

Your Health

News from the
University of Rochester
Environmental Health
Sciences Center

Winter 2008



The Environment

Deciphering the Enigmatic AhR

Understanding Changes in Immune Function and Cellular Development



Dr. Lawrence's lab is currently focused on three possible effects of AhR activation by environmental contaminants:

- * Deregulation of immune function
- * Environmental influences on immune programming
- * Deregulation of developmental regulation using the mammary gland as a model system

Environmental pollutants can change the way cells in the body function. Many of our Center's researchers are engaged in trying to understand the mechanisms by which this occurs. Some have focused on an intracellular molecule involved in gene expression (a ligand activated transcription factor known as the aryl hydrocarbon receptor (AhR)) which plays an important role in some toxic effects of environmental pollutants. AhR's biological function has eluded researchers for years, but we do know that many pollutants can bind to the receptor, which then turns on genes in the body. In addition to pollutants, many natural compounds bind to AhR. Therefore, we are exposed to molecules that activate AhR daily through ingestion and inhalation.

Dr. B. Paige Lawrence, Associate Professor of Environmental Medicine and of Microbiology and Immunology, heads an immunology lab in EHSC that studies AhR. Her work has shown that AhR may have a complex mediating effect in the body – results have demonstrated possible impacts on immune system function, such as fighting viral infections, on inflammatory responses, and on the proper development of organs. Understanding these effects increases our potential for improving medical treatments. A major focus of Dr. Lawrence's current research is to characterize molecular mechanisms by which pollutants change the immune system's ability to respond to respiratory infections.

Dr. Lawrence's Immunology Lab uses the chemical 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin) to study AhR because dioxin both activates AhR and is difficult for enzymes to break down; persistence allows researchers to study the effects of AhR without increasing pollutant dose. This research also sheds light on how dioxin interacts with the body.

[Continued on page 2](#)



Lawrence Lab, continued from cover

NIEHS Paper of the Month,
October 2008:

B.P. Lawrence, M. Denison, H. Novak, B.A. Vorderstrasse, N. Harrer, W. Neruda, C. Reichel and M. Woisetschläger (2008) Activation of the aryl hydrocarbon receptor is essential for mediating the anti-inflammatory effects of a novel low molecular weight compound. *Blood* 112: 1158 – 1165.

Dr. Lawrence and her colleagues recently published a study in *Blood*, in which they discuss the potential for targeting AhR with anti-inflammatory medications. The paper was awarded “Paper of the Month” from the National Institute of Environmental Health Sciences. Dr. Lawrence had been contacted by scientists at Novartis with a collaboration offer: the pharmaceutical researchers were developing a new treatment and noticed that AhR might be playing a role in the biological process of inflammation reduction. Novartis scientists contacted Dr. Lawrence with a request to carry out a study to determine whether this was true. Dr. Lawrence’s study revealed that the drug decreased inflammation through activation of AhR, which indicates that molecules other than environmental pollutants are able to bind to the receptor. These results have increased the potential for targeting AhR in anti-inflammatory medications that may be able to help treat a number of health conditions.

Environmental Health Sciences Center Faculty Websites

The Community Outreach and Education Core (COEC) is piloting new faculty websites in 2009 that describe the work done here at the Environmental Health Sciences Center in a way that is understandable to community members, health interest groups, clinicians and researchers in other fields. Our goal is to design faculty web pages so that anyone who visits these sites – such as potential graduate students, community members or collaborators – will be able to better understand and appreciate our scientists’ work. Dr. Shaw-Ree Chen, Research Assistant Professor of Environmental Medicine and Assistant Director of the Life Sciences Learning Center, has created simple animations and illustrations to help clarify scientific concepts described in the text. These animations are designed to help non-specialists understand the biological processes the researcher is investigating.

Dr. Paige Lawrence’s website is a prototype for this project. Excerpts from her new web page with samples of the images and animations of her research on AhR are on page 3 of this newsletter. If you would like to see more, please visit:

<http://www.lifesciences.envmed.rochester.edu/test/index.html>. We invite feedback on these sites to inform updating of other EHSC faculty pages.

EHSC Faculty Website Prototype

New faculty web pages will include three main components:

- I. Conventionalized text to describe researchers' work
- II. 2-D animations to help clarify more technical concepts
- III. Rich graphics to illustrate common concepts

Please visit <http://www.lifesciences.envmed.rochester.edu/test/index.html> to view the complete page and watch animations; We invite feedback on these sites to inform updating of other EHSC faculty pages.

In our studies, maternal exposure to dioxins have been found to be toxic to function of her offspring's immune system. These pollutants essentially "reprogram" the fetal immune system, which then develops differently than it would have without exposure to the chemical. Current research aims to determine how the inappropriate activation of AhR during development changes the normal programming of the immune system by changing the expression of genes, with the potential of correlating these findings to human development.

PROJECTS IN THE LAB

The role of dioxin and AhR in immune response

Activation of AhR reduces survival of mice infected with influenza virus



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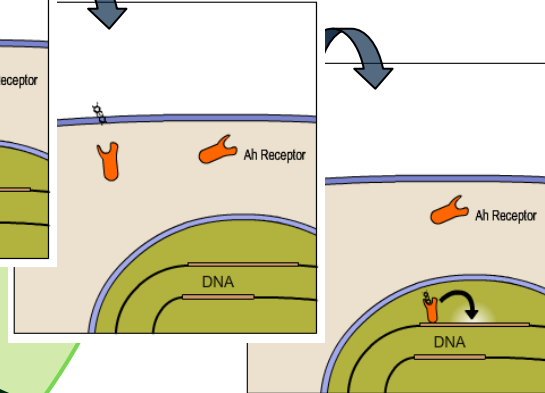
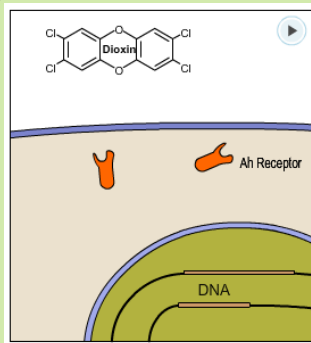


Dendritic cells in the lung are involved in breaking up viruses and presenting parts of those viruses to naive T cells. An activated T cell goes on to develop into Cytotoxic T cells. These cytotoxic T cells can kill off infected cells, thus reducing the number of viruses in the body.

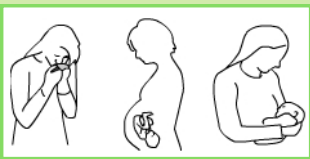
When AhR is inappropriately activated in dendritic cells, our hypothesis is that naive T cells cannot be activated because there are cellular changes brought on by AhR activation that prevent the dendritic cell from activating naive CD8+ T cells.



(For more publications, see below)
2007. Environmental toxicology and mechanisms of antiviral immune responses. *Vital Immunol. Summer 2002*;2(1):242.

Dioxins enter the cell membrane and can bind to the the Ah Receptor. This binding triggers AhR to modify the activation of currently unknown genes.



III



Exposure of pregnant mice to dioxins affected mammary gland differentiation and lactogenesis  ↔  Impact of dioxin in human lactogenesis is unknown

On October 18, the University of Rochester hosted the 21st Rochester Conference on "Critical Issues in Neurotoxicology Research" as part of the 25th International Neurotoxicology Conference to highlight the impacts made by several of these Rochester scientists. The day was dedicated as a *festschrift* to the contributions of Dr. Bernard (Bernie) Weiss in the field of behavioral and developmental neurotoxicology. The *festschrift* is a tradition with German origins to celebrate a researcher's contributions to scientific knowledge over their entire career.

Bernie established his first lab at the Air Force School of Aviation Medicine, and later moved to Johns Hopkins University where he was a leader in the study of drug effects on behavior. In 1965 he was recruited to the University of Rochester's new toxicology program. Bernie published key findings that are still cited over 30 years later, and has gained worldwide recognition for his work in behavioral toxicology. His research has been a driving force in the study of environmental toxicology. For instance, Bernie led a workshop in 1974 to illustrate the variety of methods that might be used in chemical safety evaluations under the Toxic Substances Control Act (TSCA). Because of his involvement, behavior is acknowledged by the TSCA as a valid index of environmental health, on the same scale as cancer and reproductive disorders.

Bernie has been an active researcher in many areas of toxicology, delving into a vast array of subjects such as drugs, metals, food, inhalants, industrial agents and hormones. His interests in such diverse topics led him to many 'firsts.' For instance, Bernie was one of the first scientists to use computers in behavioral studies, and the first to document consistent responses by children to food additives. Students and colleagues alike attest to Bernie's dedication in the field of behavioral toxicology and to his remarkable contributions over the last half century.

Weiss *Festschrift*



We are all gamblers. We scheme to conquer chance, to beguile it into surrender, to lull it into forgiveness. In the end, it subdues us; but without malice, and at times to our advantage. Like other lives, mine has been hostage to random collisions....[this science] is buoyed by new visions, a ferment of disciplines, and energetic young scientists. The best of them have become oblivious to traditional disciplinary boundaries, scorn disciplinary chauvinism and perceive their advanced degrees as hunting licenses. They sniff the eddies of chance for opportunities. Neurotoxicology will continue to be an adventure as long as its practitioners remain adventurers.

Dr. Bernard Weiss,
Neurotoxicology, Issue 2

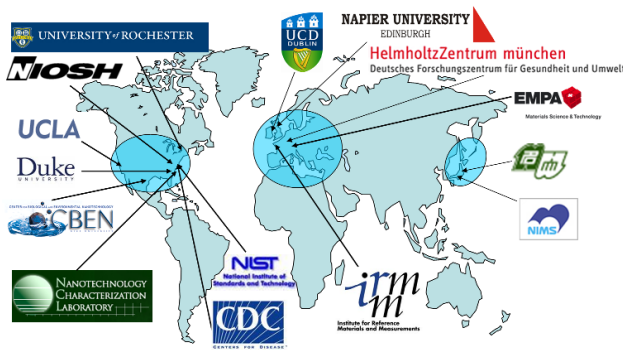
EHSC News

In early September **Dr. Shanna Swan** (PI) and **Dr. Peter Szilagyi** (co-PI) were awarded a contract from the National Institute of Child Health and Human Development (NICHD) to host a National Children's Study (NCS) Location. NCS is the largest long-term study of environmental and genetic effects on children's health in the U.S. The program will follow 100,000 children from before birth to age 21 to better understand how genetic and environmental factors affect children's health and development. Swan and Szilagyi will work with a team from the University of Rochester Medical Center to recruit 1000 women from Monroe County to participate in the NCS.

The International Alliance for NanoEHS Harmonization (IANH) was officially announced on September 9th at the 2008 Nanotox Conference in Zürich, Switzerland; the list of members includes materials scientists and toxicologists from Europe, Japan and the United States involved in nanotoxicological research. The purpose of the Alliance is to promote consistent results in nanomaterials safety testing.

Dr. Günter Oberdörster and **Dr. Alison Elder** (Department of Environmental Medicine) are involved in this new alliance.

Nanotechnology holds great potential to contribute new products that meet society's needs, but many scientists are concerned about the potential health and environmental impacts of these poorly understood particles. Past studies on the effects of these particles have produced contradictory findings, and scientists have concluded that variances in testing protocols, materials and procedures have led to irreproducible (and inconclusive) results. Understanding the need for international collaboration, leading scientists have unified to establish standardized testing procedures. The use of a 'round-robin' approach that centers on common procedures and well-characterized materials will help to identify and correct inconsistencies between laboratories to assure reproducibility in testing outcomes. The Alliance intends to publish the results of this round-robin testing so that the root causes of inconsistencies and corrective strategies can be shared with the larger community. The Alliance is currently funded through the pooled resources of its members, but additional funding is being sought.



Global Partners and Collaborators of the International Alliance for NanoEHS Harmonization. Image from <http://nanoehsalliance.org/sections/PartnersCollaborators>

Dr. Betina Lew and **Dr. B. Paige Lawrence** received a \$15,000 "Seed the Scientist" grant from the Art beCAUSE Breast Cancer Foundation for their project entitled "In utero exposure to TCDD and development of breast cancer." TCDD, a type of dioxin, activates the Aryl hydrocarbon Receptor (AhR), which can lead to breast cancer later in life. Scientists do not fully understand the mechanisms through which activation of AhR affects health, and AhR research has focused on characterizing its role in the body. This particular study looks at the possibility of deregulating the AhR to prevent breast cancer development. The researchers' work is also supported by EHSC pilot project funding.

EHSC News

Dr. Carolyn J. Baglole in the Lung Biology and Disease Program recently published two papers on the effects of tobacco smoke on the lungs. While it is well-known that smoking can lead to significant health impacts, the biological mechanisms by which the lung is affected are not well known. By understanding these mechanisms, scientists may be able to develop more effective treatments for cigarette smoke-related pulmonary diseases such as lung cancer. Dr. Baglole and her colleagues published in the *Journal of Biological Chemistry* their finding that the aryl hydrocarbon receptor (AhR) appears to limit some of the negative inflammatory effects of tobacco smoke through the regulation of the NF- κ B family member RelB. Another paper Dr. Baglole published in the *American Journal of Physiology* discusses how heme oxygenase-1, a cytoprotective enzyme, is controlled in lung cells in response to cigarette smoke. Insight into the regulation of proteins related to cell survival and inflammation may provide new therapeutic targets to treat tobacco-associated lung disease.



Baglole CJ, Maggirwar SB, Gasiewicz TA, Thatcher TH, Phipps RP and Sime PJ. The aryl hydrocarbon receptor attenuates tobacco smoke-induced cyclooxygenase-2 and prostaglandin production in lung fibroblasts through regulation of the NF- κ B family member RelB. *J Biol Chem.* 283 (43): 28944-28957, 2008.

Baglole CJ, Sime PJ, Phipps RP. Cigarette smoke-induced expression of heme oxygenase-1 in human lung fibroblasts is regulated by intracellular glutathione. *Am J Physiol Lung Cell Mol Physiol.* 295: L624-636, 2008.

Dr. Marc Williams, Assistant Professor of Medicine and Environmental Medicine was recently recognized as an international leader in the field of immunology. Dr. Williams was instated to the Faculty of 1000, Section on Innate Immunity. Faculty of 1000 is an expert forum of manuscript review and evaluation to promote significant advances in the biological and medical sciences. Faculty of 1000 members critique and highlight not only the upper echelon of scientific and medical journals, but also high-impact papers from more specialized journals. Dr. Williams has also been appointed to the editorial advisory boards of three additional journals in the fields of development and stem cell biology and immunology: *The Open Stem Cell Journal*; *Trends in Developmental Biology*; *Current Trends in Immunology*. He holds appointments on the editorial boards of *Biomarker Insights* and the *Journal of Receptor, Ligand and Channel Research*, and serves as an Associate Editor on the boards of *Stem Cells and Development* and *The Journal of Innate Immunity*.



If you have questions or comments about this newsletter, please contact Valerie_George@urmc.rochester.edu