



## References on Neurodegenerative Studies Using ALZET® Osmotic Pumps

### 1. ALS

**Q7006:** R. Malik, *et al.* The molecular tweezer CLR01 inhibits aberrant superoxide dismutase 1 (SOD1) self-assembly in vitro and in the G93A-SOD1 mouse model of ALS. *J Biol Chem* 2019;294(10):3501-3513

**Agents:** CLR01 **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 6 weeks;

**ALZET Comments:** Dose (0, 0.5, or 5.0 mg/kg); 0.9% saline used; Controls received mp w/ vehicle; animal info (Transgenic B6SJL-Tg mice); behavioral testing (grip-strength test, rotarod test); half-life: 1-2 hours (p.5); CLR01 is a broad-spectrum inhibitor of the self-assembly and toxicity of amyloid proteins; enzyme inhibitor (superoxide dismutase 1 (SOD1)); neurodegenerative (amyotrophic lateral sclerosis);

**Q7540:** S. Watanabe, *et al.* Intracerebroventricular administration of Cystatin C ameliorates disease in SOD1-linked amyotrophic lateral sclerosis mice. *J Neurochem* 2018;145(1):80-89

**Agents:** Cystatin C, Recombinant human **Vehicle:** PBS; **Route:** CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 1004; **Duration:** 4 weeks;

**ALZET Comments:** Dose (66 ng/day); Controls received mp w/ vehicle; animal info (100-day-old, transgenic SOD1G93A, male $\geq$ 30g and female $\geq$ 20g); stability verified by (influenza hemagglutinin (HA)-tagged CysC administration for 1 week); CysC is an endogenous protease inhibitor; enzyme inhibitor (cathepsin); ALZET brain infusion kit used; neurodegenerative (ALS); "After 1 week of continuous HA-tagged CysC administration using an osmotic pump, the CysC was successfully delivered to the lumbar spinal cord and was predominantly distributed in the ventral horn neurons (Fig. 1b and c), whereas CysC was rarely found in neurons of the dorsal horn. These data indicate that intracerebroventricular administration was sufficient to deliver CysC to lower motor neurons in the lumbar spinal cord." pg.82; implanted pump remained on the back of mice until end-stage; "the disease end-stage was determined as the time when animals in a lateral position were unable to right themselves within 20s" p.81; Therapeutic indication (Bunina body formation and regulation of AMPK/PGC-1 $\alpha$  pathway);

**Q7312:** N. Tsuburaya, *et al.* A small-molecule inhibitor of SOD1-Derlin-1 interaction ameliorates pathology in an ALS mouse model. *Nat Commun* 2018;9(1):2668

**Agents:** SOD1-Derlin-1 inhibitor #56-40, SOD1-Derlin-1 inhibitor #56-59 **Vehicle:** DMSO; **Route:** CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 2006; **Duration:** 58 weeks;

**ALZET Comments:** Dose (1 mM #56-40 or 3 mM #56-59); Controls received mp w/ vehicle; animal info (22 weeks, male, C57BL/6); behavioral testing (rotarod performance); pumps replaced every 6 weeks until mouse showed paralysis onset; long-term study; stability verified by (in-vitro immunoprecipitation assay); 3-Amino-N-(4-pyridyl)-6-(3-pyridyl)thieno[2,3-b]pyridine-2-carboxamide aka #56-40; N-Allyl-3-amino-N-phenyl-6-(pyridin-3-yl)thieno[2,3-b]pyridine-2-carboxamide aka #56-59; enzyme inhibitor (SOD1-Derlin-1 interaction); ALZET brain infusion kit 3 used; neurodegenerative (Amyotrophic lateral sclerosis);

**Q7208:** J. J. Riehm, *et al.* Poloxamer 188 decreases membrane toxicity of mutant SOD1 and ameliorates pathology observed in SOD1 mouse model for ALS. *Neurobiol Dis* 2018;115(115-126

**Agents:** Poloxamer 188 **Vehicle:** Not Stated; **Route:** CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 2006, 1004; **Duration:** 42 days;

**ALZET Comments:** Dose (1.5 pM/h); Controls received mp w/ vehicle; animal info (40-55 day old male B6SJL-Tg(SOD1\*G93A)1Gur/J mice); neurodegenerative (amyotrophic lateral sclerosis);

**Q7210:** M. Maier, *et al.* A human-derived antibody targets misfolded SOD1 and ameliorates motor symptoms in mouse models of amyotrophic lateral sclerosis. *Sci Transl Med* 2018;10(470):

**Agents:** miSOD1, alpha- **Vehicle:** PBS; **Route:** CSF/CNS (left ventricle); **Species:** Mice; **Pump:** 1004; **Duration:** 20, 30, 40, 55, 70, 80 days;

**ALZET Comments:** Dose (0.1 mg/kg/day); Controls received mp w/ vehicle; animal info (Mice, 60 days of age); pumps replaced every 28 days; ALZET brain infusion kit used; neurodegenerative (amyotrophic lateral sclerosis); Therapeutic indication (amyotrophic lateral sclerosis);



## 2. Alzheimer's

**Q8510:** M. Gonzalez-Prieto, *et al.* Microglial CX3CR1 production increases in Alzheimer's disease and is regulated by noradrenaline. *Glia* 2021;69(1):73-90

**Agents:** Reboxetine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 28 days;

**ALZET Comments:** Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (7 month old male WT and heterozygous 5xFAD mice); half-life (p. 2; 12.5 hr); neurodegenerative (Alzheimer's);

**Q8361:** E. E. Parks, *et al.* Interleukin 6 reduces allopregnanolone synthesis in the brain and contributes to age-related cognitive decline in mice. *J Lipid Res* 2020;61(10):1308-1319

**Agents:** Interleukin-6 **Vehicle:** Saline; **Route:** CNS/CSF; **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

**ALZET Comments:** Dose (100 ng/day); Controls received mp w/ vehicle; animal info (Male, C57BL/6N); neurodegenerative (Alzheimer's Disease);

**Q8494:** L. Park, *et al.* tPA Deficiency Underlies Neurovascular Coupling Dysfunction by Amyloid-beta. *J Neurosci* 2020;40(42):8160-8173

**Agents:** PAI-039 **Vehicle:** Not stated; **Route:** CNS/CSF; **Species:** Mice; **Pump:** 1004; **Duration:** 4 weeks;

**ALZET Comments:** Dose (42 ng/kg/min); Controls received mp w/ vehicle; animal info (10-11 months old); behavioral testing (Maze Test, Novel Object Recognition Test); enzyme inhibitor (PAI-1 inhibitor); Brain coordinates (-0.22 mm lateral, 0.8 mm, dorsal 2 mm); neurodegenerative (Alzheimer's Disease);

**Q8624:** N. Lax, *et al.* Systemic microbial TLR2 agonists induce neurodegeneration in Alzheimer's disease mice. *J Neuroinflammation* 2020;17(1):55

**Agents:** Zymosan; CU-CPT22 **Vehicle:** Not stated; **Route:** CSF/CNS (intracerebral); IV; **Species:** Mice; **Pump:** 1007D; 1004; 1002; **Duration:** 1 week; 28 days; 2 weeks;

**ALZET Comments:** Dose (25 ug zymosan; 10 ug/day CU-CPT22); animal info (male and female 5xFAD mice); CU-CPT22 aka Toll-like receptor 2 antagonist; Brain coordinates (A = 0, L = 1, H = 2.5); neurodegenerative (Alzheimer's disease);

**Q8611:** M. Krishnan, *et al.* beta-hydroxybutyrate Impedes the Progression of Alzheimer's Disease and Atherosclerosis in ApoE-Deficient Mice. *Nutrients* 2020;12(2):

**Agents:** Beta-hydroxybutyrate **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 8 weeks;

**ALZET Comments:** Dose (1.5 mmol/kg/day); Controls received mp w/ vehicle; animal info (Six-week-old male ApoE<sup>-/-</sup> and C57BL/6J mice); pumps replaced every 4 weeks; Beta-hydroxybutyrate aka B-OHB; neurodegenerative (Alzheimer's Disease);

## 3. Ataxia

**Q1073:** C. R. Foster, *et al.* Ataxia telangiectasia mutated kinase plays a protective role in beta-adrenergic receptor-stimulated cardiac myocyte apoptosis and myocardial remodeling. *MOLECULAR AND CELLULAR BIOCHEMISTRY* 2011;353(1-2):13-22

**ALZET Comments:** Isoproterenol, I-; SC; Mice; 7 days; Animal info (4 mo old, male, female, wt, hKO).

**P6477:** S. E. Browne, *et al.* Treatment with a catalytic antioxidant corrects the neurobehavioral defect in ataxia-telangiectasia mice. *Free Radical Biology and Medicine* 2004;36(7):938-942

**ALZET Comments:** EUK-189; Mannitol; SC; Mice; 2004; 56, 84 days; Controls received mp w/ vehicle; long-term study; pumps replaced every 28 days; no stress (see pg.941); cancer (thymoma); EUK-189 is a synthetic catalytic antioxidant w/ both catalase & superoxide dismutase activities; neurodegenerative (ataxia telangiectasia).

## 4. Huntington's



**Q8479:** J. Ganz, *et al.* A novel specific PERK activator reduces toxicity and extends survival in Huntington's disease models. *Sci Rep* 2020;10(1):6875

**Agents:** MK-28 **Vehicle:** DMSO; PEG-400; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 2 weeks; 28 days;  
**ALZET Comments:** Dose (6 mg/kg; 1 mg/kg); Controls received mp w/ vehicle; animal info (B6 wild type mice; four-week-old mice); behavioral testing (Rotarod test); MK-28 aka small molecule PERK activator; neurodegenerative (Huntington's disease);

**Q8389:** G. Birolini, *et al.* Striatal infusion of cholesterol promotes dose-dependent behavioral benefits and exerts disease-modifying effects in Huntington's disease mice. *EMBO Mol Med* 2020;12(10):e12519

**Agents:** cyclodextrin, methyl-b **Vehicle:** CSF, Artificial; **Route:** CSF/CNS (corpus striatum); **Species:** Mice; **Pump:** 1004; **Duration:** 28 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (wild-type mice, 5 weeks old); behavioral testing (Rotarod, Activity Cage, Novel object recognition (NOR) test); methyl-b-cyclodextrin aka MBCD; ALZET brain infusion kit 3 used; Brain coordinates (stereotaxic coordinates 1.75 mm mediolateral, 0.5 mm anteroposterior, 3 mm dorsoventral);

**Q7602:** E. Paldino, *et al.* Modulation of Phospho-CREB by Systemically Administered Recombinant BDNF in the Hippocampus of the R6/2 Mouse Model of Huntington's Disease. *Neurosci J* 2019;2019(8363274

**Agents:** neurotrophic factor, Recombinant brain derived **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 4 weeks;

**ALZET Comments:** Dose (4 ug/d); Controls received mp w/ vehicle; animal info (4 week old, Male); neurodegenerative (Huntington's Disease);

**Q6969:** A. U. Joshi, *et al.* Drp1/Fis1-mediated mitochondrial fragmentation leads to lysosomal dysfunction in cardiac models of Huntington's disease. *J Mol Cell Cardiol* 2019;127(125-133

**Agents:** P110 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 8 weeks;

**ALZET Comments:** Dose ((3 mg/Kg/day); animal info (5-week old Hemizygous R6/2 HD mice); P110 is a Drp1/Fis1 interaction peptide inhibitor; neurodegenerative (Huntington's);

**Q7587:** Y. T. Hsu, *et al.* Enhanced Na<sup>(+)</sup>-K<sup>(+)</sup>-2Cl<sup>(-)</sup> cotransporter 1 underlies motor dysfunction in huntington's disease. *Mov Disord* 2019;34(6):845-857

**Agents:** XPro1595 **Vehicle:** Saline; **Route:** CSF/CNS (lateral ventricle); **Species:** Mice; **Pump:** 1004; **Duration:** 4 weeks;

**ALZET Comments:** "Dose (0.08 mg/kg/day); Controls received mp w/ vehicle; animal info (6.5 weeks, Transgenic R6/2); XPro1595 is a dominant-negative inhibitor of soluble TNF-alpha; ALZET brain infusion kit 3 used; neurodegenerative (Huntington's); Therapeutic indication (disease progression in HD due to inflammation); "

## 5. Neimann

**Q3736:** L. Trovo, *et al.* Improvement of biochemical and behavioral defects in the Niemann-Pick type A mouse by intraventricular infusion of MARCKS. *NEUROBIOLOGY OF DISEASE* 2015;73(319-326

**ALZET Comments:** MARCKS peptide; Saline, sterile; CSF/CNS; Mice; 1004; Control animals received mp w/ vehicle; animal info (ASMko, 4 mo old); peptides; ALZET brain infusion kit 3 used; cyanoacrylate used; behavioral testing (accelerating rotarod); MARCKS is a protein required for PI(4,5)P2 membrane clustering and hydrolysis.

**Q3991:** N. Marschalek, *et al.* The natural history of cerebellar degeneration of Niemann-Pick C mice monitored in vitro. *Neuropathology and Applied Neurobiology* 2014;40(933-945

**ALZET Comments:** Cyclodextrin, 2-hydroxypropyl-B-; CSF/CNS; Mice; Animal info (NPC); pumps mentioned in introduction.

**Q1986:** C. Cabeza, *et al.* Cholinergic Abnormalities, Endosomal Alterations and Up-Regulation of Nerve Growth Factor Signaling in Niemann-Pick Type C Disease. *Molecular Neurodegeneration* 2012;7(;):U1-U18

**ALZET Comments:** Nerve growth factor; CSF, artificial; CSF/CNS; Mice; 1002; 7 days; Controls received mp w/ vehicle; animal info (BALB/c, NPC/1 -/-); aCSF recipe; brain infusion kit used.



**P9265:** M. Zhang, *et al.* Mitogen-activated protein kinase activity may not be necessary for the neuropathology of Niemann-Pick type C mice. *Journal of Neurochemistry* 2008;107(3):814-822

**ALZET Comments:** PD-98059; DMSO; saline; dye, Evan's blue; CSF/CNS; Mice; 1002; 2 weeks; Controls received mp w/ vehicle; functionality of mp verified by dye infusion; dose-response (fig. 1); enzyme inhibitor (MAPK/ERK 1); brain tissue distribution; animal info (female, BALB/c, Nctr-Npc, 5 wks old); 50% DMSO used; behavioral testing (limb motor activity/coat hanger test).

**P6916:** M. Zhang, *et al.* Cyclin-dependent kinase inhibitors attenuate protein hyperphosphorylation, cytoskeletal lesion formation, and motor defects in Niemann-Pick type C mice. *American Journal of Pathology* 2004;165(3):843-853

**ALZET Comments:** Roscovitine; olomoucine; iso-olomoucine; DMSO; CSF/CNS; Mice; 1002; 2, 4 weeks; Pumps replaced every 2 weeks for 4 week infusions; enzyme inhibitor (CDK); neurodegenerative (Alzheimer's disease, Amyotrophic Lateral Sclerosis, Niemann-Pick Type C disease); lynch coil used to accommodate 75% DMSO.

## 6. Parkinson

**Q8626:** C. Lecours, *et al.* Levodopa partially rescues microglial numerical, morphological, and phagolysosomal alterations in a monkey model of Parkinson's disease. *Brain Behav Immun* 2020;90(81-96

**Agents:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine **Vehicle:** Saline; **Route:** SC; **Species:** Monkey; **Pump:** Not stated; **Duration:** 2 weeks;

**ALZET Comments:** Dose (0.5 mg/day); animal info (adult female monkeys, 4 to 11 years old, 2.4 to 4.6 kg); 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine aka MPTP; neurodegenerative (Parkinson's Disease);

**Q8332:** D. Alarcon-Aris, *et al.* Anti-alpha-synuclein ASO delivered to monoamine neurons prevents alpha-synuclein accumulation in a Parkinson's disease-like mouse model and in monkeys. *EBioMedicine* 2020;59(102944

**Agents:** Oligonucleotides, antisense **Vehicle:** CSF, Artificial; **Route:** CNS/CSF (lateral ventricle); **Species:** Mice; Primate; **Pump:** 1004; 2ML4; **Duration:** 28 days;

**ALZET Comments:** Dose (30 ug/day; 100 ug/day; 1 mg/day); Controls received mp w/ vehicle; animal info (Eight-week-old wild-type male C57BL/6J mice; male and female hesus macaques, 20 years or older); antisense oligonucleotides aka IND-ASO; ALZET brain infusion kit 3 used; Brain coordinates (antero-posterior -0.34, medial-lateral -1.0 and dorsal-ventral -2.2 in mm); neurodegenerative (Parkinson's disease);

**Q7684:** K. C. Wu, *et al.* Down-regulation of natural resistance-associated macrophage protein-1 (Nramp1) is associated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)/1-methyl-4-phenylpyridinium (MPP(+)) -induced alpha-synuclein accumulation and neurotoxicity. *Neuropathol Appl Neurobiol* 2019;45(2):157-173

**Agents:** pyridine, 1-methyl-4-phenyl-1,2,3,6-tetrahydro **Vehicle:** Saline; **Route:** IP; **Species:** Mice; **Pump:** 2002; **Duration:** 14 days;

**ALZET Comments:** Dose (30 mg/kg/day); Controls received mp w/ vehicle; animal info (Male C57BL/6 mice 6-8 weeks old); MPTP aka 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; neurodegenerative (Parkinson's);

**Q7668:** S. Song, *et al.* Loss of Brain Norepinephrine Elicits Neuroinflammation-Mediated Oxidative Injury and Selective Caudo-Rostral Neurodegeneration. *Mol Neurobiol* 2019;56(4):2653-2669

**Agents:** Diphenyleiiodonium **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 3 months;

**ALZET Comments:** Dose (10 ng/kg/day); Controls received mp w/ vehicle; animal info (C57/BL, 3 months old, Male); DPI aka Diphenyleiiodonium ; enzyme inhibitor (NOX2 inhibitor); neurodegenerative (Parkinson's Disease);

**Q7376:** I. Miyazaki, *et al.* Effects of Enteric Environmental Modification by Coffee Components on Neurodegeneration in Rotenone-Treated Mice. *Cells* 2019;8(3):

**Agents:** Rotenone **Vehicle:** DMSO, PEG; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;



**ALZET Comments:** Dose (2.5 mg/kg/day); 50 DMSO: 50 PEG used; Controls received mp w/ vehicle; animal info (male C57BL/6J mice nine weeks old; approximately 25 g); enzyme inhibitor (Rotenone is a mitochondrial complex I inhibitor); neurodegenerative (Parkinson's disease);