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

Dasatinib


**Agents:** Dasatinib  
**Vehicle:** Not Stated  
**Route:** CSF/CNS  
**Species:** Mice  
**Pump:** 2002  
**Duration:** 14 days  
**ALZET Comments:** Dose (2 uM); Dasatinib aka Tyrosine Kinase Inhibitor; enzyme inhibitor (Tyrosine Kinase Inhibitor); cancer

**Q7794:** R. W. D’Amico, *et al.* Saracatinib and Dasatinib Fail To Prevent Heritable Pulmonary Arterial Hypertension. bioRxiv 2018;345447

**Agents:** Dasatinib, Saracatinib  
**Vehicle:** DMSO; 16-OHE  
**Route:** SC  
**Species:** Mice  
**Pump:** 1004  
**Duration:** 4 weeks  
**ALZET Comments:** Dose (1 mg/kg/day); 50% DMSO/50% 16α-hydroxyestrone (16-OHE) used; Controls received mp w/ vehicle; animal info (10-14 weeks old)cardiovascular

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

**Agents:** Dasatinib; everolimus  
**Vehicle:** DMSO; ethanol anhydrous; CSF, artificial  
**Route:** CSF/CNS (brain stem)  
**Species:** Rat  
**Pump:** 2001  
**Duration:** 7 days  
**ALZET Comments:** 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)

**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

**Agents:** Dasatinib  
**Vehicle:** DMSO; saline  
**Route:** IP  
**Species:** Mice  
**Pump:** 1004  
**Duration:** 4 weeks  
**ALZET Comments:** Controls received mp w/ vehicle; animal info (male, C57BL6, 3 months old); 50% DMSO used; no stress

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

**Agents:** Dasatinib; oligomer, amyloid beta (1-42)  
**Vehicle:** HEPES  
**Route:** CSF/CNS  
**Species:** Mice  
**Pump:** 1004  
**Duration:** 14 days  
**ALZET Comments:** 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)

**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

**Agents:** Dasatinib  
**Vehicle:** DMSO; HEPES  
**Route:** SC  
**Species:** Mice  
**Pump:** 1004  
**Duration:** 28 days  
**ALZET Comments:** Controls received mp w/ vehicle; animal info (female, APP/PS1, 13 mo old)


**Agents:** Dasatinib; imatinib mesylate  
**Vehicle:** DMSO; water; PBS  
**Route:** SC  
**Species:** Mice  
**Duration:** 4 days  
**ALZET Comments:** 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)
Erlotinib
**Agents:** Erlotinib **Vehicle:** DMSO; **Route:** IP; **Species:** Mice; **Pump:** 1003D; **Duration:** 48 hours;
**ALZET Comments:** 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);

Imatinib (Gleevec)
**Agents:** Imatinib **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 28 days;
**ALZET Comments:** Controls received mp w/ vehicle; animal info (Pathogen-free, male C57BL/6 and Balb/c mice, 20-24 g); Imatinib aka GNP-HClm; toxicology;

**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);

**Agents:** Nilotinib; Imatinib **Vehicle:** Ethanol:PEG300: Cremophor EL; Sterile water; **Route:** IV injection; Gavage; **Species:** Mice; Guinea pigs; Prairie Dogs; Cynomolgus monkeys; **Pump:** Not Stated; **Duration:** Not Stated;
**ALZET Comments:** Nilotinib 1.5:4.5:20 (ethanol:PEG300:Cremophor) in 3.7% dextrose solution used; animal info (Mice C57BL/6, 20g both genders; Prairie dogs wild caught male black tailed, 1-2 years; Guinea pigs male hartley 450-650g); half-life (p.1,8); Resultant plasma level (Figure 1 nilotinib, Figure 2 imatinib); enzyme inhibitor (tyrosine kinase (TKI)); good methods (elimination half-lives were quite short (1–2 h). Thus, further testing of these agents in C57BL/6 mice is feasible but may require a continuous delivery system such as an Alzet® mini pump.); didn’t use Alzet pmup, but recommends using it in future studies of these agents in mice or guinea pigs;

**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

**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);

**Agents:** Imatinib mesylate **Vehicle:** Water; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **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);

**Agents:** Imatinib **Vehicle:** CSF, artificial; **Route:** CSF/CNS (intrathecal); **Species:** Mice (transgenic); **Pump:** 1007D; **Duration:** 1 week;

**ALZET Comments:** 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 akd Gleevec; used dental cement; enzyme inhibitor (tyrosine kinase);


**Agents:** Imatinib mesylate **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Mice; **Pump:** Not Stated; **Duration:** 5 weeks;

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


**Agents:** Dasatinib; imatinib mesylate **Vehicle:** DMSO; water; PBS; **Route:** SC; **Species:** Mice;; **Duration:** 4 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (6 wks old, female, C57/BL6); 50% DMSO used; one group contained a mixture of dasatinib and imatinib mesylate in a single pump; enzyme inhibitor (tyrosine kinase, Src Abl)


**Agents:** Imatinib **Vehicle:** Water; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (male, C57BL/6, 6 wks old); enzyme inhibitor (tyrosine kinase);


**Agents:** Imatinib mesylate **Vehicle:** PBS; **Route:** SC; **Species:** Mice (nude); **Pump:** 2004; **Duration:** 28 days;

**ALZET Comments:** 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;


**Agents:** Gleevec **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** Not Stated;

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


**Agents:** Imatinib mesylate **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice (transgenic); **Pump:** 2001; **Duration:** 1,3,4,5,7 days;

**ALZET Comments:** 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);


**Agents:** Imatinib mesylate; Hydroxyurea **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 7, 14 days;

**ALZET Comments:** Half-life (p. 1948) hydroxyurea < 1 hour in rats; enzyme inhibitor (ribonucleotide reductase, tyrosine kinase); cancer (glioblastoma); animal info (Hanover Wistar, 270-310 grams);

**Agents:** Imatinib mesylate  
**Vehicle:** PBS;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** 1007D; 1002;  
**Duration:** 5, 8, 15 days;  

**ALZET Comments:** Controls received mp w/ vehicle; no stress (see pg. 738); enzyme inhibitor (Abl-family kinase, tyrosine kinase); animal info (female, C57/BL, 6 wk. old); agent formerly known as STI571; virology; Gleevec


**Agents:** Imatinib mesylate; Inhibitor 2  
**Vehicle:** Saline; DMSO;  
**Route:** CSF/CNS (Intrathecal);  
**Species:** Guinea pig (albino);  
**Pump:** 2001;  
**Duration:** 7 days;  

**ALZET Comments:** Controls received mp w/ vehicle; inhibitor 2 was dissolved in DMSO; “it has been shown that STI571 does not penetrate the blood-brain barrier efficiently, we therefore delivered (p. 12447) each inhibitor intrathecally over 7 days by means of implanted osmotic minipumps.”; neurodegenerative (Alzheimer’s disease)

PD153035


**Agents:** PD153035; ZD1839  
**Vehicle:** DMSO;  
**Route:** CSF/CNS;  
**Species:** Rat;  
**Pump:** 2002;  
**Duration:** 14 days;  

**ALZET Comments:** 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);


**Agents:** PD153035; 4557W  
**Vehicle:** DMSO; artificial perilymph;  
**Route:** Ear (cochlea);  
**Species:** Guinea pig;  
**Pump:** 2002;  
**Duration:** 14 days;  

**ALZET Comments:** 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)


**Agents:** PD153035; OSI-774  
**Vehicle:** DMSO; Saline;  
**Route:** CSF/CNS;  
**Species:** Rat;  
**Pump:** 2002;  
**Duration:** 14 days;  

**ALZET Comments:** 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)

PP2


**Agents:** PP2; PP3  
**Vehicle:** DMSO; Saline;  
**Route:** CSF/CNS (intrathecal);  
**Species:** Rat;  
**Pump:** 2001;  
**Duration:** 7 days;  

**ALZET Comments:** 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; enzyme inhibitor (tyrosine kinase)


**Agents:** PP2  
**Vehicle:** Not Stated;  
**Route:** CSF/CNS;  
**Species:** Rat;  
**Pump:** Not Stated;  
**Duration:** 11 days;  

**ALZET Comments:** Enzyme inhibitor (tyrosine kinase); PP2 is 4-aminocyclopropyl-7-(t-butyl) pyrazolo[3,4-d]pyrimidine
Sorafenib


**Agents:** Sorafenib; sunitinib  
**Vehicle:** DMSO; saline  
**Route:** IP  
**Species:** Not Stated  
**Pump:** 1003D  
**Duration:** Not Stated  

**ALZET Comments:** 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


**Agents:** Sorafenib  
**Vehicle:** DMSO;  
**Route:** IP  
**Species:** Mice  
**Pump:** 1003D  
**Duration:** 48 hours  

**ALZET Comments:** 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\text{app} = k_0/C_s, where, k_0 is the rate of infusion into the peritoneal cavity normalized to body weight (ng/h/kg), and C_s is the plasma concentration at steady state (ng/ml).”; enzyme inhibitor (biaryl-urea RAF kinase, tyrosine kinase); cancer (glioma); chemotherapeutic

Sunitinib


**Agents:** Sunitinib malate  
**Vehicle:** DMSO;  
**Route:** CSF/CNS (intrathecal)  
**Species:** Mice  
**Pump:** 1002  
**Duration:** 2 weeks  

**ALZET Comments:** Dose (30 µg/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);


**Agents:** Sunitinib  
**Vehicle:** DMSO;  
**Route:** IP  
**Species:** Mice (transgenic); mice (knockout)  
**Pump:** 1003D  
**Duration:** 48 hours  

**ALZET Comments:** Controls received mp w/ vehicle; Bosutinib aka SKI-606; Enzyme inhibitor (tyrosine kinase); dependence;


**Agents:** Sorafenib; sunitinib  
**Vehicle:** DMSO; saline;  
**Route:** IP;  
**Species:** Not Stated  
**Pump:** 1003D  
**Duration:** Not Stated  

**ALZET Comments:** 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

Other TK Inhibitors


**Agents:** Bosutinib  
**Vehicle:** Saline;  
**Route:** SC;  
**Species:** Mice;  
**Pump:** 2006;  
**Duration:** 42 days  

**ALZET Comments:** Dose (2.5, 5.0, or 10.0 mg/kg/day); Controls received mp w/ vehicle; Bosutinib aka SKI-606; Enzyme inhibitor (tyrosine kinase); dependence;


**Agents:** AG879  
**Vehicle:** DMSO;  
**Route:** IP;  
**Species:** Mice;  
**Pump:** 1002;  
**Duration:** Not Stated  

**ALZET Comments:** Dose (5 mg/kg/day); animal info (immunocompetent female BALB/c mice, 4 to 6 weeks old, 20g); AG879 is a TrkA inhibitor; enzyme inhibitor (Tyrosine kinase A); cancer (Breast cancer);
Agents: Apigenin, FIPI, NOPT Vehicle: DMSO; Route: SC; Species: Mice; Pump: Not Stated; Duration: 4, 5 weeks;
ALZET Comments: 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

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

Agents: TT-232 Vehicle: Acetic acid; sodium acetate; water; mannitol; Route: IV; SC; Species: Mice; Pump: 2002; Duration: 14, 28 days;
ALZET Comments: 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)

Agents: Decorin, recomb. human Vehicle: PBS; Route: CSF/CNS (intrathecal); Species: Rat; Pump: 2001; Duration: 8 days;
ALZET Comments: 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
Agents: FPT III; KN-93; Genistein Vehicle: Saline; Route: IP; Species: Rat; Pump: 2ML1; Duration: 6 days;
ALZET Comments: Controls received mp w/ vehicle; enzyme inhibitor (tyrosine kinase, CaMKII); cardiovascular; ischemia (cardiac)

Agents: AG-1296; PP1 Vehicle: Not Stated; Route: IV (vena cava); Species: Rat; Pump: 2001D; Duration: 10 days;
ALZET Comments: AG-1296 and PP1 are selective PDGF-B receptor tyrosine kinase and SRC inhibitors; enzyme inhibitor (tyrosine kinase)

Agents: CR4 Vehicle: DMSO; medium; Route: SC; Species: Mice; Pump: 2001; Duration: 14,21 days;
ALZET Comments: 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)

**Agents:** Brain-derived neurotrophic factor; K252a  
**Vehicle:** CSF, artificial; BSA; DMSO  
**Route:** CSF/CNS (suprachiasmatic nucleus)  
**Species:** Rat  
**Pump:** 2004  
**Duration:** 28 days  

**ALZET Comments:** 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