
Pamela J. Lein, Ph.D.

Lein, Pamela J., Ph.D., Professor, Department of Molecular Biosciences, School of Veterinary Medicine; Chair, UC Davis Pharmacology and Toxicology Graduate Group

Education

B.S., Biological Sciences, Cornell University, 1981

M.S., Environmental Health, East Tennessee State University, 1983

Ph.D., Pharmacology and Toxicology, State University of New York, Buffalo

Biography

Dr. Lein is a developmental neurobiologist with research interested in the molecular and cellular mechanisms by which environmental stressors modulate neurodevelopment. Her current research focuses on: (1) interactions between genetic alterations in ryanodine receptors and environmental factors that modulate calcium signaling that alter normal patterns of neuronal connectivity in the developing brain; (2) novel biomarkers and medical countermeasures for organophosphorus anticholinesterase-induced neurotoxicity; and (3) the influence of neuroimmune interactions on neuronal morphogenesis and synapse formation. The ultimate goal this research is to identify environmental stressors that can be readily controlled to decrease the incidence and/or severity of neurodevelopmental disorders. Dr. Lein has developed a well-funded, collaborative and interdisciplinary research program with colleagues across the university, as well as nationally and internationally. She is the Chair of the Graduate Group in Pharmacology and Toxicology at UC Davis, and a member of the MIND Institute.

Publications

Bucelli RC, Gonsiorek EA, Kim W-Y, Bruun D, Rabin RA, Higgins D, **Lein PJ**. Statins decrease expression of the proinflammatory neuropeptides calcitonin gene-related peptide and substance P in sensory neurons. *J Pharmacol Exp Therap* 324(3): 1172-1180, 2008.

Proskocil BJ, Bruun DA, Lorton JK, Blensly KA, Jacoby DB, **Lein PJ**, Fryer AD. Antigen sensitization influences organophosphorus pesticide-induced airway hyperreactivity. *Environ Health Perspect* 116(3): 381-388, 2008.

Yang D, Howard A, Bruun D, Ajua-Alemanj M, Pickart C, **Lein PJ**. Chlorpyrifos and chlorpyrifos-oxon inhibit axon outgrowth by disrupting the morphogenic activity of acetylcholinesterase. *Toxicol Appl Pharmacol* 228: 32-41, 2008.

Dziennis S, Yang D, Cheng J, Anderson K, Alkayed NJ, Hurn PD, **Lein PJ**. Developmental exposure to polychlorinated biphenyls influences stroke outcome in adult rats. *Environ Health Perspect*. 116(4): 474-480, 2008.

Boswell B, **Lein P**, Musil L. Cross-talk between FGF and BMPs regulates gap junction-mediated intercellular communication in lens cells. *Mol Biol Cell*. 19:2631-2641, 2008.

Pessah IN, Seegal RF, **Lein PJ**, LaSalle J, Yee BK, Van De Water J, Berman RF. Immunologic and neurodevelopmental susceptibilities of autism. *Neurotoxicol*. 29:532-545, 2008.

Andres DA, Shi GX, Bruun D, Barnhart C, **Lein PJ**. Rit Signaling Contributes to Interferon- γ -Induced Dendritic Retraction via p38 MAP Kinase Activation. *J Neurochem*. 107:1436-1447, 2008.

Kim WY, Gonsiorek EA, Barnhart C, Davare MA, Engebose AJ, Lauridsen H, Bruun D, Lesiak A, Wayman G, Bucelli RC, Higgins D, **Lein PJ**. Statins decrease dendritic arborization in rat sympathetic neurons by blocking RhoA activation. *J Neurochem*. 108:1057-1071, 2009.

Yang D, Kim KH, Phimister A, Bachstetter AD, Ward TR, Stackman RW, Mervis RF, Wisniewski AB, Klein SL, Kodavanti PRS, Anderson KA, Wayman G, Pessah IN, **Lein PJ**. Developmental exposure to PCBs interferes with experience-dependent dendritic plasticity and ryanodine receptor expression in weanling rats. *Environ Health Perspect*. 117:426-435, 2009.

Halladay A, Amaral D, Aschner M, Bolivar V, Bowman A, DiCicco-Bloom E, Hyman S, Keller F, **Lein P**, Pessah I, Restifo L, Threadgill DW. Animal models of autism spectrum disorders: Information for toxicologists. *Neurotoxicol*. 30:811-821, 2009.

Pessah IN, Cherednichenko G, **Lein PJ**. Minding the calcium store: Ryanodine receptor activation as a convergent mechanism of PCB toxicity. *Pharmacol Therap*. 125(2):260-285, 2010.

Yang D, **Lein PJ**. Polychlorinated biphenyls increase apoptosis in the developing rat brain. *Curr Neurobiol*. 1 (1): 69-76, 2010.

Farahat FM, Olson JR, Fenske RA, Galvin K, Bonner MR, Rohlman DS, **Lein PJ**, Anger WK. Chlorpyrifos exposures in Egyptian cotton field workers. *Neurotoxicol*. 31:297-304, 2010.

Proskocil BJ, Bruun DA, Thompson CM, Fryer AD, **Lein PJ**. Organophosphorus pesticides decrease M2 muscarinic receptor function in guinea pig airway nerves via indirect mechanisms. *PLoS ONE* 5(5): e10562. Doi:10.1371/journal.pone.0010562, 2010.

Yang D, Bruun DA, Andres DA, **Lein PJ**. Method for shipping live adherent cultures of dissociated rat hippocampal neurons. *Current Neurobiol* 1 (2): 95-98, 2010.

Crofton KM, Mundy WR, **Lein PJ**, Price-Bal A, Coecke S, Seiler A, Knaut H, Buzanska L, Goldberg A. Recommendations for Developing Alternative Test Methods for Screening and Prioritization of Chemicals for Developmental Neurotoxicity. *ALTex* 28(1): 9-15, 2011.

Rohlman DS, Anger WK, **Lein PJ**. Correlating neurobehavioral performance with biomarkers of organophosphorus pesticide exposure. *Neurotoxicol* 32:268-276, 2011.

Grodzki ACG, Ghogha A, Mangini L, Fryer AD, **Lein PJ**. γ -Interferon increases M2 muscarinic receptor expression in cultured sympathetic neurons. *Current Neurobiol* 2(1): 23-29, 2011.

Kim KH, Bose D, Ghogha A, Riehl J, Zhang R, Barnhart CD, **Lein PJ**, Pessah IN. *Para*- and *ortho*-substitutions are key determinants of brominated diphenyl ether activity toward ryanodine receptors and neurotoxicity. *Environ Health Perspect* 119:519-526, 2011.

Abdu E, Bruun DA, Yang D, Yang J, Inceoglu B, Hammock BD, Alkayed N, **Lein PJ**. Epoxyeicosatrienoic acids enhance axonal growth in primary sensory and cortical neuronal cell cultures. *J Neurochem* 117:632-642, 2011.

Yang D, Lauridsen H, Buels K, Chi L-H, La Du J, Bruun DA, Olson JR, Tanguay RL, **Lein PJ**. Chlorpyrifos-oxon disrupts zebrafish axonal growth and motor behavior. *Toxicol Sci* 121:46-59, 2011.

Farahat FM, Ellison CA, Bonner MR, McGarrigle B, Crane AL, Fenske RA, Lasarev M, Rohlman DS, Anger WK, **Lein PJ**, Olson JR. Biomarkers of chlorpyrifos exposure and effect in Egyptian cotton field workers. *Environ Health Perspect*, 119:801-806, 2011.

Li Y*, **Lein PJ***, Liu C, Bruun D, Tewolde T, Ford G, Ford BD. Spatiotemporal pattern of neuronal injury induced by DFP in rats: A model for delayed neuronal cell death following acute OP intoxication. *Toxicol Appl Pharmacol*, 253:261-269, 2011. * these authors contributed equally to this work.

Garred MM, Wang MM, Guo X, Harrington CA and **Lein PJ**. Transcriptional responses of cultured rat sympathetic neuron during BMP-7-induced dendritic growth. *PLoS ONE*, 6(7): e21754. doi:10.1371/journal.pone.0021754, 2011.

Ellison CA, Smith JN, **Lein PJ**, Olson JR. Pharmacokinetics and pharmacodynamics of chlorpyrifos in adult male Long-Evans rats following repeated subcutaneous exposure to chlorpyrifos. *Toxicol* 287:137-144, 2011.

Lein PJ, Barnhart CD, Pessah IN. Acute hippocampal slice preparation and hippocampal slice cultures. *Methods Mol Biol* 758:115-34, 2011.

Ellison CA, Abou El-Ella SS, Tawfik M, **Lein PJ**, Olson JR. Allele and genotype frequencies of CYP2B6 and CYP2C19 polymorphisms in Egyptian agricultural workers. *J Toxicol Environ Health, Part A*. 75:232-241, 2012.

Van Thriel C, Westerink R, Beste C, Bale A, **Lein PJ**, Leist M. Translating neurobehavioral endpoints of developmental neurotoxicity tests into *in vitro* assays and readouts. *Neurotoxicol*, in press, 2012.

Ghogha A, Bruun DA, **Lein PJ**. BMP-induced dendritic growth in cultured sympathetic neurons. *JoVE*, in press, 2012.

Lein PJ, Bonner MR, Farahat FM, Olson JR, Rohlman DS, Fenske RA, Lattal M, Lasarev MR, Galvin K, Farahat TM and Anger WK. Experimental strategy for translational studies of organophosphorus pesticide neurotoxicity based on real-world occupational exposures to chlorpyrifos. *Neurotoxicol*, in press, 2012.

Banks CN, **Lein PJ**. A review of experimental evidence linking neurotoxic organophosphorus compounds and inflammation. *Neurotoxicol*, in press, 2012.

Zolkowska D, Banks CN, Dhir A, Inceoglu B, Sanborn JR, McCoy MR, Bruun DA, Hammock BD, **Lein PJ**, Rogawski MA. Characterization of seizures induced by acute and repeated exposure to tetramethylenedisulfotetramine. *J Pharmacol Exp Therap*, in press, 2012.

Presentations

Cell and Molecular Mechanisms of PCB Developmental Neurotoxicity, invited presentation, Microbiology and Environmental Toxicology, University of California, Santa Cruz, CA, January 2012.

Influence of the immune system on neurodevelopment, invited presentation, 27th International Neurotoxicology Conference, Research Triangle Park, NC October 2011.

Identification of novel therapeutic approaches for TETS and OP intoxication, invited presentation, 5th Annual CounterACT Network Research Symposium, Washington, D.C., June 2011.

In vitro endpoints of relevance to organophosphorus pesticide-induced neurobehavioral deficits, invited presentation, International Neurotoxicology Association, Xi'an, China, June 2011.

Atopic Status Determines Inflammatory Cell Mediators in Organophosphorus Pesticide-Induced Airway Hyperreactivity, invited presentation, Lung Research Day Symposium, University of California, Davis, CA, April 2011.

Novel Neuroprotectants in OP-Induced Neurotoxicity, invited presentation, National SAVMA (Student Chapter of the American Veterinary Medical Association) Symposium, University of California, Davis, CA, March 2011.

Polychlorinated Biphenyls (PCBs) Modulate Neuronal Connectivity via Ryanodine Receptor-Dependent Mechanisms, invited presentation, Washington State University School of Veterinary Medicine, Pullman, WA, February 2011.

Organophosphorus Pesticides: Environmental Risk Factors for Autism Spectrum Disorders, invited presentation, UC Davis MIND Institute, Sacramento, CA, January 2011.

Organophosphorus Pesticides and Neurodevelopmental Disorders, invited presentation, SUNY at Buffalo, Buffalo, NY, November 2010.

Cellular and molecular mechanisms of organophosphorus pesticide-induced airway hyperreactivity, invited presentation, Center for Comparative Respiratory Biology and Medicine, UC Davis, CA May 2010.

Cellular and molecular mechanisms of organophosphorus pesticide-induced airway hyperreactivity, invited presentation, Molecular Microbiology and Immunology, UC Davis, CA, April 2010.

In vitro and other methods for identifying developmental neurotoxicants, invited presentation, Human Health Hazard Indicators Workshop, California Environmental Protection Agency, Sacramento, CA, March 2010.

Organophosphorus Pesticides and Neurodevelopmental Disorders, invited presentation, Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic College of Medicine, Rochester, MN, January 2010.

The yin and yang of dendritic growth: bone morphogenetic proteins and proinflammatory cytokines, invited presentation, Center for Neuroscience Research at the Children's National Medical Center, Washington, D.C., December 2009.

In vitro toxicity testing: perspective of an academic scientist, invited presentation, Toxicity Testing in the 21st Century: Can We Make the Business Case for Alternatives? University of Chicago Law School, Chicago, IL, November 2009.

Interference of neuronal morphogenesis by organophosphorus pesticides: potential relevance to autism spectrum disorders, invited presentation, Interdisciplinary Faculty of Toxicology, Texas A&M, College Station, TX, November 2009.

Regulation of dendritic growth by cytokines, invited presentation, Neuroscience & Physiology Program, SUNY at Syracuse, Syracuse, NY, October 2009.

Overview of Developmental Neurotoxicity Testing (DNT): problems and approaches for minimizing animal use and maximizing data collection, invited presentation, World Congress 7, Rome Italy, September 2009.

Novel neuroprotectants in OP-induced neurotoxicity, invited presentation, Annual Force Health Protection Conference, Albuquerque, NM, August 2009.

Developmental neurotoxicity of organophosphorus pesticides: neuronal morphogenesis as a target, invited presentation, Integrated Toxicology and Environmental Health Program, Duke University, Durham, NC, March 2009.

Polychlorinated biphenyls (PCBs) modulate neuronal connectivity, Center in Molecular Toxicology, Vanderbilt University School of Medicine, Nashville, TN, March 2009.

Research Funding

Principal Investigator (MPI): Biomarkers of Organophosphorus Pesticide-Induced Neurotoxicity, NIH NIEHS, 06/01/08 – 04/30/12, \$425,000 annual direct. *The main objective of this project is to test the hypotheses that OP-induced neurobehavioral deficits in humans are dose-related and that biomarkers of oxidative stress and inflammation are better predictors of neurobehavioral deficits than cholinesterase inhibition.*

Principal Investigator (MPI): Molecular and Cellular Basis of PCB Developmental Neurotoxicity, NIH/NIEHS, 12/01/0 – 11/30/13, \$303,639 annual direct. *This project examines how homologous missense mutations R176C-RyR1 and Q176R-RyR2 influence developmental neurotoxicity to susceptibility to three non-coplanar PCB congeners. In vitro and in vivo studies are determining how these congeners alter dendritic growth and plasticity and functional aspects of Ca²⁺ signaling.*

Principal Investigator (MPI): Enantioselective Metabolism Influences PCB Developmental Neurotoxicity, NIH/NIEHS, 12/1/09 – 11/30/14, \$319,549 annual direct. *The primary goal of the project is to explore whether the PCB atropisomers have differential potency and efficacy towards ryanodine receptors.*

Investigator: NIH Superfund Basic Research Program: NIH/NIEHS, 04/01/05 – 03/31/10, \$2,411,679 annual direct. The major goal of this project is to provide technical expertise in the area of receptor-based and cell-based assays to Program members.

Principal Investigator (MPI): Role of Macrophages in Organophosphorus Pesticide-Induced Airway Hyperreactivity, NIH NIEHS, 07/1/10-06/30/15, \$215,000 annual direct. The main goal is to test the hypothesis that airway macrophages mediate organophosphorus pesticide-induced airway hyperreactivity in non-atopic hosts.

Principal Investigator (MPI): Identification of novel therapeutic approaches to TETS and OP intoxication, NIH NINDS, 10/01/2010 – 09/30/2012, \$250,000 annual direct. The goal is to obtain preliminary data in support of our hypothesis that AMPA receptor (AMPA-R) antagonists and/or inhibitors of soluble epoxide hydrolases (sEHi) will significantly improve clinical management of acute TETS and parathion intoxication by extending the therapeutic window, enhancing neuroprotection and providing therapeutic efficacy against diverse chemical threat agents.

Community Service

Steering Committee, NIH CounterACT Program, 2011 - present
External Advisory Panel, NIEHS Core Center of Excellence, URochester, 2011 - present
Executive Committee, The Marion Miller Endowment Fund, 2011 - present
Judge, UC Davis Interdisciplinary Graduate and Professional Student Symposium, April 2011
Student Affairs Committee, UC Davis School of Veterinary Medicine, 2010 – 2012
Chair, Pharmacology and Toxicology (PTX) Graduate Group, 2010 – 2013
Director, NIEHS Training Grant, Advanced Training in Environmental Tox, 2010 - present
Chemical and Laboratory Safety Committee, 2010 – present
Graduate student recruitment, Neuroscience Graduate Group, 2010-2011
OECD Advisory Group on Toxicogenomics and Molecular Screening in Developmental Neurotoxicity Testing (DNT), 2009 - present
Fellowship Reviewer, Graduate Council, Support & Welfare Committee, 2009-2010
United State Environmental Protection Agency, Scientific Advisory Panel, 2004 - present
Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University, 2000 - present

Awards and Honors

Elected President, Society of Toxicology, Neurotoxicology Specialty Section, 2012-2013
Elected Vice-President, Society of Toxicology, Neurotoxicology Specialty Section, 2011-2012
Vice-President-Elect, Society of Toxicology, Neurotoxicology Specialty Section, 2010-2011
Elected Counselor, Society of Toxicology, Neurotoxicology Specialty Section, 2005-2007