stimulated insulin secretion or other functional measurement[e]	GSIS – 14-fold increase from 3 mM to 11 mM glucose	GSIS – 2.4-fold increase from 3 mM to 11 mM glucose	GSIS – 6.4-fold increase from 3 mM to 11 mM glucose	GSIS – 10.2-fold increase from 3 mM to 11 mM glucose				
Handpicked to purity? Please select yes/no from drop down list	Yes	Yes	Yes	Yes				
Additional notes	NIL	NIL	NIL	NIL				

[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