

Russell A. Prough, Ph.D.

Professor

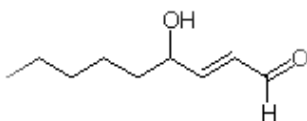
Department of Biochemistry & Molecular
Biology
School of Medicine

Research Activities:

The research pursued in Dr. Prough's laboratory focuses on the study of the mechanism of modulation of the enzyme activity of various drug/carcinogen metabolizing enzymes by various steroid hormones and sterols. For example, Tom Geoghegan and I are studying the effect of dehydroepiandrosterone (DHEA) and its metabolites on regulation of the cytochromes P450; DHEA and DHEA sulfate are major circulating sterols in humans and some primates (5-10 μ M concentration). DHEA is also a peroxisome proliferator, but regulates other enzyme systems in addition to those regulated by the peroxisome proliferator activated receptor alpha (PPAR α). PPAR and other members of subfamily III of the steroid hormone receptors may interact and modulate their respective action as mediators of the process of gene expression. We have noted that DHEA may alter the phosphorylation status of PPAR α

and other nuclear receptors by inducing protein phosphatases, specifically protein phosphatase 2A. This action appears to be different than the action of other peroxisome proliferating agents, and may account for the action of DHEA in inducing PPAR target genes. The molecular regulation of PP2A by sterols

is under study. Another collaborative project involves the study of aldehyde toxicity in cardiovascular tissues, in conjunction with Aruni Bhatnagar, Sumanth Prahbu, Sanjay Srivastava, and Stanley D'Souza. Our project studies the metabolism of acrolein, 4-hydroxynonenal and trans-2-hexenal in vascular tissues and how these agents regulate of enzyme systems in cardiovascular tissue. In addition, the effects of aldehydes on expression of those cytochromes P450 that metabolize arachidonic acid to various signaling molecules is under study to elucidate how they affect vasoactive action and proliferation and/or development of vascular smooth muscle and endothelial cells. Aldehydes serve as both substrates for some of these hemoproteins, as well as mechanism-based inactivators of CYP function. The role of aldehyde dehydrogenases and glutathione S-transferases in clearance of aldehydes is also under study, evaluating the various isozymes of these enzymes are regulated in mouse and human.



4-Hydroxynonenal (4-HNE)

Grants Funded:

Role: Project Leader

Title: Aldehyde Metabolism and Cardiovascular Disease

Funding Agency: NIEHS/NIH

Direct Costs Funded: \$169,385

Role: Co-Investigator

Title: Molecular Epidemiology of Environmental/Occupational Disease

Funding Agency: NIEHS/NIH

Direct Costs Funded: \$228,552

Role: Co-Principal Investigator

Title: NIEHS Summer Environmental Health Sciences Training Program

Funding Agency: NIEHS/NIH

Direct Costs Funded: \$28,725

Role: Mentor

Title: NIDDK Summer Endocrinology Research Training Program

Funding Agency: NIEHS/NIH

Direct Costs Funded: \$28,725

Role: Director

Title: Career Development of Environmental Health Investigators Project

Funding Agency: NIEHS/NIH

Role: Investigator

Title: DHEA: PPAR-Dependent and Independent Mechanisms of Action

Funding Agency: NIH/NIDDK

Role: Project Leader

Title: University of Louisville's Clinical and Translational Science Institute

Funding Agency: Translational Technology and Resources

Direct Costs Funded: \$340,594

Peer-reviewed Publications:

K.Cameron Falkner and **Russell A. Prough**, Regulation of the rat glutathione S-transferase A2 gene by glucocorticoids: Crosstalk through C/EBPs, *Drug Metabolism Reviews*, 39, 371-388 (2007) [PMID: 17786629; PMCID pending].

Amunom, L.J. Stephens, V. Tamasi, D.J. Conklin, A. Bhatnagar, S. Srivastava, M.V. Martin, F.P. Guengerich, and **R.A. Prough**, Cytochromes P450 catalyze oxidation of α,β -unsaturated aldehydes, *Archives of Biochemistry & Biophysics*, 464, 187-96 (2007) [PMID: 17599801; PMCID pending]

K. Kohalmy, V. Tamasi, L. Kobori, E. Sarvary, J.-M. Pascussi, P. Porrogi, D. Rozman, **R.A. Prough**, U.A. Meyer, and K. Monostory,

Dehydroepiandrosterone induces human CYP2B6 through the constitutive androstane receptor, *Drug Metabolism and Disposition*, 35, 495-501 (2007). [PMID: 17591676; PMCID pending].

D. Conklin, **R. Prough** and A. Bhatnagar, Aldehyde Metabolism in the Cardiovascular System *Molecular Biosystems*, 2, 136-150 (2007).
V. Tamasi, S. Webb, T. Geoghegan, E. Vila, and **R. Prough**. PPAR α Regulation by Dehydroepiandrosterone, In: *Proceedings of the 15th International Conference on Cytochromes P450 – Biochemistry, Biophysics and Functional Genomics, Medimond, Bologna, Italy*, pp. 23-29 (2007).

K.C. Falkner, J.T. Ritter, and **R. A. Prough**, Regulation of the rat UDP-glucosyltransferase 1A6 by glucocorticoids involving a cryptic glucocorticoid response element, *Drug Metabolism and Disposition*, 36, 409-17 (2008) [PMID: 18039810; PMCID pending]

V. Tamasi, K.K. Michael Miller, S.L. Ripp, E. Vila, T.E. Geoghegan, and **R.A. Prough**, Phosphorylation of Serine 6, 12, and 21 regulates murine PPAR α action, *Molecular Pharmacology* 73, 968-76 (2008) [PMID: 18079279; PMCID pending].

J. Cai, B.G. Hill, A. Bhatnagar, W.M. Pierce, Jr., and **R.A. Prough**, Bioactivation and Protein Modification Reactions of Unsaturated Aldehydes, In: *Advances in Bioactivation Research* (A. Elfarra, Ed.), Springer Science+Business Media, New York, NY IN PRESS (2008).

S.J. Webb, K.C. Falkner, T.E. Geoghegan, and **R.A. Prough**, Convergence of Multiple Nuclear Receptors and Metabolic Signaling Pathways in Xenobiotic and Nutrient Metabolism, In: *Volume 2, Cellular and Molecular Toxicology* (Ed., Kenneth S. Ramos) of the *2nd Edition of Comprehensive Toxicology* (Ed.-Chief, C.A. McQueen), IN PRESS, Elsevier, Oxford, UK (2009).

