



ALZET® Osmotic Pumps References from 2010-2018: Injection-Infusion Comparison

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 (800) 692-2990 (U.S. & Canada), or (408) 367-4036. You may also contact us via e-mail at alzet@direct.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.



Recent References (2010-2018) Comparing Injection versus Infusion Using ALZET® Osmotic Pumps

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

ALZET Comments: Microglial healing peptide1-AcN; Saline; SC; Mice; 2001D; 24 hours; 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);.

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

ALZET Comments: Epirubicin; IP; Rat; 1003D; 12-72 hours; 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

ALZET Comments: Nicotine Hydrogen Tartate; SC; Rat (pregnant); 2006; 6 weeks; Dose (4 mg/kg/day); animal info (timed-pregnant Sprague Dawley (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

ALZET Comments: Manganese Chloride; PBS; SC; Mice; 1002; 8 days; 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 Discov* 2017;7(7):750-765

ALZET Comments: Plerixafor; AMD3100; cabozantinib; Mice; 1007D; 3 days; 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

ALZET Comments: HA22- PE24 recombinant immunotoxin; Citrate buffer; IP; Mice; 1007D; 7 days; 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/mlPlasma. 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

ALZET Comments: Porphyrin, Mn; PBS; SC; Mice; 1004; 2-6 weeks; 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

ALZET Comments: TLR4 receptor inhibitor RS-LPS; agonist lipopolysaccharide; isoproterenol; Saline, pyrogen-free; SC; Rat; 14 days; 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

ALZET Comments: FTY720; SC; Mice; 1007D; 7 days; 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 ();.

Q6473: Gravius A, *et al.* Further pharmacological characterization of eltoprazine: focus on its anxiolytic, anorexic, and adverse effect potential. *Acta Neurobiol Exp (Wars)* 2017;77(1):77-85

ALZET Comments: Eltoprazine; Water; SC; Rat; 2ML2; Dose (8 mg/kg/day); animal info (male Sprague Dawley rats weighing 180–200 g); behavioral testing (elevated plus testing); comparison of twice daily SC injections (1 mg/kg) vs mp; Eltoprazine aka 1 (2,3 dihydro 1,4 benzodioxin 8 yl)piperazine; neurodegenerative (Parkinson's disease);.

Q5327: G. Futamura, *et al.* Evaluation of a novel sodium borocaptate-containing unnatural amino acid as a boron delivery agent for neutron capture therapy of the F98 rat glioma. *Radiat Oncol* 2017;12(1):26

ALZET Comments: Boron-10 containing sodium borocaptate, ACBC-BSH (Boron-10 derivative); CSF/CNS; Rat; 2001D; 24 hours; ALZET brain infusion kit used; comparison of IV injections vs mp; cancer (F98 glioma); brain tissue distribution; "we succeeded in achieving a high accumulation of boron in the tumors of rats in which ACBC-BSH was administered by CED, compared with ACBC-BSH administered intravenously" pg. 9 ; ACBC-BSH is a boron-10 containing sodium borocaptate derivative, 1-amino-3-fluorocyclobutane-1-carboxylic acid; Dose (1.2 mg/kg);.

Q6414: L. D. BonDurant, *et al.* FGF21 Regulates Metabolism Through Adipose-Dependent and -Independent Mechanisms. *Cell Metab* 2017;25(4):935-944 e4

ALZET Comments: Fibroblast growth factor-21, recomb. human; SC; Mice (knockout); 2 weeks; Dose (1 mg/kg/day); Controls received mp w/ vehicle; animal info (16–18 week old WT and KLB AdipoKO male mice on HFD for 12 weeks); comparison of IP injection vs mp;.

Q5942: A. Akopian, *et al.* Targeting neuronal gap junctions in mouse retina offers neuroprotection in glaucoma. *J Clin Invest* 2017;127(7):2647-2661

ALZET Comments: meclofenamic acid; SC; Mice; 2004; 8 weeks; animal info (3-4 months); pumps replaced every 4 weeks; comparison of injection vs mp; neurodegenerative (glaucoma); stress/adverse reaction: We found that animals in which subcutaneous minipumps were inserted for MFA delivery had significant problems swimming the water maze, which compromised the ability to assess the visual behavioral tests (page 2659); Therapeutic indication (Glaucoma); Dose ((5, 10, and 20 mg/kg/d));.

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

ALZET Comments: insulin; buffer solution; SC; Rat; 28 days; 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

ALZET Comments: Insulin, Insulin Detemir; Saline; SC; Mice; 8 days; 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);.

Q5052: G. Murlidharan, *et al.* CNS-restricted Transduction and CRISPR/Cas9-mediated Gene Deletion with an Engineered AAV Vector. Mol Ther Nucleic Acids 2016;5(7):

ALZET Comments: Viral vector, adeno-associated (AAV9, AAV2g0); Gene, CBh-ScGFP; CSF/CNS (intrathecal); Mice; 2001D; 24 hrs; animal info (8 weeks old C57/Bl6 male mice); comparison of IT bolus injections vs mp; ALZET mouse intrathecal catheter used (lumbar cannulation); gene therapy;.

Q6625: G. Mulas, *et al.* Differential induction of dyskinesia and neuroinflammation by pulsatile versus continuous L-DOPA delivery in the 6-OHDA model of Parkinson's disease. Exp Neurol 2016;286(83-92

ALZET Comments: L-DOPA; Benserazide; SC; Rat; 2ML2; 2 weeks; Dose (12mg/kg/day); animal info (6-OHDA-lesioned male Sprague-Dawley rats weighing 275-300g); comparison of pulsatile injections vs mp; neurodegenerative (Parkinson's disease);.

Q6693: S. Liao, *et al.* Comparison of pulsatile vs. continuous administration of human placental growth hormone in female C57BL/6J mice. Endocrine 2016;54(1):169-181

ALZET Comments: Growth hormone, placental variant; SC; Mice; 1007D; 1 week; Dose (2 or 5 mg/kg/day); Controls received mp w/ vehicle; animal info (Female C57BL/6J mice); functionality of mp verified by measurement of residual volume; comparison of sc injections vs mp;.

Q6577: F. Klaus, *et al.* Differential effects of peripheral and brain tumor necrosis factor on inflammation, sickness, emotional behavior and memory in mice. Brain Behav Immun 2016;58(310-326

ALZET Comments: Tumor necrosis factor, murine; PBS; BSA; SC; Mice; 1007D; 7 days; Dose (20 ng/g/day); 0.5% BSA used; animal info (10-12 week old Male C57BL/6J mice weighing 25-30g); comparison of injection vs mp;.

Q6570: F. A. Kassa, *et al.* Absence of apolipoprotein E protects mice from cerebral malaria. Sci Rep 2016;6(33615

ALZET Comments: Octasaccharide, heparin; Saline; IP; Mice (knockout); 4 weeks; Dose (50 µg/kg/hr); Controls received mp w/ vehicle; animal info (ApoE^{-/-} mice); comparison of daily injections vs mp; AutoClip & Reflex wound closure; Therapeutic indication (cerebral malaria);.

Q6480: C. W. Huang, *et al.* Role of n-3 Polyunsaturated Fatty Acids in Ameliorating the Obesity-Induced Metabolic Syndrome in Animal Models and Humans. Int J Mol Sci 2016;17(10):

ALZET Comments: Docosahexaenoic acid; Docosahexaenoic acid, 17R/S hydroxy; Saline; BSA; Ethanol; Mice; 15 days; Dose (Docosahexaenoic acid: 4 µg/g; 17-HDHA 50 ng/g); animal info (Male C57BL/6J wild-type mice. Male BKS.Cg-Dock 7m⁺/+Lepr^{db}/J (db/db) mice and Lean nondiabetic littermates (db/+)); comparison of injections vs mp; diabetes;.

Q5861: I. V. Guzova, *et al.* HSP70-based anti-cancer immunotherapy. Hum Vaccin Immunother 2016;12(10):2529-2535

ALZET Comments: HSP70, human recomb.; CSF/CNS (intratumoral); Rat; comparison of intracranial injections vs mp; cancer (Glioma); peptides; “Such injections, particularly those done using an osmotic pump, caused a significant delay in tumor growth and increase the survival of tumor-bearing animals.” pg 2532; Therapeutic indication (Cancer, Glioma);.

Q5352: G. S. Forkuo, *et al.* Development of GABAA Receptor Subtype-Selective Imidazobenzodiazepines as Novel Asthma Treatments. Mol Pharm 2016;13(6):2026-38



ALZET Comments: XHE-III-74EE; SC; mice; 1007D; 7 days; Dexamethasone used as positive control; animal info (Ova S/C Balb/c mice); functionality of mp verified by plasma level; comparison of injection vs mp (pg. 2035); “Pump delivery of XHE-III-74EE was effective in reducing AHR at low concentrations of methacholine” (pg 2032); “The response was more significant for a continuous release using implanted minipumps, which delivered blood concentration of 27.2 ng/mL of XHE-III-74EE compared to a cmax of 216 ng/mL with a twice daily i.p. injections” (pg. 2035); Reduces airway hyper-responsiveness in mice; Dose (20 mg/kg/day); Resultant plasma level (27.2 ± 2.7 ng/g);.

Q5786: G. Dezfuli, *et al.* Evidence for the role of beta2* nAChR desensitization in regulating body weight in obese mice. *Neuropharmacology* 2016;110(Pt A):165-174

ALZET Comments: Nicotine; Saline; SC; Mice; 2002; Controls received mp w/ vehicle; animal info (15 weeks old) ; pumps replaced every 2 weeks (at the end of the initial 14-day treatment period, the pump was removed and a new pump was implanted with a higher dose. This was repeated for the third and highest dose of nicotine);pumps replaced every 2 weeks (at the end of the initial 14-day treatment period, the pump was removed and a new pump was implanted with a higher dose. This was repeated for the third and highest dose of nicotine);comparison of twice daily SC injections vs mp;dose-response (18, 36, 72 mg/kg);good methods (2.3. Osmotic pump placement pg. 166); dependence;Therapeutic indication (Nicotine, body weight, food intake); Dose (18, 36, 72 mg/kg);.

Q5760: V. Caolo, *et al.* CXCL1 microspheres: a novel tool to stimulate arteriogenesis. *Drug Deliv* 2016;23(8):2919-2926

ALZET Comments: CXCL1; Saline; IP, Perivascular (femoral artery); Mice; 1004; 28 days; Controls received mp w/ vehicle; comparison of IM injection vs mp; ischemia (induced hind leg ischemia); Therapeutic indication (Drug delivery, arteriogenesis, peripheral artery disease);.

Q6479: M. Arvaniti, *et al.* Functional interaction between Lypd6 and nicotinic acetylcholine receptors. *J Neurochem* 2016;138(6):806-20

ALZET Comments: Nicotine hydrogen tartrate; Saline; SC; Rat (pregnant); 2006; 6 weeks; Dose (4 mg/kg/day); animal info (Sprague Dawley pregnant dams weighing 200-250g); comparison of injections vs mp;.

Q4660: T. T. Yan, *et al.* Daily Injection But Not Continuous Infusion of Apomorphine Inhibits Form-Deprivation Myopia in Mice. *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE* 2015;56(2475-2485

ALZET Comments: Apomorphine; SC; Mice; 1002; 4 weeks; Controls received mp w/ vehicle; animal info (male, C57Bl6, 4 weeks old); functionality of mp verified by residual volume; pumps replaced every 2 weeks; comparison of injection vs mp;.

Q5288: S. Villapol, *et al.* Neurorestoration after traumatic brain injury through angiotensin II receptor blockage. *Brain* 2015;138(Pt 11):3299-315

ALZET Comments: Candesartan; Saline, Physiological; SC; mice; 1004; 30 days; Controls received IP injection; animal info (C57BL/6Ncr male mice weighing 20-25g); comparison of injection vs mp; comparison of injection vs mp; Dose (pg. 3301);.

Q4032: M. C. O'Sullivan, *et al.* Dibenzosuberyl substituted polyamines and analogs of clomipramine as effective inhibitors of trypanothione reductase; molecular docking, and assessment of trypanocidal activities. *BIOORGANIC & MEDICINAL CHEMISTRY* 2015;23(996-1010

ALZET Comments: Compound 7; Mice; 3 days; Animal info (female, Swiss-Webster); comparison of injection vs mp; toxicology;.

Q4538: S. Morita, *et al.* Vascular endothelial growth factor-dependent angiogenesis and dynamic vascular plasticity in the sensory circumventricular organs of adult mouse brain. *CELL AND TISSUE RESEARCH* 2015;359(865-884

ALZET Comments: Ara-C; Saline; CSF/CNS; Mice; 2002; 10 days; Controls received mp w/ vehicle; animal info (male, C57BL6J, adult, P70-P84); comparison of IP injection vs mp; cardiovascular; “This infusion method is effective for suppressing cell proliferation in the subventricular zone and minimizes surgery damage to brain tissues” pg 867;.

Q4709: M. Grimm, *et al.* CaMKIIdelta mediates beta-adrenergic effects on RyR2 phosphorylation and SR Ca(2+) leak and the pathophysiological response to chronic beta-adrenergic stimulation. *JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY* 2015;85(282-291



ALZET Comments: Isoproterenol; SC; Mice; 2004; 2 weeks; 4 weeks; Animal info (male, Black Swiss, 8-12 weeks old); comparison of injection vs mp; cardiovascular;.

Q4157: M. Walser, *et al.* Different modes of GH administration influence gene expression in the male rat brain. *Journal of Endocrinology* 2014;222(181-190

ALZET Comments: Growth hormone, recombinant bovine; PBS; glycerol; sodium azide; SC; Rat; 2004; 7 days; Animal info (male, Sprague Dawley, hypophysectomized); 0.02% sodium azide used; 1.6% glycerol used; comparison of injection vs mp; replacement therapy (hypophysectomy);.

Q4140: A. Y. Tilahun, *et al.* Systemic Inflammatory Response Elicited by Superantigen Destabilizes T Regulatory Cells, Rendering Them Ineffective during Toxic Shock Syndrome. *Journal of Immunology* 2014;193(2919-2930

ALZET Comments: Interleukin-2, murine; antibody, anti-interleukin-2; PBS; SC; Mice (transgenic); 10 days; Controls received mp w/ vehicle; animal info (HLA-DR3); comparison of injection vs mp; immunology;.

R0319: M. Silindir, *et al.* The benefits of pramipexole selection in the treatment of Parkinson's disease. *NEUROLOGICAL SCIENCES* 2014;35(1505-1511

ALZET Comments: Pramipexole; Rat; Comparison of injections vs mp; "While higher therapeutic benefit in early morning akinesia was obtained with pramipexole CR (continuous release via ALZET pumps), motor impairment was reversed for several hours with pramipexole IR (instant release via injections)" pg 1508.

Q4096: A. Shah, *et al.* Influence of acute or chronic administration of ovarian hormones on the effects of desipramine in the forced swim test in female rats. *Psychopharmacology* 2014;231(3685-3694

ALZET Comments: Desipramine hydrochloride; Water, distilled; IP; Rat; 2ML4; 18 days; Controls received mp w/ vehicle; animal info (female, Sprague Dawley, 250-350g, ovariectomized); functionality of mp verified by serum levels; comparison of injection vs mp; dose-response (pg 3690); post op. care (penicillin and saline injection; atipamezol 1 mg/kg); behavioral testing (forced swimming test; locomotor activity); replacement therapy (estradiol pellets); solutions filtered through 0.9 um nitrocellulose filters; pumps primed at room temperature saline; used sutures;.

Q4069: B. Roche, *et al.* Parathyroid Hormone 1-84 Targets Bone Vascular Structure and Perfusion in Mice: Impacts of Its Administration Regimen and of Ovariectomy. *Journal of Bone and Mineral Research* 2014;29(1608-1618

ALZET Comments: Parathyroid hormone (1-84); SC; Mice; 14 days; Controls received mp w/ vehicle; animal info (female, C57BL6, 4 months old, ovariectomized); comparison of injection vs mp; cardiovascular;.

Q4036: M. Pabba, *et al.* NMDA Receptors Are Upregulated and Trafficked to the Plasma Membrane after Sigma-1 Receptor Activation in the Rat Hippocampus. *Journal of Neuroscience* 2014;34(11325-11338

ALZET Comments: BD1047; BD1063; PBS; SC; Rat; 2 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 4-6 weeks); comparison of injection vs mp;.

Q3589: A. Ojima, *et al.* DNA aptamer raised against advanced glycation end products inhibits melanoma growth in nude mice. *LABORATORY INVESTIGATION* 2014;94(4):422-429

ALZET Comments: AGE-aptamer; IP; Mice (nude); 1004; 43 days; Controls received mp w/ control aptamer; animal info (female, nude, athymic, 6 weeks old); comparison of IP injection vs mp; cancer (G361 melanoma); gene therapy; AGE-aptamer aka advanced glycation end products;.

Q3964: R. Lee, *et al.* Bleomycin delivery by osmotic minipump: similarity to human scleroderma interstitial lung disease. *AMERICAN JOURNAL OF PHYSIOLOGY-LUNG CELLULAR AND MOLECULAR PHYSIOLOGY* 2014;306(L736-L748

ALZET Comments: Bleomycin; Saline; SC; Mice; 1007D; 10 days; Controls received mp w/ vehicle; animal info (male, CD1, 10 weeks old); comparison of injection vs mp; immunology; "the pump model provides additional major benefits compared with the direct model. Much less weight loss and mortality is observed in the pump model than in the direct model. Therefore, besides the fact that the pump model is more humane, it also benefits the researcher because it allows the number of surviving animals in treatment groups to be accurately predicted, thereby making analyses of biochemical and



cell biological parameters at the end of an experiment more meaningful." pg L747; pumps removed after 10 days; human scleroderma interstitial lung disease model;.

Q3961: R. Lee, *et al.* Caveolin-1 regulates chemokine receptor 5-mediated contribution of bone marrow-derived cells to dermal fibrosis. FRONTIERS IN PHARMACOLOGY 2014;5(U1-U14)

ALZET Comments: Bleomycin; Saline; SC; Mice; 1007D; 10 days; Controls received mp w/ vehicle; animal info (male, CD1, 10 weeks old); comparison of injection vs mp; "Recently, we found that systemic bleomycin delivery using subcutaneously implanted osmotic minipumps can produce a very useful mouse model for SSC in which fibrosis is observed in the skin, lungs, and a variety of other internal organs" pg 2; "We recently compared two methods of delivering bleomycin [Direct Model (directly into the lungs) and Pump Model (systemic delivery using implanted osmotic minipumps)]and found that the lung disease induced in the Pump Model was distinct from the disease induced in the Direct Model and more similar to the lung disease observed in SSC patients" pg 4; pumps removed after 10 days;.

Q3507: H. Y. Hsiao, *et al.* Inhibition of soluble tumor necrosis factor is therapeutic in Huntington's disease. Human Molecular Genetics 2014;23(4328-4344)

ALZET Comments: XPro1595; CSF/CNS; Mice; 2004; 28 days; Controls received mp w/ saline; animal info (WT or R62, 7.5-11.5 weeks old); ALZET brain infusion kit 3 used; comparison of IP injections vs mp ICV infusion; neurodegenerative (Huntington's disease); behavioral testing (rotarod performance, beam walking, foot claspings, t-maze); "Our data also showed that an i.p. injection of XPro1595 further decreased the BW of R6/2 mice, whereas an i.c.v. infusion of a dominant negative inhibitor of soluble TNF- α (XPro1595) did not affect the BW... i.c.v. delivery of XPro1595 appeared to be safer and more effective for treating HD." pg 4334; XPro1595 is a selective inhibitor of soluble TNF;.

Q3884: J. Gao, *et al.* Differential effects of intermittent versus continuous haloperidol treatment throughout adolescence on haloperidol sensitization and social behavior in adulthood. PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY 2014;54(67-75)

ALZET Comments: Haloperidol; Water, sterile; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, PND44-71); comparison of injection vs mp; post op. care (incision cleaned with 75% ethanol); behavioral testing (two-way avoidance conditioning apparatus; locomotor activity monitoring apparatus; avoidance training); dependence; used 9mm wound clips; pumps wiped with 75% ethanol; pumps removed after 28 days;.

Q3906: B. D. Furman, *et al.* Targeting pro-inflammatory cytokines following joint injury: acute intra-articular inhibition of interleukin-1 following knee injury prevents post-traumatic arthritis. ARTHRITIS RESEARCH & THERAPY 2014;16(U305-U319)

ALZET Comments: Interleukin-1 receptor antagonist; Saline; SC; Mice; 2004; 4 weeks; Controls received mp w/ vehicle; animal info (male, C57BL6, 8 weeks old); functionality of mp verified by serum levels; comparison of injection vs mp; stress/adverse reaction: (see pg. 4); post op. care (buprenorphine); "...no significant differences were detected for any of the outcome measures in mice receiving systemic saline via osmotic pump or IP injections.." pg 4; pumps removed after 28 days;.

Q3456: M. E. Diaz, *et al.* GH administration patterns differently regulate epidermal growth factor signaling. Journal of Endocrinology 2014;221(309-323)

ALZET Comments: Growth hormone, porcine; SC; Mice; 1007D; 5 days; Controls received mp w/ saline; animal info (Swiss-Webster, 3-4 months old, 26-30g); functionality of mp verified by plasma levels; comparison of SC injection BID vs mp; toxicology; "The results indicate that sustained delivery systems that allow continuous GH plasma patterns would be beneficial in terms of treatment safety with regard to the actions of GH on EGFR signaling and its promitogenic activity." pg 309.

Q4703: M. Benadiba, *et al.* Growth inhibitory effects of the Diruthenium-Ibuprofen compound, [Ru(2)Cl(Ibp)(4)], in human glioma cells in vitro and in the rat C6 orthotopic glioma in vivo 1993. JOURNAL OF BIOLOGICAL INORGANIC CHEMISTRY 2014;19(1025-1035)

ALZET Comments: Diruthenium-ibuprofen; Ethanol; CSF, artificial; CSF/CNS (intratumoral); Rat; 2002; 14 days; Animal info (female, Wistar, 250-350g); ALZET brain infusion kit used; 15% ethanol used; comparison of injection vs mp; cancer (glioma); tissue perfusion (intratumoral, glioma); "Using the orthotopic C6 model the effects of either chronic 14-day



treatment by intra-peritoneal injection of chronic 14-day intra-tumour infusion by an Alzet osmotic pump attached to a brain infusion cannula were tested. Tumour growth was reduced by both routes of administration with the osmotic pump appearing to be the less harmful route in terms of haematological responses." pg 1033; Diruthenium-Ibuprofen aka Rulbp;.

Q2878: N. Zhidkov, *et al.* Continuous Intraperitoneal Carboplatin Delivery for the Treatment of Late-Stage Ovarian Cancer. MOLECULAR PHARMACEUTICS 2013;10(9):3315-3322

ALZET Comments: Carboplatin; PBS; IP; Mice (SCID); 1002; 14 days; Controls received mp w/ saline; toxicology; animal info (6-8 week old female SCID); comparison of bolus injection vs mp; cancer (ovarian).

Q6778: K. E. Stevens, *et al.* Intermittent versus continuous central administration of clozapine in DBA/2 mice, improvement in sensory inhibition deficits. Schizophr Res 2013;149(1-3):121-6

ALZET Comments: Clozapine; Saline; CSF/CNS (lateral ventricle); Mice; 1002; 24 hours; Dose (0, 3, 7.5, 15 or 30 µg/day); Controls received mp w/ vehicle; animal info (DBA/2 mice (20–25 g)); comparison of once-per-day injection vs mp; ALZET brain infusion kit 3 used; Brain coordinates ([0.9 mm anterior to bregma, 0.1 mm lateral to midline and –2.0 mm from the brain surface); cyanoacrylate adhesive;.

Q3164: V. Rajagopalan, *et al.* Altered ubiquitin-proteasome signaling in right ventricular hypertrophy and failure. American Journal of Physiology-Heart and Circulatory Physiology 2013;305(4):H551-H562

ALZET Comments: MG132; DMSO; saline; SC; Mice; 7 days; Controls received mp w/ vehicle; animal info (Male, FVB/N, 8-10 week); functionality of mp verified by comparing enzyme activity vs injection; 10% DMSO used; comparison of IP injection (once per day and three times per day) vs mp; cardiovascular; "Because of concern that the short half-life of the drug would result in incomplete inhibition of the targeted enzymes, we conducted additional studies comparing three methods of administration: once daily intraperitoneally, three times daily intraperitoneally, or via continuous subcutaneous delivery via Alzet osmotic minipump (Durect, Cupertino, CA), delivering the same total daily dose. These studies demonstrated equal efficacy of enzyme inhibition, so all further studies with epoxomicin were conducted using the once daily intraperitoneal approach" pg H552; Pumps used only in initial study, was replaced with injection once per day. MG132 is a proteasome inhibitor;.

Q6740: D. M. Pechlivanova, *et al.* The role of the angiotensin AT2 receptor on the diurnal variations of nociception and motor coordination in rats. Peptides 2013;39(152-6

ALZET Comments: CGP 42112A; PD123319; Saline; sterile; CSF/CNS (lateral ventricle); Rat; 2002; 14 days; Dose (12 µg/rat/day (CGP 42112A); 10 µg/rat/day (PD123319)); Controls received mp w/ vehicle; animal info (12 week old Adult male Wistar rats); comparison of injection vs mp; CGP 42112A is a selective peptide AT2 agonist; PD 123319 is a nonpeptide AT2 receptor antagonist; peptides; ALZET brain infusion kit 2 used; Brain coordinates (1 mm lateral and 3 mm posterior to Bregma and 4 mm deep from skull surface); cyanoacrylate adhesive;.

Q3254: O. T. W. Ng, *et al.* Small Interfering RNA Specific for N-Methyl-D-Aspartate Receptor 2B Offers Neuroprotection to Dopamine Neurons through Activation of MAP Kinase. NEURO SIGNALS 2013;21(1-2):42-54

ALZET Comments: RNA, small interfering; Saline, SilentFect; CSF/CNS (striatum); Rat; 2001; 1 week; Animal info (male, Sprague Dawley, 200-250g); ALZET brain infusion kit 2 used; comparison of single injection vs mp "In summary, single injection of siRNA into PD models showed no significant effect in ameliorating the motor syndrome and protection in TH-positive neurons. However, continuous infusion of NR2B-specific siRNA can effectively ameliorate the motor symptoms, attenuate the dopaminergic cell loss in the striatum and SN regions, and promote the ERK1/2 signaling pathway in parkinsonian models." pg53; neurodegenerative (Parkinson's disease); "Moreover, by using the osmotic minipump connecting with canals, this method can be easily transplanted into patients, and allow the siRNA to be infused to the target site directly at a steady and slow rate. The direct delivery has the advantages of reducing any undesired systemic side effects and lowering the dose requirement for efficacy" pg 53 ; Primed at 37C saline overnight.

R0360: B. Newland, *et al.* Biomaterial approaches to gene therapies for neurodegenerative disorders of the CNS. Biomaterials Science 2013;1(6):556

ALZET Comments: Lipofectin; CSF/CNS (septum); Rat; 14 days; comparison of single stereotactic injection vs mp; enzyme inhibitor (beta-galactosidase);.



Q6727: S. Mann, *et al.* Chronic olanzapine administration in rats: effect of route of administration on weight, food intake and body composition. *Pharmacol Biochem Behav* 2013;103(4):717-22

ALZET Comments: Olanzapine; Acetic acid; sodium hydroxide; SC; Rat; 2ML2; 14 days; Dose (7.5 mg/kg/day); 2% acetic acid solution, buffered with 1 N NaOH used; Controls received mp w/ vehicle; animal info (Forty-eight female Sprague–Dawley rats weighing 200–225 g); comparison of IP and SC injections vs mp;

Q2577: L. Kagan, *et al.* Mechanisms of Subcutaneous Absorption of Rituximab in Rats. *Drug Metabolism and Disposition* 2013;41(1):248-255

ALZET Comments: Rituximab; SC; Rat; 10 days; Animal info (Wistar, male, wks old, 350-375 g); PK study; The pharmacokinetic simulation for a s.c. infusion of a 40 mg/kg dose over a 10-day period using parameters obtained for rituximab administered alone predicted that serum concentrations should be comparable with or higher than those after bolus injection after approximately 6 days of the infusion... Interestingly, the observed enhancement of absorption was greater than that predicted by the model." pg 253; comparison of IP injections vs mp; pk study.

Q3076: M. E. Gentle, *et al.* Epithelial Cell TGFbeta Signaling Induces Acute Tubular Injury and Interstitial Inflammation. *Journal of the American Society of Nephrology* 2013;24(5):787-799

ALZET Comments: MitoTEMPO; Saline; SC; Mice; 1007D; 5 days; Controls received mp w/ vehicle; animal info (Pax8-rtTA/TetO-TBRI(ADD) hybrid); comparison of subcutaneous injection vs mp "Similar results were seen with mini-pumps and subcutaneous injection." pg 796; immunology;

Q3072: J. N. Freeman, *et al.* Chronic central ghrelin infusion reduces blood pressure and heart rate despite increasing appetite and promoting weight gain in normotensive and hypertensive rats. *Peptides* 2013;42(;):35-42

ALZET Comments: Ghrelin; Saline; CSF/CNS; Rat; 2002; 10 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley & Spontaneous Hypertensive Rats, 275-330 g); comparison of IV infusion vs mp "the same dose of ghrelin was administered intravenously for 7 days to test if any potential spillover of ghrelin into the systemic circulation could account for its hypotensive effects, however no significant change in HR, BP or food intake was observed during the 7-day treatment period" (see pg. 39-40, Fig 3); stress/adverse reaction: (see pg. 39); behavioral testing (air-jet stress test); cardiovascular; peptides; Cannula placement verified via dipsogenic response to ICV injection of 100 ng Angiotensin II; used tygon tubing for catheter.

Q4967: M. A. Fischer, *et al.* Flaviviruses are sensitive to inhibition of thymidine synthesis pathways. *J Virol* 2013;87(17):9411-9

ALZET Comments: Methotrexate, Floxuridine; DMSO; SC; Mice; 50% DMSO used; animal info (AG129 mice); comparison of IP injections vs mp; Agents are small-molecule inhibitors of dengue virus; immunology;

Q2911: K. Fifel, *et al.* Lack of long-term changes in circadian, locomotor, and cognitive functions in acute and chronic MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse models of parkinson's disease. *Chronobiology International* 2013;30(6):741-755

ALZET Comments: MPTP; SC; Mice; 1004; 28 days; Animal Info (MPTP mouse model of parkinsonism, 26g, 152 days old); comparison of injection vs mp. (Pg. 7); good methods (pg. 2); Neurodegenerative (Parkinson's disease); behavioral testing (radial arm water maze, spatial learning and memory); no stress/adverse effects (pg. 743).

Q5536: T. Chen, *et al.* Population pharmacodynamic modeling of exenatide after 2-week treatment in STZ/NA diabetic rats. *J Pharm Sci* 2013;102(10):3844-51

ALZET Comments: Exenatide; Saline; SC; Rat; 2002; 2 weeks; Controls received mp w/ saline; animal info (300-325g); comparison of twice daily SC injection vs mp; half-life (p.3844); diabetes; Therapeutic indication (Diabetes); Dose (20 g/kg).

Q5535: A. Chakrabarty, *et al.* Angiotensin II receptor type 2 activation is required for cutaneous sensory hyperinnervation and hypersensitivity in a rat hind paw model of inflammatory pain. *J Pain* 2013;14(10):1053-65



ALZET Comments: PD123319; Water, distilled; IP; Rat; 2001; 7 days; Controls received mp w/ (DI water); animal info (female, 60 days, 190-200g); comparison of single IP injection vs mp; behavioral testing (Thermal sensitivity, mechanical sensitivity); PD123319 is an AT2 antagonist; Therapeutic indication (Inflammatory pain); Dose (5 mg/kg/d);.

Q5668: M. V. Sofroniew. Transgenic techniques for cell ablation or molecular deletion to investigate functions of astrocytes and other GFAP-expressing cell types. *Methods Mol Biol* 2012;814(531-44

ALZET Comments: Ganciclovir; Saline; SC; Mice (transgenic); 7, 21, 42 days; animal info (mGFAP-TK mice, 30 grams); comparison of daily injections vs mp; Dose (10 mg/kg/day);.

Q2159: R. A. Rissman, *et al.* Corticotropin-releasing factor receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation. *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA* 2012;109(16):6277-6282

ALZET Comments: R121919; Ethanol; cremaphor EL; Mice; 14 days; Animal info (CRFR KO, male, 15-22 wks old); antalarmin is a CRFR1 selective antagonist; comparison of IP injections vs mp; "Minipump delivery was the most effective technique" pg 6278; neurodegenerative (Alzheimer's disease); behavioral testing (restraint test).

Q1748: L. Weiss, *et al.* Preimplantation factor (PIF) analog prevents type I diabetes mellitus (T1DM) development by preserving pancreatic function in NOD mice. *Endocrine* 2011;40(1):41-54

ALZET Comments: Preimplantation factor, synthetic analog; SC; Mice (NOD); 40 days; 4 weeks; Controls received mp w/ PBS; animal info (female, diabetic, NOD, 6-7 wks old); peptides; comparison of injections vs mp.

Q1752: E. Soltysinska, *et al.* Myocardial structural, contractile and electrophysiological changes in the guinea-pig heart failure model induced by chronic sympathetic activation. *Experimental Physiology* 2011;96(7):647-663

ALZET Comments: Isoprenaline hydrochloride; Saline; Ascorbic acid; SC; Guinea pig; 16, 32 days; Controls received mp w/ vehicle; animal info (Dunkin-Hartley, 300-350 g); comparison of SC injections vs mp.

Q1224: X. W. Ma, *et al.* Distinct actions of intermittent and sustained beta-adrenoceptor stimulation on cardiac remodeling. *Science China-Life Sciences* 2011;54(6):493-501

ALZET Comments: Isoproterenol; Ascorbic acid; SC; Mice; 14 days; Controls received mp w/ vehicle; animal info (10 wks old, BALB/c); comparison of sc injections vs mp.

Q0855: H. Kondo, *et al.* Continuous Treatment with a Low-Dose beta-Agonist Reduces Bone Mass by Increasing Bone Resorption Without Suppressing Bone Formation. *Calcified Tissue International* 2011;88(1):23-32

ALZET Comments: Isoprenaline; SC; Mice; 2002; 2 weeks; Controls received mp w/ vehicle; animal info (C57BL/6J, 10 wks old); comparison of injections vs mp; "concentrations produced by continuous administration and intermittent administration are quite different as the blood concentration of isoprenaline increased within an hour and decreased within a few hours after intermittent intraperitoneal "Even if the same doses are administered each day, the blood administration, whereas the blood concentration of isoprenaline remained stable during continuous intrasubcutaneous treatment using the Alzet model 2002 at 0.5 μ L/h." pg 28.

Q0902: A. M. Bedard, *et al.* Continuous, but not Intermittent, Antipsychotic Drug Delivery Intensifies the Pursuit of Reward Cues. *Neuropsychopharmacology* 2011;36(6):1248-1259

ALZET Comments: Haloperidol; Acetic acid, glacial; water; SC; Rat; 2ML2; 19 days; Controls received mp w/ vehicle; animal info (male, Sprague-Dawley, 200-225 g); comparison of injections vs mp.

Q1536: L. Ansel, *et al.* Peripheral kisspeptin reverses short photoperiod-induced gonadal regression in Syrian hamsters by promoting GnRH release. *REPRODUCTION* 2011;142(3):417-425

ALZET Comments: Kisspeptin 54; Ringer's solution; SC; Hamster; 2004; 4 weeks; Controls received mp w/ vehicle; animal info (male, Syrian, Siberian, SD, 8-10 wks old); peptides; comparison of injections vs mp.



Q0860: S. I. Masunaga, *et al.* Adverse effect of mild temperature hyperthermia combined with hexamethylenetetramine compared to its effect combined with tirapazamine in the treatment of solid tumors. *EXPERIMENTAL AND THERAPEUTIC MEDICINE* 2010;1(1):169-174

ALZET Comments: Uridine, 5-bromo-2'-deoxy-; tirapazamine; hexamethylenetetramine; Saline, physiological; SC; IP; Mice; 5 days; 24 hours; Animal info (syngeneic female C3H/He, 8-11 wks old); comparison of IP injections vs mp; cancer; "Continuous administration of HMTA and TPZ resulted in higher radio- and cisplatin-sensitizing effects than intraperitoneal single administration." pg 169.

Q0475: H. Ma, *et al.* Intradermal alpha 1-antitrypsin therapy avoids fatal anaphylaxis, prevents type 1 diabetes and reverses hyperglycaemia in the NOD mouse model of the disease. *Diabetologia* 2010;53(10):2198-2204

ALZET Comments: Antitrypsin, human, alpha-1; SC; Mice (NOD); 7 days; Animal info (8 wks old, female, NOD); comparison of IP, SC injections vs mp; diabetes; hAAT also known as Prolastin; "...repeated administration of hAAT may lead to fatal anaphylaxis in NOD mice... Delivery of AAT by an osmotic pump resulted in a twofold increase of the AUC 0-7days suggesting a possible clinical application in large animals and in humans." pg 2202.

Q1030: L. la Santina, *et al.* Effect of HCN Channel Inhibition on Retinal Morphology and Function in Normal and Dystrophic Rodents. *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE* 2010;51(2):1016-1023

ALZET Comments: Ivabradine; Saline; SC; Rat; 2ML4; 3 weeks; Controls received mp w/ vehicle; animal info (adult, Long Evans); functionality of mp verified by residual volume; comparison of acute injections vs mp; "This instance is the first in which the effects of acute and long-term delivery of an HCN-inhibitor have been compared, showing that the consequences of the two different dosing approaches are similar and always reversible." pg 1022.

Q1591: Y. M. Hua, *et al.* Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. *GENES & DEVELOPMENT* 2010;24(15):1634-1644

ALZET Comments: Oligonucleotide, antisense; Saline; CSF/CNS; Mice; 1007D; 7 days; Controls received mp w/ vehicle; animal info (SMA Type III, adult, 3-4 mo old); antisense (10-27); "Although the inability of ASOs to cross the BBB limits the utility of systemic administration, well-established implantable catheters and pump technology can overcome this obstacle." pg 1641 ; comparison of injections vs mp.

Q1642: R. Griggs, *et al.* Intermittent methylphenidate during adolescent development produces locomotor hyperactivity and an enhanced response to cocaine compared to continuous treatment in rats. *Pharmacology Biochemistry and Behavior* 2010;96(2):166-174

ALZET Comments: Methylphenidate; Saline, physiological, sterile; SC; Rat; 2ML4; 28 days; Animal info (Sprague Dawley, male, 100-124 g, PND 32-35); comparison of injections vs mp; pharmacokinetic. PK study; "rats in the continuous MPH condition did not exhibit these effects. Collectively, these data indicate that sustained release formulations of MPH used in the treatment of ADHD may yield fewer problematic effects compared to the immediate release formulations." pg 173.

Q0092: B. Ferger, *et al.* Continuous Dopaminergic Stimulation by Pramipexole Is Effective to Treat Early Morning Akinesia in Animal Models of Parkinson's Disease: A Pharmacokinetic-Pharmacodynamic Study Using in Vivo Microdialysis in Rats. *Synapse* 2010;64(7):533-541

ALZET Comments: Pramipexole; Saline; SC; Rat; 1007D; 2004; 2, 14 days; Controls received mp w/ vehicle; animal info (male, Wistar, 250-300 g.); comparison of SC injections vs mp; neurodegenerative (Parkinson's Disease); "...this study highlights the potential benefit of CDS (continuous dopaminergic stimulation) using PPX-CR and the advantage over PPX-IR in two symptomatic PD models" pg 540; half-life "long" pg 534; haloperidol-induced catalepsy; pk study.

R0352: A. A. Boulton. *Animal Models of Dementia.* Springer Protocols 2010;48(1-721

ALZET Comments: Amphetamine sulfate; Dopamine; Propylene Glycol; SC; CSF/CNS (nucleus accumbens); Rat; 2ML2; 14 days; comparison of injections and sytastic pellet vs mp; pulsed delivery; PE tubing contained drug and a dye in short sections interspersed with a substance immiscible with drug, to allow 12 hour infusions of drug and 12-hour infusions of the inert substance (perfluorodecalin) throughout a 14 day infusion period.; pumps primed in a physiological saline solution at 37°C for 4 hours.