Figure. S1: SerpinB1 is secreted in a Caspase-1-dependent manner (related to Fig. 1)

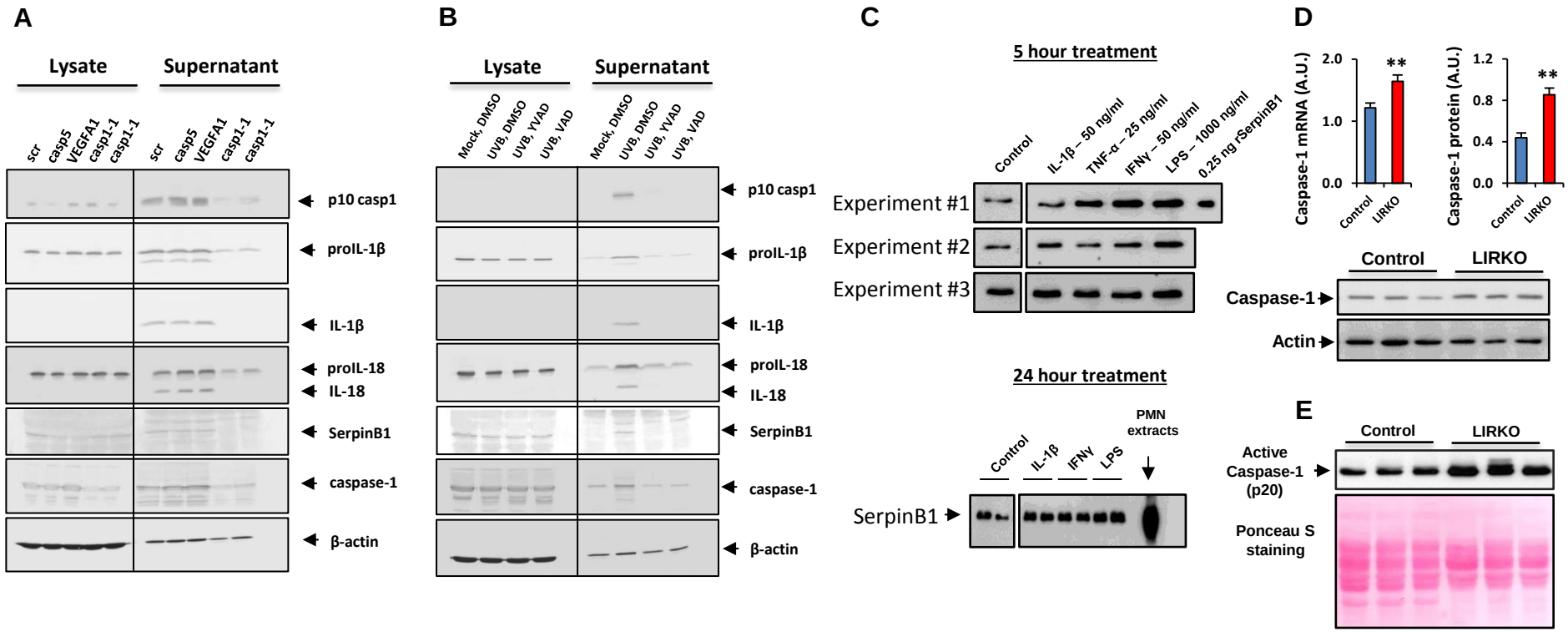
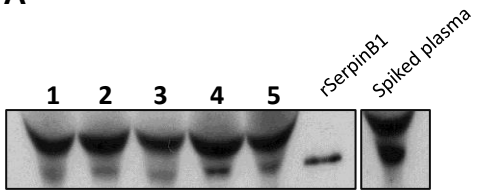


Figure S1. SerpinB1 is secreted in a caspase-1-dependent manner. A. Human primary keratinocytes were transfected with control (scrambled, scr), unrelated (caspase-5, casp5 or VEGFA1) or siRNA specific for caspase-1 mRNA (casp-1-1 and casp1-2). After two days keratinocytes were irradiated with UVB. Five h later, cell lysates and supernatants were harvested, the latter were concentrated by acetone precipitation and analyzed for expression/release of indicated proteins by Western blot. **B.** Human primary keratinocytes were treated with the caspase-1 inhibitor YVAD (20 μM), the pan-caspase-1 inhibitor VAD (10 μM) or the solvent DMSO. Five h after UVB irradiation or mock treatment cell lysates and supernatants were harvested and expression/release of the indicated proteins was assessed as described in (A). **C.** HepG2 cells were starved for 16 hours in DMEM media containing 5 mM glucose, 100U/ml penicillin and 100μg/ml streptomycin. Cells were thereafter stimulated for 5 h (upper panel) or 24 h (lower panel) with Interleukin-1β (IL-1 β: 50ng/ml), Interferon γ (IFNγ: 50ng/ml) or Lipopolysaccharide (LPS: 1μg/ml). Supernatants were collected for western blotting to assess SerpinB1 levels. Recombinant SerpinB1 (rSerpinB1) and polymorphonuclear cell (PMN) extracts were used as positive controls for SerpinB1 blotting. **D.** Relative quantification of liver Caspase-1 mRNA and protein (top panel). Data represent mean ± SEM. $^{**}p \leq 0.01$, (n=4-5 in each group). Analysis of Caspase-1 by western blot in liver lysates derived from 3-month-old male control or LIRKO mice (lower panel). **E**. Analysis of active Caspase-1 (p20) by western blot in liver explant conditioned media (LECM) derived from 3-month-old male control or LIRKO mice (top panel). Ponceau S staining of the membrane (lower panel).

Figure. S2: Relevance of SerpinB1 in Man (related to Fig. 1)

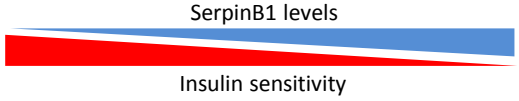
A



ID#	SerpinB1 (ng/ml)
1	13.2
2	10.7
3	9.7
4	21
5	11.7
6	12.4
7	9.6
8	11.9
9	14.1
10	14.4
11	13.6
12	14.0
13	17.2
14	27.7
15	20.2

Range of SerpinB1 levels	9.6 - 21.0 ng/ml
Mean ± SEM	12.8 ± 1.0 ng/ml
Inter-assay variation	16.4%
Intra-assay variation	13.6%

B



Characteristics	Mean±SD
Age (years)	44.8±12.7
Gender (M/F)	22/27
BMI (kg/m^2)	30.5±7.7
HbA1c (%)	5.5±0.6
Fasting glucose (mg/dl)	98.0±12.6
CISI [dl x ml (µU x mg)]	3.9±2.5

Outcome Variable	SerpinB1	
R^2	0.15	
Model P-value	0.026	
Covariates	BMI	CISI
β-estimate	0.72	1.68
Standard Error	0.28	0.74
Covariate P-value	0.014	0.028

C

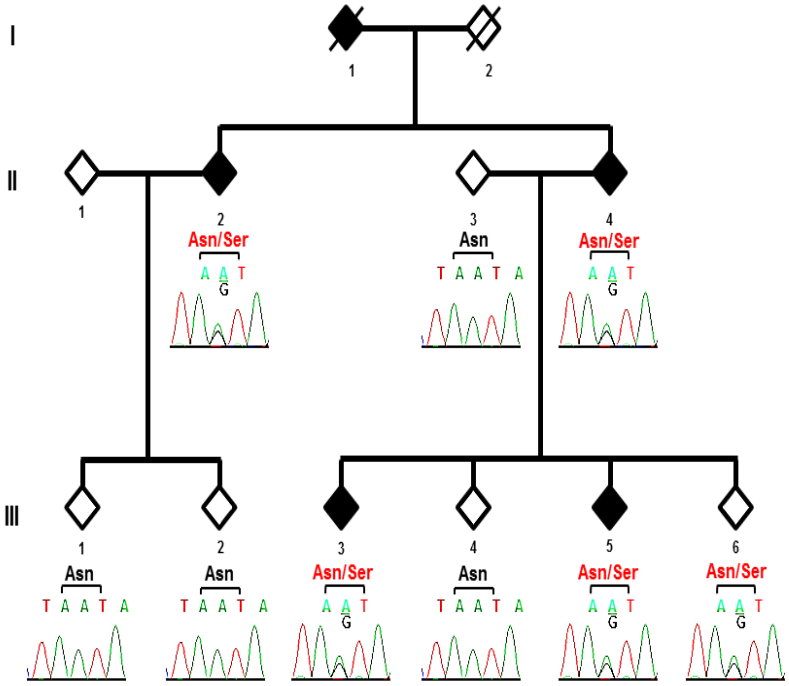


Figure S2. Relevance of SerpinB1 in Man. A. ELISA assay of SerpinB1 in human plasma. Quantification of SerpinB1 by western blot (upper panel) and ELISA (lower panel) of plasma samples from cohort 1 consisting of 15 healthy individuals. Age (years): 51.1±13.7; Gender (M/F): 5/10. Recombinant SerpinB1 (rSerpinB1) and spiked plasma was used as reference for Serpinb1 protein migration in Western blot analyses (upper panel). Inter- and intra-assay variations are provided. **B.** Correlation between circulating levels of SerpinB1 and insulin sensitivity in cohort 2 consisting of 49 individuals with one or more risk factor for diabetes, with variable degrees of insulin sensitivity. CISI: Composite Insulin Sensitivity Index. **C.** Co-segregation of the genetic SerpinB1 variant rs114597282 and diabetes in a family pedigree. Filled symbols represent diabetic individuals; empty symbols correspond to non-diabetic family members. All four diabetic members were carriers of the variant. One non-penetrant (III-6) is present in the youngest generation. Asn: asparagine; Ser: serine: T:thymidine, A:alanine; G:guaninine.

Figure. S3: Effects of GW311616A on extra-pancreatic tissue proliferation (related to Fig. 2)

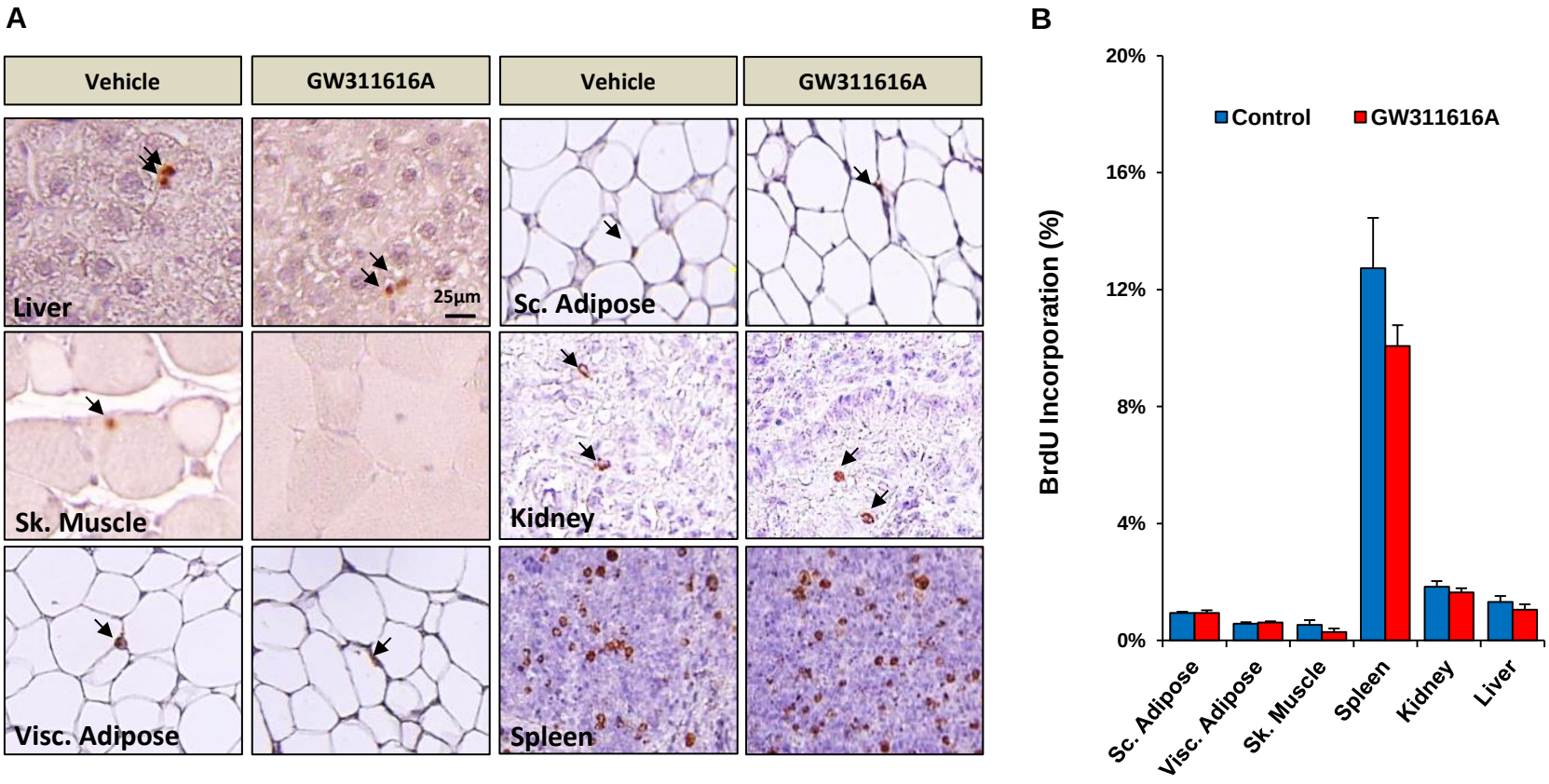


Figure. S3: Effects of GW311616A on extra-pancreatic tissue proliferation. Five to six-week old male C57BL6 mice were treated with GW311616A for 2 weeks and injected with BrdU (100 mg/kg. body weight) prior to sacrificing animals. **A.** Tissues were harvested and analyzed by immunostaining for BrdU and H&E staining. Representative images of BrdU+ nuclei in indicated tissues: liver, kidney, spleen, visceral (Visc.), subcutaneous (Sc.) adipose tissue and skeletal muscle (Sk). **B**. Quantification of BrdU+ cells of tissues in (A). Arrows indicate proliferating cells. Data represent mean ± SEM. (n=4-5 in each group), *p* is not significant.

Figure. S4: Effects of Sivelestat on β- and α-cell proliferation *in vivo* (related to Fig. 2)

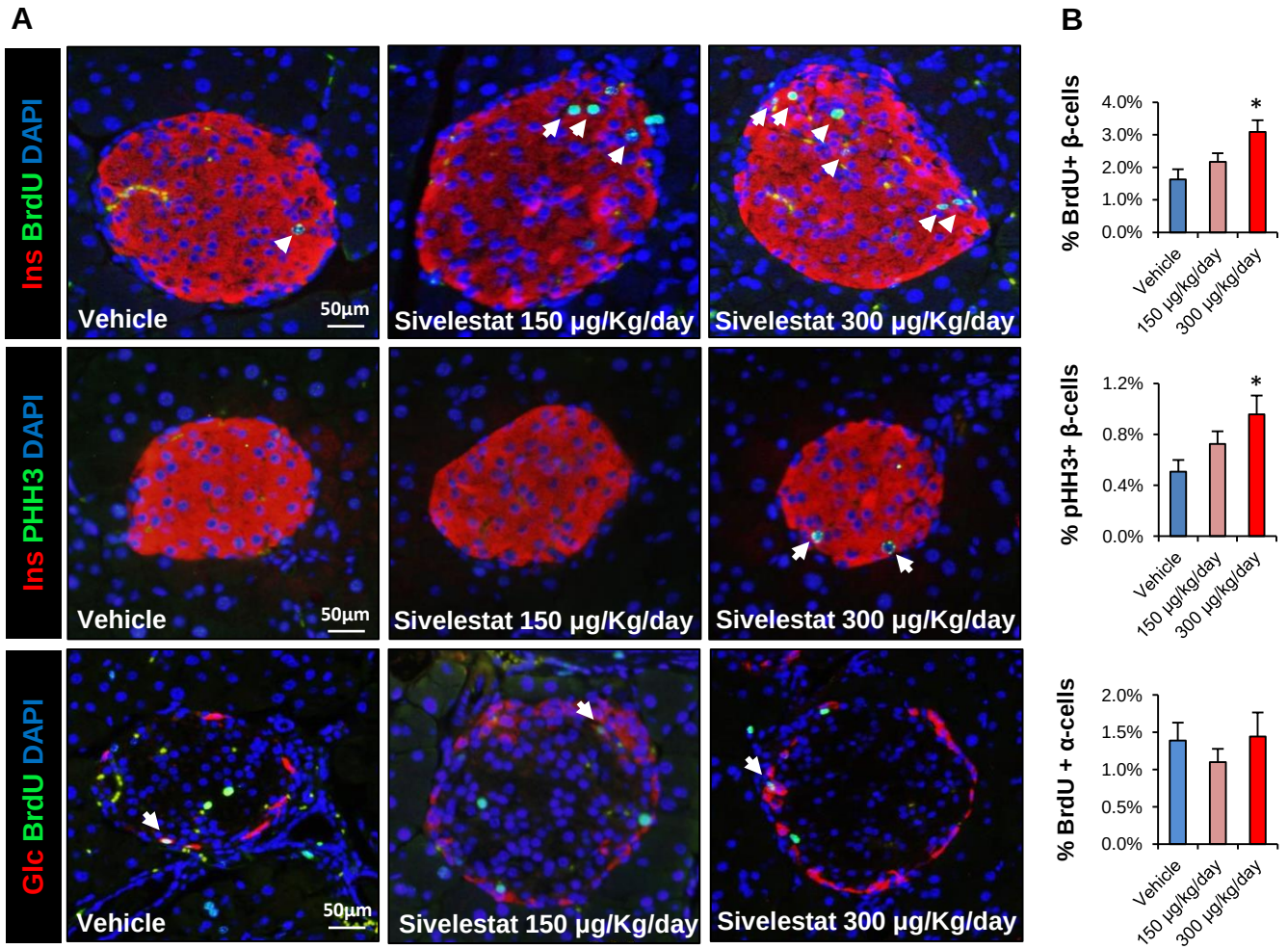


Figure S4. Effects of Sivelestat on β- and α-cell proliferation *in vivo*. Sivelestat was dissolved in 50% DMSO and administered by osmotic pumps at a dose of 150 or 300 µg/kg/day. Control mice were infused with DMSO 50% alone. After two weeks, pancreases were harvested and analyzed by fluorescent immunostaining for insulin/BrdU, insulin/pHH3 or glucagon/BrdU. **A.** Pancreatic sections immunostained for insulin/BrdU/DAPI, insulin/pHH3/DAPI, or glucagon/BrdU/DAPI as indicated. **B.** Quantification of BrdU+ insulin+ cells (top pannel), pHH+ insulin+ cells (middle pannel) and glucagon+ BrdU+ cells (lower panel). Between 400 to 900 glucagon+ cells were counted per animal. Arrows indicate proliferating cells. Data represent mean ± SEM. * $p \leq 0.05$, (n=4 in each group)

Figure. S5: SerpinB1 deficiency leads to maladaptive β-cell proliferation in insulin resistant states (related to Fig. 4)

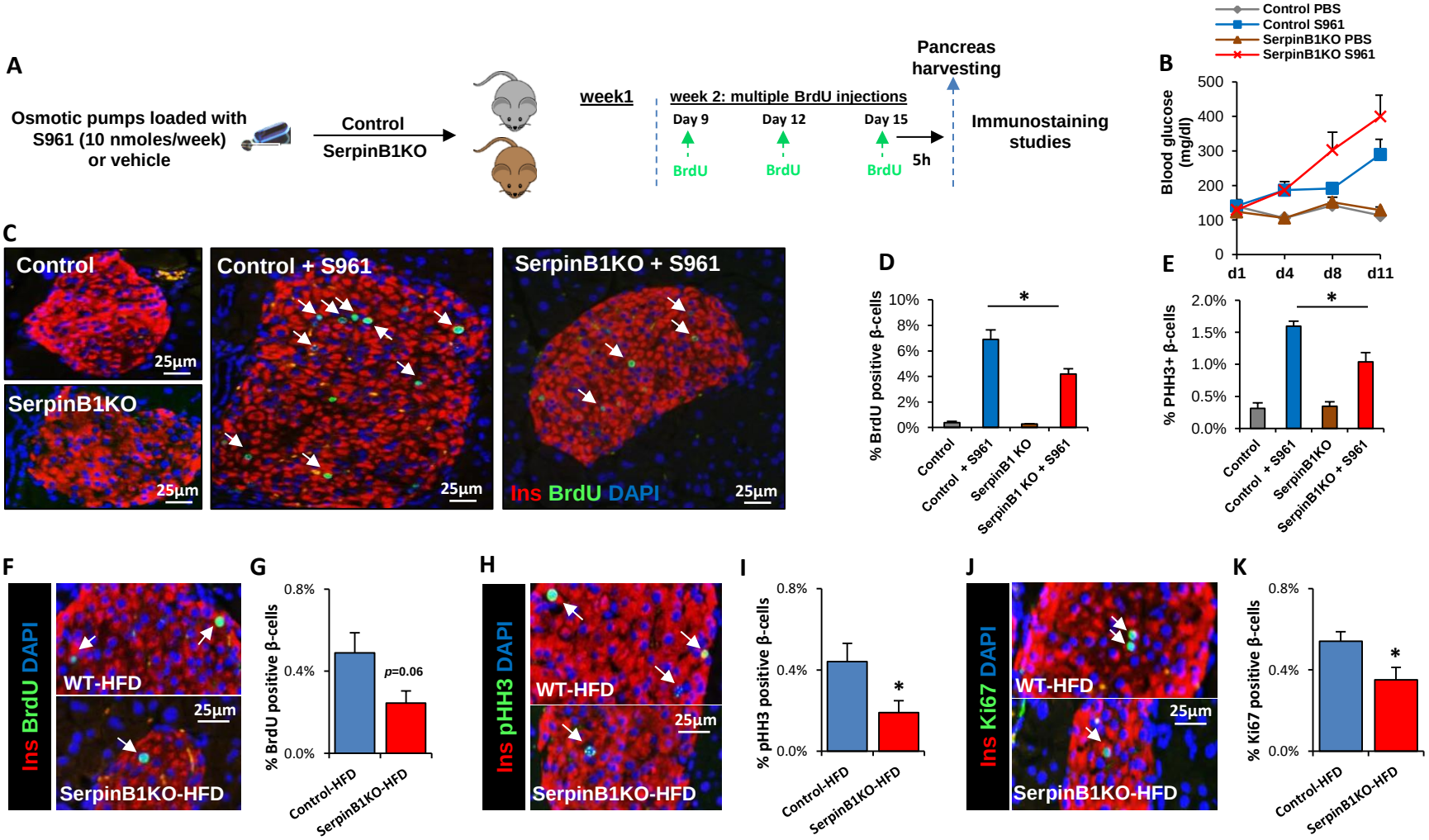


Figure S5. SerpinB1 deficiency leads to maladaptive β-cell proliferation in insulin resistant states: A. Schematic of S961 studies (A-E). Fifteen week old control or *serpinb1a* $^{-/-}$ (serpinB1KO) male mice were anesthetized, and osmotic pumps (ALZET) containing 100 µl of phosphate-buffered saline (PBS) or S961 (10 nmoles/week for two weeks) were implanted subcutaneously. One week after recovery, mice were injected with BrdU (100 mg/kg body weight). **B.** Blood glucose measurements prior to (day 1, d1) and 3, 8 and 11 days after injection of PBS or S961. **C.** Representative images of pancreases immunostained for BrdU, insulin and DAPI. **D.** Quantification of BrdU+ insulin+ cells (in **C**). **E.** Quantification of pHH3+ insulin+ cells. Data in D and E represent mean ± SEM. *p ≤ 0.05 (n=3 per group) For HFD study, 15-16 week old control or serpinB1KO male mice were fed HFD for 10 weeks and injected with BrdU (100 mg/Kg body weight) 5 h before sacrifice. **F.** Representative images of BrdU+ insulin+ cells in pancreatic sections harvested from HFD-control and HFD-serpinB1KO. **G.** Quantification of BrdU+ insulin+ cells (in F). **H.** Representative images of pHH3+ insulin+ cells in pancreatic sections harvested from HFD-control and HFD-serpinB1KO. **H.** Quantification of pHH3+ insulin+ cells (in G). **J.** Representative images of Ki67+ insulin+ cells in pancreatic sections harvested from HFD-control and HFD-serpinB1KO. **K.** Quantification of Ki67+insulin+ cells (in J). Data in G, I and K represent mean ± SEM. *p ≤ 0.05, (n=5-6 in each group). Arrows point to proliferating β-cells.

Table. S1: characteristics of individuals used in exome sequencing studies (related to Fig. S2C)

Generation	ID#	Age (years)	Age at diagnosis (years)	BMI	Medication
I	1	Unknown	Unknown	Unknown	Unknown
	2	Unknown	Unknown	Unknown	Unknown
II	1	Unknown	Unknown	Unknown	Unknown
	2	66	65	27.37	Diet
	3	57	Unknown	28.33	Unknown
	4	59	29	24.99	Insulin
III	1	36	Unknown	Unknown	Unknown
	2	42	Unknown	25.77	Unknown
	3	38	14	20.22	Insulin
	4	36	Unknown	25.92	Unknown
	5	31	29	24.44	Oral
	6	25	Unknown	30.53	Unknown

Table. S2: characteristics of islet donors used for *in vitro* studies with recombinant SerpinB1 (related to Fig. 2I and 2J)

Donor UNOS ID	Gender	Ethnicity/Race	Age (years)	BMI	Diabetic donor status	Islet purity (%)	Islet viability (%)	Islet source
ABBA069	Male	White	49	25.1	No	90	94	University of Illinois
ABDG134	Male	White	36	26.0	No	85	95	Sharp/Lacy institute
ABD1375	Female	White	47	25.0	No	70	95	University of Pennsylvenia
ABED363	Male	White	45	36.4	No	85	99	University of Wisconsin
ABEY495	Female	White	49	30.3	No	95	99	University of Wisconsin
ACDW320	Male	African-American	47	35.5	No	90	92	University of Illinois
ACFZ416A	Male	Asian	60	27.3	No	90	95	Scharp/Lacy Institute

Table. S3: characteristics of islet donors used for *in vitro* and *in vivo* studies with Sivelestat (related to Fig. 2K-M and Fig. 2N-O)

Donor UNOS ID	Gender	Ethnicity/Race	Age (years)	BMI	Diabetic donor status	Islet purity (%)	Islet viability (%)	Islet source
ACFZ416A	Male	Asian	60	27.3	No	90	95	Sharp/Lacy institute
ACGJ257A	Male	Hispanic/Latino	65	24.2	No	80	100	Southern California Islet Cell Resources Center

Supplementary Procedures:

Animals: All mice studied were 6-8-wk old males on the C57BL/6 background except where indicated otherwise. Mice were housed in pathogen-free facilities and maintained in the Animal Care Facilities at Joslin Diabetes Center, Boston, MA, Foster Biomedical Research Laboratory, Brandeis University, Waltham, MA or Boston Children's Hospital. Studies conducted and protocols used were approved by the Institutional Animal Care and Use Committees of the Joslin Diabetes Center and/or Brandeis University and/or Boston Children's Hospital and were in accordance with National Institutes of Health guidelines. LIRKO mice were generated by crossing Albumin-*Cre* to $IR^{flox/flox}$ on a mixed genetic background and were back-crossed for more than fifteen generations on the C57BL/6 background. LIRKO mice (Albumin-$Cre^{+/-}$,$IR^{flox/flox}$) and their littermate Lox controls (Albumin-$Cre^{-/-}$,$IR^{flox/flox}$) were genotyped as described (Okada et al., 2007). *SerpinB1*-deficient (*serpinb1a*$^{-/-}$) mice were generated on 129S6/SvEv/Tac (129S6) background and were back-crossed for at least 10 generations onto C57BL/6J background (Benarafa et al., 2011). Wild-type mice used as controls were obtained from Jackson Labs and maintained with *serpinB1a*$^{-/-}$ mice in the animal facility of Boston Children's Hospital.

Zebrafish lines and generation of serpinb1-overexpressing zebrafish: Zebrafish embryos, larvae, and adult fish were maintained under standard conditions at the Karolinska Institute. The transgenic zebrafish lines Tg(ins:CFP-NTR)^{s892}, Tg(ins:kaede)^{s949}, Tg(ins:H2B-GFP;ins:dsRed)^{s960}, and Tg(ins:Flag-NTR)^{s950} were used. Mosaic transgenic zebrafish were generated using the Tol2 transposon system (Kwan et al., 2007). The coding sequence of serpinb1 (ENSDARG00000055416) was amplified by PCR from zebrafish cDNA and first cloned into the middle-entry vector pDONR221; i.e. cloned using a forward primer containing an attB1 adapter, a Kozak sequence (as denoted by lower case letters in the listed sequences), and the upstream coding sequence of the serpinb1, 5'-GGGGACAAGTTTGTACAAAAAAGCAGGCTgccaccATGGAGGGAGTCTCTCGTGC-3', together with a reverse primer containing an attB2 adapter and the downstream coding sequence of the serpinb1, 5'-

GGGGACCACTTTGTACAAGAAAGCTGGGTTTAAGATGGGCCCCTGAATC-3'. The serpinb1-expression construct was then generated by LR recombination by using p5E-bactin, p3E-polyA, the middle-entry vector containing serpinb1, and the destination vector pDestTol2CG; a vector backbone containing the beta-actin promoter driving ubiquitous serpinb1-overexpression, as well as an internal control (the cmlc2 promoter driving GFP expression in the heart) for visualizing the transposon-mediated integration of the construct into the genome. Subsequently, 10-15 pg of the serpinb1-expression vector and 20 pg of transposase mRNA were injected into 1-2 cell-stage embryos, which expressed on average 3-7 fold higher levels of serpinb1 than controls, as determined by quantitative RT-PCR. To this end, total RNA was extracted from individual embryos at 6 dpf by using Trizol (Invitrogen) and treated with DNaseI. cDNA for RT-PCR experiments was synthesized using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems), and the relative expression levels were determined by SYBR-based RT-PCR (Bio-Rad). The mRNA expression level of serpinb1 was normalized to the eef1a1l1 mRNA level, as an internal standard. The primers used for RT-PCR were as follows: serpinb1 5'-AAACCAGAAAGAGAACAGACC-3' and 5'-CAACTCGCTCTCCAGCTTC-3'; eef1a1l1 5'- GTGCTGTGCTGATTGTTGCT-3' and 5'- TGTATGCGCTGACTTCCTTG-3'.

Fluorescence analysis and quantification of β-cell regeneration and proliferation: We ablated β-cells in Tg(ins:CFP-NTR) and Tg(ins:Flag-NTR) zebrafish larvae by incubating the larvae in eggwater supplemented with 10 mM metronidazole (Sigma), 1% DMSO (VWR), and 0.2 mM 1-phenyl-2-thiourea (PTU, Acros Organics) from 3-4 dpf. The fluorescent β-cells in Tg(ins:kaede) larvae were quantified by using a wide-field microscope. β-cell proliferation was assessed by adding 5 mM EdU to eggwater supplemented with 10mM Hepes (Thermo), and measuring EdU incorporation with the Click-iT EdU 647 imaging kit (Invitrogen) according to the manufacturer's protocol. The fluorescent β-cells in Tg(ins:H2B-GFP) larvae, as well as the EdU-positive cells, were quantified by using a Leica SP8 confocal microscope. The Tg(ins:H2B-GFP) was amplified by immunofluorescence using anti-GFP (Aves Labs) and secondary Alexa 488 antibodies (Life Technologies). The whole endocrine portion of the pancreas was

scanned in every larva that was examined. Results are presented as mean values ± SEM. P values < 0.05 were considered statistically significant. Statistical analyses were carried out by t-tests when two groups were analyzed, and by ANOVA when more than two groups were analyzed.

Proteins: Full length untagged recombinant human SerpinB1 (rSerpinB1) was expressed in insect cells, purified by anion chromatography and gel filtration and stored at -80°C in 20 mM Tris-HCl, pH 7.4, 500 mM NaCl, 2 mM mercaptoethanol, 1 mM EDTA at 1-2 mg/ml (Cooley et al., 1998). Mercaptoethanol (2 mM) was added prior to use. Ovalbumin (SerpinB14) purified from chicken egg white was obtained from Sigma-Aldrich, stored in PBS at -20°C at 1mg/ml.

LECM and HCM preparation: The preparation of liver explant-conditioned media (LECM) and hepatocyte conditioned media (HCM) have been described earlier (El Ouaamari et al., 2013). Briefly, mice were anesthetized with Avertin (240 mg/kg intraperitoneally), and 100 mg liver explants were washed twice in cold PBS, incubated for 30 min in PBS at 37°C, and then cultured in serum-free Dulbecco's modified Eagle's medium (DMEM) with 5.5 mM glucose. After 3 days, LECM were collected, centrifuged, and kept at −80°C. For HCM, mice were anesthetized as above; the portal vein was cannulated and the liver was perfused with EGTA solution (5.4 mM KCl, 0.44 mM KH_2PO_4, 140 mM NaCl, 0.34 mM Na_2HPO_4, and 0.5 mM EGTA [pH 7.4]) and digested with DMEM containing 0.075% type I collagenase (Sigma, catalog#C0130) for 5 min at 37°C. Hepatocytes were washed twice in Hepatocyte Wash Medium (Invitrogen, catalog #17704024). The hepatocytes were seeded in collagen-coated 6-well plates (BD BioCoat, catalog#354400) at a density of 10^6 cells/well in 25 mM glucose-containing DMEM and 10% FBS (v/v). Sixteen hours later, hepatocytes were cultured for 24 hours in serum-free DMEM containing 5.5 mM glucose. HCM was collected, centrifuged, and kept at −80°C.

LC-MS/MS based proteomics: Proteomic analyses were performed as previously described (Zhou et al., 2010). Briefly, for a given sample type (liver, LECM, HCM, or plasma), equal amounts of proteins from each biological replicate were denatured,

alkylated, and digested with trypsin. Digests of liver and plasma were further fractionated by cation exchange chromatography, and all peptide samples were analyzed by LC-MS/MS. Peptides were identified from MS/MS data by database searching algorithm MS-GF+ (Kim et al., 2010) against the Uniprot murine protein database with <1% false discovery rate. Protein abundances were quantified based on spectral count information.

Mouse Islet Studies: Islets were isolated from 6-8 week old wild type C57BL/6 male mice) using intraductal collagenase technique (El Ouaamari et al., 2013). Islets were handpicked and cultured overnight in RPMI 1640 media containing 7 mM glucose and 10% fetal bovine serum (FBS) and penicillin/streptomycin (1% v/v). After 3h-starvation in RPMI 1640 media containing 3 mM glucose and 0.1%BSA, islets were stimulated as indicated (with recombinant proteins or small molecules) for 48h and then embedded in agarose and paraffin, sectioned and used for immunostaining studies as described below and in (El Ouaamari et al., 2013).

Phosphoproteomics analysis: Islets were isolated as described above and were cultured overnight in RPMI-1640 media, 10% FBS, 7mM glucose, and 250 size-matched islets were hand-picked for each reaction. After washing in PBS, islets were starved in RPMI-1640 media with 0.1% BSA and 3 mM glucose for 3 hr. The islets were then placed in fresh RPMI-1640 media with 0.1% BSA and 5 mM glucose in Eppendorf tubes and stimulated with 1µg/ml ovalbumin (control) or recombinant SerpinB1 for 10, 30 or 120 min at 37 ºC, immediately placed on ice and washed twice with ice-cold PBS before snap-freezing for storage at -80 ºC for subsequent phosphoproteomics analysis or validation of findings by Western blot. For phosphoproteomics the frozen islets were lysed with 8M urea containing phosphatase inhibitors (Sigma-Aldrich, P5726), and the proteins were reduced, alkylated and digested by trypsin as described (Mertins et al., 2014). Peptides were labeled with 6-plex TMT reagents (Thermo Scientific, San Jose, CA) according to the manufacturer's instructions. Phosphopeptides were enriched using immobilized metal affinity chromatography (IMAC) using Magnetic Fe^{3+}-NTA-agarose beads (Qiagen, Valencia, CA). Phosphopeptides were analyzed by LC-MS/MS as described (Mertins et al., 2014). Peptides were identified from MS/MS spectra using

database searching algorithm MS-GF+ (Kim et al., 2010) against a murine protein database from Uniprot with <1% false discovery rate. TMT reporter ion intensities were extracted for relative quantification. To validate the phosphoproteomics findings, frozen SerpinB1- treated and ovalbumin-treated islets were lysed in RIPA buffer (150mM NaCl, 10mM Tris, pH 7.2, 1% Triton X-100, 1% deoxycholate, 5mM EDTA) containing 200µM orthovanadate, protease and phosphatase inhibitors (Sigma-Aldrich) (Liew et al., 2014). Lysates were precleared at 13000 rpm, 15min, 4°C and total protein concentration was determined using BCA assays (Pierce). Samples were resuspended in reducing SDS-PAGE sample buffer, boiled and resolved by SDS-polyacrylamide gel electrophoresis. Then proteins were transferred onto nitrocellulose membranes (Schleicher & Schuell), blocked in 5% milk in TBS/T (TBS containing 0.1% Tween) and incubated with primary antibodies overnight at 4°C. pMAPK3, total MAPK3 and total GSK3 antibodies are from Cell Signaling. pPRKAR2B and total PRKAR2B are from Santa Cruz. pGSK3 antibody is from Millipore.

SerpinB1 ELISA assay: Ninety-six-well plates (Costar 3591, Corning, flat bottom, polystyrene) were coated with 3 µg/ml purified IgY of chicken anti SerpinB1 in carbonate/bicarbonate buffer pH 9.6 overnight at 4^{o}C. The antibodies were custom generated by Gallus Immunotech (Fergus, Ontario) by immunizing hens with recombinant human SerpinB1 in CFA and boosting with SerpinB1 coupled to keyhole limpet hemagglutinin (KLH) in IFA. IgY was purified from yolks of immune eggs. All other steps were carried out at room temperature. The plates were washed with PBS/0.05% Tween-20 (PBS-Tween), blocked with 1% BSA (Sigma-Aldrich) for 1 hr and washed with PBS-Tween. Recombinant SerpinB1 standards ranging from 1-100 ng/ml were used along with 5 and 10 fold dilutions of human plasma samples (100 µl/well), incubated for 1 hr on a rocking platform, and the plates were washed with PBS-Tween. ELA-5 mouse monoclonal antibody to human SerpinB1 (Benarafa et al., 2011) at 2 µg/ml in PBS-Tween with 0.1% BSA was added and incubated for 1 hr. The plates were washed with PBS-Tween, and secondary goat anti-mouse Ig HRP conjugated antibodies (BioRad) at 1:3000 dilution in PBS-Tween-0.1% BSA was added and incubated for 1 hr with rocking. Plates were washed with PBS-Tween and fresh 3,3′,5,5′-tetramethylbenzidine solution (TMB Peroxidase EIA Substrate Kit, BioRad)

(100 µl/well) was added and incubated until deep blue color appeared (approximately 5 min). The reaction was stopped by adding 100 µl/ well of 1N sulfuric acid, and OD450 nm was measured on a MRX TC Plate Reader (Dynex Technologies).

Human Studies: Studies were approved by the Joslin Diabetes Center Institutional Review Board, all participants provided written informed consent. Two cohorts were recruited. The first cohort used to validate measurement of serpinB1 in plasma included 15 adults with no known diabetes and HbA1c below 6.5%. The second cohort included 49 adults with one or more risk factor for type 2 diabetes (first degree relative with disease; previous gestational diabetes; history of abnormal non-diagnostic glucose; ethnic minority; BMI above 30 kg/m^2; irregular menses; or history of hypertension, dyslipidemia or coronary heart disease). Fasting blood was obtained and participants underwent 75 gram oral glucose tolerance test.

SDS-PAGE and Western blotting: Tissue samples were lysed in RIPA buffer and total protein concentration was determined using BCA assay (Pierce). Samples were resuspended in Laemmli buffer with β-mercaptoethanol, boiled and resolved by SDS-polyacrylamide gel electrophoresis. Proteins were transferred onto nitrocellulose membranes, blocked in PBS containing 5% BSA and 0.1% Tween 20 and incubated with rabbit antiserum to human SerpinB1 (Rees et al., 1999) or actin (Santa Cruz, sc-1615) for overnight or one hour, respectively or with mouse monoclonal to human α1-antitrypsin (SerpinA1) (Santa Cruz 48D2). Secondary goat anti-rabbit (Santa Cruz, sc-2054) or goat anti-mouse (Santa Cruz, sc-2055) was used thereafter. We also used antibodies to caspase-1 (M20) (sc-514) and active caspase-1 (AG-20B-0042-C100). Protein bands were quantified by ImageJ software. In select experiments, proteins were transferred onto PVDF, and total proteins was stained with colloidal gold (Biorad).

RT-PCR: For real time experiments, total RNAs were extracted using RNeasy Mini Kit (QIAGEN). One µg RNA was used for a reverse transcription step using high-capacity cDNA Archive Kit (Applied Biosystems). cDNA was analyzed by ABI 7900HT system (Applied Biosystems). TBP was used as an internal control. Primers for SerpinB1: 5′-GCTGCTACAGGAGGCATTGC-3′ (forward) and 5′-CGGATGGTCCACTGTGAATTC-3′ (reverse), for TBP; 5’-ACCCTTCACCAATGACTCCTATG-3’ (forward) and 5’-

ATGATGACTGCAGCAAATCGC-3' (reverse) and for caspase-1; 5′-ACA AGG CAC GGG ACC TAT G-3′ (forward) and 5′ TCC CAG TCA GTC CTG GAA ATG-3' (reverse)

S961 studies: Sixteen-week-old serpinB1KO and age-matched wild-type male mice were anesthetized and infused with PBS alone or PBS with the insulin receptor antagonist S961 at the dose of 10 nmoles/week for two weeks. Infusion was carried out using osmotic pumps (ALZET) implanted subcutaneously.

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