References Using the ALZET® Osmotic Pumps In Xenograft Models

Agents: DFP-10917 Vehicle: Not Stated; Route: SC; Species: Mice; Pump: Not Stated; Duration: 1, 3, 14 days;
ALZET Comments: Dose (4.5, 8, 30 mg/kg/day); Controls received no treatment; animal info (5 weeks, male, BALB/c Jcl-nu, 17.2-24.6g); comparison of bolus injection vs mp; DFP-10917 AKA 2'-C-cyano-2'-deoxy-1-beta-D-arabino-pentofranocytosine is a 2'-deoxycytidine analog with antitumor activity; cancer (tumor xenografts); Infusion of agent occurred on three regimens: 24 consecutive hours on days 1 and 8, for 3 consecutive days on days 1 and 15, or for 14 consecutive days (p.852); Therapeutic indication (“regression of tumor growth without any toxicities on human solid and hematological tumor xenografts compared to clinically available deoxycytidine analogs.” p.858);

Agents: YM155 Vehicle: Saline; Route: SC; Species: Mice (SCID); Pump: 1003D; Duration: 2 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (female, SCID, 4-6 weeks old); cancer (oral squamous cell carcinoma, SCC9); xenograft model; Pumps infused for 3 days per week for two weeks; Therapeutic indication (oral squamous cell carcinoma); Dose (50 mg/kg);

Q5357: F. Muller, et al. Paclitaxel synergizes with exposure time adjusted CD22-targeting immunotoxins against B-cell malignancies. ONCOTARGET 2017;1-12
Agents: HA22- PE24 recombinant immunotoxin Vehicle: Citrate buffer; Route: IP; Species: Mice; Pump: 1007D; Duration: 7 days;
ALZET Comments: 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.

Agents: Doxorubicin hydrochloride Vehicle: PBS; Route: IP; Species: Mice; Pump: 1007D; Duration: 7 days;
ALZET Comments: Controls received mp w/ vehicle; cancer (Sarcoma); Therapeutic indication (Cancer; soft tissue sarcoma; xenograft model);

Agents: C-type natriuretic peptide; Route: SC; Species: Mice (nude); Pump: 1003D; Duration: 3 days; 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, C57BL6 or BALB/c nu/ny, 5 weeks old); functionality of mp verified by plasma levels (figure 4B); cancer (rhabdomyosarcoma RD-GC-B); xenograft model; Dose (2.5 ug/kg/min); Resultant plasma level (~600 pmol/L; see figure 4B);

Q5078: Y. Uchi, et al. CXCL12 expression promotes esophageal squamous cell carcinoma proliferation and worsens the prognosis. BMC Cancer 2016;16(514
Agents: AMD3100 Vehicle: Not Stated; Route: SC; Species: Mice (nude); Pump: 2001; Duration: 14 days;
ALZET Comments: Controls received mp w/ 0.1% BSA; animal info (female, BALB/c nude, 6 weeks old); pumps replaced every week; cancer (Esophageal squamous cell carcinoma TE4); xenograft model;

**Agents:** Fenofibrate; Glucose, 2-Deoxy

**Vehicle:** Saline; **Route:** SC; **Species:** Mouse; **Pump:** Not Stated; **Duration:** 62 Days;

**ALZET Comments:** Controls received mp w/ vehicle and oral gavage; cancer (human melanoma xenograft model); dose-response (pg 36469); toxicology; “slow-release pump seems to be an effective way to deliver 2-DG” pg 36470; Oral gavage vs. mp; dose given via mp requires 3 times lower total dose than IP injection (3x/week); Therapeutic indication (tumor growth); Dose (FF 100 mg/kg/day, 41 ug/ml/hr);


**Agents:** Digoxin

**Vehicle:** Promethylcellulose, Tween80, DMSO; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** Not Stated;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (NSG mice); 0.5% used Promethylcellulose, 0.2% Tween80 used, 5% DMSO; cancer (xenograft models); dose-response (pg. 14); Dose (10 mg/kg/day);


**Agents:** Paclitaxel

**Vehicle:** Cremophor EL, Ethanol; **Route:** IP; **Species:** Mice (SCID); **Pump:** 1004; **Duration:** 2 weeks;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (SCID mice 6–8 weeks old); functionality of mp verified by bioluminescence imaging to check metastatic spread; 50% Cremophor, 50% ethanol used; cancer (Cholangiocarcinoma); Xenograft model; Dose (2.6 mg/kg/d);


**Agents:** Fenoldopam

**Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 1 week, 3 weeks;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (Eight-week-old female athymic nu/nu mice; inoculated with MDA-MB-231 cells or SUM159 cells); functionality of mp verified by measurement of tumor volumes; cancer (breast cancer); dose-response (pg. 3109); Xenograft models; Dose (400 ng/kg/min or 133 ng/kg/min);


**Agents:** Eg5 inhibitor

**Vehicle:** DMSO, captsiol; **Route:** SC; **Species:** Rat (Nude); **Duration:** 1 day, 2 days, 3 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (human transitional cell carcinoma (TCC) cell line MGHU3 in nude rats); 50% DMSO, 60% captsiol used; cancer (bladder); dose-response (pg 667-669); enzyme inhibitor (kinesin-5 inhibitor); human transitional cell carcinoma (TCC) cell line MGHU3; xenograft model; Dose (1.375 mg/kg/d, 2.75 mg/kg/d, 4.6 mg/kg/d);

Q5320: M. Benlloch, et al. Pterostilbene Decreases the Antioxidant Defenses of Aggressive Cancer Cells In Vivo: A Physiological Glucocorticoids- and Nrf2-Dependent Mechanism. Antioxidants & Redox Signaling 2016;24(17):974-90

**Agents:** Pterostilbene, Corticosterone

**Vehicle:** DMSO, Ethanol; PEG400; **Route:** IV (jugular); **Species:** Mice; **Duration:** 35 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info Female nu/nu nude mice (6–8 weeks); Vehicle solution DMSO and ethanol at 2:1 ratio; functionality of mp verified by plasma levels, pg 979; functionality of mp verified by plasma levels, pg 979; Pterostilbene is a natural dimethoxylated analog of resveratrol; Mice xenograft models; Dose (50 mg/ml Pter; 0.3 ug/hr corticosterone); Resultant plasma level (pg. 979);


**Agents:** Synstatin(IGF1R), Synstatin(IGF1R-T)

**Vehicle:** PBS; **Route:** SC; **Species:** Mice (NUDE); **Pump:** 2004; **Duration:** 4 weeks;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (6- to 8-week-old female, athymic Foxn1nu outbred nude mice); functionality of mp verified by tumor volume measurements; cancer (Multiple Myeloma); dose-response (pg. 4989-4990); Xenograft model; Dose (3.6 mg/kg/d); Resultant plasma level (30 umol/L); Interesting (Evidence of tumor elimination);

Agents: PZ09 Vehicle: Not Stated; Route: CSF/CNS (lateral ventricle); Species: mice; Pump: Not Stated; Duration: 7, 14 days;
ALZET Comments: animal info (Six- to 8-week-old female NOD-SCID, TNFa−/−, and control mice); dose-response (pg. 2-5); tissue perfusion (brain, glioblastomas); PZ09 aka small-molecule, benzimidazole adenosine triphosphate–competitive aPKC inhibitor; xenografts; Dose: 10 uM PZ09


Agents: Irinotecan Vehicle: Not Stated; Route: SC; Species: Mice (nude); Pump: 2001D; Duration: 24 hours;
ALZET Comments: animal info (athymic, nude)); functionality of mp verified by plasma levels; cancer (neuroblastoma; HSJD-NB-003 or HSJD-NB-004); xenograft model; Dose (130 ug/h);


Agents: SecinH3 Vehicle: DMSO; glycerol; Route: SC; Species: Mice; Pump: 2001; Duration: 16 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Arf6 flox/flox, 8 weeks old); pumps replaced every 4 days; 50% DMSO used; 50% glycerol; cancer (B16 melanoma or LLC); xenograft model;


Agents: TAS-102 Vehicle: Saline; Route: SC; Species: Mice (nude); Pump: 1002; Duration: Not Stated;
ALZET Comments: Controls received no treatment; animal info (5 week old, male nude mice, BALB/cA); functionality of mp verified by tumor volume measurements; cancer (colorectal cancer; xenograft model); Cell lines used: CRC cell lines DLD-1, HT-29, HCT116, KM20C and SW480; small cell lung cancer cells Lu-134; breast cancer cells MC-2 and MX-1; TAS-102 is a novel nucleoside antitumor agent containing trifluoridine (FTD) and tipiracil hydrochloride (TPI); Therapeutic indication (colorectal cancer);


Agents: Follicle stimulating hormone, porcine Vehicle: Not Stated; Route: Not Stated; Species: Mice; Pump: 2004; Duration: 2 weeks;
ALZET Comments: animal info (nude mice); functionality of mp verified by tissue levels; cancer (glioblastoma multiforme); Xenograft study; Dose (62.5 U/mL);


Agents: Plasmid, miR-211-overexpressing; Plasmid, MMP-9 Vehicle: Not Stated; Route: CSF/CNS; Species: Mice (Nude); Pump: 2004; Duration: 6 weeks;
ALZET Comments: animal info (nude mice); functionality of mp verified by tissue levels; cancer (glioblastoma multiforme);


Agents: DTATEGF, immunotoxin Vehicle: Not Stated; Route: SC; Species: Mice; Pump: 1007D; Duration: 7 days;
ALZET Comments: Controls received mp w/ DT; animal info (human metastatic non-small cell lung cancer (NSCLC) brain tumor mouse xenograft model.); functionality of mp verified by BLI; cancer (PC9-BrM3 intracranial tumor); advantage of using mp (In this study we performed CED via a micro-osmotic pump system in a mouse model and showed that there are several advantages of this delivery technique: (1) the infusion pressure can allow continuous infusion of a solution at a constant rate; (2) it delivers solutions continuously for several days without the need for an external connection or frequent handling of animals; (3) the pump caused less stress to the mice and was well tolerated; and (4) humans are immunized to DT, so that immunotoxins given by CED to the CNS are immunologically privileged)

**Agents:** GMX1777  **Vehicle:** NaCl;  **Route:** IV (jugular);  **Species:** Mice (nude; SCID);  **Pump:** 2001D;  **Duration:** 24 hours;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (BalbC nude, CB17, SCID/SCID, female); comparison of 72 h infusion pump vs 24 h mp; cancer (refractory solid tumors and lymphomas); "The 24 h infusion was the most effective administration schedule identified in mouse xenograft models" pg 352-353; cancer; chemo therapeutic


**Agents:** AZD1152  **Vehicle:** Not Stated;  **Route:** SC;  **Species:** Mice;  **Pump:** 2001D;  **Duration:** 48 hours;

**ALZET Comments:** Controls received mp w/ vehicle; dose-response (p. 3684); comparison of IV or IP injections; enzyme inhibitor (aurora B kinase); cancer; xenograft; animal info (male, 8-12 weeks old, Swiss athymic)


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

**ALZET Comments:** Controls received mp w/ vehicle; plasma levels taken; dose-response (p. 3941); cancer (lung); tumors implanted in right flank; M3 receptor antagonist; xenograft; animal info (6-7 weeks old)


**Agents:** AZD1152  **Vehicle:** Tris buffer;  **Route:** SC;  **Species:** Mice (nude);  **Pump:** 2001D;  **Duration:** 48 hours;

**ALZET Comments:** Enzyme inhibitor (aurora kinase); cancer; animal info (male, Swiss, nu/nu); PK data; xenograft; tumor cells on dorsal flank


**Agents:** JTE-607  **Vehicle:** Cyclohexatin, 2-hydroxypropyl-b-;  **Route:** SC;  **Species:** Mice (SCID);  **Pump:** 2004;  **Duration:** 7 days;

**ALZET Comments:** Controls received mp w/ vehicle; plasma levels taken; dose-response (p. 1386); cancer (leukemia); animal info (5-7 weeks old, SCID); xenograft; multiple cytokine inhibitor; antileukemic; "Administration of JTE-607 using osmotic pumps reduced the number of leukemic cells...and significantly prolonged the mouse survival..." p. 1386; 30% cyclohexatin used


**Agents:** Thioredoxin, human recomb.  **Vehicle:** Not Stated;  **Route:** SC;  **Species:** Mice (nude);  **Pump:** 2002;  **Duration:** 2 weeks;

**ALZET Comments:** Controls received mp w/ PBS; plasma levels taken; cancer (colon, carcinoma); peptides; animal info (female, 6 weeks old, nude); xenograft


**Agents:** Oblimersen  **Vehicle:** Saline;  **Route:** SC;  **Species:** Mice (SCID);  **Pump:** 2004;  **Duration:** 28 days;

**ALZET Comments:** Stress/adverse reaction: (see pg. 2907), infection (pumps are provided sterile); cancer (lymphoma); animal info (5-7 weeks old, SCID); xenograft; bcl-2 antisense molecule


**Agents:** Follicle-stimulating hormone, porcine  **Vehicle:** Saline;  **Route:** SC;  **Species:** Mice (nude);  **Pump:** 2004;  **Duration:** 7, 14 days;

**ALZET Comments:** Controls received no hormone treatment; replacement therapy (ovariectomy); dose-response (pg. 280); animal info (female, Crj: CD1-Foxn1nu, 5-6 wk old); ovarian xenografts
**Agents:** ST1646 **Vehicle:** Saline; **Route:** SC; **Species:** Mice (nude); **Pump:** 2002; **Duration:** 14 days;
**ALZET Comments:** Controls received mp w/ vehicle; animal info (CD1); tumor cells were placed SC in the right flank, while the pump was placed SC in the left flank; ST1646 delivery via an osmotic pump inhibited the growth and vascularization of tumor xenografts originating from the injection of alpha v beta 3 alpha v beta 5-expressing human ovarian carcinoma cells in nude mice.

**Agents:** Testosterone; estradiol; progestosterone; flutamide **Vehicle:** Cylodextrin, 2-beta-hydroxypropyl; **Route:** SC; **Species:** Mice (nude); **Pump:** 2004; **Duration:** 4 weeks;
**ALZET Comments:** Replacement therapy (castration); cancer (prostate); CWR22 xenograft used; flutamide is an anti-androgen; animal info (5-6 week old, nude, ORX).

**Agents:** oligonucleotide, antisense **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 14 days;
**ALZET Comments:** Controls received no treatment or mp w/ control oligonucleotides; animal info (6-weeks, SCID/NOD-hu); antisense ((ISIS 16009, 5’-CTA CGC TTT CCA CGC ACA GT-3’), (ISIS 15999, 5’-TCC CGG TTG CTC TGA GAC AT-3’)); cancer (leukemia); pump model not stated although study listed 200μl capacity; Therapeutic indication (chemosensitization of tumor xenografts);

**Agents:** Cisplatin **Vehicle:** Not Stated; **Route:** IV (saphenous); IA (saphenous); **Species:** Rat (nude); **Pump:** 2ML1; **Duration:** 6 days;
**ALZET Comments:** tissue perfusion (tumor xenograft); cancer.

**Agents:** Antibody, 791T/36; Immunoglobulin, IgG2b; Radio-isotopes **Vehicle:** 125I tracer; 131I tracer; Saline; **Route:** SC; **Species:** Mice (nude); **Pump:** 2002; **Duration:** 5, 15 days;
**ALZET Comments:** dose-response; half-life; mp implanted contralaterally to xenografted tumors; concomitant and simult. infusion; 125I tracer used with IgG2b; comparison of sc, iv injections vs. mp infusion; functionality of mp verified by chromatography; stability; cancer.