



References on the Administration of Statin Class Drugs Using ALZET® Osmotic Pumps

1. Atorvastatin

Q5389: D. Atrahimovich, *et al.* Punicalagin Decreases Serum Glucose Levels and Increases PON1 Activity and HDL Anti-Inflammatory Values in Balb/c Mice Fed a High-Fat Diet. *Oxid Med Cell Longev* 2018;2018(2673076)

Agents: Punicalagin, Quercetin, Atorvastatin **Vehicle:** water, distilled, Tween 80; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 28 days;

ALZET Comments: Dose (punicalagin 140µg/100 µl, quercetin 42µg/100 µl, atorvastatin 15mg/100 µl); 2% Tween 80 used; Controls received mp w/ vehicle; animal info (male Balb/c mice, 8 weeks old); no stress: Mouse BW was not affected by sc-implanted pump treatments. (see pg. 3);

Q6650: X. M. Ren, *et al.* Atorvastatin Alleviates Experimental Diabetic Cardiomyopathy by Regulating the GSK-3beta-PP2Ac-NF-kappaB Signaling Axis. *PLoS One* 2016;11(11):e0166740

Agents: Atorvastatin calcium **Vehicle:** **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 12 weeks;

ALZET Comments: Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Male C57BL/6 mice (8 wk old, 18±22 g)); cardiovascular; diabetes; Therapeutic indication (diabetic cardiomyopathy);

Q1170: T. Kishi, *et al.* Sympathoinhibition Induced by Centrally Administered Atorvastatin Is Associated With Alteration of NAD(P)H and Mn Superoxide Dismutase Activity in Rostral Ventrolateral Medulla of Stroke-Prone Spontaneously Hypertensive Rats. *Journal of Cardiovascular Pharmacology* 2010;55(2):184-190

Agents: Atorvastatin **Vehicle:** DMSO; CSF, artificial; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 1003D; **Duration:** 14 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, SHRSP/Izm, WKY, 14-16 wksold)

2. Fluvastatin

Q7262: C. P. Richter, *et al.* Fluvastatin protects cochleae from damage by high-level noise. *Sci Rep* 2018;8(1):3033

Agents: Fluvastatin **Vehicle:** DMSO, Ringer's Solution; **Route:** Ear (cochlea); **Species:** Guinea Pig; **Pump:** 2004; **Duration:** 28 days;

ALZET Comments: Dose (fluvastatin 50 µM); animal info (Outbred Hartley guinea pigs of both sexes 200–500 g); post op. care (Buprenex); Cannula used;

P3443: A. Corsini, *et al.* Non-lipid-related effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Cardiology* 1996;87(458-468)

Agents: Mevalonate; Fluvastatin **Vehicle:** Saline, physiological; **Route:** IP; perivascular (arterial collar); **Species:** **Pump:** **Duration:** 5 days;

ALZET Comments: tissue perfusion (lesion site-carotid collar); enzyme inhibitor (HMG-CoA reductase)

P3457: M. R. Soma, *et al.* Inhibition of isoprenoid biosynthesis and arterial smooth-muscle cell proliferation. *J. Cardiovasc. Pharmacol* 1995;25(S 4):S20-S24

Agents: Mevalonate; Fluvastatin **Vehicle:** **Route:** IP; perivascular (arterial collar); **Species:** rabbit; **Pump:** **Duration:** no duration posted;

ALZET Comments: controls received mp w/ saline; tissue perfusion (carotid artery collar); cardiovascular; enzyme inhibitor (HMG-CoA reductase)



3. Lovastatin

Q4310: M. A. Assaggaf, *et al.* Prevention of Phenytoin-Induced Gingival Overgrowth by Lovastatin in Mice. AMERICAN JOURNAL OF PATHOLOGY 2015;185(1588-1599)

Agents: Phenytoin; lovastatin **Vehicle:** Water; propylene glycol; ethanol; **Route:** SC; **Species:** Mice; **Pump:** 2002; **Duration:** 12 weeks;

ALZET Comments: Controls received mp w/ vehicle or saline; animal info (male, BALB/cByJ, 8 weeks old); 9% ethanol used; 41% propylene glycol used; long-term study; phenytoin and lovastatin inside one pump; used autoclips; pumps primed in 37C saline overnight;

P2086: J. Joles, *et al.* Subcutaneous administration of HMG-CoA reductase inhibitors in hyperlipidaemic and normal rats. Lab. Anim 1992;26(269-280)

Agents: Lovastatin; Pravastatin; Liposomes; Simvastatin **Vehicle:** Propylene glycol; **Route:** **Species:** Rat; **Pump:** 2ML4; **Duration:** no duration posted;

ALZET Comments: comparison of injections and oral administration vs. mp; stress/adverse reaction: local cystic reaction to simvastatin and lovastatin (p. 271, 275); enzyme inhibitor (HMG-CoA reductase), sc injections of simvastatin also caused subcutaneous toxicity

4. Pravastatin

Q1240: V. Monceau, *et al.* Modulation of the Rho/ROCK Pathway in Heart and Lung after Thorax Irradiation Reveals Targets to Improve Normal Tissue Toxicity. CURRENT DRUG TARGETS 2010;11(11):1395-1404 Pravastatin; Y-27632

Agents: Pravastatin; Y-27632 **Vehicle:** DMSO; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 2 weeks;

ALZET Comments: Animal info (female, C57BL6); enzyme inhibitor (ROCK, Rho-associated protein kinase); 10% DMSO used

P9274: H. Zaher, *et al.* Targeted disruption of murine organic anion-transporting polypeptide 1b2 (oatp1b2/Slco1b2) significantly alters disposition of prototypical drug substrates pravastatin and rifampin. MOLECULAR PHARMACOLOGY 2008;74(2):320-329

Agents: Rifampin; pravastatin **Vehicle:** Water; DMSO; **Route:** SC; **Species:** Mice; **Pump:** 2001D; **Duration:** 24 hours;

ALZET Comments: Functionality of mp verified by plasma concentrations; dose-response (fig. 5); comparison of IV injections vs. mp; animal info (male, DBA1/lacJ, wt, Slco1b2 -/-, 9-14 wks old); 0.5% DMSO used

P2086: J. Joles, *et al.* Subcutaneous administration of HMG-CoA reductase inhibitors in hyperlipidaemic and normal rats. Lab. Anim 1992;26(269-280)

Agents: Lovastatin; Pravastatin; Liposomes; Simvastatin **Vehicle:** Propylene glycol; **Route:** **Species:** Rat; **Pump:** 2ML4; **Duration:** no duration posted;

ALZET Comments: comparison of injections and oral administration vs. mp; stress/adverse reaction: local cystic reaction to simvastatin and lovastatin (p. 271, 275); enzyme inhibitor (HMG-CoA reductase), sc injections of simvastatin also caused subcutaneous toxicity

5. Rosuvastatin

Q4414: P. Escudero, *et al.* Combined treatment with bexarotene and rosuvastatin reduces angiotensin-II-induced abdominal aortic aneurysm in apoE(-/-) mice and angiogenesis. BRITISH JOURNAL OF PHARMACOLOGY 2015;172(2946-2960)

Agents: Rosuvastatin, Angiotensin II **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 5 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (apoE -/-, 8 weeks old); cardiovascular; peptides; "Because the s.c. administration of the statin using an osmotic minipump allows 100% drug bioavailability and its p.o. administration results in 34.5% bioavailability in mice (Peng et al., 2009), we chose the former route to ensure a full dosage effect." pg 2948; comparison of mp vs. oral gavage



Q3875: P. Escudero, *et al.* Combined Sub-Optimal Doses of Rosuvastatin and Bexarotene Impair Angiotensin II-Induced Arterial Mononuclear Cell Adhesion Through Inhibition of Nox5 Signaling Pathways and Increased RXR/PPARalpha and RXR/PPARgamma Interactions. *ANTIOXIDANTS & REDOX SIGNALING* 2015;22(901-920

Agents: Angiotensin II; Rosuvastatin **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Duration: 14 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL6 or ApoE -/-, 23-30g); cardiovascular; peptides; antihypertensive;

Q3783: E. Kilic, *et al.* HMG-CoA reductase inhibition promotes neurological recovery, peri-lesional tissue remodeling, and contralesional pyramidal tract plasticity after focal cerebral ischemia. *Frontiers in Cellular Neuroscience* 2014;8(U1-U10

Agents: Rosuvastatin **Vehicle:** NaCl; **Route:** CSF/CNS; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;

ALZET Comments: Control animals received mp w/ vehicle; animal info (C57BL6/J, 23-25 g); ALZET brain infusion kit 3 used; enzyme inhibitor (HMG-CoA reductase)

6. Simvastatin

Q6593: E. M. Masko, *et al.* Evidence for Feedback Regulation Following Cholesterol Lowering Therapy in a Prostate Cancer Xenograft Model. *Prostate* 2017;77(5):446-457

Agents: Simvastatin **Vehicle:** DMSO; PBS; **Route:** SC; **Species:** Mice (nude); **Pump:** 2006; **Duration:** **ALZET Comments:** Dose (11 mg/kg/day); 40% DMSO, 60% PBS used; Controls received mp w/ vehicle; animal info (6 week old male Athymic Nude-Foxn1Nu mice);

Q3283: S. Morishita, *et al.* Systemic Simvastatin Rescues Retinal Ganglion Cells from Optic Nerve Injury Possibly through Suppression of Astroglial NF-kappaB Activation. *PLoS One* 2014;9(1):U528-U538

Agents: Simvastatin **Vehicle:** Polyethylene glycol; **Route:** SC; **Species:** Rat; **Pump:** **Duration:** **ALZET Comments:** Control animals received mp w/ vehicle; animal info (9 wks old, male, Wistar)

Q0763: P. Wei, *et al.* Simvastatin Reverses Podocyte Injury but not Mesangial Expansion in Early Stage Type 2 Diabetes Mellitus. *RENAL FAILURE* 2009;31(6):503-513

Agents: Simvastatin **Vehicle:** Ethanol; **Route:** SC; **Species:** Mice; **Pump:** **Duration:** 4 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (C57BL/6, male, 26 wks old); 60% ethanol used

P9177: E. Holmberg, *et al.* Statins decrease chondroitin sulfate proteoglycan expression and acute astrocyte activation in central nervous system injury. *Experimental Neurology* 2008;214(1):78-86

Agents: Simvastatin **Vehicle:** **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2004; **Duration:** 4 weeks;

ALZET Comments: Comparison of PO gavage vs. mp; ALZET brain infusion kit used; post op. care (buprenorphine); animal info (female, Long Evans, adult, 200-22 g.); cannula placement confirmed by preparing cryosections of the brain at the lateral ventricle and verifying the presence of a cavity created by the cannula; spinal cord injury

P9024: B. Skoglund, *et al.* Locally applied Simvastatin improves fracture healing in mice. *BMC MUSCULOSKELETAL DISORDERS* 2007;8(1):U1-U6

Agents: Simvastatin **Vehicle:** PEG 400; **Route:** SC; bone (femur); **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;

ALZET Comments: Comparison of SC injections vs. SC mp vs. localized delivery; half-life (p. 2 of 6) "about 2 hours in humans"; animal info (mature, male, Balb-C); tissue perfusion (femur); compound passed through sterile filter before filling in pumps; silicone tube used; "continuous systemic delivery resulted in a 160% larger force at failure."; "Continuous local delivery... resulted in a 170% larger force at failure as well as a twofold larger energy uptake."

P7913: A. K. Banes-Berceli, *et al.* Effect of simvastatin on high glucose- and angiotensin II-induced activation of the JAK/STAT pathway in mesangial cells. *American Journal of Physiology-Renal Physiology* 2006;291(1):F116-F121

Agents: Simvastatin **Vehicle:** Water, distilled; **Route:** SC; **Species:** Rat; **Pump:** **Duration:** **ALZET Comments:** Controls received no treatment; animal info (male, Sprague-Dawley, 225-250 g)



P2086: J. Joles, *et al.* Subcutaneous administration of HMG-CoA reductase inhibitors in hyperlipidaemic and normal rats. *Lab. Anim* 1992;26(269-280)

Agents: Lovastatin; Pravastatin; Liposomes; Simvastatin **Vehicle:** Propylene glycol; **Route:** **Species:** Rat; **Pump:** 2ML4;

Duration: no duration posted;

ALZET Comments: comparison of injections and oral administration vs. mp; stress/adverse reaction: local cystic reaction to simvastatin and lovastatin (p. 271, 275); enzyme inhibitor (HMG-CoA reductase), sc injections of simvastatin also caused subcutaneous toxicity

7. Pitavastatin

P9421: N. Kobayashi, *et al.* Cardioprotective Effects of Pitavastatin on Cardiac Performance and Remodeling in Failing Rat Hearts. *American Journal of Hypertension* 2009;22(2):176-182

Agents: Pitavastatin; Wortmannin; Y-27632 **Vehicle:** DMSO; saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 7 weeks;

ALZET Comments: Controls received mp w/ vehicle; long-term study; pumps replaced; enzyme inhibitor (phosphatidyl inositol 3-kinase, Rho kinase); cardiovascular; multiple pumps per animal (2); animal info (male, Dahl S, Dahl R, 11 wks old); 8% DMSO used