



Recent References (2018-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)

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:** Large white x landrace; **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:** 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."

Q11251: K. T. Brown, *et al.* Toll-like receptor 4 antagonists reduce cocaine-primed reinstatement of drug seeking. *Psychopharmacology* 2023;240(7):1587-1600

Agents: Naltrexone **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Strain:** Sprague-Dawley; **Pump:** 2ML1; 2ML2; **Duration:** 7; 14 days;

ALZET Comments: Dose: 15 mg/kg/day; Controls received mp w/ vehicle; animal info (Male; Weighed 330-350 g); comparison of acute injection vs mp; dependence; testing cocaine self-administration after pump implant

Q11173: D. E. Leisman, *et al.* Angiotensin II enhances bacterial clearance via myeloid signaling in a murine sepsis model. *Proceedings of the National Academy of Sciences* 2022;119(34):e2211370119

Agents: Angiotensin II, synthetic **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Strain:** C57BL/6; **Pump:** 1003D; **Duration:** 6 hours; 24 hours;

ALZET Comments: Dose: 10 ng/kg/min; 0.9% saline used; Controls received mp w/ vehicle; animal info: Male C57BL/6 mice aged 12 to 14 wk; comparison of SC injection vs mp; toxicology;



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); 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; **Strain:** Not Stated; **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:** Not Stated; **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 Nephrylsin 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; **Strain:** Wistar; **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,); 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.);

Q6792: G. M. Shackelford, *et al.* Continuous and bolus intraventricular topotecan prolong survival in a mouse model of leptomeningeal medulloblastoma. *PLoS One* 2019;14(1):e0206394
Agents: Topotecan **Vehicle:** Saline; **Route:** CSF/CNS (ventricle); **Species:** Mice; **Strain:** J:NU (homozygous for the Foxn1nu mutation); **Pump:** 2004; **Duration:** 28 days;
ALZET Comments: Dose (5.28 µg/day); Controls received mp w/ vehicle; animal info (mice ; comparison of bolus dosing injection vs mp; cancer (Leptomeningeal medulloblastoma);



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; **Strain:** Sprague-Dawley (SD); **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 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;

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; **Strain:** C57BL/6; **Pump:** 2001; **Duration:** 14 days; **ALZET Comments:** Dose (100 mg/kg); Controls received i.p. injection w/ DMSO; animal info (7 weeks, female,); 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;

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; **Strain:** Long-Evans; **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,); 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:** C57BL/6NTac; **Pump:** 2004; **Duration:** 3 weeks; **ALZET Comments:** Dose (1.5 mg/kg/day); Controls received mp w/ vehicle; animal info (8 weeks, male,); 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-piperidinyl]-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; **Strain:** C57BL/6J; **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,); 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; **Strain:** C57BL/6; **Pump:** Not Stated; **Duration:** 2, 7 days; **ALZET Comments:** Dose (60 mg/kg/day); animal info (2-3 months, male,); 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; **Strain:** FVB; **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,); 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 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Strain:** C57BL/6; **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; 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; vehicle used, but identity not stated;

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; **Strain:** Agrp-IRES-cre; Agrp-IRES-cre::LSL-Cas9-GFP; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (454 ng/µl); Controls received mp w/ vehicle; animal info (4-8 weeks,); 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; **Strain:** C57BL/6; BALB/c; **Pump:** Not Stated; **Duration:** 28d

ALZET Comments: Dose (2 mg/kg/day); Controls did not receive mp; animal info (male,); 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; **Strain:** ApoE(-/-); **Pump:** Not Stated; **Duration:** 2 weeks;

ALZET Comments: Dose (25 mg/kg/day); Controls received mp w/ vehicle; animal info (8 weeks, male, , 23-27g); comparison of IP injection of Notoginsenoside R1 vs mp; cardiovascular; isoproterenol used to induce myocardial hypertrophy and fibrosis;

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: Ang II **Vehicle:** Saline, Sterile; **Route:** SC; **Species:** Mice; **Strain:** C57BL/6; SMKO; **Pump:** 2004; **Duration:** 5, 28 days

ALZET Comments: Dose (1000 ng/kg/min); Controls did not receive mp; animal info (10-30 weeks, female,); comparison of IP injection vs mp; cardiovascular;

Q8780: A. Willeford, *et al.* CaMKIIdelta-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; **Strain:** Camk2d(fl/fl), CaMKIIdelta KO; Nlrp3(-/-); **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (1.5 µg/kg/min); Controls received mp w/ vehicle; animal info (8-12 weeks, male,); comparison of IP injection vs mp; cardiovascular; immunology; AngII used to induce inflammatory and fibrotic responses;



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; **Strain:** Athymic, nu/nu; **Pump:** 2002; **Duration:** 14 days;

ALZET Comments: Dose (0.36, 1.2, 3.6 µg); Controls did not receive tumor injection and received mp w/ vehicle; animal info (); 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 µg, 18.0 µg, and 36.0 µg 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; **Strain:** C57/BL6J; **Pump:** 2001D; **Duration:** 40, 42 hours;

ALZET Comments: Dose ($1 \cdot 10^{11}$, $2 \cdot 10^{12}$ GC in 200 µL); Controls received mp w/ vehicle; animal info (6 weeks, male and female, C57BL/6J, 20g); post op. care (200 µL 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;

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):411-420

Agents: Manganese Chloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Strain:** B6129SF1/Tac; **Pump:** 1004; **Duration:** 15 d

ALZET Comments: Dose (25, 50 mg/kg/day); Controls received mp w/ vehicle; animal info (10-12 weeks, male,); 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, Diphtheria; reserpine; captopril; norepinephrine **Vehicle:** PBS; **Route:** Intrasplenic; **Species:** Mice; **Strain:** Apoe(-/-); **Pump:** 1002; **Duration:** 1, 2, 3 weeks;

ALZET Comments: "Dose ((ICI-118,551 12 mg/kg/hr), (Diphtheria 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,); comparison of intrasplenic 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; Diphtheria toxin used to deplete TH+ leukocytes. Splenic nerves were depleted by intrasplenic DT using mp for 7 days; Therapeutic indication (ICI-118,551 reduced splenic GMP proliferation and inflammatory myeloid cell generation); "



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; **Strain:** C57Bl6/J; **Pump:** 2001D; **Duration:** 24 hours;

ALZET Comments: Dose (0.5, 1, or 2 mg/ml); Controls received mp w/ vehicle; animal info (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);

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; **Strain:** Sprague-Dawley; **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, , 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; **Strain:** BALB/cA Jcl-nu; **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, , 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 Pharmacal Research* 2018;85(98-103

Agents: Raloxifene **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice (ovariectomized); **Strain:** ddY strain; **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,); 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; **Strain:** CD-1; **Pump:** Not Stated; **Duration:** 6 days;

ALZET Comments: Dose (20, 45 or 120 mg/kg/day); Controls received mp w/ vehicle; animal info (male, , 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 ± 126ng/g), (Med 426±87 ng/g), (High 1703±665 ng/g));