



References on the Administration of Tyrosine Kinase Inhibitors Using ALZET® Osmotic Pumps

1. Dasatinib

Q4317: S. Balasubramanian, *et al.* Dasatinib Attenuates Pressure Overload Induced Cardiac Fibrosis in a Murine Transverse Aortic Constriction Model. *PLoS One* 2015;10(U407-U425)

ALZET Comments: Dasatinib; DMSO; saline; IP; Mice; 1004; 4 weeks; Controls received mp w/ vehicle; animal info (male, C57BL6, 3 months old); 50% DMSO used; no stress (see pg. 4); cardiovascular;.

Q2100: G. Dhawan, *et al.* Inhibition of Src kinase activity attenuates amyloid associated microgliosis in a murine model of Alzheimer's disease. *Journal of Neuroinflammation* 2012;9(;):U1-U17

ALZET Comments: Dasatinib; DMSO; HEPES; SC; Mice; 1004; 28 days; Controls received mp w/ vehicle; animal info (female, APP/PS1, 13 mo old); neurodegenerative (Alzheimer's disease).

Q3781: S. L. Ho, *et al.* Toxicity evaluation of prolonged convection-enhanced delivery of small-molecule kinase inhibitors in naive rat brainstem. *Childs Nervous System* 2015;31(221-226)

ALZET Comments: Dasatinib; everolimus; DMSO; ethanol anhydrous; CSF, artificial; CSF/CNS (brain stem); Rat; 2001; 7 days; Control animals received mp w/ aCSF and coomassie blue; animal info (Sprague-Dawley, 188-250 g); convection-enhanced delivery; Plastics One cannula used; "an Elizabethan collar was placed on animals to prevent disturbance of cannula" pg 222; "brainstem targeting using pCED to infuse single and multi-drug therapy was well tolerated in these rats" pg 221; enzyme inhibitor (receptor tyrosine kinase).

Q1444: P. M. Reeves, *et al.* Variola and Monkeypox Viruses Utilize Conserved Mechanisms of Virion Motility and Release That Depend on Abl and Src Family Tyrosine Kinases. *JOURNAL OF VIROLOGY* 2011;85(1):21-31

ALZET Comments: Dasatinib; imatinib mesylate; DMSO; water; PBS; SC; Mice; 4 days; Controls received mp w/ vehicle; animal info (6 wks old, female, C57/BL6); 50% DMSO used; dasatinib also known as BMS-354825; one group contained a mixture of dasatinib and imatinib mesylate in a single pump; imatinib mesylate also known as STI-571; enzyme inhibitor (tyrosine kinase, Src Abl).

Q2412: G. Dhawan, *et al.* Amyloid-beta oligomers stimulate microglia through a tyrosine kinase dependent mechanism. *NEUROBIOLOGY OF AGING* 2012;33(10):2247-2261

ALZET Comments: Dasatinib; oligomer, amyloid beta (1-42); HEPES; CSF/CNS; Mice; 1004; 14 days; Control animals received mp w/ vehicle; animal info (C57BL/6, female, 12 mo old); ALZET brain infusion kit used; neurodegenerative (Alzheimer's disease); peptide; enzyme inhibitor (tyrosine kinase).

2. Erlotinib

Q2576: S. Agarwal, *et al.* Function of the Blood-Brain Barrier and Restriction of Drug Delivery to Invasive Glioma Cells: Findings in an Orthotopic Rat Xenograft Model of Glioma. *Drug Metabolism and Disposition* 2013;41(1):33-39

ALZET Comments: Erlotinib; DMSO; IP; Mice; 1003D; 48 hours; Animal info (Mdr1ab -/-, Bcrp1 -/-, 8-10 wks old); wound clips used; half-life ("approximately 1 hour") pg 34; cancer (glioma); "Erlotinib half-life in mice has been reported to be approximately 1 hour (Marchetti et al., 2008), so an infusion lasting 48 hours was considered to be sufficient to attain steady state in both the brain and plasma." pg 34; chemotherapeutic; enzyme inhibitor (tyrosine kinase);.

3. Imatinib (Gleevec)

Q8295: R. C. Nayak, *et al.* The signaling axis atypical protein kinase C lambda/iota-Satb2 mediates leukemic transformation of B-cell progenitors. *Nat Commun* 2019;10(1):46

Agents: PKC inhibitor, Imatinib, or both **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2002; **Duration:** 14 days;



ALZET Comments: Dose (PKC inhibitor- 0.5 mM, Imatinib-1 mM); Controls received mp w/ vehicle; gene therapy;

Q6168: R. C. Nayak, *et al.* The signaling axis atypical protein kinase C lambda/iota-Satb2 mediates leukemic transformation of B-cell progenitors. *Nat Commun* 2019;10(1):1-16

Agents: Ro-31-8220; imatinib **Vehicle:** PBS; **Route:** SC; **Species:** Mice (transgenic); **Pump:** 2002; **Duration:** 14 days;

ALZET Comments: Dose (Ro-31-8220 (1 mM); imatinib (0.5 mM)); Controls received mp w/ vehicle; animal info (6-12 week old transgenic mice); enzyme inhibitor (Protein Kinase C);

Q6491: Tucheng Sun, *et al.* Imatinib inhibits angiotensin II-induced aortic dissection through the c-Abl signaling pathway. *International Journal for Clinical Experimental Pathology* 2017;10(5):5316-5324

Agents: Angiotensin II; Imatinib mesylate **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 2 weeks;

ALZET Comments: Dose (Angiotensin II: 3 mg/kg/day; Angiotensin II + Imatinib mesylate: 60 mg/kg per day); 0.9% saline used; Controls received mp w/ vehicle; animal info (12-30 week old C57BL/6 male mice weighing 25-35g); enzyme inhibitor (tyrosine kinase, c-Abl); cardiovascular; Pump incorrectly noted as model #1014D

Q5735: R. Callahan, *et al.* Original Research: Featured Article: Imatinib mesylate (Gleevec) inhibits Notch and c-Myc signaling: Five-day treatment permanently rescues mammary development. *Experimental Biology and Medicine* 2017;242(1):53-67

Agents: Imatinib mesylate **Vehicle:** Saline; **Route:** SC; **Species:** Mice (pregnant); **Pump:** 2001; **Duration:** 5 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (10 weeks old); cancer (Breast); Imatinib mesylate a.k.a Gleevec ; Therapeutic indication (Mammary gland development, Breast cancer); Dose (21 mg/mouse/week); enzyme inhibitor (tyrosine kinase);

Q4546: R. J. Napier, *et al.* Low Doses of Imatinib Induce Myelopoiesis and Enhance Host Anti-microbial Immunity. *PLoS Pathogens* 2015;11(U1651-U1677)

Agents: Imatinib mesylate **Vehicle:** Water; **Route:** SC; **Species:** Mice; **Pump:** 1007D; 2002; **Duration:** 28 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, C57BL6, 6 weeks old); functionality of mp verified by serum levels; dose-response (pg.9); immunology; enzyme inhibitor (tyrosine kinase);

4. PD153035

Q2985: M. Mizuno, *et al.* ErbB inhibitors ameliorate behavioral impairments of an animal model for schizophrenia: implication of their dopamine-modulatory actions. *TRANSLATIONAL PSYCHIATRY* 2013;3(;):U74-U84

ALZET Comments: PD153035; ZD1839; DMSO; CSF/CNS; Rat; 2002; 14 days; Animal info (male Sprague-Dawley rats); post op. care (topical antiseptic (50mg/day)); behavioral testing (7 days after mp implantation); 10-20% DMSO used; enzyme inhibitor (EGF receptor tyrosine kinase);.

Q1665: F. Watanabe, *et al.* Signaling through erbB receptors is a critical functional regulator in the mature cochlea. *European Journal of Neuroscience* 2010;32(5):717-724

ALZET Comments: PD153035; 4557W; DMSO; artificial perilymph; Ear (cochlea); Guinea pig; 2002; Controls received mp w/ artificial perilymph; animal info (female, pigmented, 250-500 g); functionality of mp verified by residual volume; tissue perfusion (intracochlear); 0.1% DMSO used; enzyme inhibitor (tyrosine kinase).

Q0890: M. Mizuno, *et al.* Antipsychotic Potential of Quinazoline ErbB1 Inhibitors in a Schizophrenia Model Established With Neonatal Hippocampal Lesioning. *JOURNAL OF PHARMACOLOGICAL SCIENCES* 2010;114(3):320-331

ALZET Comments: PD153035; ZD1839; OSI-774; DMSO; saline; CSF/CNS; Rat; 2002; 14 days; Controls received mp w/ vehicle; animal info (male, Sprague-Dawley); behavioral testing (locomotor activity test, acoustic startle test, contextual conditioning); 10% DMSO used; PD153035, OSI-774, and ZD1839 is an epidermal growth factor receptor family (ErbB1) inhibitor; enzyme inhibitor (tyrosine kinase);.



5. PP2

P8118: H. Katsura, K. Obata, T. Mizushima, J. Sakurai, K. Kobayashi, H. Yamanaka, Y. Dai, T. Fukuoka, M. Sakagami and K. Noguchi. Activation of Src-family kinases in spinal microglia contributes to mechanical hypersensitivity after nerve injury. *Journal of Neuroscience* 2006;26(34):8680-8690

ALZET Comments: PP2; PP3; DMSO; saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; Controls received mp w/ normal saline; dose-response (fig.8); enzyme inhibitor (Src-Family tyrosine kinase); animal info (male, Sprague-Dawley, 200-250g., spinal nerve ligation); 50% DMSO.

P6195: M. Mizuno, K. Yamada, J. He, A. Nakajima and T. Nabeshima. Involvement of BDNF receptor TrkB in spatial memory formation. *LEARNING & MEMORY* 2003;10(2):108-115

ALZET Comments: PP2; CSF/CNS; Rat; 11 days; Enzyme inhibitor (tyrosine kinase); PP2 is 4-amino-5-(4-chlorophenyl)-7-(t-butyl) pyrazolo [3,4-d] pyrimidine.

6. Sorafenib

Q2916: A. Z. Dudek, *et al.* Brain Metastases from Renal Cell Carcinoma in the Era of Tyrosine Kinase Inhibitors. *Clinical Genitourinary Cancer* 2013;11(2):155-160

ALZET Comments: Sorafenib; sunitinib; DMSO; saline; IP; 1003D; Animal info (Friend virus B-type (FVB) wild type, and Abcb1a/b knockout mice); cancer (renal carcinoma and brain metastases); cancer; enzyme inhibitor (tyrosine kinase); chemotherapeutic.

Q1442: S. Agarwal, *et al.* The Role of the Breast Cancer Resistance Protein (ABCG2) in the Distribution of Sorafenib to the Brain. *Journal of Pharmacology and Experimental Therapeutics* 2011;336(1):223-233

ALZET Comments: Sorafenib; DMSO; IP; Mice; 1003D; 48 hours; Animal info (FVB wild-type, Mdr1a/b $-/-$, Bcrp1 $-/-$, Mdr1a/b $-/-$, Bcrp1 $-/-$); half-life pg 226 "Sorafenib half-life in plasma and brain after an intravenous dose was determined to be 1.6 and 0.9 h, respectively. Therefore an infusion lasting 48 h was considered to be sufficiently long to attain steady state in both plasma and brain."; good methods, pg 226 "In the intraperitoneal infusion studies, the apparent plasma clearance (CLapp) was calculated by using the equation, $CL_{app} = k(0)/C_{ss}$, where, $k(0)$ is the rate of infusion into the peritoneal cavity normalized to body weight (ng/h/kg), and C_{ss} is the plasma concentration at steady state (ng/ml)."; enzyme inhibitor (biaryl-urea RAF kinase, tyrosine kinase); cancer (glioma); chemotherapeutic.

7. Sunitinib

Q4264: Y. Zhu, *et al.* Hematogenous macrophage depletion reduces the fibrotic scar and increases axonal growth after spinal cord injury. *NEUROBIOLOGY OF DISEASE* 2015;74(114-125

ALZET Comments: Sunitinib malate; DMSO; CSF/CNS (intrathecal); Mice; 1002; 2 weeks; enzyme inhibitor (tyrosine kinase); Animal info (female, 8 weeks old); functionality of mp verified by use of evans blue dye; 2.5% DMSO used; spinal cord injury; immunology; used ALZET mouse IT catheter; .

Q6739: R. K. Oberoi, *et al.* Pharmacokinetic assessment of efflux transport in sunitinib distribution to the brain. *J Pharmacol Exp Ther* 2013;347(3):755-64

ALZET Comments: Sunitinib; DMSO; IP; Mice (transgenic); mice (knockout); 1003D; 48 hours; Dose (30 μ g/h); animal info (8-10 week old wild-type and transgenic mice in which the gene for P-gp [Mdr1a/b(2/2) knockout mice], Bcrp [Bcrp1(2/2) knockout mice], and both P-gp and Bcrp [Mdr1a/b(2/2) Bcrp1(2/2) or "triple knockout" mice] was knocked out); enzyme inhibitor (tyrosine kinase);

Q2916: A. Z. Dudek, *et al.* Brain Metastases from Renal Cell Carcinoma in the Era of Tyrosine Kinase Inhibitors. *Clinical Genitourinary Cancer* 2013;11(2):155-160

ALZET Comments: Sorafenib; sunitinib; DMSO; saline; IP; 1003D; Animal info (Friend virus B-type (FVB) wild type, and Abcb1a/b knockout mice); cancer (renal carcinoma and brain metastases); cancer; enzyme inhibitor (tyrosine kinase); chemotherapeutic.



8. Other TK Inhibitors

Q5054: K. M. Henkels, *et al.* Phospholipase D (PLD) drives cell invasion, tumor growth and metastasis in a human breast cancer xenograph model. *Oncogene* 2013;32(49):5551-62

ALZET Comments: Apigenin, FIPI, NOPT; DMSO; SC; mice; 4, 5 weeks; animal info: SCID; cancer (breast); dose-response: Fig. 5; enzyme inhibitor (tyrosine kinase); half-life: >12 hrs. in humans; mp were used to study the effect of apigenin on tumor cell metastasis. Paper does not mention ALZET pump model; dose: 1.8 mg/kg/day.

Q1928: T. L. Wang, *et al.* Brain Distribution of Cediranib Is Limited by Active Efflux at the Blood-Brain Barrier. *Journal of Pharmacology and Experimental Therapeutics* 2012;341(2):386-395

ALZET Comments: Cediranib; DMSO; IP; Mice; 1003D; 72 hours; Animal info (wt, Mdr1a/b -/-, Bcrp1 -/-, and Mdr1a/b -/-, Bcrp1 -/-); cancer (glioma); enzyme inhibitor (tyrosine kinase); chemotherapeutic.

P6894: M. Tejada, *et al.* Growth Inhibitory Effect of the Somatostatin Structural Derivative (TT-232) on Leukemia Models. *Anticancer Research* 2005;25(325-330)

ALZET Comments: TT-232; Acetic acid; sodium acetate; water; mannitol; IV; SC; Mice; 2002; 14, 28 days; Dose-response (p. 328, fig 1); comparison of IP/SC injections vs. SC/IV mp; pumps replaced at day 14 for 28 day group; stability verified, 37 degrees Celsius for over 3 weeks; cancer (leukemia); TT-232 is a novel somatostatin analog; "The IV infusion for 28 days resulted in 82% growth inhibition." (p. 328); "The infusion of TT-232 by ALZET osmotic minipump resulted in 70-80% tumor growth inhibition and 20% tumor free survival." (p. 329); "...serial injections represent significant stress to the animals..." "To reduce and eliminate the above mentioned problem [stress] we used an ALZET osmotic minipump..." "Infusion from inserted ALZET minipumps maintains a constant drug level, resulting in a well defined, consistent pattern of drug exposure throughout the period of drug administration." "These studies suggest that TT-232 is a potent inhibitor of leukemia tumor in vitro and in vivo and suggest infusion treatment as a beneficial application in clinical practice." (p. 330); oligopeptide; enzyme inhibitor (tyrosine kinase); animal info (CBA/ca, immunosuppressed, female).

P6629: J. E. Davies, *et al.* Decorin Suppresses Neurocan, Brevican, Phosphacan and NG2 Expression and Promotes Axon Growth Across Adult Rat Spinal Cord Injuries. *European Journal of Neuroscience* 2004;19(1226-1242)

ALZET Comments: Decorin, recomb. human; PBS; CSF/CNS (intrathecal); Rat; 2001; 8 days; Controls received mp w/ vehicle; tissue perfusion (spinal lesion); enzyme inhibitor (tyrosine kinase); decorin is known to inhibit TGF beta and is an antagonist to EGF receptor tyrosine kinase.

P6396: I. F. Benter, *et al.* Inhibition of Ras-GTPase, but not tyrosine kinases or Ca²⁺/calmodulin-dependent protein kinase II, improves recovery of cardiac function in the globally ischemic heart. *MOLECULAR AND CELLULAR BIOCHEMISTRY* 2004;259(1-2):35-42

ALZET Comments: FPT III; KN-93; Genistein; Saline; IP; Rat; 2ML1; 6 days; Controls received mp w/ vehicle; enzyme inhibitor (tyrosine kinase, CaMKII); cardiovascular; ischemia (cardiac).

P6010: S. Q. Liu, *et al.* Pattern formation of vascular smooth muscle cells subject to nonuniform fluid shear stress: role of PDGF-β; receptor and Src. *American Journal of Physiology-Heart and Circulatory Physiology* 2003;285(3):H1081-H1090

ALZET Comments: AG-1296; PP1; IV (vena cava); Rat; 2001D; 10 days; AG-1296 and PP1 are selective PDGF-B receptor tyrosine kinase and SRC inhibitors; enzyme inhibitor (tyrosine kinase).

P6530: T. Grunberger, *et al.* Inhibition of acute lymphoblastic and myeloid leukemias by a novel kinase inhibitor. *Blood* 2003;102(12):4153-4158

ALZET Comments: CR4; DMSO; medium; SC; Mice; 2001; 14,21 days; Controls received mp w/ vehicle; pumps replaced every 7 days; CR4 was dissolved in 50% DMSO/medium and is a novel enzyme inhibitor (tyrosine kinase).

P5764: F.-Q. Liang, *et al.* Role of brain-derived neurotrophic factor in the circadian regulation of the suprachiasmatic pacemaker by light. *J Neurosci* 2000;20(8):2978-2987



ALZET Comments: Brain-derived neurotrophic factor; K252a; CSF, artificial; BSA; DMSO; CSF/CNS (suprachiasmatic nucleus); Rat; 2004; 28 days; Controls received mp w/ vehicle; comparison of acute injections vs. mp p.2979; enzyme inhibitor (tyrosine kinase); BDNF was recombinant human; dissolved in a CSF & 0.1% BSA; K252a was dissolved in DMSO; guide cannula used with a stylet; 3-day recovery period before pump implantation.