



**References on the Administration of Metalloproteinase Inhibitors
Using ALZET® Osmotic Pumps**

Q6890: X. Wang, *et al.* Liver-Selective MMP-9 Inhibition in the Rat Eliminates Ischemia-Reperfusion Injury and Accelerates Liver Regeneration. *Hepatology* 2019;69(1):314-328

Agents: 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid **Vehicle:** Not Stated; **Route:** IV (inferior mesenteric vein); IP;

Species: Rat (transgenic); **Pump:** 2ML1; 2001; **Duration:** 7 days;

ALZET Comments: Dose (100 µg/h); animal info (Male Lew-Tg(CAG-EGFP)ys); (Matrix metalloproteinases 2/9);

Q8973: H. Yu, *et al.* FOXO3a (Forkhead Transcription Factor O Subfamily Member 3a) Links Vascular Smooth Muscle Cell Apoptosis, Matrix Breakdown, Atherosclerosis, and Vascular Remodeling Through a Novel Pathway Involving MMP13 (Matrix Metalloproteinase 13). *Arteriosclerosis, Thrombosis, and Vascular Biology* 2018;38(3):555-565

Agents: WAY-170523 **Vehicle:** DMSO, PEG 400 buffered; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 3, 7 days;

ALZET Comments: Dose (7.5mg/kg/day); 50% DMSO with PEG400 used; Controls received mp w/ vehicle; animal info (5-6 months, male, ApoE(-/-) and SM22alphaFOXO3aA3ER); WAY170523 is a MMP13-selective inhibitor; enzyme inhibitor (matrix metalloproteinase 13); cardiovascular; results section states mp implanted days 0-7 while materials and methods states mp implanted days 7-10;

Q6074: S. D. Nandlall, *et al.* Assessing the Stability of Aortic Aneurysms with Pulse Wave Imaging. *Radiology*: 2016;281(3):772-782

Agents: Angiotensin II **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 30 days;

ALZET Comments: Dose (2.2 mg/kg/day or 4.4 mg/kg/day); animal info (male apolipoprotein E and tissue inhibitor of metalloproteinases-1 knockout mice); cardiovascular;

Q4464: R. P. Iyer, *et al.* Early matrix metalloproteinase-12 inhibition worsens post-myocardial infarction cardiac dysfunction by delaying inflammation resolution. *INTERNATIONAL JOURNAL OF CARDIOLOGY* 2015;185(198-208

Agents: RXP 470.1 **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 1 day; 3 days; 5 days; 7 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, C57BL6J, 3-6 months old, myocardial infarction); cardiovascular; immunology; enzyme inhibitor (matrix metalloproteinase-12);

Q3387: A. Meides, *et al.* Effects of selective MMP-13 inhibition in squamous cell carcinoma depend on estrogen. *International Journal of Cancer* 2014;135(2749-2759

Agents: MMP-13 inhibitor **Vehicle:** PEG 200; DMSO; **Route:** Not Stated; **Species:** Mice (nude); **Pump:** 2004;

ALZET Comments: Control animals received mp w/ vehicle; animal info (C57BL/6N, ovariectomized); MMP-13 inhibitor also known as compound 1, was synthesized from 2,4 pyridine dicarboxylic acid and 4-Fluoro3-Methylbenzylamine; "Delivery of the inhibitor was achieved by an osmotic minipump, as constant blood levels of inhibitor are more effective than bolus injections to fully block MMP-13 activity during long term treatments." pg 2759; dose-response; cancer; enzyme inhibitor (matrix metalloproteinases)

Q1667: S. Allard, *et al.* Impact of the NGF Maturation and Degradation Pathway on the Cortical Cholinergic System Phenotype. *Journal of Neuroscience* 2012;32(6):2002-2012

Agents: Antiplasmin, alpha-2; MMP2-9I, type 1 **Vehicle:** Saline; sodium acetate; DMSO; **Route:** CSF/CNS (medial prefrontal cortex); **Species:** Rat; **Pump:** 2002; **Duration:** 2 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (Wistar, male, 350 g); Plastics One bilateral cannula used; 1% DMSO used; enzyme inhibitor (matrix metalloproteinase); behavioral testing (water maze test); neurodegenerative (Alzheimer's disease); bilateral infusion;

Q1963: A. W. Smith, *et al.* Plasticity associated with escalated operant ethanol self-administration during acute withdrawal in ethanol-dependent rats requires intact matrix metalloproteinase systems. *Neurobiology of Learning and Memory* 2011;96(2):199-206

Agents: FN-439 **Vehicle:** Not Stated; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2006; **Duration:** Not Stated;

ALZET Comments: Controls received mp w/ artificial CSF; animal info (Wistar, adult, male); enzyme inhibitor (matrix metalloproteinase); cannula placement verified via histology with 0.6% cresyl violet, 2 ul over 60 s



Q2230: S. G. N. Mazurek, *et al.* Functional biomarkers of musculoskeletal syndrome (MSS) for early in vivo screening of selective MMP-13 inhibitors. *Journal of Pharmacological and Toxicological Methods* 2011;64(1):89-96

Agents: Marimastat **Vehicle:** DMSO; water; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 15-17 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (Sprague Dawley, male, 180-370); wound clips used; enzyme inhibitor (matrix metalloproteinase, MMP-13)

Q0682: G. Cirillo, *et al.* Reactive astrocytosis-induced perturbation of synaptic homeostasis is restored by nerve growth factor. *NEUROBIOLOGY OF DISEASE* 2011;41(3):630-639

Agents: Nerve growth factor, beta, recomb.; GM6001 **Vehicle:** CSF, artificial; albumin, rat serum; **Route:** CSF/CNS (intrathecal, subarachnoid space); **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (Sprague-Dawley, male, 250-300 g); enzyme inhibitor (metalloproteinase); PE10 connected to PE60 tubing

Q0676: M. S. Aagren, *et al.* Nonselective matrix metalloproteinase but not tumor necrosis factor-alpha inhibition effectively preserves the early critical colon anastomotic integrity. *International Journal of Colorectal Disease* 2011;26(3):329-337

Agents: GM6001; AG3340 **Vehicle:** DMSO; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** Not Stated;

ALZET Comments: Controls received mp w/ vehicle; animal info (male Sprague-Dawley, 205-360 g); enzyme inhibitor (matrix metalloproteinase, MMP); 50% DMSO used

Q0345: G. Marino, *et al.* Insulin-like growth factor 1 treatment extends longevity in a mouse model of human premature aging by restoring somatotroph axis function. *Proceedings of the National Academy of Sciences of the United States of America* 2010;107(37):16268-16273

Agents: Insulin-like growth factor-1, human, recomb. **Vehicle:** HCl; saline, isotonic, sterile; **Route:** SC; **Species:** Mice (transgenic); **Pump:** 1004; **Duration:** 56 days;

ALZET Comments: Animal info (transgenic, Zmpste24 metalloproteinase deficient); pumps replaced after 28 days

Q0871: C. A. Fernandez, *et al.* The Anti-angiogenic Peptide, Loop 6, Binds Insulin-like Growth Factor-1 Receptor. *Journal of Biological Chemistry* 2010;285(53):41886-41895

Agents: Peptide, loop 6 **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice (SCID); **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: Controls received mp w/ PBS; peptides; enzyme inhibitor (metalloproteinase); cancer; Loop 6, anti-angiogenic peptide, is a smaller domain C-terminal portion of TIMP-2

P9577: J. W. Wright, *et al.* Habituation-induced neural plasticity in the hippocampus and prefrontal cortex mediated by MMP-3. *Behavioural Brain Research* 2009;203(1):27-34

Agents: MMP-3i **Vehicle:** Not Stated; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 6 days;

ALZET Comments: Controls received mp aCSF; functionality of mp verified by residual volume; animal info (male, Sprague Dawley, 300-350g); behavioral testing (head-shake response habituation); cannula placement verified w/icv injection of fast green dye; enzyme inhibitor (metalloproteinase-3)

P9117: T. Kasaoka, *et al.* Matrix metalloproteinase inhibitor, MMI270 (CGS27023A) inhibited hematogenic metastasis of B16 melanoma cells in both experimental and spontaneous metastasis models. *Clinical & Experimental Metastasis* 2008;25(7):827-834

Agents: MMI270 **Vehicle:** DMSO; PEG 300; **Route:** SC; **Species:** Mice; **Pump:** 2004; 2004; **Duration:** 14; 21 days;

ALZET Comments: Comparison of SC injections vs. mp; enzyme inhibitor (matrix metalloproteinase); cancer (melanoma); animal info (7 wks old, BDF1, male, lymphadectomy; 50% DMSO used; 50% PEG 300 used)

P9225: J. P. H. Chow, *et al.* Metalloproteinase- and gamma-Secretase-mediated Cleavage of Protein-tyrosine Phosphatase Receptor Type Z. *Journal of Biological Chemistry* 2008;283(45):30879-30889

Agents: GM6001 **Vehicle:** DMSO; **Route:** CSF/CNS; **Species:** Mice; **Pump:** 1007D; **Duration:** 4 days;

ALZET Comments: Controls received mp w/ vehicle; enzyme inhibitor (metalloproteinase); ALZET brain infusion kit 3 used; dental cement and stay screws used; animal info (male, C57BL/6, wt, Ptp^{prz} -/-, adult); 50% DMSO used



P8704: P. Tummalapalli, *et al.* RNAi-mediated abrogation of cathepsin B and MMP-9 gene expression in a malignant meningioma cell line leads to decreased tumor growth, invasion and angiogenesis. *International Journal of Oncology* 2007;31(5):1039-1050

Agents: RNA, small interfering **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Mice (nude); **Pump:** Not Stated; **Duration:** 3-4 weeks;

ALZET Comments: Controls received no treatment; cancer (meningioma); animal info (athymic, nude); siRNA plasmid vectors targeting cathepsin B and matrix metalloproteinase MMP9

P8053: M. A. Bruno, *et al.* Activity-dependent release of precursor nerve growth factor, conversion to mature nerve growth factor, and its degradation by a protease cascade. *Proceedings of the National Academy of Sciences of the United States of America* 2006;103(17):6735-6740

Agents: Neuroserpin; GM6001 **Vehicle:** CSF, artificial, PBS; **Route:** CSF/CNS (parietal cortex); **Species:** Rat; **Pump:** 2001; **Duration:** 72 hours;

ALZET Comments: Controls received mp w/ vehicle into contralateral side; enzyme inhibitor (tpa, metalloproteinase); multiple pumps per animal (2); animal info (Fischer 344, 6 month old); Lynch coil with air-oil spacer at mp end of tubing; bilateral infusion cannulae; tissue perfusion (parietal cortex)

P6498: E. S. Nakamura, *et al.* Inhibition of lymphangiogenesis-related properties of murine lymphatic endothelial cells and lymph node metastasis of lung cancer by the matrix metalloproteinase inhibitor MMI270. *Cancer Science* 2004;95(1):25-31

Agents: MMI270 **Vehicle:** DMSO; PEG 300; **Route:** IP; **Species:** Mice; **Pump:** 2004; **Duration:** 15 days;

ALZET Comments: Controls received mp w/ vehicle; no stress (see pg.27); enzyme inhibitor (matrix metalloproteinase); cancer (lung); MMI270 was formerly termed CGS27023A; 50% DMSO used; 50% PEG 300 used; "The continuous administration of MMI270 for 15 days using an osmotic pump led to a significant decrease in the weight of tumor-metastasized lymph nodes" (p. 29)

P7054: B. Matthey, *et al.* Metalloproteinase inhibition augments antitumor efficacy of the anti-CD30 immunotoxin Ki-3(scFv)-ETA' against human lymphomas in vivo. *International Journal of Cancer* 2004;111(4):568-574

Agents: BB-3644 **Vehicle:** PBS; **Route:** SC; **Species:** Mice (SCID); **Pump:** 2001; **Duration:** 8 days;

ALZET Comments: Controls received mp w/ vehicle; comparison of IV injections vs. mp; enzyme inhibitor (metalloproteinases); cancer (lymphoma); "when BB-3644 was continuously applied via a small osmotic pump, the antitumor activity of a single dose of Ki-3(scFv)-ETA' was further enhanced with a tumor-free survival of all animals treated for more than 200 days." (p. 572)

P7036: J. P. Levesque, *et al.* Characterization of hematopoietic progenitor mobilization in protease-deficient mice. *Blood* 2004;104(1):65-72

Agents: MMI270 **Vehicle:** DMSO; PEG 300; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 6 days;

ALZET Comments: Controls received mp w/ vehicle; functionality of mp verified by serum MMI270 levels; enzyme inhibitor (metalloproteinase)

P6575: M. J. Cox, *et al.* Attenuation of oxidative stress and remodeling by cardiac inhibitor of metalloproteinase protein transfer. *Circulation* 2004;109(17):2123-2128

Agents: CIMP **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice; **Pump:** 1002; **Duration:** 4 weeks;

ALZET Comments: Controls received no treatment/sham AVF surgery; enzyme inhibitor (metalloproteinase); cardiovascular; peptides; agent also known as (metalloproteinase, cardiac inhibitor)

P5943: N. Wada, *et al.* Reduced angiogenesis in peritoneal dissemination of gastric cancer through gelatinase inhibition. *Clinical & Experimental Metastasis* 2003;20(5):431-435

Agents: Marimastat **Vehicle:** DMSO; water; **Route:** SC; **Species:** Mice (SCID); **Pump:** 2002; **Duration:** 2 weeks;

ALZET Comments: controls received mp w/ vehicle; enzyme inhibitor (matrix metalloprotease); marimastat, the broad-spectrum matrix metalloproteinase inhibitor was dissolved in 50% DMSO; angiogenesis inhibitor



P6346: N. Kawai, *et al.* Treatment of cold injury-induced brain edema with a nonspecific matrix metalloproteinase inhibitor MMI270 in rats. *Journal of Neurotrauma* 2003;20(7):649-657

Agents: MMI270 **Vehicle:** DMSO; PEG 300; **Route:** IP; **Species:** Rat; **Pump:** 2001D; 2ML1; **Duration:** 7 days; 24 hours; **ALZET Comments:** Controls received mp/ vehicle; no stress (see pg. 652); enzyme inhibitor (matrix metalloproteinase);

P5338: M. Kimata, *et al.* Matrix metalloproteinase inhibitor, marimastat, decreases peritoneal spread of gastric carcinoma in nude mice. *Japanese Journal of Cancer Research* 2002;93(7):834-841

Agents: Marimastat **Vehicle:** DMSO; **Route:** SC; **Species:** Mice (nude); **Pump:** Not Stated; **Duration:** 28 days; **ALZET Comments:** Controls received mp w/ vehicle; pumps replaced after 14 days; matrix metalloproteinase inhibitor;

P5454: P. Charoenrat, *et al.* A synthetic matrix metalloproteinase inhibitor prevents squamous carcinoma cell proliferation by interfering with epidermal growth factor receptor autocrine loops. *International Journal of Cancer* 2002;100(5):527-533

Agents: Marimastat **Vehicle:** DMSO; Water, sterile; **Route:** SC; **Species:** Mice; **Pump:** 2002; **Duration:** 17 days; **ALZET Comments:** Controls received mp w/ vehicle; cancer; enzyme inhibitor (matrix metalloproteinase)

P4811: T. Kiyama, *et al.* Effect of matrix metalloproteinase inhibition on colonic anastomotic healing in rats. *JOURNAL OF GASTROINTESTINAL SURGERY* 2001;5(303-311)

Agents: BE16627B **Vehicle:** DMSO; ethylene glycol; **Route:** SC; **Species:** Rat; **Pump:** 1003D; **Duration:** 3 days; **ALZET Comments:** Controls received mp w/ vehicle; vehicle mix was 50:50 ratio; BE16627B matrix metalloproteinase inhibitor;

P4285: M. F. Prescott, *et al.* Effect of matrix metalloproteinase inhibition on progression of atherosclerosis and aneurysm in LDL receptor-deficient mice overexpressing MMP-3, MMP-12, and MMP-13 and on restenosis in rats after balloon injury. *Annals of the New York Academy of Sciences* 1999;878(179-190)

Agents: CGS 27023A **Vehicle:** DMSO; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; 2ML4; **Duration:** 9,47 days; **ALZET Comments:** Cardiovascular; enzyme Inhibitor; CGS 27023A hydroxamic acid matrix metalloproteinase inhibitor

P4382: J. G. Conway, *et al.* Effect of matrix metalloproteinase inhibitors on tumor growth and spontaneous metastasis. *Clinical & Experimental Metastasis* 1996;14(115-124)

Agents: E-64; GI168; GI173; GI179; GI184 **Vehicle:** DMSO; Saline; Ethanol; Buffer, sodium citrate; Tappsol HPB-20; **Route:** SC; **Species:** Mice; **Pump:** 2001; 2002; **Duration:** 2, 7, 14 days; **ALZET Comments:** Controls received mp w/ vehicle; cancer; matrix metalloproteinase inhibitors; mice received 2 pumps each;

P4025: E. H. Karran, *et al.* In vivo model of cartilage degradation - effects of a matrix metalloproteinase inhibitor. *Annals of the Rheumatic Diseases* 1995;54(662-669)

Agents: MI-1; MI-2 **Vehicle:** Propylene glycol; **Route:** Cartilage, femoral head; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days; **ALZET Comments:** Tissue perfusion (femoral head cartilage); good methods (p. 663); MI-1 and MI-2 are matrix metalloproteinase inhibitors; enzyme inhibitors

P3379: J. G. Conway, *et al.* Inhibition of cartilage and bone destruction in adjuvant arthritis in the rat by a matrix metalloproteinase inhibitor. *J. Exp. Med* 1995;182(449-457)

Agents: GI168 **Vehicle:** DMSO; Sodium citrate buffer; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 2 weeks; **ALZET Comments:** controls received mp w/vehicle; dose-response (see p. 451); immunology; multiple pumps per animal (2); "GI168 had poor oral bioavailability and a short plasma t 1/2 after subcutaneous injection... so minipump delivery was evaluated." p. 451; enzyme inhibitor (matrix metalloproteinase)

P2788: K. Naito, *et al.* Inhibition of growth of human tumor cells in nude mice by a metalloproteinase inhibitor. *Int. J. Cancer* 1994;58(730-735)

Agents: BE16627B; Doxorubicin HCl **Vehicle:** DMSO; Ethylene glycol; **Route:** SC; **Species:** Mice (nude); **Pump:** 2001; 2002; **Duration:** 3 weeks, 18 days; **ALZET Comments:** controls received vehicle or no treatment; pumps replaced; stress/ adverse reaction: skin inflammation and necrosis around delivery site in mice treated with Adriamycin (pg. 733); BE166278B animals were fine; stability verified for 18 days by assay; cancer; enzyme inhibitor; BE16627B is a metalloproteinase inhibitor; 2002 replaced w/ 2001 after 20 days; adriamycin is doxorubicin HCl