



References on the Administration of Antiviral Agents Using ALZET® Osmotic Pumps

1. Acyclovir

Q3927: N. Ito, *et al.* Organic Cation Transporter/Solute Carrier Family 22a is Involved in Drug Transfer into Milk in Mice. *Journal of Pharmaceutical Sciences* 2014;103(3342-3348)

ALZET Comments: Acyclovir; cimetidine; clindamycin; metformin; terbutaline; verapamil;; IP; Mice; 1003D; 72 hours; Animal info (female, lactating, Bcrp KO or WT FVB); functionality of mp verified by plasma and milk concentrations; no stress "All mice survived the surgical procedure and appeared to be lactating normally, and all pups thrived throughout the course of the experiment." (see pg. 3343);.

Q5063: N. Ito, *et al.* Contribution of protein binding, lipid partitioning, and asymmetrical transport to drug transfer into milk in mouse versus human. *Pharm Res* 2013;30(9):2410-22

ALZET Comments: acetaminophen, cephalothin sodium salt, clindamycin hydrochloride, disopyramide phosphate salt, labetalol hydrochloride, nitrofurantoin +-propranolol hydrochloride, terbutaline hemisulfate salt, verapamil hydrochloride, Acyclovir, alprazolam, atenolol, anhydrous caffeine, cefotaxime sodium salt, cephapirin sodium salt, diltiazem hydrochloride, metronidazole, nitrazepam, prednisolone, 6-propyl-2-thiouracil, trazadone hydrochloride, chloramphenicol, cimetidine, theophylline, fluconazole, metoprolol, mirtazapine, praziquantel, quetiapine fumarate, triprolidine hydrochloride, metformin, moclobemide.; DMSO; water; IP; mice; 1003D; animal info: lactating mice, postnatal age of 14 days; functionality of mp verified by measurement of drug concentration in milk and plasma; mp were used to infuse study lactational drug transfer.

P0379: D. Myerson, *et al.* Prophylactic and therapeutic treatment with acyclovir of genital herpes in the guinea pig (41717). *Proc. Soc. Exp. Biol. Med* 1983;174(147-152)

ALZET Comments: Acyclovir, sodium; Saline; SC; Guinea pig; 2ML2; 1 week; comparison of ip inject vs. mp infusion; article states incorrectly that 2ML2 is spent after 7 days.

2. Amantadine

Q6943: E. F. Brigham, *et al.* Pharmacokinetic/Pharmacodynamic Correlation Analysis of Amantadine for Levodopa-Induced Dyskinesia. *J Pharmacol Exp Ther* 2018;367(2):373-381

ALZET Comments: Amantadine; Sodium acetate; SC; Rat; 2ML2; Dose (22.5, 45, or 83 mg/kg per day); Controls received mp w/ vehicle; animal info (Sprague-Dawley rats);.

Q3272: E. Y. K. Huang, *et al.* Amantadine Ameliorates Dopamine-Releasing Deficits and Behavioral Deficits in Rats after Fluid Percussion Injury. *PLoS One* 2014;9(1):U118-U131

ALZET Comments: Amantadine; Saline; SC; Rat; 2006; 8 weeks; Control animals received mp w/ vehicle; animal info (male, Sprague Dawley, 200-250 g, 6 wks old); long-term study.

P4224: M. B. Hesselink, *et al.* Brain penetration and in vivo recovery of NMDA receptor antagonists amantadine and memantine: a quantitative microdialysis study. *Pharmaceut. Res* 1999;16(5):637-642

ALZET Comments: Memantine; Amantadine; Water; SC; Rat; 2ML2; no duration posted; dose-response; serum levels.

P4321: M. B. Hesselink, *et al.* Adaptations of NMDA and dopamine D₂, but not of muscarinic receptors following 14 days administration of uncompetitive NMDA receptor antagonists. *Journal of Neural Transmission* 1999;106(409-421)

ALZET Comments: MK-801; Memantine; Amantadine;; Water;; SC;; Rat;; 2ML2;; 3-14 days;; controls received sham surgeries; comparison of S.C. injections vs. mp; half-life (p. 411); "In the clinical situation, depending on dosing schedule, only minor fluctuations in the steady-state plasma levels of the aminoadamantanes is observed. The only way to mimic this in animals is by continuous infusion of the drug using ALZET osmotic minipumps." (p. 411);.



P3920: L. Stitz, *et al.* Lack of antiviral effect of amantadine in borna disease virus infection. *Med Microbiol Immunol* 1998;186(195-200)

ALZET Comments: Adamantane, 1-amino-; Water, sterile distilled; SC; Rat; 2ML2; 14 days; functionality of mp verified by serum levels; comparison of oral doses vs. mp; immunology; agent is NMDA antagonist also called amantadine or 1-adamantanamide.

R0187: W. Danysz, *et al.* Aminoadamantanes as NMDA Receptor Antagonists and Antiparkinsonian Agents - Preclinical Studies. *Neurosci Biobehav Rev* 1997;21(4):455-468

ALZET Comments: Amantadine; memantine; SC; Rat; 7, 14 days; Neurodegenerative (Parkinson's disease).

3. Azidothymidine

P2211: A. F. Tarantal, *et al.* Pre and postnatal treatment of the rhesus macaque (*Macaca mulatta*) with azidothymidine: I. fetal studies. *Pediatr. Aids HIV Infection: Fetus to Adolescent* 1994;5(1):10-19

ALZET Comments: Azidothymidine; Sodium hydroxide; SC; monkey (pregnant); 2ML4; 28 days; controls received mp w/vehicle; functionality of mp verified by plasma levels of AZT; teratology; AZT is azidothymidine, also known as zidovudine; multiple pumps per animal (3-4); "Circulating levels of AZT remained constant during the course of treatment and were achieved by the first (24 hr.) sample (p. 11); antiretroviral drug.

P2093: M. Sinet, *et al.* Efficacy of continuous zidovudine infusion at early stages of retroviral infection in mice. *J. Acquir. Immune Defic. Syndr* 1992;5(577-582)

ALZET Comments: Azidothymidine; Propylene glycol; Water; SC; mice; 2001; 5 days; functionality of mp verified by plasma AZT levels; comparison of b.i.d. s.c. injections vs. mp; good methods; also called zidovudine; pK; half-life (p.577); continuous infusion significantly more effective than bolus injection; antiretroviral drug.

P1928: J. A. Bilello, *et al.* Use of a neonatal murine retrovirus model to evaluate the long-term efficacy and toxicity of antiviral agents. *Ann. N. Y. Acad. Sci* 1990;616(238-251)

ALZET Comments: Azidothymidine; mice (pregnant); 2001; 21 days; Pumps replaced after each week to achieve 3 weeks duration; immunology; teratology; oral delivery of AZT resulted in highly variable plasma levels; antiretroviral drug.

P1644: J. M. Gallo, *et al.* Pump delivery of azidothymidine: potential for constant concentrations and improved brain delivery. *J. Controlled Release* 1989;9(249-253)

ALZET Comments: Azidothymidine; IA (carotid); Rat; 2001; 3-7 days; Dose-response; blood levels; comparison of IV injections vs. mp; good methods; antiviral; alkaline pH of 11 increased solubility and stability of AZT; antiretroviral drug.

4. Ganciclovir

Q6925: S. Kalin, *et al.* CNS myeloid cells critically regulate heat hyperalgesia. *J Clin Invest* 2018;128(7):2774-2786

ALZET Comments: Ganciclovir; CSF/CNS (lateral ventricle); Mice (transgenic); 2002; 4 weeks; animal info (150- to 200-dayold adult male hemizygous CD11b-HSVTK (TK) mice (4) or their transgene-negative littermates); ALZET brain infusion kit used;

Q7124: M. Cusimano, *et al.* Selective killing of spinal cord neural stem cells impairs locomotor recovery in a mouse model of spinal cord injury. *J Neuroinflammation* 2018;15(1):58

ALZET Comments: Ganciclovir; Water; SC; Mice; 2002; 28 days; Dose (100 mg/kg/day); animal info (NestinTK); pumps replaced every 2 weeks; neurodegenerative (Spinal Chord); .

Q5714: W. Xu, *et al.* Myelin Basic Protein Regulates Primitive and Definitive Neural Stem Cell Proliferation from the Adult Spinal Cord. *Stem Cells* 2017;35(2):485-496

ALZET Comments: Ganciclovir; CSF/CNS; Mice; 1007D; 5 days; animal info (GFAP-TK); spinal cord injury;.



Q5885: R. L. Reeve, *et al.* Quiescent Oct4(+) Neural Stem Cells (NSCs) Repopulate Ablated Glial Fibrillary Acidic Protein(+) NSCs in the Adult Mouse Brain. *Stem Cells* 2017;35(9):2071-2082

ALZET Comments: Ara-C; ganciclovir; CSF/CNS; Mice; 1007D; 3 days; 7 days; 14 days; animal info (Oct4 CKO;tk);.

Q5822: M. Nakano, *et al.* NG2 glial cells regulate neuroimmunological responses to maintain neuronal function and survival. *Sci Rep* 2017;7(42041)

ALZET Comments: Ganciclovir; CSF/CNS (left lateral ventricle); Rat; SMP-300, iPRECIO; Controls animals were sham operated or infused with vehicle; animal info (NG2-HSVtk, 12-35 weeks old); ALZET brain infusion kit 1 used; immunology; Therapeutic indication (Neuroimmunology, neuroinflammation, neural development); Dose (0.01, 0.1, 0.5, 1.0, and 10 mg/ml);.

Q6356: J. Mircetic, *et al.* Development of a genetic sensor that eliminates p53 deficient cells. *Nat Commun* 2017;8(1):1463

ALZET Comments: Ganciclovir; Water; SC; Mice (nude); 2002; 14 days; Dose (20 mg/kg/day); Controls received mp w/ vehicle; animal info (12 week old NMRI (nu/nu) mice);.

Q5709: H. Williams, *et al.* Suppression of neointima formation by targeting beta-catenin/TCF pathway. *Biosci Rep* 2016;36(6):

ALZET Comments: Ganciclovir; SC; Mice; 2002; 2004; 21 days; Controls received mp w/ PBS; animal info (C57BL6J); Dose (25 mg/kg/day);.

Q4845: A. G. Kotini, *et al.* Escape Mutations, Ganciclovir Resistance, and Teratoma Formation in Human iPSCs Expressing an HSVtk Suicide Gene. *MOLECULAR THERAPY* 2016;5(**ALZET Comments:** Ganciclovir; PBS; SC; Mice (NSG); 1007D; 2 weeks; animal info (female, NSG, 8 weeks old); pumps replaced every week; cancer (teratoma); Dose (5 mg/kg/day);.

Q5285: N. H. Varvel, *et al.* Replacement of brain-resident myeloid cells does not alter cerebral amyloid-beta deposition in mouse models of Alzheimer's disease. *J Exp Med* 2015;212(11):1803-9

ALZET Comments: Valganciclovir; PBS; CSF/CNS (ventricle); mice; 2004; 2 weeks; Controls received mp w/ vehicle; animal info (Female hemizygous TK mice crossed w/ male hemizygous APPS1 or hemizygous APP23); ALZET brain infusion kit 3 used; good methods (pg. 11807); post op. care (paracetamol, i.p. 5 mg/kg daily; acetaminophen i.p. 5 mg/kg daily); brain tissue distribution; Dental cement used; Cannula placement verified via staining; anesthetized using ketamine and xylazine; Brain coordinates; from bregma: +0.1 mm anteroposterior, 1.0 mm lateral, and 2.5 mm dorsoventral; Dose (50 mg/ml);.

Q4258: D. O. Seo, *et al.* Adult Hippocampal Neurogenesis Modulates Fear Learning through Associative and Nonassociative Mechanisms. *JOURNAL OF NEUROSCIENCE* 2015;35(11330-11345)

ALZET Comments: Ganciclovir; PBS; CSF/CNS; Mice; 1002; 2 weeks; Control animals received mp w/ vehicle; animal info (8 wks old, DCX-TK transgenic, wt); ALZET brain infusion kit 3 used.

Q4578: U. Schneider, *et al.* Microglia inflict delayed brain injury after subarachnoid hemorrhage. *ACTA NEUROPATHOLOGICA* 2015;130(215-231)

ALZET Comments: Ganciclovir; CSF/CNS; Mice; 9 days; Animal info (CD11b-HSVTK, 14-14 weeks old, 22-25g); ALZET brain infusion kit used; immunology; noted 230 ul reservoir;.

Q4290: K. Rolon-Reyes, *et al.* Microglia Activate Migration of Glioma Cells through a Pyk2 Intracellular Pathway. *PLoS One* 2015;10(U2306-U2323)

ALZET Comments: Ganciclovir; CSF/CNS (intratumoral); Mice (transgenic); 2004; 7 days; Controls received mp w/ saline, normal; animal info (male, CD11b-HSVTK transgenic); ALZET brain infusion kit used; cancer (glioma GL261);.

Q5254: S. Prokop, *et al.* Impact of peripheral myeloid cells on amyloid-beta pathology in Alzheimer's disease-like mice. *J Exp Med* 2015;212(11):1811-8



ALZET Comments: Ganciclovir; CSF, artificial; CSF/CNS (lateral ventricles); mice; 2001; 10 days; Controls received mp w/ vehicle; animal info (APPPS1 transgenic mice); brain infusion cannula used; neurodegenerative (Alzheimer's); Dose (2.5 mg/ml); Therapeutic indication (Alzheimer's Disease);.

Q4509: K. J. Dixon, *et al.* Endogenous Neural Stem/Progenitor Cells Stabilize the Cortical Microenvironment after Traumatic Brain Injury. JOURNAL OF NEUROTRAUMA 2015;32(753-764

ALZET Comments: Ganciclovir sodium; SC; Mice; 1002; 4 weeks; Controls received mp w/ vehicle; animal info (CD1 nestin TK, adult); pumps replaced every 2 weeks; behavioral testing (motor function/rotarod test); traumatic brain injury;.

Q4373: K. O. Cho, *et al.* Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline. Nature Communications 2015;6(U1-U13

ALZET Comments: Ganciclovir; Water, distilled; SC; Mice; 2004; 4 weeks; Controls received mp w/ vehicle; animal info (C57BL6 or Nestin-TH, 6 weeks old); behavioral testing (epilepsy behavior, open field, memory); pumps removed after 4 weeks; epilepsy;.

Q4340: M. L. Bustos, *et al.* Depletion of Bone Marrow CCSP-Expressing Cells Delays Airway Regeneration. MOLECULAR THERAPY 2015;23(561-569

ALZET Comments: Ganciclovir; SC; Mice; 15 days; Animal info (CCK or WT);.

5. PMEAE

P1963: J. S. Lee, *et al.* Transplacental antiretroviral therapy with 9-(2-phosphonylmethoxyethyl)adenine is embryotoxic in transgenic mice. J. Acquir. Immune Defic. Syndr 1991;4(833-838

ALZET Comments: PMEAE; Mice; no duration posted; comparison of ip injections vs. mp; teratology; antiviral agent.

6. R-95288

P3720: T. Agatsuma, *et al.* Protection of hu-PBL-SCID/beige mice from HIV-1 infection by a 6-mer modified oligonucleotide, R-95288. Antiviral Res 1997;34(121-130

ALZET Comments: R-95288; Saline; IP; SC; mice (SCID); 2002; no duration posted; controls received mp w/saline; antisense; mice were transplanted w/human peripheral blood leukocytes; R-95288 protects human chimeric mice against HIV-1 infection; AIDS.

7. Ribavirin

P9134: M. C. Georges-Courbot, *et al.* Poly(I)-poly(C₁₂U) but not ribavirin prevents death in a hamster model of Nipah Virus infection. Antimicrobial Agents and Chemotherapy 2006;50(5):1768-1772

ALZET Comments: Ribavirin; 6-aza-uridine; SC; Hamster; 2ML2; 14 days; Controls received mp w/ PBS; toxicology; animal info (2 months old, golden); Ribavirin is an antiviral agent; 6-aza-uridine is a triazmenucleoside.

P5453: N. Charlier, *et al.* Infection of SCID mice with Montana Myotis leukoencephalitis virus as a model for flavivirus encephalitis. Journal of General Virology 2002;83(1887-1896

ALZET Comments: Ribavirin; SC; Mice (SCID); 2002; 14 days; Ribavirin is an antiviral; antiretroviral.

8. SID791

P3587: R. Datema, *et al.* Antiviral efficacy in vivo of the anti-human immunodeficiency virus bicyclam SDZ SID 791 (JM 3100), an inhibitor of infectious cell entry. Antimicrob. Agents Chemother 1996;40(3):750-754



ALZET Comments: SID 791; Saline, sterile; SC; Mice (SCID); mice; 2002; no duration posted; functionality of mp verified by plasma levels; dose-response; comparison of sc injections vs. mp; immunology; SID 791 is a bicyclam which inhibits HIV replication in vivo; human fetal liver & thymus transplanted into SCID mice.