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

1. Dasatinib

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;

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).

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).

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

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)

ALZET Comments: Ro-31-8220; imatinib; PBS; SC; Mice (transgenic); 2002; 14 days; 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);


ALZET Comments: Angiotensin II; Imatinib mesylate; Saline; SC; Mice; 1002; 2 weeks; 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.


ALZET Comments: Imatinib mesylate; Saline; SC; Mice (pregnant); 2001; 5 days; 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);


ALZET Comments: Imatinib mesylate; Water; SC; Mice; 1007D; 2002; 28 days; 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);


ALZET Comments: Imatinib; CSF, artificial; CSF/CNS (intrathecal); Mice (transgenic); 1007D; 1 week; Controls received mp w/ vehicle; animal info (triple transgenic ABBP, PS1, P301L); neurodegenerative (Alzheimer’s); "Since it is known that the drug does not penetrate the blood-brain barrier efficiently, it is possible that the contradictory results reflect this property of the drug. For this reason in the current study, we delivered Imatinib by means of implanted osmotic minipumps directly in the brains of the triple transgenic mice" pg 730; Imatinib aka STI571 a.kd Gleevec; used dental cement; enzyme inhibitor (tyrosine kinase);


ALZET Comments: Imatinib mesylate; Mice; 5 weeks; Controls received mp w/ vehicle; animal info (SHT-2b -/-, adult, 7-9 wks old); imatinib mesylate also known as Gleevec or STI-571; hypoxia; enzyme inhibitor (tyrosine kinase);


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).


ALZET Comments: Imatinib; Water; SC; Mice; 1007D; 7 days; Controls received mp w/ vehicle; animal info (male, C57BL/6, 6 wks old); enzyme inhibitor (tyrosine kinase);

**ALZET Comments:** Imatinib mesylate; PBS; SC; Mice (nude); 2004; 28 days; Controls received mp w/ vehicle; cancer (Plexiform neurofibromas); enzyme inhibitor (receptor tyrosine kinase); stress/adverse reaction: (see pg 13) "because of inflammation at the ALZET pump site, four mice of the treatment group had to be discontinued"; animal info (female, athymic nu/nu Balb/c); agent also known as Glivec or Gleevec.


**ALZET Comments:** Gleevec; SC; Mice; Enzyme inhibitor (tyrosine kinase); Review, pg. 121, ref #21; compound also known as ST-571.

**P8330:** A. Raafat, *et al.* Kit and PDGFR-alpha activities are necessary for Notch4/Int3-induced tumorigenesis. ONCOGENE 2007;26(5):662-672

**ALZET Comments:** Imatinib mesylate; SC; Mice (transgenic); 2001; 1,3,4,5,7 days; Controls received mp w/ water; dose-response (fig 2); no stress (see pg. 663); cancer (mammary); animal info (female, FVB/N, 10 wks old); antiangiogenic; "Continuous release of Gleevec for a week resulted in 33% inhibition of tumor growth by day 2 and 66% by day 4." (p. 668); 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(1):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**


**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


**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.


**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, Clapp = k0/Css, where, k(0) is the rate of infusion into the peritoneal cavity normalized to body weight (ng/h/kg), and Css is the plasma concentration at steady state (ng/ml)."; enzyme inhibitor (biaryl-urea RAF kinase, tyrosine kinase); cancer (glioma); chemotherapeutic.

7. Sunitinib


**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.


**ALZET Comments**: Sunitinib; DMSO; IP; Mice (transgenic); mice (knockout); 1003D; 48 hours; Dose (30 µg/h); animal info (8-10 week old wild-type and transgenmic 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);


**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


**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.


**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.
**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).

**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).

**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).

**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).

**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.