



Recent References (2015-Present) on Gene Therapy Research
Using ALZET® Osmotic Pumps

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:** CSF/CNS (right lateral ventricle); **Species:** Mice; **Pump:** 1007D; **Duration:** 10 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); "In our C9BAC mice, we were not able to safely perform ICV bolus injections with more than 10 nmol of LNA-modified ASO3 due to induction of severe motor phenotypes. To overcome this limitation, we use osmotic pumps to compare the potency of ASO3 and ASO5" pg3; gene therapy

Q10379: L. A. Ezerskiy, *et al.* Astrocytic 4R tau expression drives astrocyte reactivity and dysfunction. *JCI Insight* 2022;7(1):

Agents: Oligonucleotide, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS (right ventricle); **Species:** Mice; **Pump:** Not Stated; **ALZET Comments:** Dose (15 ug/d); animal info (hTau); Brain coordinates (1.1 mm lateral; 0.5 mm posterior; 2.5 mm ventral from bregma); neurodegenerative (); Therapeutic indication (neurodegenerative diseases); gene therapy

Q10357: M. D. C. de Arriba, *et al.* FPR2 DNA Aptamers for Targeted Therapy of Wound Repair. *Journal of Investigative Dermatology* 2022;142(8):2238-2248 e8

Agents: Aptamer, FPR2 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 6 days;

ALZET Comments: Dose (10 uM); animal info (FPR2 aptamer-treated mice); stability of aptamer in pump verified by qPCR; FPR2 aptamer acting as FPR2 agonist; gene therapy

Q10411: F. B. Bengur, *et al.* Spironolactone Mitigates Fibrosis and Improves Healing of Burn Wounds. *Plastic and Reconstructive Surgery* 2022;

Agents: Aldosterone **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: animal info (Female; 4 weeks old; 2 total); gene therapy; Therapeutic indication (Hypertrophic collagen deposition);

Q8486: O. Gawrys, *et al.* Polyprenol-Based Lipofecting Agents for In Vivo Delivery of Therapeutic DNA to Treat Hypertensive Rats. *Biochemical Genetics* 2021;59(1):62-82

Agents: Polyprenol-based lipoinfecting agent **Vehicle:** Glucose; **Route:** Renal medulla; **Species:** Rat; **Pump:** 2001; **Duration:** 1 week;

ALZET Comments: 5% glucose used; Controls received mp w/ vehicle; animal info (Male, adult spontaneously hypertensive rats, 16 weeks old, 299 +- 4); Blood pressure measured via telemetry transmitters; vascular endothelial growth factor aka VEGF-A; ALZET brain infusion kit 2 used; gene therapy;

R0396: Y. Li, *et al.* Strategies and materials of "SMART" non-viral vectors: Overcoming the barriers for brain gene therapy. *Nano Today* 2020;35(Agents: RNA, small interfering **Route:** CSF/CNS (intratumoral); **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Dose: (350 ug/kg); neurodegenerative (brain diseases); gene therapy;

Q8686: I. A. Akkouh, *et al.* Exploring lithium's transcriptional mechanisms of action in bipolar disorder: a multi-step study. *Neuropsychopharmacology* 2020;45(6):947-955

Agents: Lithium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 4 days;

ALZET Comments: Dose (84.8 mg/kg/day); Controls received mp w/ vehicle; animal info (Female, Sprague Dawley); gene therapy;



R0372: J. Hong, *et al.* Relaxin gene therapy: A promising new treatment option for various diseases with aberrant fibrosis or irregular angiogenesis. *Molecular and Cellular Endocrinology* 2019;

Agents: Relaxin, human recomb. **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat (pregnant);

ALZET Comments: Dose (2000 ng/h); Resultant plasma level (RLX level close to 0.5 ng/mL); gene therapy;

Q7455: R. E. De la Vega, *et al.* Specific, Sensitive, and Stable Reporting of Human Mesenchymal Stromal Cell Chondrogenesis. *Tissue Engineering Part C Methods* 2019;25(3):176-190

Agents: FK-506, SEW2871 **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;

ALZET Comments: Dose (0.15 mg/kg/day- FK-506, 0.075 mg/kg/day- SEW2871); Controls received mp w/ vehicle; animal info (Male, 14 weeks old, Fischer-344); gene therapy;

Q8779: S. Wang, *et al.* miR3383p mediates gluconeogenesis via targeting of PP4R1 in hepatocytes. *Molecular Medicine Reports* 2018;18(4):4129-4137

Agents: Tumor necrosis factor, alpha **Vehicle:** Saline; **Route:** Not Stated; **Species:** Mice; **Pump:** Not Stated; **Duration:** 2 weeks;

ALZET Comments: Dose (15 µg/ml at 0.5 µl/h); Controls received mp w/ vehicle; animal info (16 weeks, male, C57BL/6J, 30g); gene therapy; diabetes; pump route and model not stated. mp used for TNF-alpha-induced insulin resistance model;

Q8775: D. Wang, *et al.* Slow Infusion of Recombinant Adeno-Associated Viruses into the Mouse Cerebrospinal Fluid Space. *Human Gene Therapy Methods* 2018;29(2):75-85

Agents: Virus, recombinant adeno-associated **Vehicle:** Saline; **Route:** CSF/CNS (subarachnoid space); CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 2001D; **Duration:** 40, 42 hours;

ALZET Comments: Dose ($1 \cdot 10^{11}$, $2 \cdot 10^{12}$ GC in 200 µL); Controls received mp w/ vehicle; animal info (6 weeks, male and female, C57BL/6J, 20g); post op. care (200 µL of 0.9% saline by i.p. injection); comparison of IT injection vs mp; recombinant adeno-associated viruses (rAAVs) packaged in several serotypes such as AAV9 and AAV.rh10 can cross the BBB and transduce neurons and glia in rodents and nonhuman primates; Brain coordinates ((-0.9, -0.2) for the left ventricle, or (+0.9, -0.2) for the right ventricle); Cannula placement verified via stereotaxic frame; cyanoacrylate adhesive for icv delivery (Loctite); gene therapy; good methods (detailed pump installation instructions for IT and ICV delivery of agent on p.77-83); "IT pump infusion resulted in more widespread and higher transduction of the spinal cord than a bolus IT injection" pg.83; recombinant adeno-associated virus serotype 9 (rAAV9) used for examples;

Q7242: Y. Takeda, *et al.* Epigenetic Regulation of Aldosterone Synthase Gene by Sodium and Angiotensin II. *J Am Heart Assoc* 2018;7(10):

Agents: Angiotensin II, Candesartan **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 4 weeks;

ALZET Comments: Dose (Ang II 200 ng/kg/min, Candesartan 1mg/kg/day); animal info (Male, Wistar, 6 weeks old); Candesartan aka Ang II type 1 receptor antagonist; gene therapy;

Q7266: K. Taguchi, *et al.* RAGE-aptamer attenuates deoxycorticosterone acetate/salt-induced renal injury in mice. *Sci Rep* 2018;8(1):2686

Agents: DNA aptamer (RAGE) **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2006; **Duration:** 21 days;

ALZET Comments: Dose (2×10^{-4} ug/day); Controls received mp w/ vehicle; animal info (8 week old, male, C57BL/6J); RAGE-apt is a DNA aptamer against the advanced glycation end products receptor; gene therapy;

Q7223: J. Lu, *et al.* CIC-2 knockdown prevents cerebrovascular remodeling via inhibition of the Wnt/beta-catenin signaling pathway. *Cellular & Molecular Biology Letters* 2018;23(29)

Agents: Angiotensin II **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** Not Stated;

ALZET Comments: Dose (1.5 mg/kg/day); Controls received mp w/ vehicle; animal info (Male, 12 weeks old, 20-25 g, C57BL/6); gene therapy;

Q8078: F. Li, *et al.* Loss of renal SNX5 results in impaired IDE activity and insulin resistance in mice. *Diabetologia* 2018;61(3):727-737

Agents: SNX5-specific or non silencing snRNA **Vehicle:** Not stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (3 ug/day); animal info (Male, C57BL/6J, 1 year old); SNX5-specific aka sorting nexin 5 ; gene therapy;



Q8058: A. Kuroda, *et al.* Minocycline Directly Enhances the Self-Renewal of Adult Neural Precursor Cells. *Neurochem Res* 2018;43(1):219-226

Agents: Minocycline **Vehicle:** Saline; **Route:** CSF/CNS (Lateral ventricle); **Species:** Mice; **Pump:** 1007; **Duration:** 7 days;
ALZET Comments: "Dose (0.6 uL/h); Controls received mp w/ vehicle; animal info (20-30 weeks old, Male); Brain coordinates (0.3 mm posterior to Bregma, 0.8 mm lateral, and 2.7 mm below the surface of the skull); bilateral cannula used; cyanoacrylate adhesive; gene therapy; "

Q7149: K. Kamio, *et al.* Resolution of bleomycin-induced murine pulmonary fibrosis via a splenic lymphocyte subpopulation. *Respir Res* 2018;19(1):71

Agents: Bleomycin **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Dose (100 mg/kg/day); Controls received mp w/ vehicle; animal info (C57BL/6); gene therapy;

Q7139: Y. Gao, *et al.* The histone methyltransferase DOT1L inhibits osteoclastogenesis and protects against osteoporosis. *Cell Death & Disease* 2018;9(2):33

Agents: EPZ5676 **Vehicle:** DMSO, Water; **Route:** SC; **Species:** Mice; **Pump:** 2006, 2002; **Duration:** 8 weeks;
ALZET Comments: Dose (1.6 mg/d); 50% DMSO used; Controls received mp w/ vehicle; animal info (Eight-week-old, female, FVB/N); Model 2006 pumps replaced with Model 2002 after six weeks; long-term study; EPZ5676 aka small molecule inhibitor;

Q7138: S. Galic, *et al.* AMPK signaling to acetyl-CoA carboxylase is required for fasting- and cold-induced appetite but not thermogenesis. *eLife Journal* 2018;7(**Agents:** Ghrelin, N-octanoylated **Vehicle:** Ghrelin, N-octanoylated; **Route:** SC; **Species:** Mouse; **Pump:** 2002; **Duration:** 14 days;

ALZET Comments: Dose (30 ug/day); Controls received mp w/ vehicle; animal info (Male, ACC DKI); Peptide, recombinant protein aka N-octanoylated murine ghrelin; gene therapy;

Q7137: K. Fujita, *et al.* Targeting Tyro3 ameliorates a model of PGRN-mutant FTLTDP via tau-mediated synaptic pathology. *Nature Communications* 2018;9(1):433

Agents: Gö6976 **Vehicle:** PBS; **Route:** CSF/CNS (intrathecal); **Species:** Mouse; **Pump:** 2006; **Duration:** 2 weeks;
ALZET Comments: Dose (0.15 ul/h); animal info (PGRN-KI and C57BL/6J, 10-12 weeks old); behavioral testing (Morris water maze test, Fear-conditioning, Probe test, Rotarod test, Open-field test, Light-dark box test); enzyme inhibitor (PKC inhibitor);

Q7109: S. Chakraborty, *et al.* Dexamethasone-induced Intra-Uterine Growth Restriction impacts NOSTRIN and its downstream effector genes in the rat mesometrial uterus. *Scientific Reports* 2018;8(1):8342

Agents: Dexamethasone **Vehicle:** Ethanol; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: Dose (200 ug/kg/day); 10% ethanol used; Controls received mp w/ vehicle; animal info (SD, 8-10 wk old);

Q10089: Y. P. Bai, *et al.* Induction of microRNA-199 by Nitric Oxide in Endothelial Cells Is Required for Nitrovasodilator Resistance via Targeting of Prostaglandin I2 Synthase. *Circulation* 2018;138(4):397-411

Agents: Control antagomirs; GTN; miR 199a/b **Route:** SC; **Species:** Mice; **Pump:** 1003D; **Duration:** 3 days; 2 weeks;
ALZET Comments: Dose (antagomirs/miR 199 a/b 80mg/kg body weight; GTN 100mg/kg/day); Controls received mp w/ control antagomirs or control antagomirs + GTN; animal info (male Apoe+, 8-12wks old, 20-30g); GTN aka Nitroglycerin; antagomir aka RNA complimentary to specific miRNA; gene therapy; cardiovascular; pumps were used in part 1,2,5 and 6 of the study, this study identified PTGIS mRNA as a new target of miR-199a/b, and discovered a novel mechanism by which nitric esters cause nitrate tolerance. Mechanistically, NO derived from organic nitrates induces the endogenous expression of miR-199a/b in endothelial cells, which represses PTGIS gene expression, resulting in PGI2 deficiency and thromboxane receptor activation. Consequently, organic nitrates induce nitrate tolerance and nitrovasodilator resistance;

Q5940: Y. Zou, *et al.* Prenatal levonorgestrel exposure induces autism-like behavior in offspring through ERbeta suppression in the amygdala. *Mol Autism* 2017;8(46)

Agents: Lentivirus, ER beta **Vehicle:** CSF, artificial; **Route:** CSF/CNS (amygdala); **Species:** Rat; **Pump:** 2002; **Duration:** 2 weeks;
ALZET Comments: Controls received mp w/ empty lentivirus; animal info (male, Sprague Dawley, 8 weeks old); functionality of mp verified by India ink injection; behavioral testing (marbles burying test, social interaction, elevated plus maze, open-field test); gene therapy; Used Plastics One cannula;



- Q5829:** N. Martinez-Sanchez, *et al.* Thyroid hormones induce browning of white fat. *J Endocrinol* 2017;232(2):351-362
Agents: Thyroxin, L-, Adenovirus vector; Gene, green fluorescent protein; Gene, AMP-activated protein kinase **Vehicle:** Saline;
Route: CSF/CNS (hypothalamus); **Species:** Rat; **Pump:** 1007D; **Duration:** 7, 21 days;
ALZET Comments: bilateral cannula used; animal info (200-250g); Therapeutic indication (Browning, thyroid hormones);
- Q5052:** G. Murlidharan, *et al.* CNS-restricted Transduction and CRISPR/Cas9-mediated Gene Deletion with an Engineered AAV Vector. *Mol Ther Nucleic Acids* 2016;5(7):
Agents: Viral vector, adeno-associated (AAV9, AAV2g0); Gene, CBh-ScGFP **Vehicle:** Not Stated; **Route:** CSF/CNS (intrathecal);
Species: Mice; **Pump:** 2001D; **Duration:** 24 hrs;
ALZET Comments: animal info (8 weeks old C57/BL6 male mice); comparison of IT bolus injections vs mp; ALZET mouse intrathecal catheter used (lumbar cannulation); gene therapy;
- Q5158:** M. Gujrati, *et al.* Multifunctional pH-Sensitive Amino Lipids for siRNA Delivery. *Bioconjugate Chemistry* 2016;27(1):19-35
Agents: RNA, small interfering/EHCO; PEGylated EHCO **Species:** Mice (nude); **Duration:** 14 days;
ALZET Comments: Controls received treated with nonspecific PEGylated EHCO/siGFP nanoparticles (PEGGFP) and non-PEGylated EHCO/HIF-1 α ; cancer; gene therapy, RNA nanoparticle infusion; peptides; "These results indicate that PEGylation can significantly improve the stability of EHCO/siRNA nanoparticles during storage in solution, possibly by preventing the aggregation of the nanoparticles and providing better protection to the siRNA cargo from degradation" (pg 31);
- Q5312:** K. Caviness, *et al.* Complex Interplay of the UL136 Isoforms Balances Cytomegalovirus Replication and Latency. *MBio* 2016;7(2):e01986
Agents: Granulocyte-colony stimulating factor; AMD3100 **Route:** IP; **Species:** Mice (NOD/SCID); **Pump:** 1007D; **Duration:** 1 week;
ALZET Comments: animal info (NOD-scid humanized (huNSG) mice); gene therapy; immunology; Engraftment of human CD45+ cells; viral persistence; Dose (300mg/ml Colony-stim; 125 ug AMD3100);
- Q5625:** J. Benoit, *et al.* Epigenetic stability in the adult mouse cortex under conditions of pharmacologically induced histone acetylation. *Brain Structure and Function* 2016;221(8):3963-3978
Agents: Trichostatin A **Vehicle:** DMSO, water; **Route:** SC; **Species:** Mice; **Pump:** 2002; **Duration:** 14 days, 28 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (6 months old); Subset of pumps replaced every 2 weeks;
- Q5279:** Y. Sztainberg, *et al.* Reversal of phenotypes in MECP2 duplication mice using genetic rescue or antisense oligonucleotides. *Nature* 2015;528(7580):123-6
Agents: Oligonucleotide, antisense MECP2 **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** mice; **Pump:** 1004; **Duration:** 28 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (FVB/N pure background); functionality of mp verified by EEG; ALZET brain infusion kit 3 used; ALZET brain infusion kit 3 used; good methods (pg. 6); gene therapy; Dose (500 ug); Brain coordinates; AP = - 0.2 mm, ML = 1 mm, DV = - 3 mm
- Q4242:** A. L. Mathes, *et al.* CpGB DNA activates dermal macrophages and specifically recruits inflammatory monocytes into the skin. *Experimental Dermatology* 2015;24(133-139
Agents: CpGB DNA **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 7 days; 28 days;
ALZET Comments: Controls received mp w/ PBS; animal info (male, C57BL6 or TNFa -/- or IFNg -/- or CXCR3 -/- or CCR5 -/- or CCL2 -/- or TLR9 -/-); functionality of mp verified by immunofluorescence at pump outlet; gene therapy; immunology; CpGB DNA is a TLR9 ligand;
- Q5143:** A. C. Dusabineza, *et al.* Hepatic Stellate Cells Improve Engraftment of Human Primary Hepatocytes: A Preclinical Transplantation Study in an Animal Model. *Cell Transplantation* 2015;24(12):2557-71
Agents: Uridine, bromodeoxy- **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice; **Pump:** 1004; **Duration:** 6 hours; 4 weeks;
ALZET Comments: animal info: SCID mice, females, 20-24 g; GFP+ transgenic mice, males, 35-44 g; gene therapy;