



Recent References (2015-2020) on the Administration of Insulin Using ALZET® Osmotic Pumps

Q8217: T. Katahira, *et al.* Conversion of pancreatic alpha cells into insulin-producing cells modulated by beta-cell insufficiency and supplemental insulin administration. *Biochem Biophys Res Commun* 2020;521(1):178-183

Agents: Insulin **Vehicle:** Saline; **Route:** Not stated; **Species:** Mice; **Pump:** Not stated; **Duration:** 2 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL/6J male mice, 6 or 7 weeks of age); diabetes;

Q7653: H. Zhu, *et al.* Insulin Therapy for Gestational Diabetes Mellitus Does Not Fully Protect Offspring From Diet-Induced Metabolic Disorders. *Diabetes* 2019;68(4):696-708

Agents: Insulin, recombinant human **Vehicle:** Saline; **Route:** SC; **Species:** Mice (Pregnant); **Pump:** 1007D; **Duration:** 1 week;

ALZET Comments: Dose (0.35 IU/day); Controls received mp w/ vehicle; animal info (6-8 weeks, female, ICR, 26-28g);

diabetes; Pumps were implanted on day 14.5 or 15 of pregnancy. Pups were fostered by normal females until the age of 3 weeks. "To maintain stable glycemic levels, INS dams received another injection of 0.1 units of long-acting insulin (Levemir; Novo Nordisk) ~1h before the fed state (darkness) during late gestation." p.697;

Q7634: B. P. Tooke, *et al.* Hypothalamic POMC or MC4R deficiency impairs counterregulatory responses to hypoglycemia in mice. *Mol Metab* 2019;20(194-204

Agents: Insulin; Melanotan **Vehicle:** PBS; **Route:** SC; CSF/CNS (Paraventricular Nucleus of Hypothalamus); **Species:** Mice;

Pump: 2002; 1002; **Duration:** 14 days;

ALZET Comments: Dose (10 U/kg/day); Controls received mp w/ vehicle; Brain coordinates (bregma: anteroposterior, 0.70; mediolateral, -0.22; dorsoventral, 4.80 mm); bilateral cannula used; diabetes; BIK: Plastics1, 3280PD/V/SPC;

Q8373: S. Pushpakumar, *et al.* Hydrogen Sulfide Protects Hyperhomocysteinemia-Induced Renal Damage by Modulation of Caveolin and eNOS Interaction. *Sci Rep* 2019;9(1):2223

Agents: Fluoresceinyl isothiocyanate-Insulin **Vehicle:** Not stated; **Route:** SC; **Species:** Mice; **Pump:** 2001D; **Duration:** 1 day;

ALZET Comments: animal info (C57BL/6J, 8-12 weeks old, 25 g); Fluoresceinyl isothiocyanate-Inulin aka FITC-Inulin; dependence;

Q7570: Z. Li, *et al.* mTOR Signaling in X/A-Like Cells Contributes to Lipid Homeostasis in Mice. *Hepatology* 2019;69(2):860-875

Agents: Ghrelin, acyl-; Insulin **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 14 days;

ALZET Comments: Dose (11 nmol/kg/d); Controls received mp w/ vehicle; animal info (Four-week-old male mice); obesity;

Q8204: A. P. Gupta, *et al.* Pancreastatin inhibitor PSTi8 attenuates hyperinsulinemia induced obesity and inflammation mediated insulin resistance via MAPK/NOX3-JNK pathway. *Eur J Pharmacol* 2019;864(172723

Agents: Insulin Glargine, Pancreastatin Inhibitor **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;

ALZET Comments: Dose (1 mg/kg/day or 30 U/kg/day); Controls received mp w/ vehicle; animal info (male C57BL/6 male mice (20 ± 2 g)); Pancreastatin Inhibitor aka PSTi8; diabetes;

Q6881: W. Deng, *et al.* Insulin ameliorates pulmonary edema through the upregulation of epithelial sodium channel via the PI3K/SGK1 pathway in mice with lipopolysaccharide-induced lung injury. *Mol Med Rep* 2019;

Agents: Insulin, human **Vehicle:** PBS; **Route:** IV (jugular); **Species:** Mice; **Pump:** Not Stated; **Duration:** 24 hours;

ALZET Comments: Dose (Human Insulin (.01 U/kg/day); Controls received mp w/ vehicle; animal info (C3H/HeN mice, aged 7-9 weeks); ALZET internal jugular vein catheter used; cardiovascular;

Q7977: F. Adel, *et al.* Insulin Therapy in a Rat Model of Diabetic Cardiomyopathy Is Associated with Attenuation of the Cgmp System. *Journal of the American College of Cardiology* 2019;73(9):

Agents: insulin **Vehicle:** saline; **Route:** SC; **Species:** Rat; **Pump:** Not stated; **Duration:** 1 month;

ALZET Comments: Dose (11.5 µg/kg/day); Controls received mp w/ vehicle; animal info (male, Wistar); cardiovascular; diabetes;



Q7160: Y. W. Yu, *et al.* Glucose-Dependent Insulinotropic Polypeptide Mitigates 6-OHDA-Induced Behavioral Impairments in Parkinsonian Rats. *Int J Mol Sci* 2018;19(4):

Agents: Glucose-dependent insulinotropic polypeptide **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 2 weeks;

ALZET Comments: Dose (7.8 or 15 nmol/kg/day); Controls received mp w/ vehicle; behavioral testing (Open field test); functionality of mp verified by plasma levels; Resultant plasma level (GIP administration at 15 nmol/kg/day resulted in total GIP plasma levels of 203.9 pmol/L); neurodegenerative (Parkinson's);

Q6914: Y. Mori, *et al.* Glucose-Dependent Insulinotropic Polypeptide Suppresses Peripheral Arterial Remodeling in Male Mice. *Endocrinology* 2018;159(7):2717-2732

Agents: Glucose-dependent insulinotropic polypeptide **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice (knockout); **Pump:** 1002; **Duration:** Not Stated;

ALZET Comments: Dose (GIP(1–42) and GIP(3–42) were 50 nmol/kg/d, except for experiment 2, where GIP(1–42) at 25 nmol/kg/d was also administered); animal info (Seven-week-old male C57BL/6 (wild-type) and db/db mice); peptides; cardiovascular;

Q8056: D. Kumar, *et al.* Chronic hyperinsulinemia promotes meta-inflammation and extracellular matrix deposition in adipose tissue: Implications of nitric oxide. *Mol Cell Endocrinol* 2018;477(15-28

Agents: Insulin **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not stated; **Duration:** 8 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (8-10 weeks old, 20-24 g, C57BL/6J, Male); pumps replaced every 4 weeks; diabetes;

Q7021: H. Hvid, *et al.* Activation of insulin receptors and IGF-1 receptors in COLO-205 colon cancer xenografts by insulin and insulin analogue X10 does not enhance growth under normo- or hypoglycaemic conditions. *Diabetologia* 2018;61(11):2447-2457

Agents: Insulin, human; X10 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice (nude); **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: Dose (insulin at 27 nmol/kg/d; X10 at 41 nmol/kg/d); Controls received mp w/ vehicle; animal info (male BALB/c nude mice); X10 is an insulin analog; cancer (colon); diabetes;

Q7755: R. W. Holdcraft, *et al.* A model for determining an effective in vivo dose of transplanted islets based on in vitro insulin secretion. *Xenotransplantation* 2018;25(6):e12443

Agents: Insulin, recomb. human **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 3-5 days;

ALZET Comments: Dose ((female 1.5-2.0 U/day), (males 3.0-4.5 U/day)); Controls consisted of rats that did not become diabetic during the initial study period; animal info (male and female, BioBreeding diabetes-prone); Multiple pumps per animal (2 if hyperglycemic state observed. see p.4); comparison of macrobead implant vs mp; diabetes; Pilot study for CGM calibration 3-5 days followed by 1 or 3 month study using microbeads. Pump models not stated but duration length was listed at 7 or 14 days;

Q7903: J. M. Gladding, *et al.* The Effect of Intrahippocampal Insulin Infusion on Spatial Cognitive Function and Markers of Neuroinflammation in Diet-induced Obesity. *Front Endocrinol (Lausanne)* 2018;9(752

Agents: Insulin, Humulin N **Vehicle:** Saline; **Route:** CNS/CSF (third ventricle); **Species:** Mice; **Pump:** 2004; **Duration:** 28 days;

ALZET Comments: Dose (2.64 ul/day); Controls received mp w/ vehicle; animal info (Male, 8 weeks old, C57BL/6J); post op. care (Analgesia); behavioral testing (Morris Water Maze Test, Y Maze Test); ALZET brain infusion kit (not stated) used; Brain coordinates (AP–2.0mm, ML +/-1.8mm, DV–1.6mm from dura); bilateral cannula used; dependence;

Q7812: M. B. Fluitt, *et al.* Chronic Insulin Infusion Down-Regulates Circulating and Urinary Nitric Oxide (NO) Levels Despite Molecular Changes in the Kidney Predicting Greater Endothelial NO Synthase Activity in Mice. *Int J Mol Sci* 2018;19(10):

Agents: insulin **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Dose (50 U/kg/d); Controls received mp w/ vehicle; animal info (4-7 months, male, TALLYHO/Jng); replacement therapy (insulin); "Systolic BP was significantly higher in the insulin-infused mice during the early time period of infusion; however this arose primarily due to the fact that systolic BP levels tended to fall in vehicle-infused mice. We do



not fully understand this response, but it may reflect recovery from the surgeries to implant the radiotelemetry transmitter and osmotic pumps." p.8;

Q7088: N. C. Boisvert, *et al.* Hyperfiltration in ubiquitin C-terminal hydrolase L1-deleted mice. *Clinical Science* 2018;132(13):1453-1470

Agents: Insulin (Humulin R) **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Dose (8.33 $\mu\text{mol/ml}$); Controls received mp w/ vehicle; animal info (Uchl1-/-mice, 9-11-week-old, male); diabetes;

Q5997: K. M. Thrailkill, *et al.* The impact of SGLT2 inhibitors, compared with insulin, on diabetic bone disease in a mouse model of type 1 diabetes. *Bone* 2017;94(141-151)

Agents: Insulin (Humulin R) **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 9 weeks;

ALZET Comments: Controls were untreated diabetic mice; animal info (12 weeks); functionality of mp verified by insulin serum levels using a mouse ultrasensitive insulin ELISA; Does not indicate replacement; diabetes; 145Therapeutic indication (Diabetes); Dose (0.125 units/day);

Q5962: H. Okamoto, *et al.* Glucagon receptor inhibition normalizes blood glucose in severe insulin-resistant mice. *Proc Natl Acad Sci U S A* 2017;114(10):2753-2758

Agents: S961 insulin receptor antagonist **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 2002; **Duration:** 14 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL/6 mice, 10-wk old males); Dose (20 nmol/wk);

Q5825: K. P. Mori, *et al.* Increase of Total Nephron Albumin Filtration and Reabsorption in Diabetic Nephropathy. *J Am Soc Nephrol* 2017;28(1):278-289

Agents: Insulin **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: animal info (Akita, 14 weeks) ; diabetes; Therapeutic indication (Diabetes, Nephrology);

Q6298: C. K. Katashima, *et al.* iNOS promotes hypothalamic insulin resistance associated with deregulation of energy balance and obesity in rodents. *Sci Rep* 2017;7(1):9265

Agents: S-nitrosoglutathione; insulin; glutathione **Vehicle:** Not Stated; **Route:** CSF/CNS (third ventricle); **Species:** Rat; mice; **Pump:** 1002; 2002; **Duration:** 1 week;

ALZET Comments: Dose (GSNO (50 μM)/insulin (0.033 $\text{UI}/\mu\text{L}$) and GSH (50 μM)/insulin (0.033 $\text{UI}/\mu\text{L}$)); animal info (Male 4-week-old Wistar rats, Swiss, C57BL/6 and iNOS-null (iNOS-/-) mice); S-nitrosoglutathione is an NO donor; Brain coordinates (rats DV: -8.5 mm and AP: - 0.5 mm; mice DV: -5 mm and AP: -1.8 mm);

Q5505: Y. W. Yu, *et al.* Glucose-Dependent Insulinotropic Polypeptide Ameliorates Mild Traumatic Brain Injury-Induced Cognitive and Sensorimotor Deficits and Neuroinflammation in Rats. *J Neurotrauma* 2016;33(22):2044-2054

Agents: Glucose-dependent insulinotropic polypeptide **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** Not Stated;

Duration: 7 days; 2 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-300g, adult); functionality of mp verified by plasma levels (pg 2049); behavioral testing (Morris water maze; recognition memory test; beam walking test; novel object recognition); peptides; traumatic brain injury; Dose (21.58 or 38.85 $\mu\text{g/kg/day}$); Resultant plasma level (58.6 +/- 11.8 pmol/L);

Q4817: Stephanie Dal, *et al.* Oxidative stress status and liver tissue defenses in diabetic rats during intensive subcutaneous insulin therapy. *Experimental Biology and Medicine* 2016;241(184-192)

Agents: Insulin **Vehicle:** Not Stated; **Route:** SC; **Species:** Rats; **Pump:** 2006; **Duration:** 1 week; 4 weeks;

ALZET Comments: animal info (male, Wistar, 180-200g, STZ); immunology; diabetes; "The intensive subcutaneous insulin administration performed using a mini pump in our study led to an improvement in the metabolic control of diabetic rats, as confirmed by a decrease in fructosamine levels and an increase in body weight after four weeks of treatment. Moreover, blood insulin concentration was maintained at the same level throughout the study attesting to the efficiency of this therapy." pg 189; Dose (2 $\text{UI}/200\text{g/day}$);



Q5196: A. Schaschkow, *et al.* Impact of the Type of Continuous Insulin Administration on Metabolism in a Diabetic Rat Model. *J Diabetes Res* 2016;2016(8310516)

Agents: insulin **Vehicle:** buffer solution; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 28 days;
ALZET Comments: animal info (male, Lewis, STZ injection); comparison of injection of insulin vs mp; post op. care (Baytril 10 mg/kg QD for 7 days); diabetes; pumps primed for 24 hours in 37C saline; "...continuous insulin delivery by pumps restored normoglycaemia, which induced the reduction of both reactive oxygen species and macrophage infiltration into the liver and omentum. Injections controlled the glucose levels for only a short period of time and therefore tissue stress and inflammation were elevated." pg 1; "pumps require no daily injection and facilitate rat follow-up. Well-being of the animals and the homogeneity of the results permit researchers to limit the numbers of animals and experiments used to build solid and reproducible results." pg 8; Dose (4 IU/day);

Q5601: T. Sartorius, *et al.* Sustained Treatment with Insulin Detemir in Mice Alters Brain Activity and Locomotion. *PLoS One* 2016;11(9):e0162124

Agents: Insulin, Insulin Detemir **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 8 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (10-15 week); comparison of daily s.c. injections vs mp; behavioral testing (Locomotion); Therapeutic indication (Insulin-dependent brain activity); Dose (.6 U/d);

Q6647: S. Rajan, *et al.* Chronic hyperinsulinemia reduces insulin sensitivity and metabolic functions of brown adipocyte. *J Endocrinol* 2016;230(3):275-90

Agents: Insulin, glargine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 8 weeks;
ALZET Comments: Dose (0.6 U/day); animal info (C57BL/6 mice); pumps replaced every 4 weeks; diabetes;

Q5381: K. Kohashi, *et al.* A Dipeptidyl Peptidase-4 Inhibitor but not Incretins Suppresses Abdominal Aortic Aneurysms in Angiotensin II-Infused Apolipoprotein E-Null mice. *Journal of Atherosclerosis and Thrombosis* 2016;23(4):441-454

Agents: Angiotensin II; Glucagon-like peptide-1; Glucose-dependent insulinotropic polypeptide **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (ApoE^{-/-} mice, 9 weeks old); functionality of mp verified by plasma levels, blood pressure; pumps replaced every 2 weeks; cardiovascular; atherosclerosis; peptides; Pathophysiology similarities btwn abdominal aortic aneurysms, atherosclerosis; blood pressure measure via tail-cuff method; Dose (2000 ng/kg/min AngII, 2.16 nmol/kg/day GLP-1, 25 nmol/kg/day GIP); Resultant blood pressure (Start: 104 mmHg, End: 118 mmHg);

Q5548: K. Kohashi, *et al.* A Dipeptidyl Peptidase-4 Inhibitor but not Incretins Suppresses Abdominal Aortic Aneurysms in Angiotensin II-Infused Apolipoprotein E-Null Mice. *Journal of Atherosclerosis and Thrombosis* 2016;23(4):441-454

Agents: Angiotensin II, Glucagon-like peptide-1, Glucose-Dependent Insulinotropic Polypeptide **Vehicle:** Saline; **Route:** SC; **Species:** Mice (knockout); **Pump:** 1002; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (13 weeks old); pumps replaced every 2 weeks; Multiple pumps per animal (2); one for either Ang II, GLP-1 or GIP; enzyme inhibitor (Dipeptidyl Peptidase-4 inhibitor); Therapeutic indication (Abdominal aortic aneurysm); Dose (Angiotensin II: 2000 ng/kg/min, Angiotensin II + GIP: 25 nmol/kg/day, DPP-4i: 6 mg/kg/day);

Q6101: Cochran BJ, *et al.* Impact of Perturbed Pancreatic β -Cell Cholesterol Homeostasis on Adipose Tissue and Skeletal Muscle Metabolism. *Diabetes* 2016;65(12):3610-3620

Agents: Insulin (Humulin R) **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 4 weeks;
ALZET Comments: Dose: (Humulin R 0.1 units/day); Controls received mp w/ vehicle; animal info (16-week-old male mice); Resultant plasma level (p. 3615); diabetes;

Q5627: M. P. Bhatt, *et al.* C-peptide protects against hyperglycemic memory and vascular endothelial cell apoptosis. *J Endocrinol* 2016;231(1):97-108

Agents: C-peptide, human; insulin, human recombinant **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;



ALZET Comments: Controls underwent sham operations; animal info (6 weeks old, diabetic (non-fasting blood glucose >16mM, polyuria, and glycosuria)); diabetes; Therapeutic indication (Vasculopathy, Hyperglycemic memory); Dose (35 pmol/min/kg);

Q5778: Pancreatic β -Cells Express the Fetal Islet Hormone Gastrin in Rodent and Human Diabetes. *Diabetes* 2016;66(2):
Agents: S961, Insulin receptor antagonist **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (6 weeks old);diabetes; Average blood glucose level at sacrifice, 515 mg/dL Therapeutic indication (Glucose tolerance, Diabetes);Dose (12 nmol);

Q4939: N. M. Templeman, *et al.* Suppression of hyperinsulinaemia in growing female mice provides long-term protection against obesity. *Diabetologia* 2015;58(10):2392-402
Agents: Insulin2, murine peptide **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 28 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (Ins1 -/-; 25 weeks old); functionality of mp verified by plasma insulin; peptides; diabetes; Dose (0.1 U/day);

Q4039: G. Pandey, *et al.* Insulin Regulates Nitric Oxide Production in the Kidney Collecting Duct Cells. *Journal of Biological Chemistry* 2015;590(5582-5591
Agents: Insulin (Humulin R) **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 14 days; 28 days;
ALZET Comments: Animal info (male, C57BL6J, 5 months old); cardiovascular;

Q5241: Keunhee Oh, *et al.* In Vivo Differentiation of Therapeutic Insulin-Producing Cells from Bone Marrow Cells via Extracellular Vesicle-Mimetic Nanovesicles. *ACS Nano* 2015;9(12):11718-11727
Agents: Insulin **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice (NOD); **Pump:** Not Stated; **Duration:** 14 days;
ALZET Comments: animal info (BALB/c, NOD male mice, aged 7-10 wks); functionality of mp verified by blood glucose levels; diabetes; Dose (0.14 units/day);

Q3779: G. T. Dodd, *et al.* Leptin and Insulin Act on POMC Neurons to Promote the Browning of White Fat. *Cell* 2015;160(88-104
Agents: Leptin; insulin, human **Vehicle:** Not Stated; **Route:** CSF/CNS; CSF/CNS (intra-arcuate nucleus of the hypothalamus); **Species:** Mice; **Pump:** 1002; **Duration:** 6 days;
ALZET Comments: Control animals received mp w/ vehicle; animal info (8 wks old, C57BL/6); ALZET brain infusion kit (3) used; Plastics One bilateral cannula used with PEG tubing and a Y connector

R0323: W. R. Crowley, *et al.* Neuroendocrine Regulation of Lactation and Milk Production. *Comprehensive Physiology* 2015;5(255-291
Agents: Leptin; insulin **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Animal info (female);

Q3794: L. Adzovic, *et al.* Insulin improves memory and reduces chronic neuroinflammation in the hippocampus of young but not aged brains. *Journal of Neuroinflammation* 2015;12(U1-U10
Agents: Insulin, recombinant cat; endotoxin, LPS **Vehicle:** CSF, artificial; **Route:** CSF/CNS (fourth ventricle); **Species:** Rat; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, F-344, 3 months old, 21 months old); bilateral cannula used; behavioral testing (morris water maze); tissue perfusion (fourth ventricle); bilateral infusion; used tygon tubing to attach cannula to pump;