



Recent References (2017-Present) Comparing Injection versus Infusion Using ALZET® Osmotic Pumps

ALZET pumps allow researchers to understand and optimize the key determinants of drug action. These determinants are the level of drug exposure and its duration, and the spatial distribution of drug relative to the target tissue. By manipulating these variables, drug effects can be optimized early in preclinical development, allowing clinical studies to be conducted at lower cost and with better results.

A drug's therapeutic index is a ratio reflecting the quotient of its therapeutic effects and adverse effects. Varying the schedule of administration can have a major influence on the therapeutic index of some drugs. Relative to bolus dosing, constant infusion can:

- increase efficacy,
- reduce side effects, or
- both increase efficacy and reduce side effects.

All of these changes can increase a drug's therapeutic index, improving its value as a pharmaceutical. One cannot assume, however, that infusion regimens are superior to injections for all drugs. The relationship between dose, regimen, and drug effect must be carefully explored for each drug. Dose-response testing, where the effects of one or more schedules of injections are compared with the effects of constant infusion, helps elucidate schedule-dependent drug effects. This type of testing has been termed the injection-infusion comparison (IIC) protocol. This protocol is an established method for optimizing the effectiveness of anticancer agents, and it is important in the preclinical testing of proteins, peptides, and other recombinant DNA products.

The references which follow explore the schedule or regimen dependence of a drug's therapeutic index. The notes following each reference detail the substance(s) infused, the route of administration, the animal model used, the vehicle for infusion, the pump model used, the duration of infusion, and notable technical achievements or results.

This list does not include references in this category from before 2010. To obtain a complete list of references published since 1975, please contact ALZET Technical Services at alzet@durect.com.

A more complete review of the injection-infusion comparison protocol can be found in the following references:

R0050 Fara J, and Urquhart J. *The Value of Infusion and Injection Regimens in Assessing Efficacy and Toxicity of Drugs.* *Trends Pharmacol Sci* 5 (1): pp. 21-25, 1984.

R0051 Urquhart J, Fara J, and Willis KL. *Rate-controlled Delivery Systems in Drug and Hormone Research.* *Ann Rev Pharmacol Toxicol* 24: pp. 199-236, 1984.



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Q11003: H. L. Song, *et al.* Monoclonal antibody Y01 prevents tauopathy progression induced by lysine 280-acetylated tau in cell and mouse models. *Journal of Clinical Investigation* 2023;133(8):

Agents: Monoclonal antibody Y01 **Vehicle:** PBS; **Route:** CSF/CNS (right lateral ventricle); **Species:** Mice; **Strain:** tau-P301L; **Pump:** Not Stated; **Duration:** 28 days;

ALZET Comments: Dose (1.9 mg/ml); Controls received mp w/ vehicle; animal info: 8 months; comparison of ip injection vs mp; ALZET brain infusion kit used; Brain coordinates: 0.58 mm posterior to bregma, 1 mm lateral to the midline, and 2 mm from the skull surface; behavioral testing (Nest building test; Y maze; Morris water maze); neurodegenerative (Alzheimer's disease)

Q10994: D. Selvakumar, *et al.* Delivery of Cardioactive Therapeutics in a Porcine Myocardial Infarction Model. *Journal of Visual Experiment* 2023;192):

Agents: Platelet-derived growth factor-AB, human **Vehicle:** Saline; **Route:** IV (jugular); **Species:** Pig; **Strain:** Not Stated; **Pump:** 2ML1; 2ML2; 2ML4; **Duration:** 7 days;

ALZET Comments: Dose: Controls received mp w/ vehicle; animal info: Pre-pubescent large white x landrace gilts, 18-20 kg, post op. care: 0.2 mg/kg of meloxicam SC; comparison of injections (thoracotomy, transepical, percutaneous transendocardial) vs mp; functionality of mp verified by recomb protein serum concentration (ELISA); cardiovascular (myocardial infarction); good methods p. 8, 13 fig. 2; no stress; "Jugular vein minipump insertion provides a safe and reliable method of PDGF delivery over a 7 day time period." p. 13

Q10992: A. Saoudi, *et al.* Investigating the Impact of Delivery Routes for Exon Skipping Therapies in the CNS of DMD Mouse Models. *Cells* 2023;12(6):

Agents: Oligonucleotides, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS (intracerebroventricular); **Species:** Mice; **Strain:** hDMD; mdx52; **Pump:** 1002; **Duration:** 2 weeks;

ALZET Comments: Dose (~700 nmol); animal info: 6–8-week-old mdx52 and WT mice; comparison of bolus injection vs mp; neurodegenerative (neurological disorder); brain tissue distribution

Q11059: K. Momenzadeh, *et al.* Propylene glycol and Kolliphor as solvents for systemic delivery of cannabinoids via intraperitoneal and subcutaneous routes in preclinical studies: a comparative technical note. *Journal of Cannabis Research* 2023;5(1):24

Agents: Tetrahydrocannabinol; cannabinoids **Vehicle:** Propylene glycol; Kolliphor; ethanol; saline; **Route:** IP; SC; **Species:** Rat; **Strain:** Sprague-Dawley; **Pump:** 2ML4; **Duration:** 8 weeks;

ALZET Comments: Dose (20 mg/kg); controls received mp w/ vehicle; animal info (13-week male (approximately 330 g); post op. care (Enrofloxacin); pumps replaced after 4 weeks; comparison of injection vs mp; stress/adverse reaction: (see pg.3-5); used sterile technique and changed solvent; "We conclude that subcutaneous delivery utilizing osmotic pumps with Kolliphor as a solvent provides viable and consistent route of administration for long-term systemic cannabinoid delivery in the preclinical context."

Q11104: K. Karimi Galougahi, *et al.* beta3 adrenergic agonism: A novel pathway which improves right ventricular-pulmonary arterial hemodynamics in pulmonary arterial hypertension. *Physiological Reports* 2023;11(1):e15549

Agents: CL316243 **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Mice; **Strain:** FVB/N; **Pump:** Not Stated; **Duration:** 2 weeks;

ALZET Comments: Dose (40µg/kg/h); Controls received mp w/ vehicle; animal info (Male Weighed 20-25 g; 10-16 weeks old); comparison of injection vs mp; comparison of gavage vs mp; receptor agonist (CL316243 is a B3 AR agonist);cardiovascular; Therapeutic indication (Pulmonary arterial hypertension);



Q10924: M. Ji, *et al.* Vaspin Ameliorates Cardiac Remodeling by Suppressing Phosphoinositide 3-Kinase/Protein Kinase B Pathway to Improve Oxidative Stress in Heart Failure Rats. *Journal of Cardiovascular Pharmacology* 2022;80(3):442-452
Agents: Angiotensin II **Vehicle:** Saline; **Route:** IP; **Species:** Rat; **Strain:** Sprague–Dawley; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Dose: (500 ng/kg/minute); Controls received mp w/ vehicle; animal info (Male (SD) rats (160–180 g); comparison of _ vs mp; (i.p. injection); Blood pressure measurement results (see pg. 3 table 2); Angiotensin II aka (Ang II); cardiovascular;

Q10488: F. Alzoughool, *et al.* Impact of Sustained Exogenous Irisin Myokine Administration on Muscle and Myocyte Integrity in Sprague Dawley Rats. *Metabolites* 2022;12(10):
Agents: Irisin, human recombinant **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2006; **Duration:** 42 days;
ALZET Comments: Dose (0.25 ug/ul)); animal info (Female; Weighed about 250 g); comparison of sc injection vs mp

Q10097: A. L. Koch, *et al.* Comparison of the effects of osmotic pump implantation with subcutaneous injection for administration of drugs after total body irradiation in mice. *Laboratory Animals Limited* 2021;55(2):142-149
Agents: Saline, sterile **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Strain:** Not Stated; **Pump:** 1004; **Duration:** 30 days;
ALZET Comments: post op. care triple antibiotic ointment administered twice a day; comparison of sc injection vs mp;

R0410: S. Ren, *et al.* Implantation of an Isoproterenol Mini-Pump to Induce Heart Failure in Mice. *JoVE* 2020;
Agents: Isoproterenol **Vehicle:** Saline; **Route:** IP; **Species:** Mice; **Strain:** Pump: 1004; **Duration:** 3 weeks; 4 weeks;
ALZET Comments: Dose (30 mg/kg/day); 0.9% saline used; Controls received mp w/ vehicle; animal info (9+ week old female, 18+ grams, no max body weight); post op. care (dedicated intubator to keep warm and dry, carprofen 5 mg/kg s.c. every 48 h as needed to minimize pain, 0.25 mg/ml amoxicillin in drinking water for 5 days to prevent surgical site infections); comparison of daily injections vs mp; cardiovascular (ISO administration induce cardiac failure); good methods (preparation, filling, priming, surgical implantation) pgs. 2-5; "The overall goal of this method is to induce heart failure in mice using an implanted mini pump that releases ISO continuously to mimic chronic sympathetic activation found in heart failure patients." pg. 2; "Continuous administration causes immediate hypotension on the day of pump implantation followed by normalization of blood pressure to mild hypertension by day 220. The overall hemodynamic trends more closely mimic chronically activated sympathetic hormones in heart failure patients. " pg. 7; susceptibility to ISO is variable among mouse strains;

Q7654: I. A. Zhuravin, *et al.* Regulation of Neprilysin Activity and Cognitive Functions in Rats After Prenatal Hypoxia. *Neurochem Res* 2019;44(6):1387-1398
Agents: epigallocatechin-3-gallate **Vehicle:** Saline; **Route:** CSF/CNS (parietal cortex); **Species:** Rat; **Pump:** Not Stated; **Duration:** 4 weeks;
ALZET Comments: Dose (0.25 µL/h of 10⁻³ M); Controls received mp w/ vehicle; animal info (4 months, Wistar); behavioral testing (novel object recognition test); comparison of oral administration vs mp; EGCG is a green tea catechin; Brain coordinates (Bregma=+0.20; L=3; H=1 mm); neurodegenerative (Alzheimer's); organisms used were offspring of rats submitted to prenatal hypoxia. Oral EGCG administration via drinking water was more beneficial than intracranial injection resulting in better cognitive outcome on memory test; Therapeutic indication (protect hippocampal formation and spatial memory in aged rats through an increase in NEP activity in blood plasma, Cx and Hip along with increased number of labile dendritic spines in their hippocampal CA1 area.);

Q7377: N. Morozumi, *et al.* ASB20123: A novel C-type natriuretic peptide derivative for treatment of growth failure and dwarfism. *PLoS One* 2019;14(2):e0212680
Agents: ASB20123 **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 1 week, 12 weeks;
ALZET Comments: Dose (0.05, 0.15 mg/kg/day); dose-response (fig 5); Controls received mp w/ vehicle; animal info (Seven-week-old male SD rats); comparison of injections vs mp "We also analyzed whether continuous sc infusion of ASB20123 to rats could accelerate skeletal growth, compared to the effects of multiple sc bolus injections"; long-term study; ASB20123 is a CNP/ghrelin chimeric peptide, composed of CNP(1-22) and human ghrelin (12-28, E17D); peptides; replacement therapy (dwarf);



Q7620: N. Kokuho, *et al.* Analyses of alveolar epithelial injury via lipid-related stress in mammalian target of rapamycin inhibitor-induced lung disease. *Lab Invest* 2019;99(6):853-865

Agents: Bleomycin hydrochloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 14 days;
ALZET Comments: Dose (100 mg/kg); Controls received i.p. injection w/ DMSO; animal info (7 weeks, female, C57BL/6); comparison of i.p. temsirolimus injection vs mp; BLM causes marked inflammation and epithelial injury in the lung; immunology; BLM dissolved in saline for pump (injury group) although controls used i.p. injected DMSO;

Q7582: B. Hunter, *et al.* (352) Sex Differences in Sensory Processing: The Role of Stimulus Modality and Psychological Factors. *The Journal of Pain* 2019;20(4):

Agents: fentanyl **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 5 days;
ALZET Comments: Dose (0.01mg/kg/hr); Controls received mp w/ vehicle; animal info (male, Sprague-Dawley); comparison of oxycodone and morphine injection vs mp; opioids administered 1 hour, 10 days, or 28 days post-CCI (chronic constriction injury) surgery;

Q7586: K. A. Horton, *et al.* Systemic Blockade of the CB1 Receptor Augments Hippocampal Gene Expression Involved in Synaptic Plasticity but Perturbs Hippocampus-Dependent Learning Task. *Cannabis and Cannabinoid Research* 2019;4(1):33-41

Agents: rimonabant **Vehicle:** saline; DMSO; Tween-80 buffer; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 28 days;
ALZET Comments: Dose (1.0 mg/kg/day); 10% DMSO and 0.1% Tween-80 in sterile saline used; Controls received mp w/ vehicle; animal info (male, Long-Evans); behavioral testing (DNMS cognitive task); comparison of intraperitoneal injection vs mp; rimonabant is a CB1 receptor antagonist; "Moreover, no performance deficits were observed in the current study using the continuous osmotic mini-pump infusion protocol." pg.39; "In three of the rimonabant treatment animals a second osmotic mini-pump was implanted because DNMS training was not successfully completed within the functional lifespan on the initial osmotic mini-pump." p.34;

Q7964: B. K. Chen, *et al.* Prophylactic efficacy of 5-HT4R agonists against stress. *Neuropsychopharmacology* 2019;45(542-552

Agents: RS 67333 **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Strain:** Pump: 2004; **Duration:** 3 weeks;
ALZET Comments: Dose (1.5 mg/kg/day); Controls received mp w/ vehicle; animal info (8 weeks, male, C57BL/6NTac); behavioral testing (elevated plus maze, novelty-suppressed feeding, sucrose splash test); comparison of acute injection vs mp; RS-67,333 (aka 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1(n-butyl)-4-piperidiny]-1-propanone HCl) is a high-affinity 5-HT4R partial agonist; Osmotic minipumps were rotated under the skin two to three times per week. "RS-67,333 was not performed in C57BL/6NTac mice, as a previous study of our own has shown that female C57BL/6NTac mice are insensitive to chronic CORT" p.20; Therapeutic indication (In C57BL/6NTac mice prophylactic RS-67,333 was effective at decreasing depressive- and anxiety-like behavior. In 129S6/SvEv mice, prophylactic RS-67,333 was effective at attenuating learned fear, but not decreasing depressive-like behavior.);

Q7951: R. Caire, *et al.* Parathyroid Hormone Remodels Bone Transitional Vessels and the Leptin Receptor-Positive Pericyte Network in Mice. *J Bone Miner Res* 2019;34(8):1487-1501

Agents: Parathyroid hormone (1-84) **Vehicle:** saline; **Route:** SC; **Species:** Mice; **Pump:** Not stated; **Duration:** 7, 14, 28 days;
ALZET Comments: Dose (100 µg/kg/day); Controls received SC injection of vehicle; animal info (4 months, female, C57BL/6J); comparison of SC injection vs mp; mp model not stated;

Q7950: W. Cai, *et al.* Translationally controlled tumor protein (TCTP) plays a pivotal role in cardiomyocyte survival through a Bnip3-dependent mechanism. *Cell Death Dis* 2019;10(8):549

Agents: isoproterenol **Vehicle:** Not stated; **Route:** SC; **Species:** Mice; **Pump:** Not stated; **Duration:** 2, 7 days;
ALZET Comments: Dose (60 mg/kg/day); animal info (2-3 months, male, C57BL/6); comparison of IP DOX injection and TAC vs mp; cardiovascular; mp used for ISO-induced heart failure model. mp model not stated;



Q7963: V. M. Breinholt, *et al.* TransCon CNP, a Sustained-Release C-Type Natriuretic Peptide Prodrug, a Potentially Safe and Efficacious New Therapeutic Modality for the Treatment of Comorbidities Associated with Fibroblast Growth Factor Receptor 3-Related Skeletal Dysplasias. *J Pharmacol Exp Ther* 2019;370(3):459-471

Agents: Peptide, C-type natriuretic **Vehicle:** Acetate Buffer; **Route:** SC; **Species:** Mice; **Pump:** 1002; 1004; **Duration:** 5 weeks; **ALZET Comments:** Dose (203 µg/kg/d); 30 mM acetate buffer (pH 4) with 5% sucrose and 1% benzylic alcohol used; Controls received mp w/ vehicle; animal info (3 weeks, male, FVB); pumps exchanged on day 15; comparison of SC injection vs mp; CNP-38 is a C-terminal 38 amino acid peptide structurally identical to endogenous CNP; peptides; "Overall growth effects on femur, tibia and spine were much stronger when CNP-38 was applied as a continuous subcutaneous infusion compared to a daily s.c. bolus injection indicating improved efficacy as a result of continuous exposure." pg.33; mp model 1002 used for days 1-15 and model 1004 for days 15-34;

Q8979: R. Yang, *et al.* A glucose-responsive insulin therapy protects animals against hypoglycemia. *JCI Insight* 2018;3(1):

Agents: Insulin, glucose-responsive; Insulin, recomb. human **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days; **ALZET Comments:** Dose ((GRI1 340 nmol/kg/day), (RHI 60 nmol/kg/day)); Controls received mp w/ vehicle; animal info (male, C57BL/6); comparison of SC injection vs mp; glucose-responsive insulin aka GRI is glycosylated insulin that has been conjugated to maltose and polymerized with concanavalin A; replacement therapy (insulin); diabetes;

Q8828: J. Xu, *et al.* Genetic identification of leptin neural circuits in energy and glucose homeostases. *Nature* 2018;556(7702):505-509

Agents: Leptin **Vehicle:** Saline; **Route:** CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days; **ALZET Comments:** Dose (454 ng/µl); Controls received mp w/ vehicle; animal info (4-8 weeks, Agrp-IRES-cre and Agrp-IRES-cre::LSL-Cas9-GFP); comparison of IP injection vs mp; Brain coordinates (AP: -0.50mm, ML:±1.3mm, DV: -2.3mm); replacement therapy (leptin);

Q8837: H. Xu, *et al.* Utility of IL-2 Complexes in Promoting the Survival of Murine Orthotopic Forelimb Vascularized Composite Allografts. *Transplantation* 2018;102(1):70-78

Agents: Rapamycin **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 28 days; **ALZET Comments:** Dose (2 mg/kg/day); Controls did not receive mp; animal info (male, C57BL/6 and BALB/c); comparison of IP injection of FK506 vs mp; immunology; RPM monotherapy was about as effective as post-Tx IL-2C in prolonging survival. Co-administration of IL-2C and post-Tx RPM had additional benefits, with pre-Tx IL-2C plus RPM causing a fivefold increase in survival, and post-Tx IL-2C plus RPM causing a threefold increase in survival;

Q8835: J. Xiao, *et al.* Notoginsenoside R1, a unique constituent of Panax notoginseng, blinds proinflammatory monocytes to protect against cardiac hypertrophy in ApoE(-/-) mice. *European Journal of Pharmacology* 2018;833(441-450

Agents: Isoproterenol **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 2 weeks; **ALZET Comments:** Dose (25 mg/kg/day); Controls received mp w/ vehicle; animal info (8 weeks, male, ApoE(-/-), 23-27g); comparison of IP injection of Notoginsenoside R1 vs mp; cardiovascular; isoproterenol used to induce myocardial hypertrophy and fibrosis;

Q8784: Y. Wu, *et al.* Downregulation of Gprotein-coupled receptor 30 in the hippocampus attenuates the neuroprotection of estrogen in the critical period hypothesis. *Molecular Medicine Reports* 2018;17(4):5716-5725

Agents: Estradiol, 17-beta- **Vehicle:** Saline, Normal; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 1, 10 weeks; **ALZET Comments:** Dose (0.025 mg/day); Controls received sham surgery; animal info (3/24 months, female, SD, 250-300g or 450-500g); comparison of ICV injection vs mp; ischemia (global cerebral ischemia); replacement therapy (estradiol); Rats received E2 10 weeks immediately post-ovariectomy, or for 1 week after 10 weeks post-ovariectomy; Therapeutic indication (EE2 must be administered during perimenopause to observe its neurological benefit within CA1 region of the hippocampus);

Q8782: E. Wolf, *et al.* Vascular type 1 angiotensin receptors control blood pressure by augmenting peripheral vascular resistance in female mice. *American Journal of Physiology Renal Physiology* 2018;315(4):F997-F1005

Agents: Angiotensin II **Vehicle:** Saline, Sterile; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 5, 28 days; **ALZET Comments:** Dose (1000 ng/kg/min); Controls did not receive mp; animal info (10-30 weeks, female, C57BL/6 and SMKO); comparison of IV injection vs mp; cardiovascular;



Q8780: A. Willeford, *et al.* CaMKII δ -mediated inflammatory gene expression and inflammasome activation in cardiomyocytes initiate inflammation and induce fibrosis. *JCI Insight* 2018;3(12):

Agents: Angiotensin II **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (1.5 μ g/kg/min); Controls received mp w/ vehicle; animal info (8-12 weeks, male, Camk2d(fl/fl), CaMKII δ KO, and Nlrp3(–/–)); comparison of IP injection vs mp; cardiovascular; immunology; AngII used to induce inflammatory and fibrotic responses;

Q6549: M. Shimamura, *et al.* Development of a novel RANKL-based peptide, microglial healing peptide1-AcN (MHP1-AcN), for treatment of ischemic stroke. *Sci Rep* 2018;8(1):17770

Agents: Microglial healing peptide1-AcN **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001D; **Duration:** 24 hours;

ALZET Comments: Dose (0.5, 1, or 2 mg/ml); Controls received mp w/ vehicle; animal info (C57BL6/J mice); comparison of intravenous injection vs mp; MHP1-AcN is a novel partial peptide of RANKL with N-terminal acetylation and C-terminal amidation; Therapeutic indication (ischemic stroke);

Q8770: W. Wang, *et al.* Intratumoral delivery of bortezomib: impact on survival in an intracranial glioma tumor model. *J Neurosurg* 2018;128(3):695-700

Agents: Bortezomib **Vehicle:** Saline; **Route:** CSF/CNS (Cranium); **Species:** Mice; **Pump:** 2002; **Duration:** 14 days;

ALZET Comments: Dose (0.36, 1.2, 3.6 μ g); Controls did not receive tumor injection and received mp w/ vehicle; animal info (athymic, nu/nu); comparison of iv injection vs mp; ALZET brain infusion kit used (model not stated); cancer (Glioblastoma); "The pump was used because it is an efficient method for intratumoral administration and circumvents the BBB." pg.698. "The mini-osmotic pump provides drug treatment directly to the brain and also bypasses the liver, thereby achieving the desired drug concentration in the glioma microenvironment while avoiding the use of high drug doses." p.699 ; "Tumor progression could not be determined using imaging because the pump interfered with imaging." p.698. "doses at 7.2 μ g, 18.0 μ g, and 36.0 μ g were toxic and fatal to the testing animals." p.698; Therapeutic indication (bortezomib can be an effective therapy for the treatment of GBM, as long as the drug is administered in such a way that the BBB is circumvented.);

Q8775: D. Wang, *et al.* Slow Infusion of Recombinant Adeno-Associated Viruses into the Mouse Cerebrospinal Fluid Space. *Human Gene Therapy Methods* 2018;29(2):75-85

Agents: Virus, recombinant adeno-associated **Vehicle:** Saline; **Route:** CSF/CNS (subarachnoid space); CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 2001D; **Duration:** 40, 42 hours;

ALZET Comments: Dose (1·10¹¹, 2·10¹² GC in 200 μ L); Controls received mp w/ vehicle; animal info (6 weeks, male and female, C57BL/6J, 20g); post op. care (200 μ L of 0.9% saline by i.p. injection); comparison of IT injection vs mp; recombinant adeno-associated viruses (rAAVs) packaged in several serotypes such as AAV9 and AAV.rh10 can cross the BBB and transduce neurons and glia in rodents and nonhuman primates; Brain coordinates ((-0.9,-0.2) for the left ventricle, or (+0.9, -0.2) for the right ventricle); Cannula placement verified via stereotaxic frame; cyanoacrylate adhesive for icv delivery (Loctite); gene therapy; good methods (detailed pump installation instructions for IT and ICV delivery of agent on p.77-83); "IT pump infusion resulted in more widespread and higher transduction of the spinal cord than a bolus IT injection" pg.83; recombinant adeno-associated virus serotype 9 (rAAV9) used for examples;

Q8756: A. E. Vozenilek, *et al.* Absence of Nicotinamide Nucleotide Transhydrogenase in C57BL/6J Mice Exacerbates Experimental Atherosclerosis. *Journal of Vascular Research* 2018;55(2):98-110

Agents: Manganese Chloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 15 days;

ALZET Comments: Dose (25, 50 mg/kg/day); Controls received mp w/ vehicle; animal info (10-12 weeks, male, B6129SF1/Tac); post op. care (2 mg/kg meloxicam for 3 days); behavioral testing (Morris Water Maze); comparison of IP injection vs mp; MRI; stress/adverse reaction: ("mice implanted with pumps swam more slowly on the first 2 days of training than the control animals. By day 3 this difference had normalized, and there was no effect of pumps, MnCl₂ treatment, or specific treatment group on swim speed." p.417. "Some mice that received MnCl₂ via osmotic pump developed skin ulceration where the solution was being released from the pump. In 4/17 cases, the ulceration was so severe that the mice had to be euthanized." p.417); "when mice are given 50 mg/kg/day MnCl₂ via osmotic pump, the useable imaging window is only from day 3 to day 5. The useable imaging window for mice receiving 25 mg/kg/day is approximately 3–14 days." p.419;



Q7932: D. A. Vousden, *et al.* Continuous manganese delivery via osmotic pumps for manganese-enhanced mouse MRI does not impair spatial learning but leads to skin ulceration. *Neuroimage* 2018;173(4):11-420

Agents: manganese chloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 15 days;

ALZET Comments: Dose (25, 50 mg/kg/day); Controls received mp w/ vehicle; animal info (10-12 weeks, male, B6129SF1/Tac); post op. care (2 mg/kg meloxicam for 3 days); behavioral testing (Morris Water Maze); comparison of IP injection vs mp; MRI; stress/adverse reaction: ("mice implanted with pumps swam more slowly on the first 2 days of training than the control animals. By day 3 this difference had normalized, and there was no effect of pumps, MnCl₂ treatment, or specific treatment group on swim speed." p.417. "Some mice that received MnCl₂ via osmotic pump developed skin ulceration where the solution was being released from the pump. In 4/17 cases, the ulceration was so severe that the mice had to be euthanized." p.417); "when mice are given 50 mg/kg/day MnCl₂ via osmotic pump, the useable imaging window is only from day 3 to day 5. The useable imaging window for mice receiving 25 mg/kg/day is approximately 3–14 days." p.419;

Q7929: S. B. Vasamsetti, *et al.* Sympathetic Neuronal Activation Triggers Myeloid Progenitor Proliferation and Differentiation. *Immunity* 2018;49(1):93-106 e7

Agents: ICI-118,551 hydrochloride; Toxin, Diptheria; reserpine; captopril; norepinephrine **Vehicle:** PBS; **Route:** Intraspinal; **Species:** Mice; **Pump:** 1002; **Duration:** 1, 2, 3 weeks;

ALZET Comments: "Dose ((ICI-118,551 12 mg/kg/hr), (Diptheria Toxin 5 mg/kg/day), (reserpine 5mg/kg/day), (captopril 6mg/kg/day), (norepinephrine 5mg/kg/day)); Controls received mp w/ vehicle; animal info (10-12 weeks, Apoe(-/-)); comparison of intraspinal injection vs mp; ICI-118,551 hydrochloride is a selective antagonist of the beta2 adrenergic receptor. angiotensin converting enzyme (ACE) inhibitor. Reserpine blocks the uptake of catecholamines into synaptic vesicles; Reserpine is an enzyme inhibitor (vesicular monoamine transporter 2); immunology; Diptheria toxin used to deplete TH+ leukocytes. Splenic nerves were depleted by intraspinal DT using mp for 7 days; Therapeutic indication (ICI-118,551 reduced splenic GMP proliferation and inflammatory myeloid cell generation); "

Q7766: A. R. Johnson, *et al.* Amphetamine maintenance differentially modulates effects of cocaine, methylenedioxypyrovalerone (MDPV), and methamphetamine on intracranial self-stimulation and nucleus accumbens dopamine in rats. *Neuropsychopharmacology* 2018;43(8):1753-1762

Agents: amphetamine **Vehicle:** saline, bacteriostatic; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 7, 13 days;

ALZET Comments: Dose (0.1 or 0.32 mg/kg/h), (2ML2 pump 0.5 µl/h); Controls received mp w/ vehicle; animal info (male, Sprague-Dawley, 300-350g); behavioral testing (operant chambers); comparison of IP injection vs mp; dependence;

Q7757: K. Iizuka, *et al.* Analysis of the prolonged infusion of DFP-10917, a deoxycytidine analog, as a therapeutic strategy for the treatment of human tumor xenografts in vivo. *Int J Oncol* 2018;52(3):851-860

Agents: DFP-10917 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1, 3, 14 days;

ALZET Comments: Dose (4.5, 8, 30 mg/kg/day); Controls received no treatment; animal info (5 weeks, male, BALB/cA Jcl-nu, 17.2-24.6g); comparison of bolus injection vs mp; DFP-10917 AKA 2'-C-cyano-2'-deoxy-1-beta-D-arabino-pentofuranocytosine is a 2'-deoxycytidine analog with antitumor activity; cancer (tumor xenografts); Infusion of agent occurred on three regimens: 24 consecutive hours on days 1 and 8, for 3 consecutive days on days 1 and 15, or for 14 consecutive days (p.852); Therapeutic indication ("regression of tumor growth without any toxicities on human solid and hematological tumor xenografts compared to clinically available deoxycytidine analogs." p.858);

Q7919: R. Ichimaru, *et al.* Raloxifene reduces the risk of local alveolar bone destruction in a mouse model of periodontitis combined with systemic postmenopausal osteoporosis. *Archives of Pharmacol Research* 2018;85(9):8-103

Agents: Raloxifene **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice (ovariectomized); **Pump:** Not Stated; **Duration:** 4 weeks;

ALZET Comments: Dose (300 µg/kg/day); Controls received sham surgery and mp w/ agent; animal info (4 weeks, female, ddY strain); comparison of local injection vs mp; "However, our study found that the in vivo local injection of raloxifene did not prevent bone resorption in a mouse model of periodontitis, although the systemic treatment of raloxifene using a mini-osmotic pump did prevent the loss of alveolar bone mass induced by LPS injection." pg.102; Therapeutic indication (raloxifene systemically maintain alveolar bone mass in a mouse model of periodontitis with osteoporosis);



Q7909: R. Hill, *et al.* Oxycodone-induced tolerance to respiratory depression: reversal by ethanol, pregabalin and protein kinase C inhibition. *Bulletin of Experimental Biology and Medicine* 2018;175(12):2492-2503

Agents: oxycodone **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 6 days;

ALZET Comments: Dose (20, 45 or 120 mg/kg/day); Controls received mp w/ vehicle; animal info (male, CD-1, 30g); comparison of IP injection vs mp; Resultant plasma level ((Low 81 ± 8 ng/ml), (Med 284 ± 147 ng/ml), (High 1670 ± 635 ng/ml)); dependence; brain levels of oxycodone include ((Low 248 ± 126 ng/g), (Med 426 ± 87 ng/g), (High 1703 ± 665 ng/g));

Q10086: R. Babaei, *et al.* Jak-TGF β cross-talk links transient adipose tissue inflammation to beige adipogenesis. *Science Signaling* 2018;11(Agents: CL-316243 **Vehicle:** Saline; **Route:** SC **Species:** Mice; **Pump:** Not Stated; **Duration:** 7 days;

ALZET Comments: Dose (1mg/kg/day); equivalent volume to agent used; Controls received mp w/ vehicle; animal info (7-12wk old, female, created adipocyte specific ATGL KO mice); comparison of injection vs mp; enzyme inhibitor (β 3-adrenoreceptor agonist); "in vivo β -adrenergic stimulation, mice were either intraperitoneally injected with CL-316243 (1 mg/kg) or equivalent volume of saline (acute treatments) or subcutaneously implanted with Alzet minipumps delivering saline or CL-316243 (1 mg/kg per day). Our model reinforces the idea that transient inflammation promotes the induction of adaptive adipose tissue remodeling"; Therapeutic indication (results provide insight into the activation of adipocyte progenitors and are relevant for the therapeutic targeting of adipose tissue inflammatory pathways.);

Q10360: R. Babaei, *et al.* Jak-TGF β cross-talk links transient adipose tissue inflammation to beige adipogenesis. *Science Signaling* 2018;11(eaai7838

Agents: CL-316243 **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 7 days;

ALZET Comments: "Dose (1mg/kg/day); equivalent volume to agent used; Controls received mp w/ vehicle; animal info (7-12wk old, female, created adipocyte specific ATGL KO mice); comparison of injection vs mp; enzyme inhibitor (β 3-adrenoreceptor agonist); in vivo β -adrenergic stimulation; Our model reinforces the idea that transient inflammation promotes the induction of adaptive adipose tissue remodeling; Therapeutic indication (results provide insight into the activation of adipocyte progenitors and are relevant for the therapeutic targeting of adipose tissue inflammatory pathways); "

Q7828: H. Haselmann, *et al.* Human Autoantibodies against the AMPA Receptor Subunit GluA2 Induce Receptor Reorganization and Memory Dysfunction. *Neuron* 2018;100(1):91-105 e9

Agents: Immunoglobulin G, human; antibody, human IgG **Vehicle:** Saline; **Route:** CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Dose (10mg/ml at 0.25 μ l/h); Controls received mp w/ vehicle; animal info (male, C57BL/6J); behavioral testing (Novel object recognition, locomotor activity box, elevated plus maze, black-and-white test); comparison of stereotactic microinjection vs mp; a-GluA2 IgG are autoantibodies against only the GluA2 subunit of the AMPAR; Brain coordinates (0.2 mm posterior and \pm 1.00 mm lateral from bregma, depth 2.2 mm); bilateral cannula used (PlasticsOne, model 3280PD-2.0/SP); neurodegenerative (Autoimmune encephalitis); immunology; purified IgG fraction and antibody sources described on page e2

Q6281: F. Yang, *et al.* Delivery of epirubicin via slow infusion as a strategy to mitigate chemotherapy-induced cardiotoxicity. *PLoS One* 2017;12(11):e0188025

Agents: Epirubicin **Vehicle:** Not Stated; **Route:** IP; **Species:** Rat; **Pump:** 1003D; **Duration:** 12-72 hours;

ALZET Comments: Dose (8 mg/kg body weight); animal info (6–9 weeks old male Sprague-Dawley rats); comparison of IV injections vs mp; "we found that continuous intravenous infusion of epirubicin using micro-pumps had less cardiotoxicity than intravenous bolus infusion of epirubicin at the same total dose of 70 mg/m² " pg. @;

Q6539: F. Wichern, *et al.* Perinatal nicotine treatment induces transient increases in NACHO protein levels in the rat frontal cortex. *Neuroscience* 2017;346(278-283

Agents: Nicotine Hydrogen Tartate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat (pregnant); **Pump:** 2006; **Duration:** 6 weeks;

ALZET Comments: Dose (4 mg/kg/day); animal info (timed-pregnant (SD) rats); comparison of injections vs mp;



Q6745: D. S. Poole, *et al.* Continuous infusion of manganese improves contrast and reduces side effects in manganese-enhanced magnetic resonance imaging studies. *Neuroimage* 2017;147(1-9

Agents: Manganese Chloride **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 8 days;

ALZET Comments: Dose (30 mg/kg and 60 mg/kg); Controls received mp w/ vehicle; animal info (10 week old C57BL/6J mice); comparison of IP injections vs mp; MRI; "Our study demonstrates that the osmotic pump is able to deliver Mn to the brain (and in a suitable amount) with contrast comparable to that achieved via IP injections. Although a higher dose does appear necessary to achieve a similar contrast, this higher dose administered via osmotic pump can be used without giving side effects. Additionally, the constant delivery of manganese ensures a stable blood level and presumably a more timing-independent manganese uptake during activation. Lastly, osmotic pump delivery ensures less animal handling during the experiment, which may be a large advantage for many studies involving behavior, fear or stress, where animal handling may have a large influence on the experimental outcome." pg.8 ;

Q6237: A. Patnaik, *et al.* Cabozantinib Eradicates Advanced Murine Prostate Cancer by Activating Antitumor Innate Immunity. *Cancer Discovery* 2017;7(7):750-765

Agents: Plerixafor; AMD3100; cabozantinib; **Species:** Mice; **Pump:** 1007D; **Duration:** 3 days;

ALZET Comments: Dose (90 mg/mL); animal info (male Pb-Cre; Ptenfl/flTrp53fl/fl mice with tumor); comparison of Plerixafor daily injection vs mp; AMD3100 is a CXCR4 inhibitor; cancer (prostate);

Q5357: F. Muller, *et al.* Paclitaxel synergizes with exposure time adjusted CD22-targeting immunotoxins against B-cell malignancies. *ONCOTARGET* 2017;1-12

Agents: HA22- PE24 **Vehicle:** Citrate buffer; **Route:** IP; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (6-8-week-old NSG mice); JeKo-1 xenograft model; Citrate buffer: 32 mM citrate, 0.65% Tween80, 5 mM EDTA; comparison of 3 times IV bolus injections vs mp; cancer (Mantle Cell Lymphoma); half-life: 15 minutes in mice (p. 4); To enable continuous drug delivery in vivo, the rIT-formulation buffer was optimized to ensure protein stability. Stability for 7-days with citrate buffer verified using WST-8 cell proliferation assay; "Continuous infusion substantially increased efficacy of LR compared to bolus dose administration." pg 4; "a well-tolerated total amount of 84 µg LR given by continuous infusion is substantially more active than the 120 µg LR given as three bolus doses QOD." (P. 5); Because rITs have a short plasma half-life in mice and men, blood levels fall quickly after a bolus dose; Dose (1 mg/ml); Immunotoxin plasma concentration was on average 45 ng/ml, correlating with an AUC of 350 ng x day/mL plasma. This steady state plasma concentration was higher than the IC50 of any of the MCL cell lines tested.

Q6147: D. Leu, *et al.* CNS bioavailability and radiation protection of normal hippocampal neurogenesis by a lipophilic Mn porphyrin-based superoxide dismutase mimic, MnTnBuOE-2-PyP(5). *Redox Biol* 2017;12(864-871

Agents: Porphyrin, Mn **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 2-6 weeks;

ALZET Comments: Dose (3 mg/kg/day); animal info (25g male C57BL/6J mice); Comparison of 2X daily injections vs mp ("Mice received either two daily subcutaneous (sc) injections (2×1.5 mg/kg) for 7–14 days, or continuous infusion for 2–6 weeks using a model 1004 Alzet® osmotic pump loaded with 28.4 mg/ml MnP"); Resultant plasma level (Fig. 1D p.865);

Q6299: P. B. Katare, *et al.* Toll-Like Receptor 4 Inhibition Improves Oxidative Stress and Mitochondrial Health in Isoproterenol-Induced Cardiac Hypertrophy in Rats. *Front Immunol* 2017;8(719

Agents: TLR4 receptor inhibitor RS-LPS; agonist lipopolysaccharide; isoproterenol **Vehicle:** Saline, pyrogen-free; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 14 days;

ALZET Comments: Dose (RS-LPS: 5 µg/day; lipopolysaccharide: 3.12 ug/day); Controls received mp w/ vehicle; animal info (Male Sprague- Dawley rats weighing 200–250 g); comparison of sc injections vs mp; cardiovascular;

Q6254: S. A. Grenald, *et al.* Targeting the S1P/S1PR1 axis mitigates cancer-induced bone pain and neuroinflammation. *Pain* 2017;158(9):1733-1742

Agents: FTY720 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (1 mg/kg/d); Controls received mp w/ vehicle; animal info (Female BALB/c mice weighing 18-20 g); comparison of single daily injection vs mp; FTY720 aka fingolimod; cancer ();