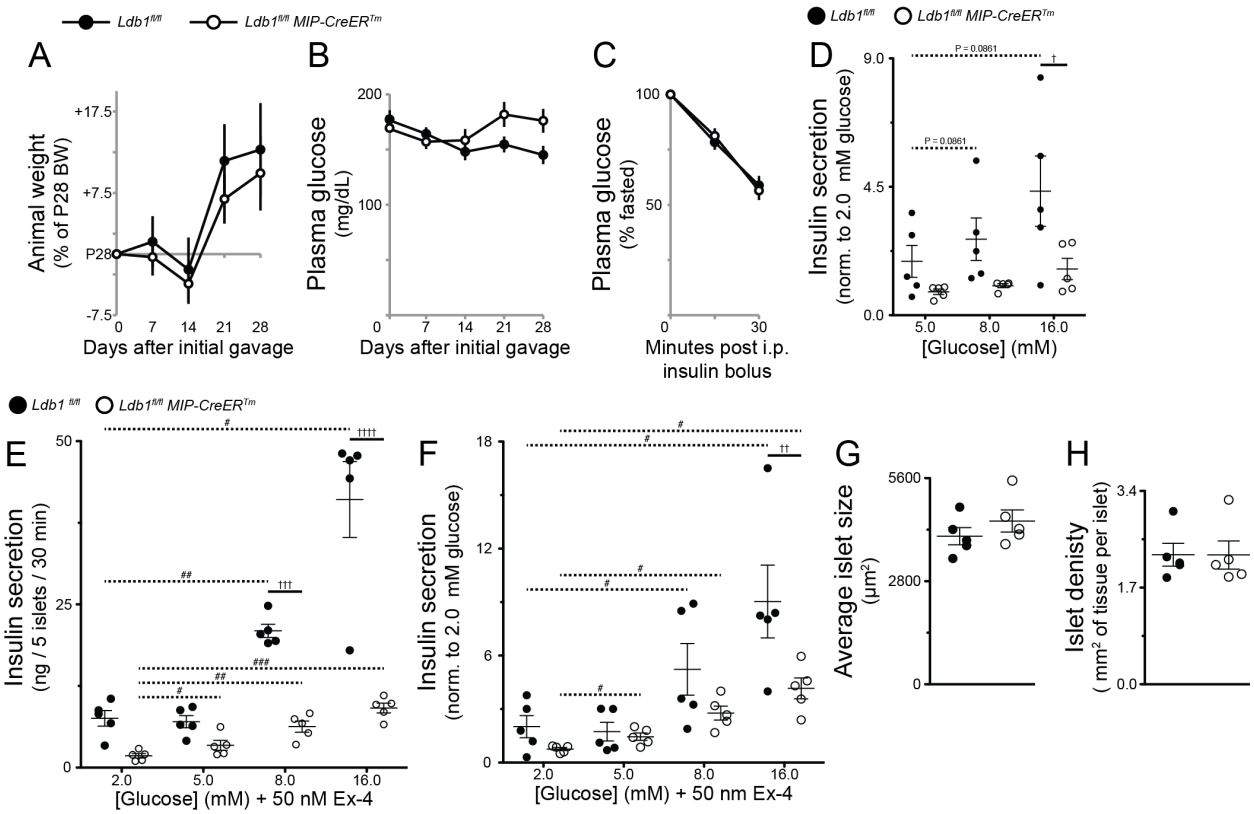
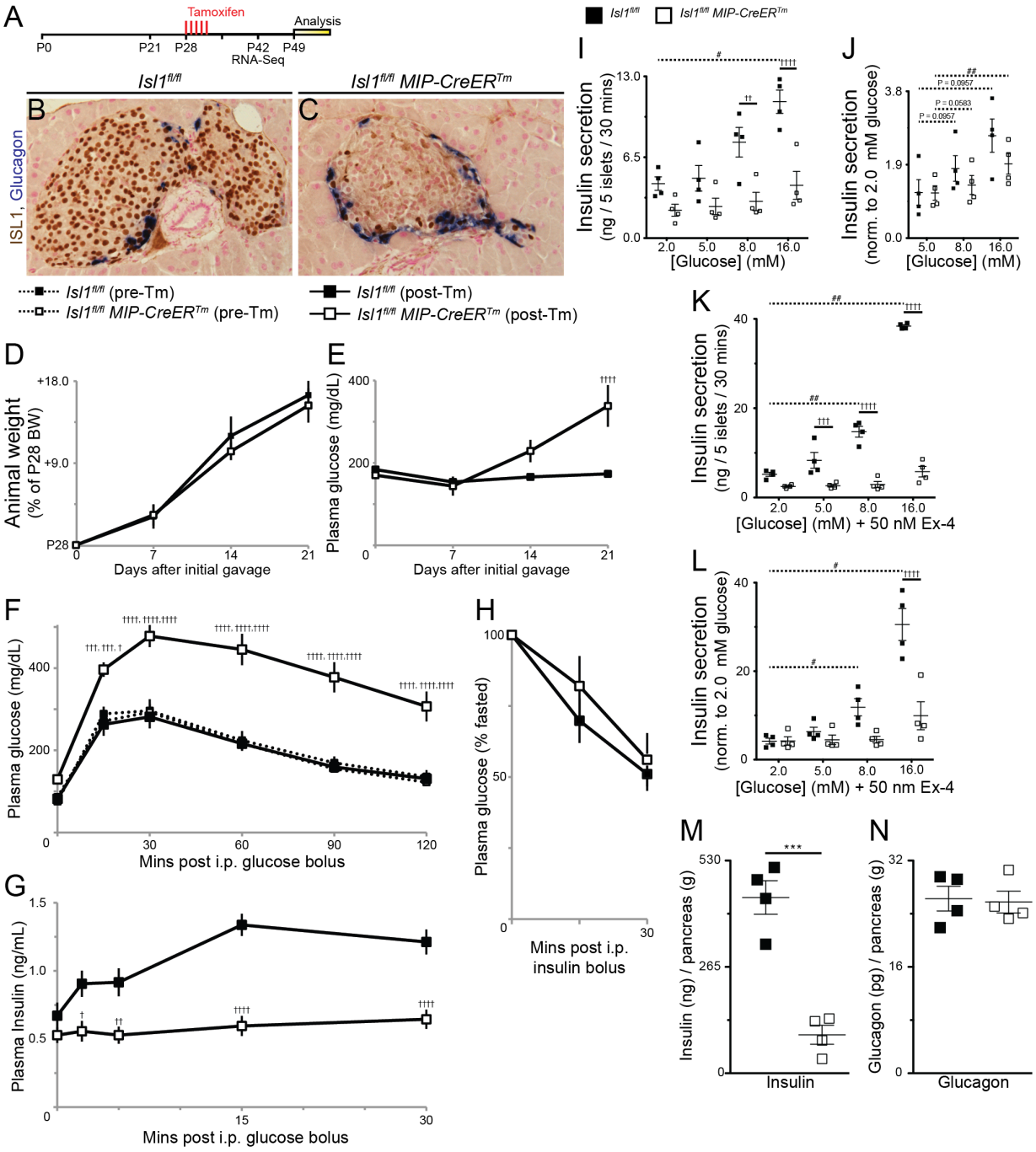
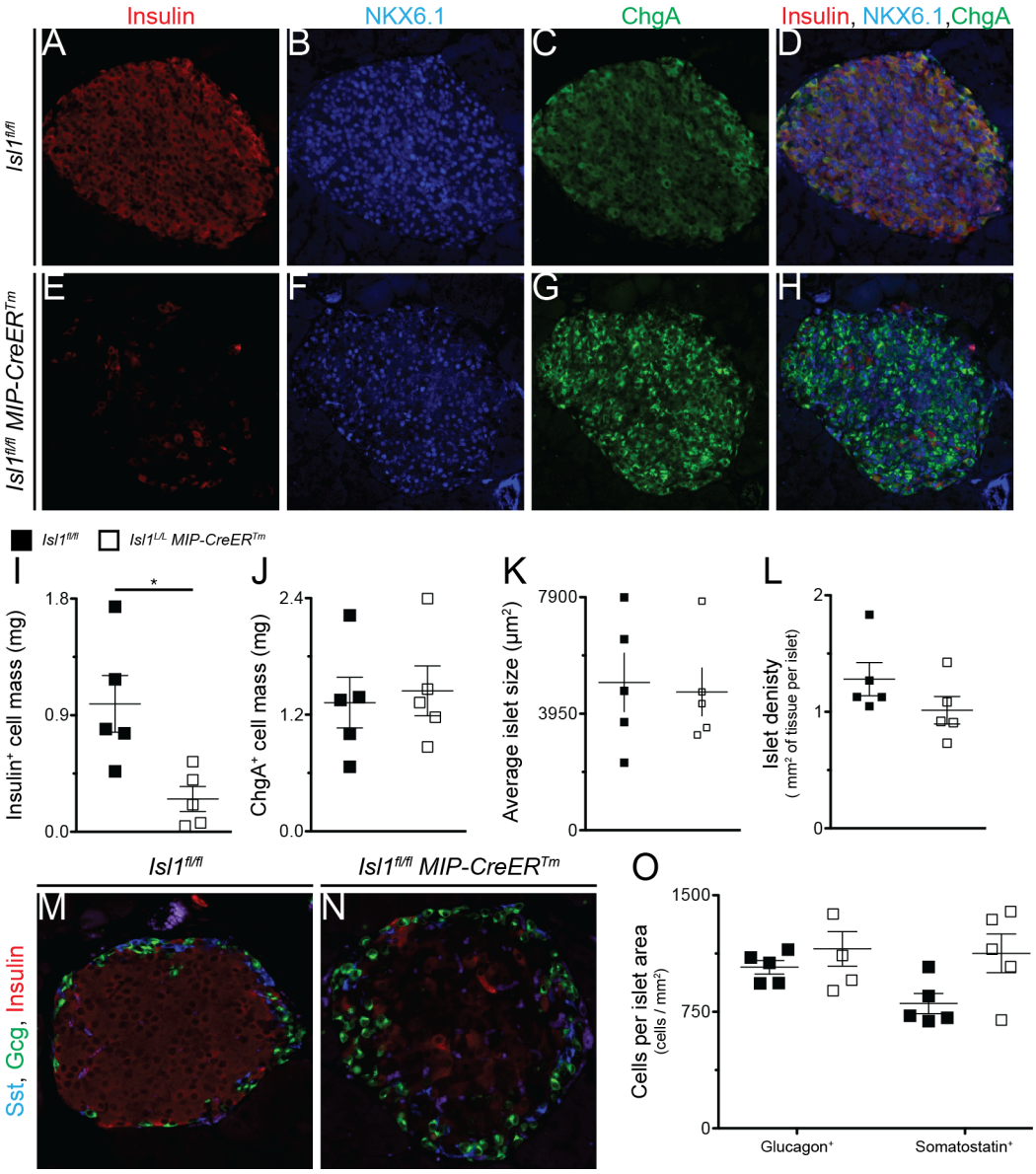


Supplemental Figure 1. Related to Figure 1. Blunted insulin secretion is the most prominent metabolic defect resulting from ablating β-cell *Ldb1*. A. Bodyweight, as a percentage of bodyweight at P28, tracked after initial Tm gavage at P28. B. Weekly random blood glucose tracked after initial Tm gavage at P28. A-B. $Ldb1^{fl/fl}$, n = 9; $Ldb1^{fl/fl}$ $MIP\text{-}CreER^{Tm}$, n = 11. C. P56 insulin tolerance test ($Ldb1^{fl/fl}$, n = 9; $Ldb1^{fl/fl}$ $MIP\text{-}CreER^{Tm}$, n = 10). D. Static glucose islet incubations: absolute insulin secretion normalized (norm.) to baseline secretion at 2.0mM glucose. E-F. Static glucose islet incubations + 50nM Ex-4: (E) absolute insulin secretion and (F) absolute insulin secretion norm. to baseline secretion at 2.0mM glucose. G. Quantified average islet size. H. Quantified pancreatic islet density. D-H. $Ldb1^{fl/fl}$, n = 5; $Ldb1^{fl/fl}$ $MIP\text{-}CreER^{Tm}$, n = 5. A-F. Repeated measures, two-way ANOVA with Bonferroni correction, † = P < 0.05 / †† = P < 0.01 / ††† = P < 0.001 / †††† = P < 0.0001. D-F. Repeated measures, one-way ANOVA with Holm-Šidák correction, $^{\#}$ = P < 0.05 / $^{\#\#}$ = P < 0.01 / $^{\#\#\#}$ = P < 0.001. (**E-F**) Only the post-hoc comparisons to the respective 2.0 mM glucose treatments were analyzed. G-H. Student's two-way t-test. Absent statistical annotation in A-H indicates comparisons that were not significant. Pooled data represent mean ± SEM.

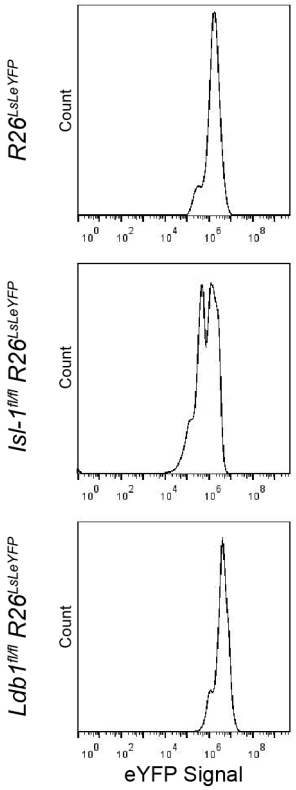


Supplemental Figure 2. Related to Figure 1. Ablating *Isl1* in the mature β-cell phenocopies *Ldb1* ablation. A. Tamoxifen administration schedule for the *Isl1*$^{fl/fl}$ and *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm} mice. Red hashes indicate tamoxifen gavages; the yellow box indicates experimental analysis window. B-C. Immunohistochemistry for ISL1 and glucagon from ~P49 pancreata. D. Bodyweight, as a percentage of bodyweight at P28, tracked after initial tamoxifen gavage. E. Weekly random blood glucose tracked after initial Tm gavage. F. IPGTTs performed at P28 prior to tamoxifen administration (pre-Tm) (*Isl1*$^{fl/fl}$, n = 6; *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm}, n = 8) and P49 following completion of tamoxifen pulse-chase (post-Tm) (*Isl1*$^{fl/fl}$, n = 7; *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm}, n = 7). Statistical annotation reflects the post-hoc comparisons at each time point in following order: post-Tm *Isl1*$^{L/L}$ *MIP-CreER*^{Tm} mice compared to 1) post-Tm

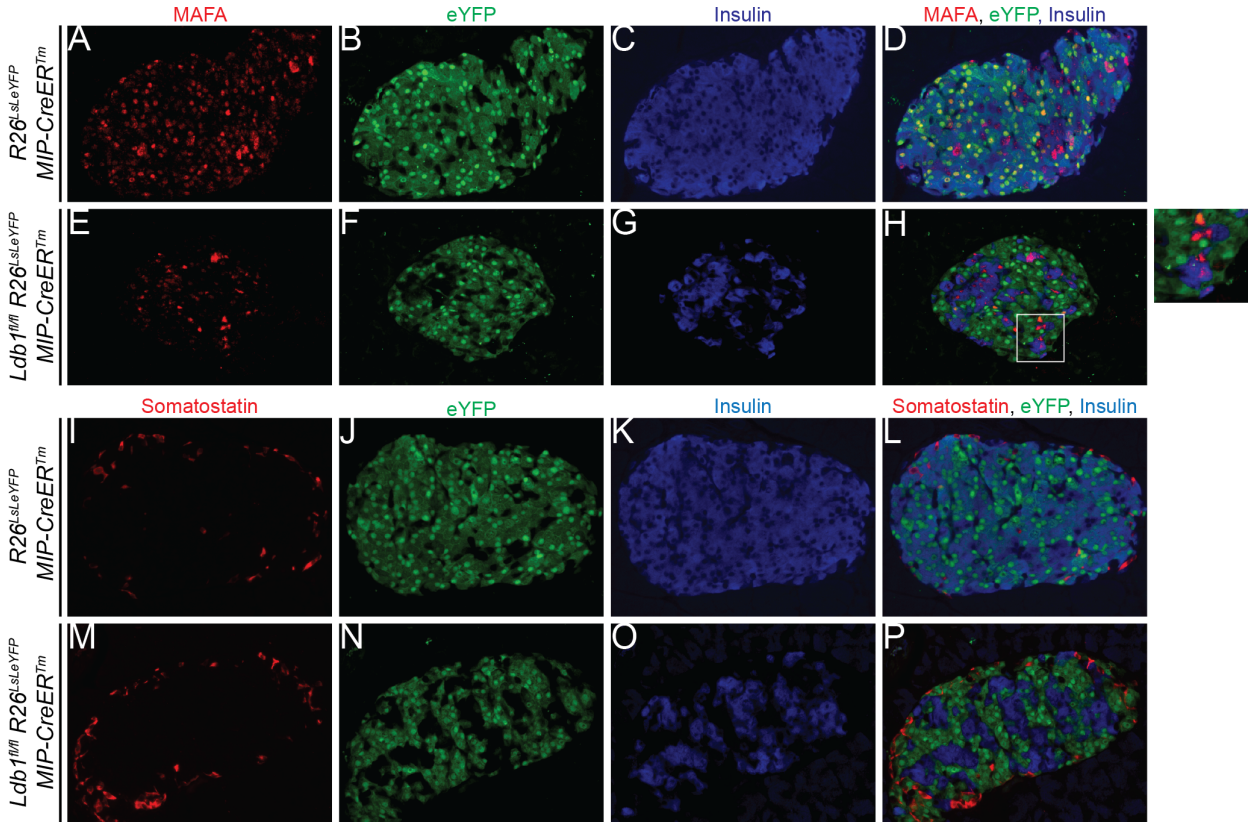
Isl1$^{fl/fl}$, 2) pre-Tm *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm} and 3) pre-Tm *Isl1*$^{fl/fl}$ mice. G. P49 GSIS assay. H. P49 insulin tolerance test (*Isl1*$^{fl/fl}$, n = 5; *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm}, n = 5). I-J. P49 static glucose islet incubations: (I) absolute insulin secretion and (J) absolute insulin secretion normalized (norm.) to baseline secretion at 2.0mM glucose. K-L. P49 static glucose islet incubations + 50nM Ex-4: (K) absolute insulin secretion and (L) absolute insulin secretion norm. to baseline secretion at 2.0mM glucose. M. Total pancreatic insulin content. N. Total pancreatic glucagon content. B-C and I-N. *Isl1*$^{fl/fl}$, n = 4; *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm}, n = 4. D-E and G. *Isl1*$^{fl/fl}$, n = 7; *Isl1*$^{fl/fl}$ *MIP-CreER*^{Tm}, n = 7. Repeated measures, two-way ANOVA with (F) Holm-Šidák or (D-E and G-L) Bonferroni correction, † = P < 0.05 / ††† = P < 0.001 / †††† = P < 0.0001. I-L. Repeated measures, one-way ANOVA with Holm-Šidák correction, $^{\#}$ = P < 0.05 / $^{\#\#}$ = P < 0.01. Only the post-hoc comparisons to the respective 2.0 mM glucose treatments were analyzed. M-N. Student's two-way t-test, *** = p < 0.001. Absent statistical annotation in D-L, and N indicates comparisons that were not significant. All images taken at 20x zoom. Pooled data represent mean ± SEM.



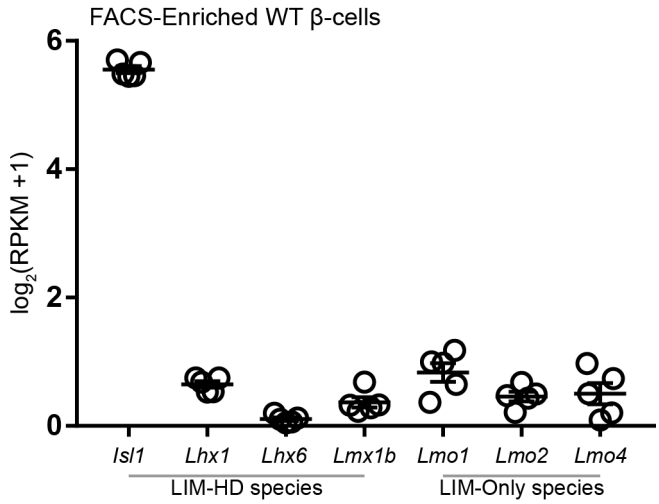
Supplemental Figure 3. Related to Figure 2. Loss of insulin after *Isl1* ablation. A-H. Co-immunofluorescence for insulin, Nkx6.1, and chromogranin A at P49. I. Quantified insulin$^+$ cell mass. J. Quantified chromogranin A$^+$ cell mass. K. Quantified average islet size. L. Quantified pancreatic islet density. M-N. Co-immunofluorescence for insulin, somatostatin, and glucagon at P49. O. Frequency of glucagon$^+$ and somatostatin$^+$ cells within chromogranin A$^+$ cells mass. A-O. *Isl1$^{fl/fl}$*, n = 5; *Isl1$^{fl/fl}$ MIP-CreER^{Tm}*, n = 5. I-L Student's two-way t-test, * = $p < 0.05$. O. Repeated measures, two-way ANOVA with Bonferroni correction. Absent statistical annotation in I-L, and O indicates comparisons that were not significant. All images taken at 20x zoom. Pooled data represent mean ± SEM.



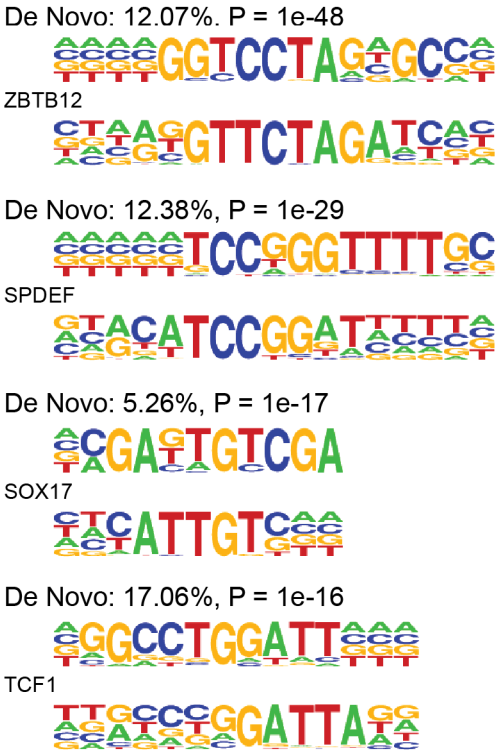
Supplemental Figure 4. Related to Figure 3. An eYFP^{+} population is absent in littermates lacking Cre recombinase. Representative FACS profiles for eYFP signal from littermates lacking Cre recombinase (n=2).



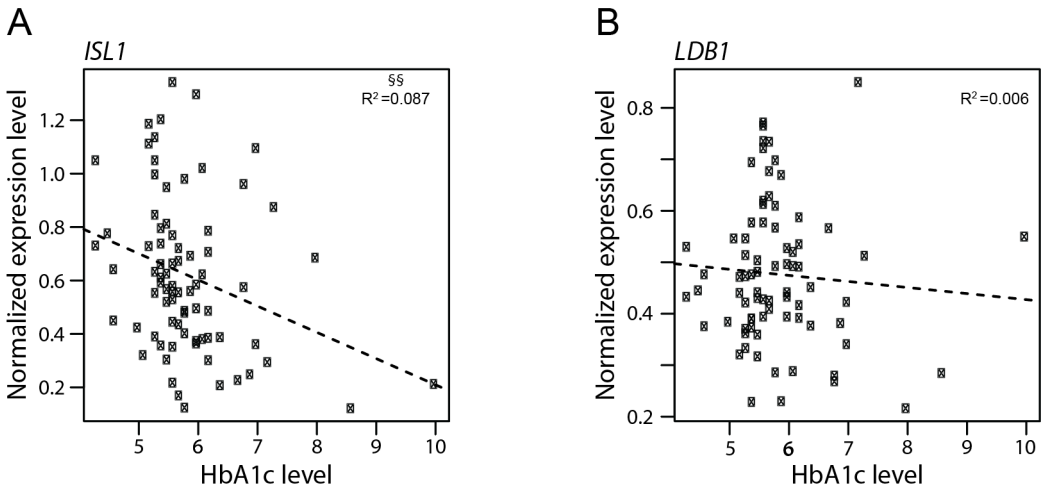
Supplemental Figure 5. Related to Figure 4. LDB1-depleted β-cells lose MAFA and do not express somatostatin. A-H. Co-immunofluorescence for MAFA, insulin, and eYFP at P56. I-P. Co-immunofluorescence for somatostatin, insulin, and eYFP at P56. A-P. *Ldb1*$^{fl/fl}$, n = 5; *Ldb1*$^{fl/fl}$ *MIP-CreER*^{Tm}, n = 5. All images taken at 20x zoom and insets at 40x zoom.



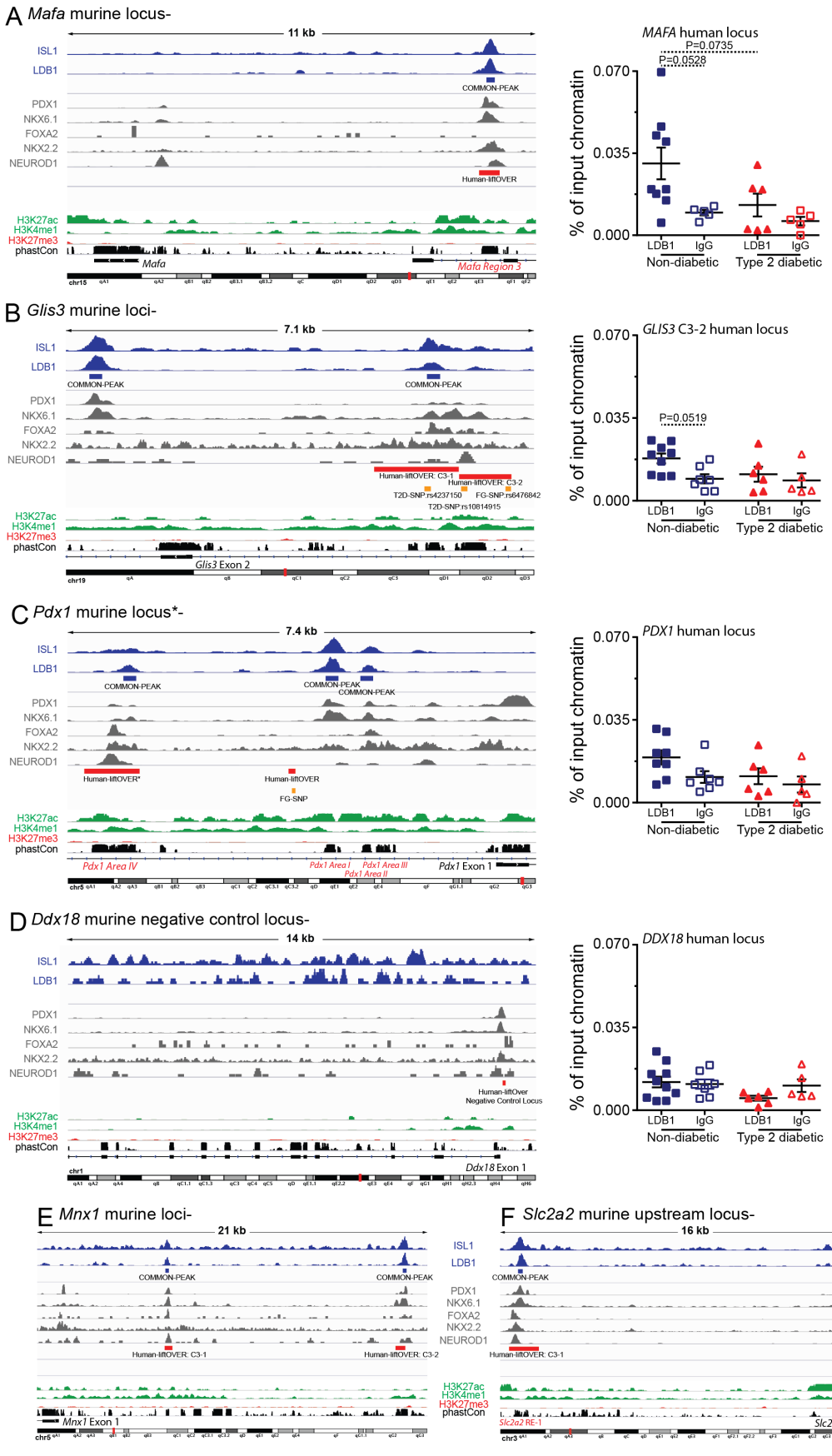
Supplemental Figure 6. Related to Figure 5. *Isl1* is the predominantly enriched transcript encoding a nuclear tandem LIM-domain factor in mature β-cells. Expression profile of nuclear LIM-HD and LMO factors detectable in FACS-enriched WT β-cells (n=5). RPKM = Reads per million normalized to sum of gene exon widths and total read depth.



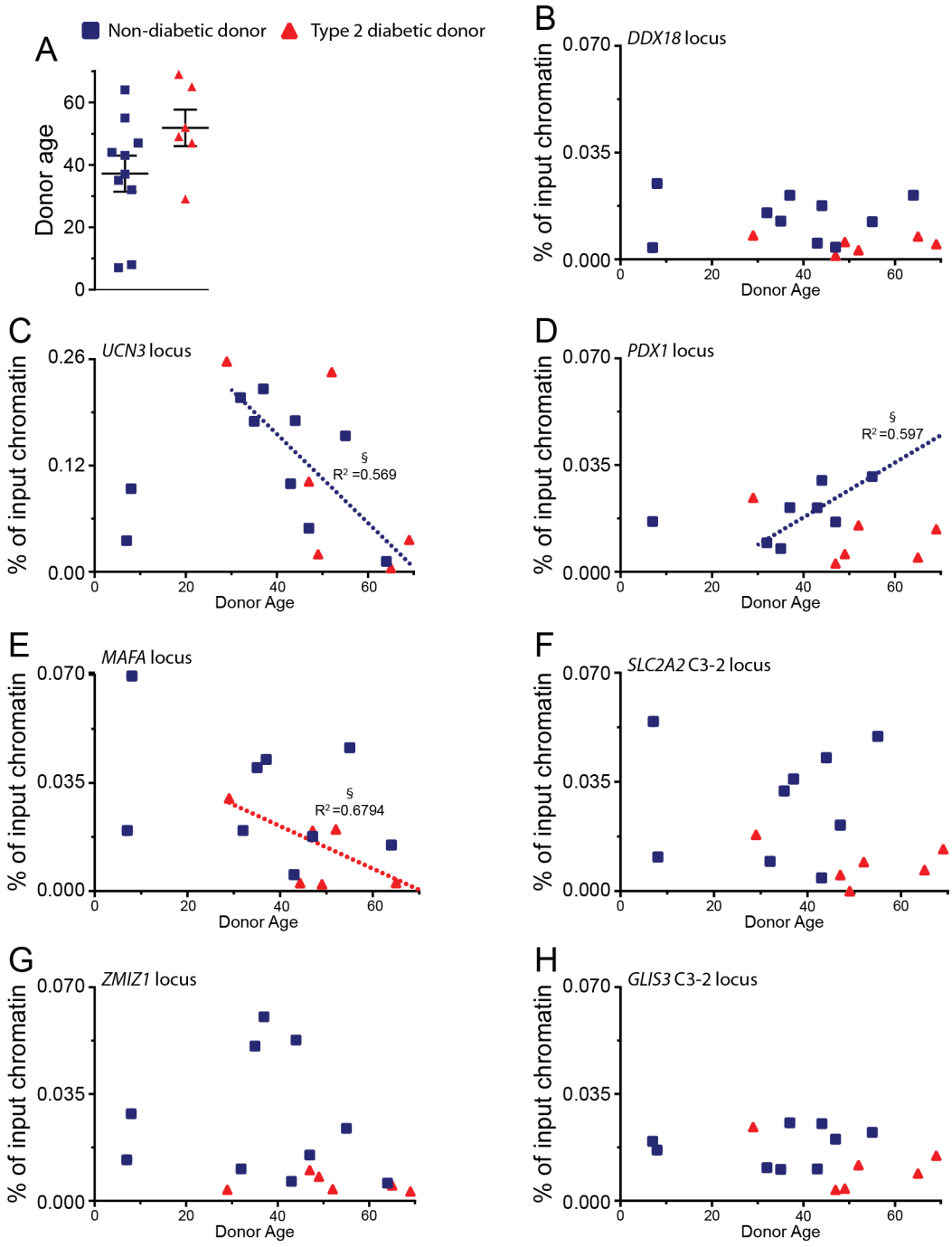
Supplemental Figure 7. Related to Figure 5. ISL1-alone peak set is not strongly enriched for de novo motifs. De Novo motif analysis of the H3K4me3-enriched, ISL1-alone peak set. The de novo motif is presented with the percent of the H3K4me3-enriched, ISL1-alone peaks containing it and the P-value. Below the respective de novo motifs are the matched consensus sequence.



Supplemental Figure 8. Related to Figure 6. *ISL1* expression in human islets decreases with increasing HbA1c levels. Reanalysis of a published 77-donor, whole islet RNA-Seq data set (1). A. *ISL1* expression plotted against donor HbA1c levels. B. *LDB1* expression plotted against donor HbA1c levels. A-B. Pearson product-moment correlation coefficient, §§ = $P < 0.01$. Dotted lines represent linear regression. Absent statistical annotation in B indicates comparisons that were not significant.


A Mafa murine locus-
11 kb
ISL1
LDB1
COMMON-PEAK
PDX1
NKX6.1
FOXA2
NKX2.2
NEUROD1
Human-liftOVER
H3K27ac
H3K4me1
H3K27me3
phastCon
Mafa
Mafa Region 3
MAFA human locus
P=0.0735
P=0.0528
% of input chromatin
0.070
0.035
0.000
LDB1
IgG
LDB1
IgG
Non-diabetic
Type 2 diabetic
B Glis3 murine loci-
7.1 kb
COMMON-PEAK
COMMON-PEAK
Human-liftOVER: C3-1
Human-liftOVER: C3-2
T2D-SNP:rs4237150
FG-SNP:rs6476842
T2D-SNP:rs10814915
Glis3 Exon 2
GLIS3 C3-2 human locus
P=0.0519
C Pdx1 murine locus*-
7.4 kb
COMMON-PEAK
COMMON-PEAK
COMMON-PEAK
Human-liftOVER*
Human-liftOVER
FG-SNP
Pdx1 Area IV
Pdx1 Area I
Pdx1 Area III
Pdx1 Area II
Pdx1 Exon 1
PDX1 human locus
D Ddx18 murine negative control locus-
14 kb
Human-liftOver
Negative Control Locus
Ddx18 Exon 1
DDX18 human locus
E Mnx1 murine loci-
21 kb
COMMON-PEAK
COMMON-PEAK
Human-liftOVER: C3-1
Human-liftOVER: C3-2
Mnx1 Exon 1
F Slc2a2 murine upstream locus-
16 kb
COMMON-PEAK
Human-liftOVER: C3-1
FG-SNP
Slc2a2 RE-1
Slc2a2 Exon 1

Supplemental Figure 9. Related to Figure 6. Selected LDB1, ISL1 common peaks corresponding to conserved human islet enhancer regions. A. Murine *Mafa* locus and ChIP-qPCR at human *MAFA* locus. B. Murine *Glis3* locus and ChIP-qPCR at human *GLIS3* C3-2 locus. C. Murine *Pdx1* locus and ChIP-qPCR at human *PDX1* locus. * indicates analyzed human enhancer. D. Murine *Ddx18* locus and ChIP-qPCR at human *DDX18* negative control locus. E. Murine *Mnx1* locus. F. Murine *Slc2a2* upstream locus. I-F. IGV windows of murine loci. LDB1 and ISL1 ChIP-seqs labeled in blue. LDB1, ISL1 common peaks are indicated by blue line segments. PDX1, NKX6.1, FOXA2, NKX2.2, and NEUROD1 ChIP-seqs are labeled in gray. Human islet regulome active enhancers: human liftOvers (indicated by red line segments); human SNP liftOvers (indicated by orange line segments). FG, fasting glycemia associated and T2D, type 2 diabetes associated. H3K27ac and H3K4me1 ChIP-seqs are labeled in green; H3K27me3 ChIP-seq is labeled in red; PhastCon (evolutionary conservation) is labeled in black. Published *cis*-elements are indicated in red text. A-D. Nondiabetic donor ChIPs are indicated by blue and white squares: LDB1 IP = blue squares (n = 10); normal goat IgG IP = white squares (n = 8). Type 2 diabetic donor ChIPs are indicated by red and white triangles: LDB1 IP = red triangles (n = 6); normal goat IgG IP = white triangles (n = 5). Pooled data represent the mean ± SEM. A-D. One-way ANOVA with Holm-Sidak correction for the following post-hoc comparisons: nondiabetic LDB1 versus nondiabetic normal goat IgG; nondiabetic LDB1 versus type 2 diabetic LDB1; type 2 diabetic LDB1 versus type 2 diabetic normal goat IgG; and nondiabetic normal goat IgG versus type 2 diabetic normal goat IgG. Absent statistical annotation in A-D indicates comparisons that were not significant. chr, chromosome. Also see Supplementary Tables 1, 3, and 4.



Supplemental Figure 10. Related to Figure 6. LDB1 enrichment at some human active enhancers correlates with age. A. Comparison of age distribution with the non-diabetic and type 2 diabetic human donor populations. B-H. LDB1 ChIP-qPCR plotted against donor age. Non-diabetic donor ChIPs: blue squares; type 2 diabetic donor ChIPs: red triangles. B. *DDX18* negative control locus. C. *UCN3* locus. D. *PDX1* locus. E. *MAFA* locus. F. *SLC2A2* C3-2 locus. G. *ZMIZ1* locus. H. *GLIS3* C3-2 locus. A-H Non-diabetics donors (n=10) and type 2 diabetic donors (n=6). A. Student's two-way t-test. B-H. Pearson product-moment correlation coefficient, § = $P < 0.05$. Child donors excluded from this analysis. C-E. Dotted lines represent linear regression of adult donor values of matching color. Pooled data represent mean ± SEM. Absent statistical annotation in A-H indicates comparisons that were not significant.

Supplemental Table 1. Related to Figure 6. Characteristics of selected human islet active enhancers analyzed for LDB1 occupancy.

C3 Element Location[A]	Gene[B]	Enumeration[C]	C3 Element "liftOver"[D]	LDB1, ISL1 Common Peak[E]	Fasting Glycemia Level-Associated SNP[F]	Type 2 Diabetes-Associated SNP[G]
8:143439203-143439699	*MAFA*	NA	15:755864473-75586962	15:75586642-75586841	NA	NA
7:157016342-157016727	*MNX1*	C3-1	5:29810809-29811213	5:29810851-29811050	NA	NA
7:157027817-157028360	*MNX1*	C3-2	5:29823480-29824014	5:29823886-29824085	NA	NA
13:27911256-27912333	*PDX1*	NA	5:148075216-148076087	5:148075827-148076026	NA	NA
3:171044539-171045825	*SLC2A2*	C3-1	3:28580712-28582005	3:28581098-28581297	NA	NA
3:170976866-170978735	*SLC2A2*	C3-2	3:28635895-28637759	3:28636082-28636281	rs1905506, rs1905504, rs7635100, rs7635470	NA
10:5356620-5357372	*UCN3*	NA	13:3994969-3998803	13:3998398-3998597	NA	NA
9:4289440-4290458	*GLIS3*	C3-1	19:28743504-28744788	19:28744310-28744509	NA	rs4237150
9:4290466-4291326	*GLIS3*	C3-2	19:28744802-28745595	NA	rs6476842	rs10814915
10:79184111-79184667	*ZMIZ1*	NA	14:26374197-26374673	14:26374451-26374650	NA	rs703977
2:117813934-117814033	*DDX18*	NA	Deleted	Negative Control Locus		

[A] Human islet active enhancer (C3 element) locus from Human Islet Regulome Browser: GRch38/hg38 (chrN:start-end) (2). [B] Gene proximal to active enhancer that also corresponds to misexpressed murine gene in transcriptomic analysis. [C] Enumeration of multiple enhancers in one locus. [D] Location of human islet active enhancer liftOver in mouse genome: NCBI37/mm9 (chrN:start-end). Human islet active enhancers were mapped to the mouse genome using the UCSC Batch Coordinate Conversion Tool (liftOver) at a 0.1 minimum ratio for bases remapping (3). [E] Location of LDB1, ISL1 common peak overlapping human islet active enhancer liftOver: NCBI37/mm9 (chrN:start-end). [F] Fasting glycemia level-associated SNPs within human islet active enhancer that liftOver to mouse. [G] Type 2 diabetes-associated SNPs within human islet active enhancer that liftOver to mouse. NA = Not Applicable

Supplemental Table 2. Related to Figure 6. Immunofluorescence human donor information.

Donor ID	Source	Sex	Age	BMI[A]	HbA1c (%)[B]	Cause of Death	T2D[C] History
T2D #78	IIDP[D]	M	59	21.2	9.4	Stroke	14 years
Non T2D #94	IIDP[D]	M	59	25.4	NA	Anoxia	NA
T2D #58	IIDP[D]	F	51	34	5.2	Stroke	15 years
Non T2d #54	IIDP[D]	F	51	21.1	5.2	Stroke	NA

[A] Donor's body mass index (BMI). [B] Donor's hemoglobin A1c (HbA1c). [C] Type 2 diabetes (T2D). [D] Integrated Islet Distribution Program (IIDP). Not applicable (NA)

Supplemental Table 3. Related to Figure 6. LDB1 ChIP non-diabetic human islet donor information.

Donor ID	Source	Sex	Race	Age	BMI[A]	HbA1c (%)[B]	Cause of Death	Islet Viability	GSIR[C]
ICRH043	UPenn[D]	M	White	7	20.6	U	Anoxia	97%	2.02
ICRH059	UPenn[D]	M	White	8	13.6	U	Head Trauma	95%	NM
ICRH073	UPenn[D]	M	White	37	27.7	5.50	Anoxia	94%	2.7
ICRH074	UPenn[D]	F	Black	44	23.8	U	Stroke	95%	1.6
ICRH090	UPenn[D]	M	Asian	35	28.5	5.30	Head Trauma	95%	3.1
ABDP112	IIDP[E]	M	Hispanic	43	22.8	5.70	Stroke	95%	1.0
ABDV142	IIDP[E]	M	White	32	23.1	U	Anoxia	95%	1.6
ABEL098	IIDP[E]	F	Black	47	26.5	5.60	Stroke	95%	2.3
AAABA479	IIDP[E]	M	White	55	28.4	U	Stroke	96%	5.5
AAAL088	IIDP[E]	M	White	64	25.4	U	U	90%	3.5

[A] Donor's body mass index (BMI). [B] Donor's hemoglobin A1c (HbA1c). [C] Glucose-stimulated insulin release (GSIR). [D] University of Pennsylvania Center for Islet transplantation (UPenn). [E] Integrated Islet Distribution Program (IIDP). U = Unknown.

Supplemental Table 4. Related to Figure 6. LDB1 ChIP type 2 diabetic human donor information.

Donor ID	Source	Sex	Race	Age	BMI[A]	HbA1c (%)[B]	Cause of Death	Islet Viability	GSIR[C]	T2D[D] History	T2D[D] Medication
ICRH017	UPenn[E]	M	White	47	28.7	7.4	Stroke	96%	U	2 years	Metformin
AAFH472	IIDP[F]	F	White	69	35	U	Stroke	92%	3.6	>10 years	U
AAFS251	IIDP[F]	M	Asian	49	23.9	6.3	Stroke	95%	10.2	20 years	"pills"[H]
ZKC263	IIDP[F]	F	White	65	28.85	U	U	90%	U	1 year	Metformin
HP13346	Prodo[G]	F	White	29	38.7	9.9	Stroke	95%	U	2 years	Metformin, Glucovance
HP14009	Prodo[G]	F	White	52	32.5	8.2	Anoxia	95%	U	U	Metformin

[A] Donor's body mass index (BMI). [B] Donor's hemoglobin A1c (HbA1c. [C] Glucose-stimulated insulin release (GSIR). [D] Type 2 diabetes (T2D). [E] University of Pennsylvania Center for Islet transplantation (UPenn). [F] Integrated Islet Distribution Program (IIDP). [G] Prodo Laboratories, Inc. (Prodo). [H] Family testament. U = Unknown.

Supplemental Table 5. Immunofluorescence/ Immunohistochemistry antisera.

Antigen	Source	Antibody	Species	Clonality	Concentration	Amplification
LDB1	Dr. Paul Love	NA	Rabbit	-	1 to 2500	TSA
LDB1	Santa Cruz	sc-11198 X	Goat	Poly	1:1000	None
NKX6.1	DSHB[A]	F55A12	Mouse (MIgG1)	Mono	1 to 3000	TSA
Insulin	Abcam	ab7842	Guinea Pig	Poly	1 to 100	None
Insulin	Dako	104840	Guinea Pig	Poly	1 to 1000	None
Somatostatin	Santa Cruz	sc-7819	Goat	Poly	1 to 250	None
Glucagon	Santa Cruz	sc-13091	Rabbit	Poly	1 to 500	None
GFP	Abcam	ab6673	Goat	Poly	1 to 250	None
GFP	Abcam	ab13970	Chicken	Poly	1 to 250	None
Chromogranin A	Abcam	ab85554	Rabbit	Poly	1 to 500	None
GLUT2	Millipore	07-1402	Rabbit	Poly	1 to 500	None
PDX1	Dr. Chris Wright	NA	Goat	-	1 to 5000	None
NEUROG3	Dr. Maike Sander	NA	Guinea Pig	-	1 to 1000	None
ISL1	DSHB[A]	39.4D5	Mouse (MIgG2b)	Mono	3µg/ml	HRP-ABC
ISL1	DSHB[A]	40.2D6	Mouse (MIgG1)	Mono	3µg/ml	HRP-ABC
MAFA	Bethyl	A300-611A	Rabbit	Poly	1 to 1000	TSA

[A] Developmental Studies Hybridoma Bank (DSHB). NA = Not Applicable.

Supplemental Table 6. IP and Western blotting antisera.

Antigen	Source	Antibody	Species	Clonality	Concentration	Use
LDB1	Santa Cruz	sc-11198 X	Goat	Poly	NA	IP[B]
NA	Santa Cruz	sc-2028	Goat	NA	NA	IP[B]
LDB1	Dr. Paul Love	-	Rabbit	-	1 to 2500	1°[C]
ISL1	DSHB[A]	39.4D5	Mouse (MIgG2b)	Mono	1µg/ml	1°[C]
PDX1	Dr. Chris Wright	-	Mouse (MIgG2b)	-	1 to 10000	1°[C]
NKX6.1	DSHB[A]	F55A12	Mouse (MIgG1)	Mono	0.5µg/ml	1°[C]
FOXA2	Abcam	ab60721	Mouse	Poly	1 to 500	1°[C]
Mouse IgG	Santa Cruz	sc-2005	Goat	Poly	1 to 3000	2°[D]
Rabbit IgG	Santa Cruz	sc-2004	Goat	Poly	1 to 3000	2°[D]
Guinea Pig IgG	Santa Cruz	sc-2438	Goat	Poly	1 to 3000	2°[D]

[A] Developmental Studies Hybridoma Bank (DSHB). [B] Immunoprecipitation (IP). [C] Western blot primary (1°). [D] Western blot secondary (2°). NA = Not Applicable.

Supplemental Table 7. ChIP-qPCR primers for selected human islet active enhancers analyzed for LDB1 occupancy.

C3 Element Location[A]	Gene[B]	Enumeration[C]	Forward-Primer (5' to 3')	Reverse-Primer (5' to 3')
8:143439203-143439699	*MAFA*	-	ACAGAAAGGGTCGTTTGCAG	CATTTGGGGCTTGGTAAATG
7:157016342-157016727	*MNX1*	C3-1	TAGCGCATTCTGACTCGAAA	AGTGCAGACTTCCTGCCATT
7:157027817-157028360	*MNX1*	C3-2	ATGCAAACGCTGACACAGAA	TGAGAGTATCTGCGCTGTGC
13:27911256-27912333	*PDX1*	-	GGGAGTTTGTCAGACCAGGA	GGCAGCGAGAAAACACTAGG
3:171044539-171045825	*SLC2A2*	C3-1	AGGCATTCTGGCTCTTTTCA	TCTGCTCCAACAGAGGAGGT
3:170976866-170978735	*SLC2A2*	C3-2	CTGGGATTTTGCTTGCTGAT	ACCGACATGTGGGGTACTGT
10:5356620-5357372	*UCN3*	-	ACAGCAGCTGAACAAAGCAA	GGCCTATTAGCCATGCTCAC
9:4289440-4290458	*GLIS3*	C3-1	GACAGGATTCCATCGGAAGA	TCGATGGAGAACAGAGGAGAA
9:4290466-4291326	*GLIS3*	C3-2	CCCATGGGCTTCTCTTGTTA	CAGCCGTGCATGAGAATAACT
10:79184111-79184667	*ZMIZ1*	-	GGATAAGTGCCCTGCAAATG	CAGTCCATGGATCAGGTGTG
Negative Control Locus[D]				
2:117813934-117814033	*DDX18*	-	TGGAATGAATGGAATTGAAGG	GGCCACTCTCCTCAGAAATACA

[A] Human islet active enhancer (C3 element) locus: GRch38/hg38 (chrN:start-end). [B] Gene proximal to active enhancer that also corresponds to misexpressed murine gene in transcriptomic analysis. [C] Enumeration of multiple enhancers in one locus. [D] Information for Negative Control Locus primer set.

Supplemental References

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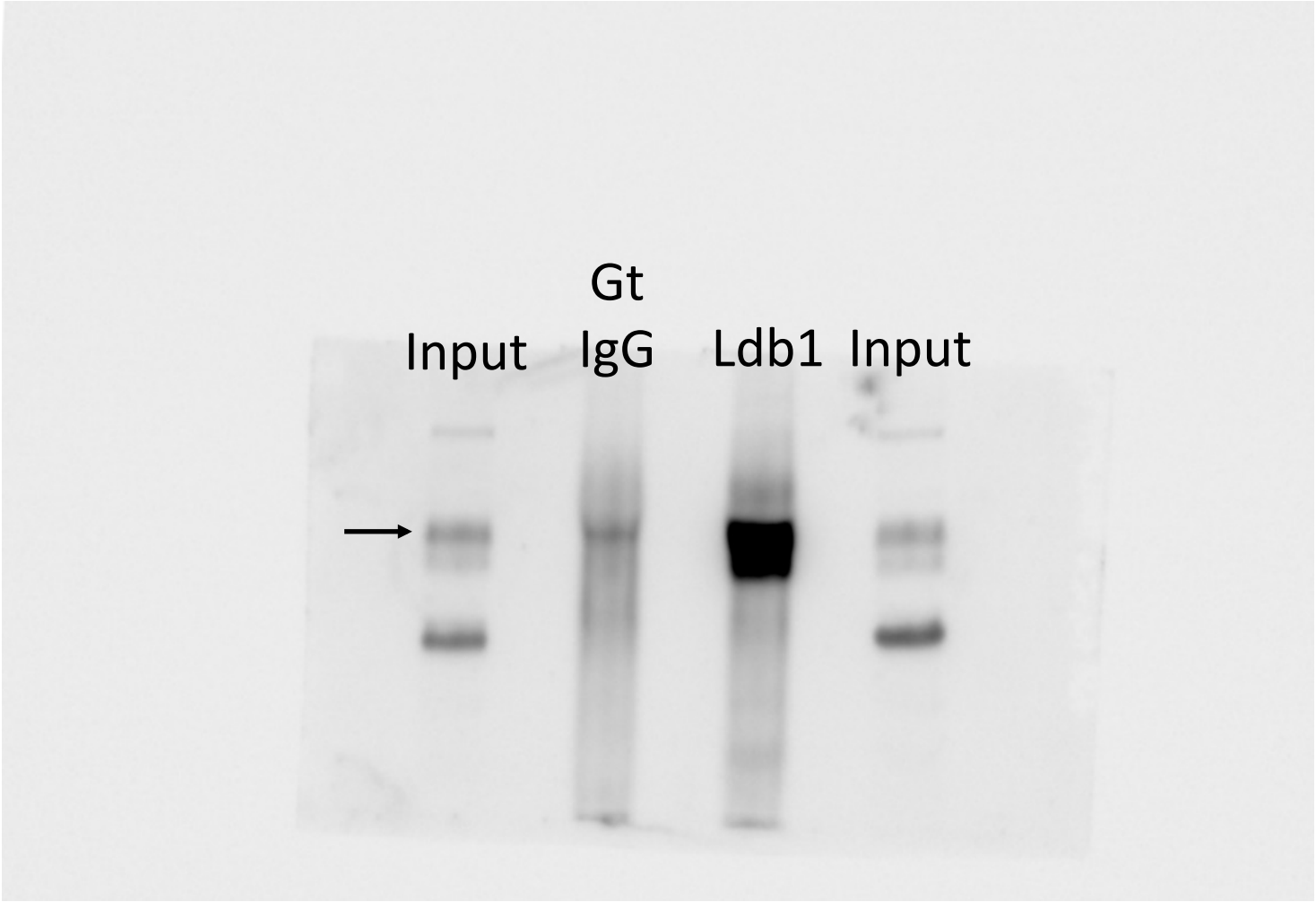
dited gel for Figure 5
DB1



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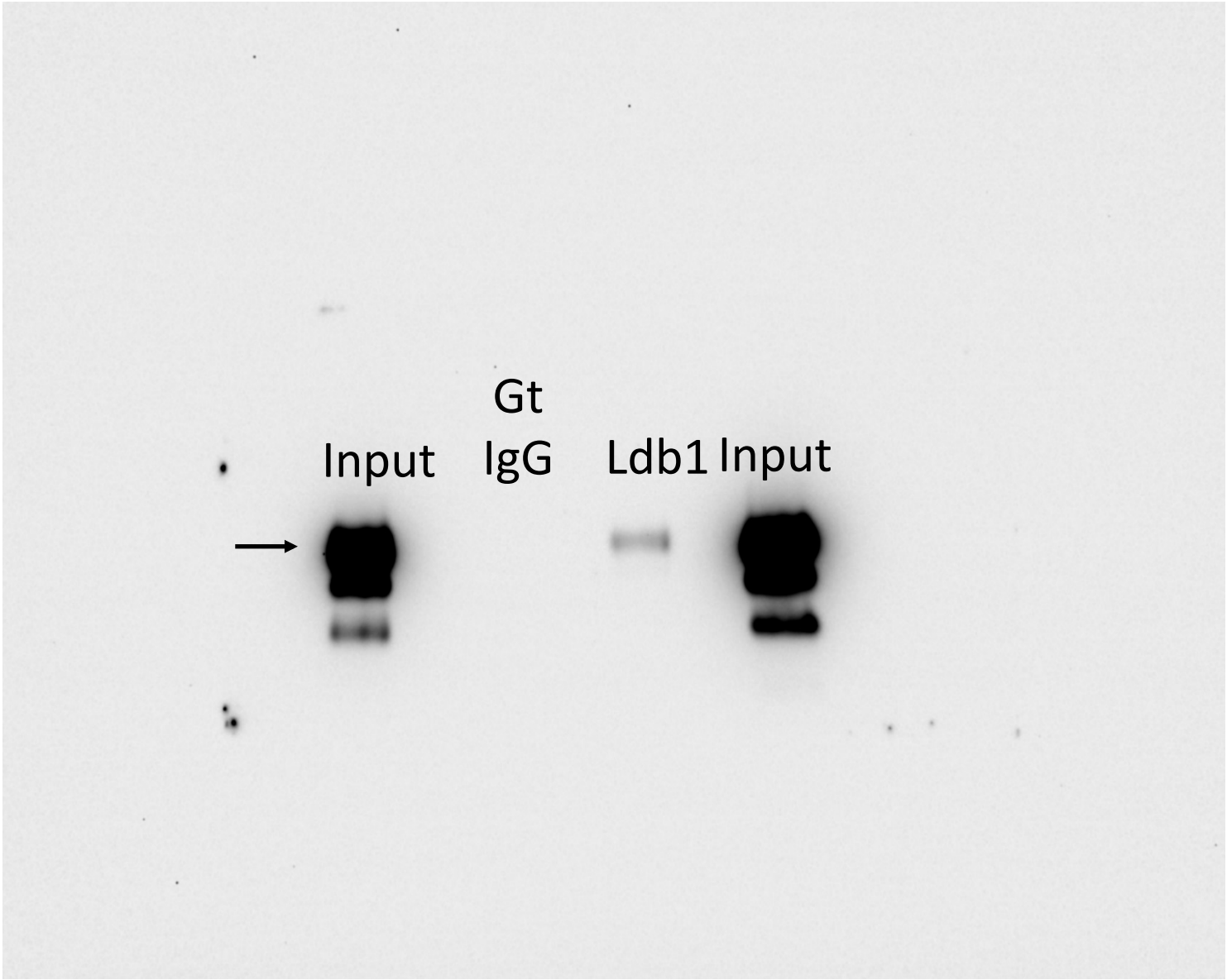
L1



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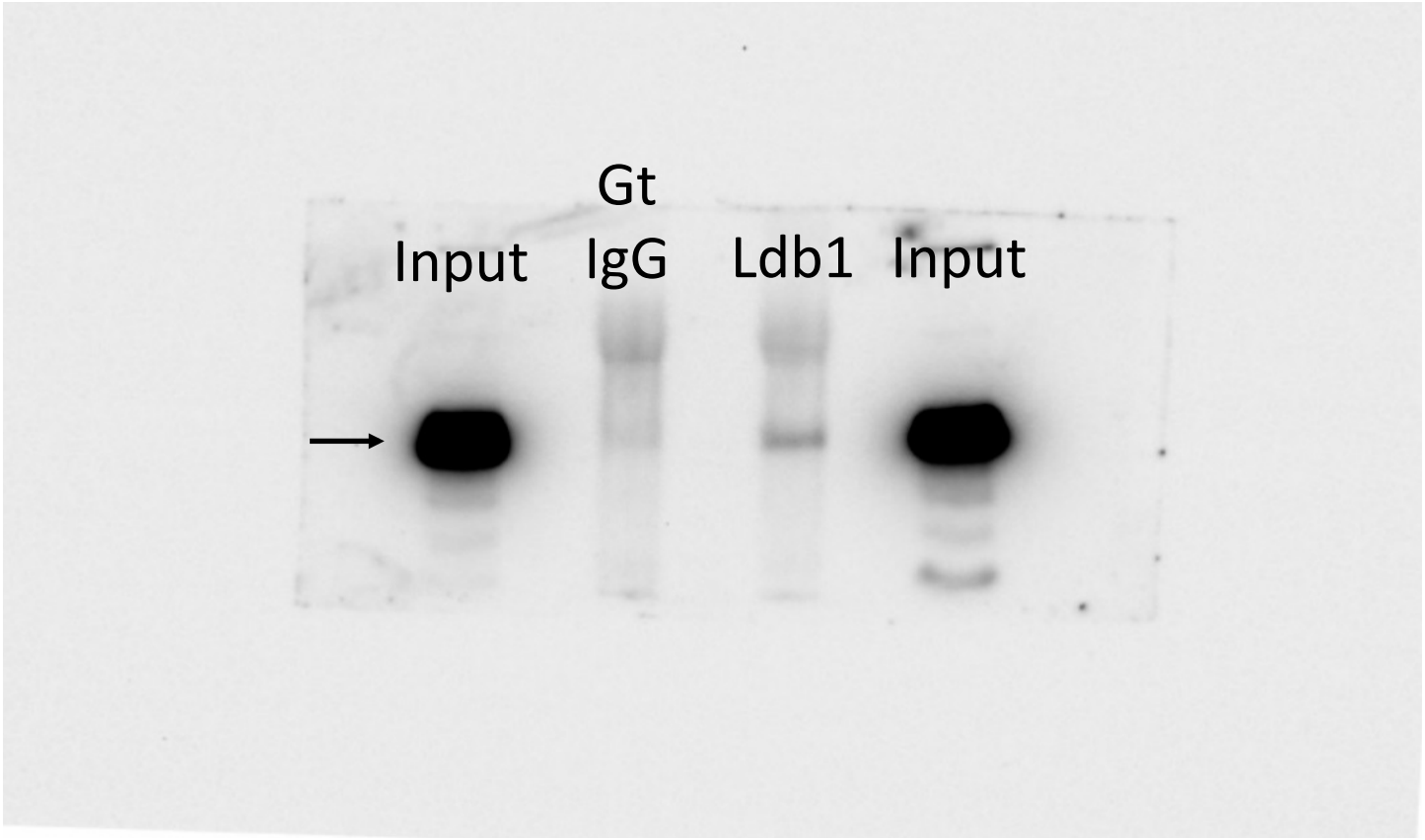

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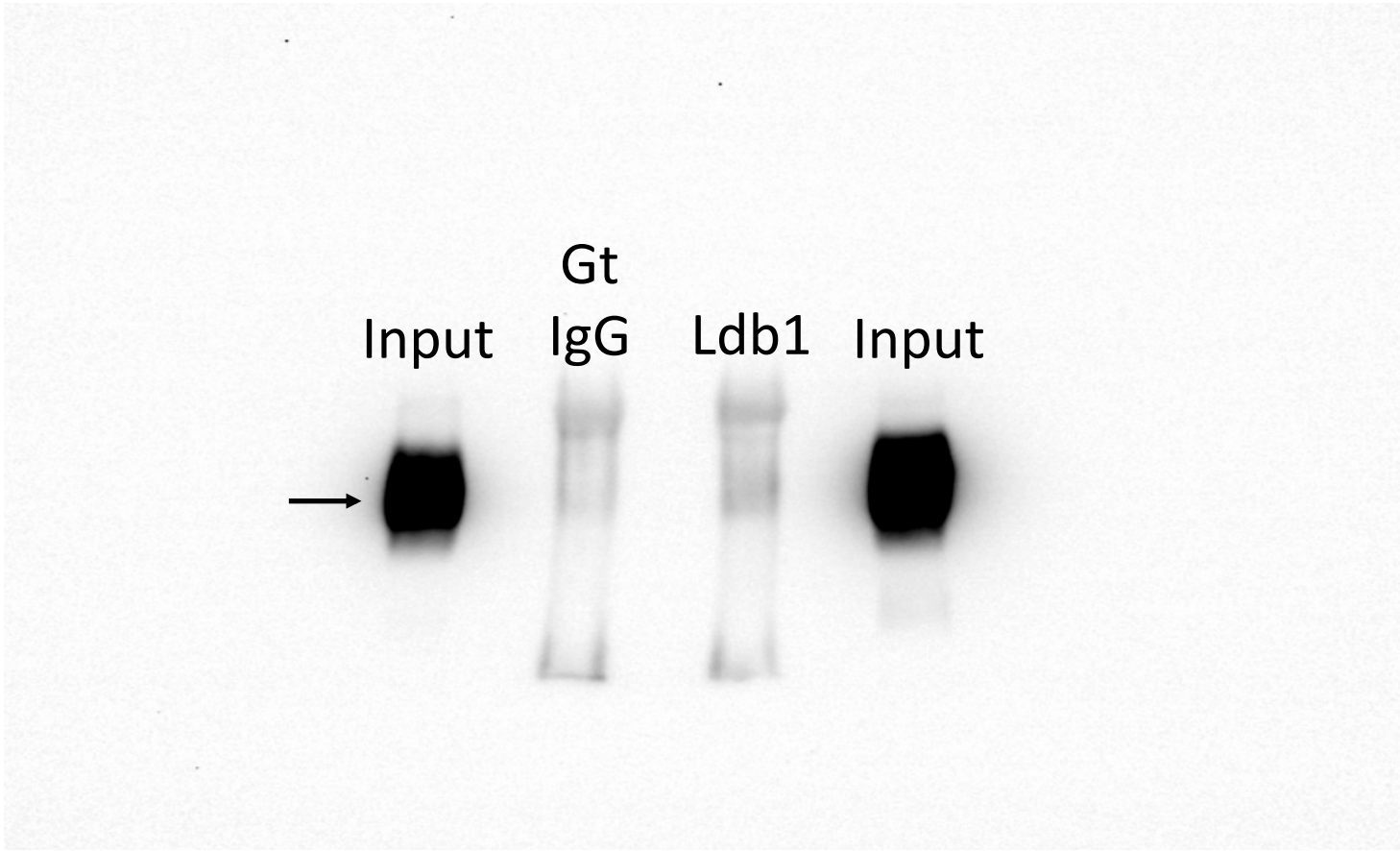
XX6.1



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OXA2