Targeted Delivery of Agents Using ALZET® Osmotic Pumps

ALZET pumps allow researchers to understand and optimize the key determinants of drug action. These determinants are the level of drug exposure and its duration, and the spatial distribution of drug relative to the target tissue. By manipulating these variables, drug effects can be optimized early in preclinical development, allowing clinical studies to be conducted at lower cost and with better results. Accumulated literature offers numerous examples of targeted delivery in which ALZET pumps expose a specific, limited region to a compound. Through a catheter introduced into the arterial blood supply of an organ, or affixed within or adjacent to the target tissue, the pump provides continuous and controlled input of a compound. A variety of organs and tissues have become target sites for drug delivery using this method.

Targeted infusion offers significant advantages over systemic administration. Daemen *et al.* (Trends Pharmacol Sci 1988;9:138) assert that "for the clinician, drug delivery should ideally be direct to its target tissue. Its distribution should be confined to the target site (thus avoiding any systemic drug effects), where it should reach high concentration." This ideal has two key facets:

- achieving sufficiently high concentrations at the target site
- minimizing systemic concentrations

To demonstrate a drug's efficacy, it must reach the target tissue at a concentration sufficient to elicit a therapeutic effect. There are many obstacles that can make it difficult to achieve sufficient concentration at the target site, such as drug metabolism, drug excretion, and permeability barriers. Infusing drug to the target tissue can circumvent these barriers, and can improve the drug's efficacy as compared with systemic administration.

Even if the concentration at the target site is sufficient, the desired effect may or may not be recognized. If the drug is administered such that significant systemic concentrations are also produced, simultaneous or cascading drug effects in multiple tissues may result. These systemic effects may alter the effect from the target tissue by diminishing, antagonizing, or simply obscuring it. Additionally, unwanted systemic effects may be toxic to the target tissue or even lethal, thus preventing the desired effect from ever developing.

References in which the following organs or tissues were infused via ALZET pumps are included in this list, with the exception of brain infusion. (References on brain infusion can be obtained at www.alzet.com or by contacting ALZET Technical Support at 1-800-692-2990 or by email at alzet@durect.com.)

Targeted Delivery of Agents
Using ALZET® Osmotic Pumps

Arterial Wall
Articular Cavity
Bladder
Bone
Brain (Solid Tissue)
Brain (Ventricles)
Ear
Esophagus
Eye
Gallbladder
Intestine
Kidney+
Liver+
Lymph Node
Mammary Gland
Muscle
Myocardial
Nerve
Ovary
Pericardial Space
Prostate
Skin
Spleen
Stomach
Testis+
Trachea
Tumor
Uterus

+ Perfused directly and via arterial supply.

The technical notes following each reference detail the substance(s) infused, route of administration, animal model studied, infusion vehicle, model of pump used, duration of infusion, and notable technical achievements or results obtained. For a more complete discussion of the capabilities of solid tissue microperfusion, consult the following reference:

R0051 Urquhart, J., Fara, J., and Willis, K.L. Rate-controlled delivery systems in drug and hormone research. Ann. Rev. Pharmacol. Toxicol. 24, 199-236, 1984.

Note: This listing does not contain abstracts in this category, nor references from before the years indicated. To obtain abstracts or additional references, contact ALZET Technical Services at (800) 692-2990 or by email at alzet@durect.com.

Recent References (2014-Present) on the Targeted Delivery of Agents Using ALZET® Osmotic Pumps

Q10600: D. Mao, *et al.* Effect and Mechanism of BDNF/TrkB Signaling on Vestibular Compensation. Bioengineered 2021;12(2):11823-11836
Agents: Brain derived neurotrophic factor, RNA, small interfering **Vehicle:** CSF, artificial; **Route:** CSF/CNS (right lateral ventricle); **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: animal info (Male Sprague Dawley; Weighed 200-250 g); behavioral testing (Rotarod test; Postural asymmetry; Head roll tilt; Nystagmus); tissue perfusion (Brain tissue); gene therapy;

Q10284: H. Tran, *et al.* Suppression of mutant C9orf72 expression by a potent mixed backbone antisense oligonucleotide. Nature Medicine 2022;28(1):117-124
Agents: Oligonucleotide, antisense **Vehicle:** PBS; **Route:** CNS/CSF (intracerebroventricular); **Species:** Mice; **Pump:** 1007D; **Duration:** 21 days;
ALZET Comments: Dose (2.5-20 nmol/day); dose-response (dose-dependent reduction in V1 and V3 repeat-containing transcripts in both the cortex and spinal cord regions after being treated with ASO3 and ASO5); animal info (C9BAC transgenic mice); antisense oligonucleotides aka ASO; antisense (oligonucleotide); ALZET brain infusion kit 3 used; bilateral cannula used; 2.5-20 nmol/day of each ASO were continuously infused over 10 d into the right lateral ventricle of age-matched heterozygous C9BAC mice through a cannula using an implanted Alzet osmotic pump; tissue perfusion (brain); neurodegenerative (ALS);(FTD) Therapeutic indication (ALS, FTD);

Q10754: J. Hu, *et al.* Trimethylamine N-Oxide Promotes Abdominal Aortic Aneurysm Formation by Aggravating Aortic Smooth Muscle Cell Senescence in Mice. Journal of Cardiovascular Translational Research 2022;15(5):1064-1074
Agents: Angiotensin II **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Dose (1000 ng/kg/min); Controls received mp w/ vehicle; animal info (Male; apoe-/- 8 weeks old); peptides; tissue perfusion (Brain tissue); cardiovascular;

Q10278: D. B. Mangarova, *et al.* Microscopic multifrequency magnetic resonance elastography of ex vivo abdominal aortic aneurysms for extracellular matrix imaging in a mouse model. Acta Biomaterialia 2022;140(389-397
Agents: Angiotensin II **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Dose (1000 ng/kg/min); animal info (8-weeks old B6.129P2- Apoetm1Unc/J (ApoE-/-) male mice); tissue perfusion (cardiac); cardiovascular;

Q7861: S. Ruoss, *et al.* Inhibition of calpain delays early muscle atrophy after rotator cuff tendon release in sheep. Physiol Rep 2018;6(21):e13833
Agents: calpeptin **Vehicle:** DMSO; **Route:** intramuscular (infraspinatus); **Species:** Sheep; **Pump:** 2ML4; **Duration:** 6 weeks;
ALZET Comments: Dose (0.75 mg/day); animal info (26.7+/-1.4 months, female, Swiss Alpine); pumps replaced at 2 weeks; calpeptin is a synthetic calpain inhibitor; enzyme inhibitor (calpain); tissue perfusion (m. infraspinatus); good methods (detailed pump implantation procedure on page 3.); Therapeutic indication (calpain inhibition prevented the early unloading adaptations, but not the subsequent initiation of rotator cuff disease); 75% DMSO used;

Q5909: L. Wang, *et al.* Sodium butyrate suppresses angiotensin II-induced hypertension by inhibition of renal (pro)renin receptor and intrarenal renin-angiotensin system. J Hypertens 2017;35(9):1899-1908
Agents: Angiotensin II; sodium butyrate **Vehicle:** Not Stated; **Route:** SC; Intrarenal (medulla); **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-300g); Multiple pumps per animal (2); replacement therapy (uniphrectomy); tissue perfusion (renal medulla); cardiovascular;
antihypertensive; peptides; Bp measured using radio telemetry (DSI); Dose (Ang II 200 ng/kg/min; NaBu 1 ug/kg/min); good bp comparison curve (pg4);

Q5333: C. Y. Tsai, *et al.* Nitrosative Stress-Induced Disruption of Baroreflex Neural Circuits in a Rat Model of Hepatic Encephalopathy: A DTI Study. Sci Rep 2017;7(40111
Agents: FeTMPyP; Tempol **Vehicle:** CSF, artificial; **Route:** CSF/CNS (intracisternal); **Species:** Rat; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male adult Sprague-Dawley rats 278 +/-28 g); FeTMPyP is an active peroxynitrite decomposition catalyst; tempol is an antioxidant; Dose: FeTMPyP (100 pmol/ul/hr); tempol (4 nmol/ul/hr); tissue perfusion (cisternae);

Q5894: S. Thammacharoen, *et al.* Effects of Hindbrain Infusion of an Estrogen Receptor Antagonist on Estrogenic Modulation of Eating Behavior. Neurophysiology 2017;49(1):72-77
Agents: ICI 182,780 **Vehicle:** DMSO; Saline; **Route:** CSF/CNS (fourth ventricle); **Species:** Rat; **Pump:** 1002;
ALZET Comments: animal info (female, Wistar, 250-300g, OVX); 1% DMSO used; post op. care (enrofloxacin IV 2.5-5 mg/kg, ibuprofen PO 15 mg/kg); replacement therapy (estradiol infusion); tissue perfusion (fourth ventricle); Cannula placement verified via injection of Evans Blue dye; Used PlasticsOne cannula;

Q5104: Q. Y. Yi, *et al.* Paraventricular Nucleus Infusion of Epigallocatechin-3-O-Gallate Improves Renovascular Hypertension. Cardiovascular Toxicology 2016;16(3):276-85
Agents: gallate, Epigallocatechin-3-O **Vehicle:** CSF, artificial; **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 1004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-275g); bilateral cannula used; post op. care (buprenorphine 0.01 mg/kg SC 12 hours post); tissue perfusion (paraventricular nucleus); tissue perfusion (paraventricular nucleus); tissue perfusion (paraventricular nucleus); Dose (20 ug/h); Brain coordinates "1.8 mm posterior, 0.4 mm lateral to the bregma and 7.9 mm ventral to the zero level" pg 277;

Q5097: K. L. Wu, *et al.* Impaired Nrf2 regulation of mitochondrial biogenesis in rostral ventrolateral medulla on hypertension induced by systemic inflammation. Free Radic Biol Med 2016;97(58-74
Agents: Endotoxin, LPS; coenzyme Q10; temple; Interleukin-1 receptor antagonist; butylhydroquinone, tert- **Vehicle:** Saline; CSF, artificial; **Route:** IP; ;CSF/CNS (cisterna magna); **Species:** Rat; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 8 weeks old, 250-280g); ALZET brain infusion kit 2 used; post op. care (IM procaine Penicillin 1000 IU); tissue perfusion (cisterna magna); cardiovascular; bp measured using tail cuff; Dose (LPS 1.2 mg/kg/day; coenzyme Q10 3.25 ug/ul/hr; tempol 5 ug/ul/hr; IL-1Ra 0.5 ug/ul/h);

Q5091: X. Wang, *et al.* Affinity-controlled protein encapsulation into sub-30 nm telodendrimer nanocarriers by multivalent and synergistic interactions. Biomaterials 2016;101(258-71
Agents: Telodendrimer nanoparticles, peptide-incorporated **Vehicle:** Not Stated; **Route:** CSF/CNS (Intratumoral); **Species:** Mice (nude); **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ free peptide; animal info (female, athymic nude NCRU-Sp/Sp, 8 weeks old); cancer (glioblastoma U87); tissue perfusion (intratumoral); pumps primed overnight at 37C; Dose (0.5 ug/h); Brain coordinates (0.5 mm anterior to bregma and 2.5 mm lateral of midline);

Q5080: J. Urra, *et al.* In vivo blockade of acetylcholinesterase increases intraovarian acetylcholine and enhances follicular development and fertility in the rat. Sci Rep 2016;6(30129
Agents: Huperzine A **Vehicle:** Not Stated; **Route:** Intraovarian (ovarian bursa); **Species:** Rat; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ saline; animal info (female, Sprague Dawley, 250-300g, hemi-OVX); tissue perfusion (ovarian bursa); enzyme inhibitor (acetylcholine esterase);

Q5212: T. Tamagawa, *et al.* Involvement of Microglial P2Y12 Signaling in Tongue Cancer Pain. J Dent Res 2016;95(10):1176-82
Agents: MRS2395 **Vehicle:** DMSO; PBS; **Route:** CSF/CNS (cisterna magna); **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Fischer, 100-200g); 25% DMSO used; cancer (tongue squamous cell carcinoma SCC-158, JCRB0231; JCRB); behavioral testing (head-withdrawal); tissue perfusion (cisterna magna); used PE tubing 0.8mm diameter; MRS2395 is an P2Y12R antagonist;

Q4895: Y. A. Syed, *et al.* Antibody-mediated neutralization of myelin-associated EphrinB3 accelerates CNS remyelination. Acta Neuropathologica 2016;131(281-298
Agents: Fc-IgG; ephrineB3, pre-clustered **Vehicle:** PBS; **Route:** CSF/CNS (caudal cerebellar peduncle); **Species:** Rats; mice; **Pump:** Not Stated; **Duration:** 11 days; 18 days;
ALZET Comments: Controls received mp w/ Fc-IgG only; animal info (Rats - female, Sprague Dawley; mice - EphrinB3 KO); neurodegenerative (multiple sclerosis); tissue perfusion (caudal cerebellar peduncle); Cannula placement verified via infusion of Evan's Blue;

Q4900: P. Q. H. Renjun Wang, MD; Rui Zhou, BSc; Zengxiang Dong, PhD;, *et al.* Sympathoexcitation in Rats With Chronic Heart Failure Depends on Homeobox D10 and MicroRNA-7b Inhibiting GABBR1 Translation in Paraventricular Nucleus. Circulation: Heart Failure 2016;9(1-10
Agents: AntagomiR-7b; RNA, small interfering GABBR1; angiotensin II **Vehicle:** Not Stated; **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 1004; 1002; **Duration:** 4 weeks; 2 weeks;
ALZET Comments: animal info (male, Wistar, 180-200g); pumps replaced after 4 weeks; bilateral cannula used; tissue perfusion (paraventricular nucleus); cardiovascular; peptides; bilateral infusion; Dose (AntagomiR-7b or Ad-siGABBR1 40 ng/h; angiotensin II 1 ng/kg/min);

Q4862: Matthew McMillin, *et al.* Bile Acid Signaling Is Involved in the Neurological Decline in a Murine Model of Acute Liver Failure. American Journal of Pathology 2016;186(2):
Agents: Vivo-morpholino **Vehicle:** Not Stated; **Route:** CSF/CNS (frontal cortex); **Species:** Mice; **Pump:** Not Stated; **Duration:** 3 days;
ALZET Comments: Controls received mp w/ mismatched control morpholino; animal info (male, C57BL6, 25-30g); tissue perfusion (frontal cortex); tissue perfusion (frontal cortex);

Q5395: T. H. Lin, *et al.* NF-kappaB decoy oligodeoxynucleotide mitigates wear particle-associated bone loss in the murine continuous infusion model. Acta Biomaterialia 2016;41(273-81
Agents: Ultra-high molecular weight polyethylene particles; oligodeoxynucleotide, decoy; oligodeoxynucleotide, scrambled; Endotoxin, LPS; Brain-derived neurotropic factor; **Vehicle:** Saline; **Route:** In Vitro (cell culture); Bone (Femur); **Species:** Mice (nude); **Pump:** 2006; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (Male athymic nude mice, 10-15 weeks old); stability verified by (in vitro experiment); dose-response (pg. 277); good methods (pg. 276); tissue perfusion (bone); Dose (15 mg/ml UHMWPE, 50uM decoy, 1 ug/ml LPS); Therapeutic indication (Bone loss, chronic inflammation);

Q5390: H. B. Li, *et al.* TLR4/MyD88/NF-kappaB signaling and PPAR-gamma within the paraventricular nucleus are involved in the effects of telmisartan in hypertension. Toxicol Appl Pharmacol 2016;305(93-102
Agents: Telmisartan; Losartan; GW9662 **Vehicle:** CSF, artificial; **Route:** CSF/CNS (Hypothalamic paraventricular nucleus); **Species:** Rat; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (12-week-old male normotensive Wistar-Kyoto); functionality of mp verified by blood pressure; bilateral cannula used; dose-response (pg. 94); post op. care (buprenorphine 0.04 mg/kg, sc); tissue perfusion (hypothalamic paraventricular nucleus); cardiovascular; antihypertensive; Dose (10 ug/hr TEL, 20 ug/hr LOS, 100 ug/hr GW); Brain coordinates (1.8mm posterior to bregma, 0.4mm from midline, and 7.9mm ventral to dura);

Q5382: D. B. Kurland, *et al.* The Sur1-Trpm4 channel regulates NOS2 transcription in TLR4-activated microglia. J Neuroinflammation 2016;13(1):130
Agents: Endotoxin, LPS **Vehicle:** Saline, normal; **Route:** CSF/CNS (striatum); **Species:** Rat; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (Male Wistar rats aged 8-12 weeks); ALZET brain infusion kit 2 used; good methods (pg. 3); tissue perfusion (striatum); model to study TLR4 activation in vivo; nitrosative/oxidative stress and neuroinflammation; Brain coordinates; 1-mm burr hole was made over the right striatum [AP, +0.75 mm; ML, +1.7 mm relative to bregma]; Dose (5 ug/day);

Q5367: F. Higuchi, *et al.* Hippocampal MicroRNA-124 Enhances Chronic Stress Resilience in Mice. J Neurosci 2016;36(27):7253-67
Agents: LMK-135, LY2090314 **Vehicle:** Water; **Route:** CSF/CNS (hippocampus); **Species:** Mice; **Pump:** 1002, 1004; **Duration:** 2 weeks, 4 weeks;
ALZET Comments: animal info (BALB mice); behavioral testing (social interaction test, forced swim test, novelty-suppressed feeding test); tissue perfusion (hippocampus); brain tissue distribution; Bilateral infusion; Dose (LMK-235 (100 nM or 1 uM), LY2090314 (10 or 100 nM));

Q6041: L. German-Castelan, *et al.* Intracellular Progesterone Receptor Mediates the Increase in Glioblastoma Growth Induced by Progesterone in the Rat Brain. Archives of Medical Science 2016;47(6):419-426
Agents: Oligodeoxynucleotide, antisense **Vehicle:** Propylene glycol; **Route:** CSF/CNS; **Species:** Rat; **Duration:** 15 days;
ALZET Comments: animal info (250-300g) ; tissue perfusion (brain tissue); Guide cannula used; Therapeutic indication (Astrocytomas, CNS tumor); Dose (0.5 ug/day);

Q5347: D. A. Figge, *et al.* Dynamic DNA Methylation Regulates Levodopa-Induced Dyskinesia. J Neurosci 2016;36(24):6514-24
Agents: RG108 **Vehicle:** Cyclodextrin, hydroxypropyl-β-; **Route:** CSF/CNS (dorsal striatum); **Species:** Rat; **Pump:** 2004;
Duration: 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male Sprague-dawley, 60 – 90 days old, 180-200 g); functionality of mp verified by behavioral testing; 5% cyclodextrin used; Plastics One unilateral guide cannula used; post op. care (7 days of care, buprenorphine and wound care for pain management); behavioral testing (forepaw adjusting steps test); tissue perfusion (brain); delayed delivery "additional polyethylene tubing was added to provide a 14 d prime of vehicle before RG-108 administration" (pg. 6515); "rats were given a unilateral dopamine lesion to the left medial forebrain bundle" (pg. 6515); Brain coordinates: anteroposterior, 0 from bregma, -3mm lateral from midline, and -3.5 mm from the dura; Dose (100 uM);

Q5311: L. Chen, *et al.* 20-HETE contributes to ischemia-induced angiogenesis. Vascular Pharmacology 2016;83(57-65
Agents: DDMS; 6,15-20-HEDGE **Vehicle:** Not Stated; **Route:** Intramuscular (hindlimb gracilis); **Species:** Mice; **Pump:** 2002, 2004; **Duration:** 32 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (Balb/c mice, 12 wk old); functionality of mp verified by blood pressure and blood perfusion scans; dose-response (pg. 61); good methods (pg. 58); ischemia (peripheral); tissue perfusion (intramuscular); Polyethylene catheter tubing used (inner ID 0.8 mm); Dose (5 mg/kg/day);

Q4673: M. Zamykal, *et al.* Inhibition of intracerebral glioblastoma growth by targeting the insulin-like growth factor 1 receptor involves different context-dependent mechanisms. NEURO-ONCOLOGY 2015;17(1076-1085
Agents: IMC-A12 **Vehicle:** Saline; **Route:** CSF/CNS (intratumoral); **Species:** Mice; **Pump:** 2004; **Duration:** 3 weeks; 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (Foxn1nu, 6-8 weeks old); cancer (glioblastoma); tissue perfusion (glioblastoma); IMC-A12 aka cixutumumab;

Q4217: K. Yuyama, *et al.* A potential function for neuronal exosomes: Sequestering intracerebral amyloid-beta peptide. FEBS Letters 2015;589(84-88
Agents: Exosome **Vehicle:** PBS; **Route:** CSF/CNS (hippocampus); **Species:** Mice; **Pump:** Not Stated; **Duration:** 14 days;
ALZET Comments: Animal info (APP or C57BL6J, 13 months old); ALZET brain infusion kit used; neurodegenerative (Alzheimer's disease); tissue perfusion (hippocampus);

Q4656: H. J. Yang, *et al.* Red peppers with moderate and severe pungency prevent the memory deficit and hepatic insulin resistance in diabetic rats with Alzheimer's disease. Nutrition & Metabolism 2015;12(U15-U26
Agents: Amyloid protein, beta (25-35) **Vehicle:** Not Stated; **Route:** CSF/CNS (hippocampus); **Species:** Rat; **Pump:** Not Stated;
Duration: 14 days;
ALZET Comments: Controls received mp w/ scrambled amyloid protein; animal info (male, Sprague Dawley, 192 +/-30g,); neurodegenerative (Alzheimer's disease); behavioral testing (locomotive activity, passive avoidance, Morris water maze); tissue perfusion (CA1 subregion of hippocampus); diabetes;

Q5008: Yael Kusne*, et al.* Targeting aPKC disables oncogenic signaling by both the EGFR and the proinflammatory cytokine TNFa in glioblastoma. Science Signaling 2015;7(338):1-15
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; gliobastomas); PZ09 aka small-molecule, benzimidazole adenosine triphosphate–competitive aPKC inhibitor; xenografts; Dose: 10 uM PZ09

Q4593: R. Stark*, et al.* Acyl Ghrelin Acts in the Brain to Control Liver Function and Peripheral Glucose Homeostasis in Male Mice. Endocrinology 2015;156(858-868
Agents: Ghrelin, acyl **Vehicle:** CSF, artificial; **Route:** CSF/CNS (third ventricle); **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, C57BL6);; tissue perfusion (third ventricle);

Q4990: T. A. Paine*, et al.* Effects of chronic inhibition of GABA synthesis on attention and impulse control. Pharmacol Biochem Behav 2015;135(97-104
Agents: Allylglycine, L- **Vehicle:** CSF, artificial; **Route:** CSF/CNS (prefrontal cortex); **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley); bilateral cannula used; Multiple pumps per animal (2); behavioral testing (standard time reaction test; locomotor activity); tissue perfusion (prefrontal cortex); enzyme inhibitor (glutamic acid decarboxylase); Dose (3.5 ug/0.5ul/h);

Q5000: H. Liu*, et al.* The distinct role of NR2B subunit in the enhancement of visual plasticity in adulthood. Mol Brain 2015;8(49
Agents: PPPA; TCN 201; Ro 25-6981 **Vehicle:** PBS; **Route:** CSF/CNS (visual cortex); **Species:** Mice; **Pump:** 1007D; 1002;
Duration: 5 days; 2 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL6); tissue perfusion (visual cortex); cyanoacrylate adhesive; brain coordinates;

Q4995: H. B. Li*, et al.* Central blockade of salusin beta attenuates hypertension and hypothalamic inflammation in spontaneously hypertensive rats. Sci Rep 2015;5(11162
Agents: Immunoglobulin G, antisalusin b **Vehicle:** Not Stated; **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 1004; **Duration:** 2 weeks;
ALZET Comments: Controls received mp w/ vehicle and control antibody; animal info (male, Wistar Kyoto, SHR, 10 weeks old); bilateral cannula used; post op. care (buprenorphine SC); tissue perfusion (paraventricular nucleus); cardiovascular; Cannula placement verified via histological analysis; bilateral infusion; bp measured using tail cuff; Dose (50, 100, 150 ng/kg/day);

Q4970: D. H. Kim*, et al.* Peptide fragment of thymosin beta4 increases hippocampal neurogenesis and facilitates spatial memory. Neuroscience 2015;310(51-62
Agents: Ac-SDKP **Vehicle:** PBS; **Route:** CSF/CNS (third ventricle); **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: animal info (male, C57BL6J, 25-28g, 8 weeks old); behavioral testing (Morris water maze); tissue perfusion (third ventricle); peptides; Cannula placement verified via histologic analysis; used Plastics one cannula; brain coordinates;

Q3920: S. C. Hopp*, et al.* Differential Neuroprotective and Anti-Inflammatory Effects of L-Type Voltage Dependent Calcium Channel and Ryanodine Receptor Antagonists in the Substantia Nigra and Locus Coeruleus. Journal of Neuroimmune Pharmacology 2015;10(35-44
Agents: Endotoxin, LPS **Vehicle:** CSF, artificial; **Route:** CSF/CNS (fourth ventricle); **Species:** Rat; **Pump:** 2004; **Duration:** 28 days;
ALZET Comments: Animal info (male, F-344, 3 months old); behavioral testing (rotarod; open field test; forced swim test); tissue perfusion (fourth ventricle); immunology;

Q3780: R. Hiramatsu, *et al.* Tetrakis(p-Carboranylthio-Tetrafluorophenyl)Chlorin (TPFC): Application for Photodynamic Therapy and Boron Neutron Capture Therapy. Journal of Pharmaceutical Sciences 2015;104(962-970
Agents: Tetrakis (pcarboranylthiotetrafluorophenyl) Chlorin **Vehicle:** Not Stated; **Route:** CSF/CNS (intratumoral); **Species:** Rat; **Pump:** 2001D; **Duration:** Not Stated;
ALZET Comments: Animal info (male, 200-250 g, F344 Fischer); ALZET brain infusion kit 2 used; TPFC, also known as Tetrakis(p-Carboranylthio-Tetrafluorophenyl)Chlorin, is a carboranyl-containing chlorin of high boron content; cancer (glioma); tissue perfusion; convection-enhanced delivery

Q4425: S. Garofalo, *et al.* Enriched environment reduces glioma growth through immune and non-immune mechanisms in mice. Nature Communications 2015;6(U26-U38
Agents: Interleukin-15; brain-derived neurotrophic factor **Vehicle:** PBS; **Route:** CSF/CNS (striatum); **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, C57BL6, 3 weeks or 2 months old); ALZET brain infusion kit 3 used; cancer (glioma, U87MG human); tissue perfusion (right striatum); immunology; pumps primed in 37C saline overnight;

Q4405: J. M. do Carmo, *et al.* Role of hindbrain melanocortin-4 receptor activity in controlling cardiovascular and metabolic functions in spontaneously hypertensive rats. JOURNAL OF HYPERTENSION 2015;33(1201-1206
Agents: SHU-9119 **Vehicle:** Not Stated; **Route:** CSF/CNS (fourth ventricle); **Species:** Rat; **Pump:** 2002; **Duration:** 10 days;
ALZET Comments: Animal info (male, Spontaneously hypertensive or Wistar-Kyoto, 275-325g, 15-17 weeks old); behavioral testing (food intake); tissue perfusion (fourth ventricle); cardiovascular; Cannula placement verified via Evan's Blue dye; bp measured using radiotelemetry (DSI);

Q3853: B. N. Desai, *et al.* Leptin in the hindbrain facilitates phosphorylation of STAT3 in the hypothalamus. American Journal of Physiology Endocrinology and Metabolism 2015;308(E351-E361
Agents: Leptin **Vehicle:** Not Stated; **Route:** CSF/CNS (third ventricle; fourth ventricle); **Species:** Rat; **Pump:** 2002; **Duration:** 6 days;
ALZET Comments: Controls received mp w/ saline; animal info (male, Sprague Dawley, 275-300g); Multiple pumps per animal (2); tissue perfusion (third ventricle; fourth ventricle); bilateral infusion; one cannula to third ventricle second cannula to fourth ventricle; used plastics one cannula;

Q5135: P. Cheng, *et al.* Protein phosphatase 2A (PP2A) activation promotes axonal growth and recovery in the CNS. J Neurol Sci 2015;359(1-2):48-56
Agents: Sphingosine, D-erythro **Vehicle:** saline; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 2 weeks;
ALZET Comments: Controls received mp w/ vehicle; sham operation; animal info: adult Sprague–Dawley (SD) male rats, 240 - 260 g; spinal cord injury; tissue perfusion (spinal cord); D-erythro-sphingosine aka DES; Dose: DES (200 µl 1 µg/ml solution)

Q4347: N. Carrier, *et al.* The Anxiolytic and Antidepressant-like Effects of Testosterone and Estrogen in Gonadectomized Male Rats. Biological Psychiatry 2015;78(259-269
Agents: Fadrozole **Vehicle:** Saline, sterile; **Route:** CSF/CNS (dentate gyrus); **Species:** Rat; **Pump:** 2004; **Duration:** Not Stated;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-270g, adult, orchidectomized); bilateral cannula used; behavioral testing (sucrose preference test, open field test); tissue perfusion (dentate gyrus); Cannula placement verified via a posteriori by sectioning on cryostat; bilateral infusion; coordinates; pumps primed for 48 hours in 37C sterile saline; used Plastics One cannula;

Q5123: R. F. Barth, *et al.* Evaluation of TK1 targeting carboranyl thymidine analogs as potential delivery agents for neutron capture therapy of brain tumors. Aqua-BioScience Monographs 2015;106(251-5
Agents: N5-2OH **Vehicle:** DMSO; **Route:** CSF/CNS (intracerebral); IV; **Species:** Rat; **Pump:** 2001D; **Duration:** 24 hr;
ALZET Comments: Controls received mp w/ vehicle, untreated controls; 35% of DMSO; cancer (brain tumor; F98 glioma model); tissue perfusion (brain tissue); brain tissue distribution; Animals were irradiated for 5 min at the MITR-II reactor; "intracerebral. administration of BPA did not increase the tumor boron uptake compared to that obtained following i.v. administration" (pg. 252); Dose: 500 ug

Q4320: E. Barbier, *et al.* DNA Methylation in the Medial Prefrontal Cortex Regulates Alcohol-Induced Behavior and Plasticity. JOURNAL OF NEUROSCIENCE 2015;35(6153-6164
Agents: RG108 **Vehicle:** Cyclodextrin, 2-hydroxypropyl-b-; **Route:** CSF/CNS; CSF/CNS (medial prefrontal cortex); **Species:** Rat; **Pump:** 2002; 2004; **Duration:** 1 week;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Wistar, 200-225g); 5% cyclodextrin used; behavioral testing (two bottle free choice; alcohol self-administration); tissue perfusion (medial prefrontal cortex); dependence;

Q3794: L. Adzovic, *et al.* Insulin improves memory and reduces chronic neuroinflammation in the hippocampus of young but not aged brains. Journal of Neuroinflammation 2015;12(U1-U10
Agents: Insulin, recombinant cat; endotoxin, LPS **Vehicle:** CSF, artificial; **Route:** CSF/CNS (fourth ventricle); **Species:** Rat; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, F-344, 3 months old, 21 months old); bilateral cannula used; behavioral testing (morris water maze); tissue perfusion (fourth ventricle); used tygon tubing to attach cannula to pump;

Q4233: Y. B. Zhou, *et al.* Intermedin in Paraventricular Nucleus Attenuates Sympathetic Activity and Blood Pressure via Nitric Oxide in Hypertensive Rats. Hypertension 2014;63(330-+
Agents: Intermedin; AM22-52 **Vehicle:** CSF, artificial; **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 1004; **Duration:** 15 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 160-180g); ALZET brain infusion kit used; tissue perfusion (paraventricular nucleus); antihypertensive; cardiovascular; Cannula placement verified via 2% Evans Blue dye injection; Intermedin aka IMD; AM22-52 is an adrenomedulllin receptor antagonist; bp measured using tail cuff;

Q4225: F. Zhang, *et al.* Apelin-13 and APJ in paraventricular nucleus contribute to hypertension via sympathetic activation and vasopressin release in spontaneously hypertensive rats. ACTA PHYSIOLOGICA 2014;212(17-27
Agents: Apelin-13 **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 1002; **Duration:** 15 days;
ALZET Comments: Controls received mp w/ saline; animal info (male, Wistar Kyoto, 13 weeks old); tissue perfusion (paraventricular nucleus); cardiovascular; "Osmotic minipumps were used for continuously delivering chemicals at controlled rate for several weeks without the need for external connections, frequent handling or repeated dosing" pg 19; bp measured using tail cuff; hypertension;

Q4216: K. Yuyama, *et al.* Decreased Amyloid-beta Pathologies by Intracerebral Loading of Glycosphingolipid-enriched Exosomes in Alzheimer Model Mice. Journal of Biological Chemistry 2014;289(24488-24498
Agents: Exosome solution, glycosphingolipid-enriched **Vehicle:** PBS; **Route:** CSF/CNS (hippocampus); **Species:** Mice (transgenic); **Pump:** 1002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (APP, 4 months old); ALZET brain infusion kit 3 used; neurodegenerative (Alzheimers); tissue perfusion (hippocampus);

Q4184: Y. W. Wu, *et al.* Central adiponectin administration reveals new regulatory mechanisms of bone metabolism in mice. American Journal of Physiology Endocrinology and Metabolism 2014;306(E1418-E1430
Agents: Adiponectin, globular; adiponectin, full-length **Vehicle:** CSF, artificial; **Route:** CSF/CNS (third ventricle); **Species:** Mice; **Pump:** Not Stated; **Duration:** 28 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, APN-KO or WT, 20-25g, 4-6 weeks old); ALZET brain infusion kit 2 used; tissue perfusion (third ventricle); cyanoacrylate adhesive; Cannula placement verified via micrograph imaging; used tygon tubing to attach BIK cannula to pump;

Q4181: K. L. H. Wu, *et al.* Role of Nitric Oxide Synthase Uncoupling at Rostral Ventrolateral Medulla in Redox-Sensitive Hypertension Associated With Metabolic Syndrome. Hypertension 2014;64(815-+
Agents: Tempol; coenzyme Q10 **Vehicle:** CSF, artificial; **Route:** CSF/CNS (cisterna magna); **Species:** Rat; **Pump:** 1007D; **Duration:** 2 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley 8 weeks old, 235-296g); post op. care (1000 IU IM); tissue perfusion (cisterna magna); cardiovascular; diabetes; used PE-10 catheter;

Q3696: M. Wosiski-Kuhn*, et al.* Glucocorticoid receptor activation impairs hippocampal plasticity by suppressing BDNF expression in obese mice. Psychoneuroendocrinology 2014;42(165-177
Agents: Corticosterone **Vehicle:** Cyclodextrin, 2-hydroxypropyl-b-; **Route:** CSF/CNS (hippocampus); **Species:** Mice; **Pump:** Not Stated; **Duration:** 2 weeks;
ALZET Comments: Controls received mp w/ vehicle and aCSF; animal info (male, C57BL6J or db/db, 5 weeks old); functionality of mp verified by hippocampal corticosterone levels; Multiple pumps per animal (2); behavioral testing (y-maze apparatus); tissue perfusion (bilateral hippocampi); immunology; Cannula placement verified via histology; used Plastics One bilateral cannula; bilateral infusion;

Q4173: Y. K. Wang*, et al.* Overexpression of angiotensin-converting enzyme 2 attenuates tonically active glutamatergic input to the rostral ventrolateral medulla in hypertensive rats. American Journal of Physiology Heart and Circulatory Physiology 2014;307(H182-H190
Agents: A779 **Vehicle:** CSF, artificial; **Route:** CSF/CNS (fourth ventricle); **Species:** Rat; **Pump:** 1007D; **Duration:** 1 week;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, SHR and WKY); tissue perfusion (fourth ventricle);

Q4141: Y. Tona*, et al.* Therapeutic potential of a gamma-secretase inhibitor for hearing restoration in a guinea pig model with noise-induced hearing loss. BMC Neuroscience 2014;15(U1-U8
Agents: MDL28170 **Vehicle:** DMSO; PBS; **Route:** Ear (cochlea); **Species:** Guinea pig; **Pump:** 1002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (Hartley strain, 350-400g); 0.3% DMSO used; tissue perfusion (cochlea); used Tefron tube with inner diameter of 180 um to cannulate cochlea; MDL28170 is a gamma-secretase inhibitor;

Q4135: E. Tavares*, et al.* Immunoneutralization of Endogenous Aminoprocalcitonin Attenuates Sepsis-Induced Acute Lung Injury and Mortality in Rats. American Journal of Pathology 2014;184(3069-3083
Agents: Antibody, anti-aminoprocalcitonin **Vehicle:** Saline; **Route:** IP; **Species:** Rat; **Pump:** 2001D; **Duration:** 18 hours;
ALZET Comments: Controls received mp w/ control antibody; animal info (male, Wistar, 280-300g); tissue perfusion (peritoneum); immunology; peptides; Catheter used to cannulate peritoneum;

Q4128: M. S. Tan*, et al.* Amyloid-beta induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease. Cell Death & Disease 2014;5(U228-U239
Agents: RNA, small interfering NLRP1; RNA, small interfering, NLRP3; RNA, small interfering caspase-1 **Vehicle:** CSF, artificial; water, RNase-free; **Route:** CSF/CNS (dorsal third ventricle); **Species:** Mice (transgenic); **Pump:** Not Stated; **Duration:** 8 weeks;
ALZET Comments: Controls received mp w/ vehicle or control RNA; animal info (male, APP/PS1); functionality of mp verified by knowckdown of targeted gene; ALZET brain infusion kit 3 used; neurodegenerative (Alzheimer's disease); no stress "This dose of NLRP1 siRNA, caspase-1 siRNA or NLRP3 siRNA infusion was well tolerated, and no signs of neurotoxicity including hind-limb paralysis, vocalization, food intake, or neuroanatomical damage were observed in preliminary study." (see pg. 10); behavioral testing (morris water maze); tissue perfusion (dorsal third ventricle); "Our study using this approach of pump-mediated siRNA infusion is efficient in downregulation of NLRP1 mRNA (by about 60%) and protein (by about 50%) levels in APP/PS1 brain. And the treatment with control siRNA did not alter cerebral NLRP1 mRNA and protein levels compared with No siRNA-treated APP/PS1 mice, excluding an effect of pump-mediated infusion on NLRP1 expression levels." pg 8;

Q3661: Q. Su*, et al.* Inhibition of reactive oxygen species in hypothalamic paraventricular nucleus attenuates the renin-angiotensin system and proinflammatory cytokines in hypertension. TOXICOLOGY AND APPLIED PHARMACOLOGY 2014;276(115-120
Agents: Tempol; angiotensin II **Vehicle:** CSF, artificial; saline, sterile; **Route:** CSF/CNS (paraventricular nuclei); **Species:** Rat; **Pump:** 1004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Sprague Dawley, adult, 250-275g); functionality of mp verified by increase bp; tissue perfusion (paraventricular nucleus); immunology; "The success rate of bilateral microinjection and vein infusion is respectively 65% and 78%." pg 116; bp measured using tail-cuff;

Q4743: K. Shinohara*, et al.* Post-acquisition hippocampal NMDA receptor blockade sustains retention of spatial reference memory in Morris water maze. Behavioural Brain Research 2014;259(;):261-267
Agents: AP5, D- **Vehicle:** CSF, artificial; **Route:** CSF/CNS (hippocampus); **Species:** Rat; **Pump:** 1007D; **Duration:** 7 days; 14 days;
ALZET Comments: Animal info (male, albino Wistar); pumps replaced every 7 days; Plastics One bilateral cannula used; Multiple pumps per animal (2); behavioral testing (morris water maze, probe test); tissue perfusion (hippocampus); Cannula placement verified via histological analysis; pumps primed for 24 hours in 37C saline; bilateral infusion;

Q3627: A. Sehgal*, et al.* Tissue-specific gene silencing monitored in circulating RNA. RNA-A PUBLICATION OF THE RNA SOCIETY 2014;20(2):143-149
Agents: RNA, small interfering **Vehicle:** PBS; **Route:** CSF/CNS (striatum); **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: Animal info (male, Sprague Dawley); neurodegenerative (Parkinson's disease); tissue perfusion (striatum); gene therapy; used Plastics One 30g cannula; primed overnight in 37C saline