



INTERFACE:

GENES AND THE ENVIRONMENT

CENTER FOR ENVIRONMENTAL GENETICS

UNIVERSITY OF CINCINNATI

2009

From the Director, Dr. Shuk-mei Ho

Wow! What a year! The American Recovery and Reinvestment Act (ARRA) certainly added a huge incentive to increase our usual grant submissions. With all of the additional work and angst, in the end, we did very well. CEG members had a great rate of success. We are still compiling a list of funded projects, but CEG-investigator highlights include three Grand Opportunity Grants on the health effects of bisphenol A (Scott Belcher, Shuk-mei Ho), and many supplemental grants in diverse research areas such as worker health and safety training (Carol Rice); air pollution and gene interaction (Grace LeMasters); lupus (Divaker Choubey); colon cancer (Peter Stambrook); UV-induced melanomas (Zalfa Abdel-Malak); hepatocellular carcinogenesis (Sara Kozma); stroke (Joseph Broderick); genetics of metabolic syndrome (Ranjan Deka); pulmonary fibrosis (William Hardie); hematological disorders (George Thomas); allergy (Gurjit Khurana Hershey); lung cancer (Marshall Anderson); cholesterol (James Heubi); genetic analysis of virus/host interactions (Malak Kotb); recruitment (Peter Embi); sodium-potassium ATPase (Jerry Lingrel); and a community based exposure study (Erin Haynes) – all hold great promise in generating new and exciting data for environmental health sciences research or provide resounding services to occupational/public health. We apologize for any awards that we've missed—look for a full report on ARRA funding in the next *Interface*.

The CEG's commitment to address the health needs of Cincinnati's inner-city neighborhoods and Ohioans' unique manufacture-based communities through collaborations with community organizations and government agencies will get an additional lift in 2010. Plans are in-the-works for more community outreach programs and interactions with other communities in our region and other Environmental Centers around the country to boost our efforts. I congratulate you all on your past years hard work whether funded or not, and wish you all the best for this coming New Year – may you all be funded at your first submission.

Epigenetic markers of transplacental exposure to traffic pollution



Dr. Shuk-mei Ho and the CEG support the efforts of young investigators such as Wan-ye Tang.

(PAHs). By exploring DNA methylation profiling of 20 cohort children, over 30 DNA sequences were identified whose methylation status was dependent on the level of maternal PAH exposure. Of these, acyl-CoA synthetase long-chain family member 3 (ACSL3) exhibited the highest concordance between the extent of methylation of its 5'-CGI in umbilical cord white blood cells (UCWBC) and the level of gene expression in matched fetal placental tissues in the initial 20 cohort children. ACSL3 was therefore chosen for further investigation in a larger sample of 56 cohort children. Methylation of the ACSL3 5'-CGI was found to be significantly associated with maternal airborne PAH exposure and with a parental report of asthma symptoms in children prior to age 5. Thus, if validated, methylated ACSL3 5'-CGI in UCWBC DNA may be a surrogate endpoint for transplacental PAH exposure and/or a potential biomarker for environmentally-related asthma. Moreover, this experimental approach may provide a blueprint for future epigenetic epidemiology studies aiming at moving the nation's health priority from curative to personalized, preventive medicine. Drs. **Wan-ye Tang** and **Linda Levin** from University of Cincinnati and Drs. Rachel Miller, Deliang Tang and Julie Herbstman, also contributed to this study, published in the February 16th issue of *PLOS One*. Dr. **Wan-ye Tang** is a new associate member of the Center for Environmental Genetics, and a recent NIEHS K99/R00 awardee.

There is growing concern of prenatal exposure to environmental pollutants and its long lasting effects on later life disease risk. Recently, it has become clear that epigenetic disruption of gene expression plays an equally important role in the development of disease and, arguably, that this process is more susceptible than the gene mutation/deletion to environmental modulation. Under the lead of **Dr. Shuk-mei Ho** and Dr. Frederica P. Perera from Columbia Center for Children's Environmental Health (CCCEH), epigenetic marks etched on the human genome were identified in fetal tissues and serve as early predictive biomarkers for later life diseases, including childhood asthma.

In a longitudinal cohort of ~700 children in New York City, the prevalence of asthma (>25%) is among the highest in the US. This high risk may in part be caused by transplacental exposure to traffic-related **polycyclic aromatic hydrocarbons**

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Role of the CYP1 enzymes in immunosuppression and cancer caused by oral benzo[a]pyrene or dioxin

In the early 1970s **Nebert** postulated the existence of a receptor inside the cell that interacts with certain chemicals in the environment; the existence of this receptor was demonstrated indirectly in 1974, and the gene encoding the receptor was identified in 1992. Chemicals (called “ligands”) that bind to this receptor include *benzo[a]pyrene* (and other moieties found in combustion processes such as cigarette smoke, roofing tar and heavily charcoal-cooked foods) and *dioxin* (2,3,7,8-tetrachlorodibenzo-*p*-dioxin; a byproduct of Agent Orange, an herbicide used to defoliate trees in Vietnam; also a byproduct of burning paper and of industrial processes to make certain soaps).

In the 1970s the Nebert laboratory discovered there were genetic differences among inbred mouse strains, in that some mice show an increased risk of toxicity and cancer when treated with dioxin or benzo[a]pyrene (**BaP**), whereas other mice do not—even though they are exposed to the same dose of BaP. The mice exhibiting increased risk were found to have a “high-affinity” aromatic hydrocarbon receptor (**AHR**), and those displaying low risk have a “poor-affinity” AHR, meaning that—at whatever dose of BaP or dioxin—more of these environmental chemicals bind to the AHR in “highly sensitive high-affinity-AHR” mice and cause an unwanted chain-reaction of events in the cell, when compared to the AHR in “highly resistant poor-affinity-AHR” mice. In 1993 the Nebert laboratory reported that these results can be explained by a small difference in the *Ahr* gene (mutation in the DNA) between the two kinds of mice.

In the earliest minutes following exposure to combustion products, BaP or dioxin, one of many chain-reaction events in the cell is the induction (up-regulation) of enzymes called CYP1A1, CYP1A2 and CYP1B1. These enzymes can transform BaP (as well as other foreign chemicals, plus (usually) unknown compounds that are naturally-occurring in the cell) to *reactive intermediates* responsible for oxidative stress, inflammation and DNA damage (all of which appear to be required for toxicity or cancer to occur). Other chain-reaction events lead to alterations in the cell cycle so that cells divide abnormally more rapidly (called “proliferation”) or die an unusual death (called “programmed cell death,” or “apoptosis”).

Between 1968 and 2000, it had been shown by hundreds of laboratories in innumerable studies (in a test tube, in cell cultures, even skin-painting experiments) that purified mouse or human CYP1A1 or CYP1B1 metabolically activate the inert BaP parent compound to reactive oxygenated intermediates that react with (by binding covalently to) cellular proteins and nucleic acids. Similarly, purified mouse or human CYP1A2 was repeatedly shown to metabolically activate 4-aminobiphenyl (**ABP**), 2-aminofluorene (**AAF**) and two charcoal-cooked meat-derived heterocyclic amine mutagens, 2-amino-3-methylimidazo[4,5-f]quinoline (**IQ**) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (**PhIP**) to reactive oxygenated intermediates that bind covalently with cellular proteins and nucleic acids to cause DNA damage and/or cancer. In fact, ABP is an occupationally hazardous chemical (in manufacturing of tires, for example) regarded as a known human carcinogen.

The dogma was that these three enzymes (CYP1A1, CYP1A2, CYP1B1) were always BAD for you. These enzymes took inert substrates (such as BaP or ABP) and activated them to nasty intermediates that damage DNA and proteins (often leading to cancer); in fact, it was a common question by graduate students after a lecture by Dr. Nebert, anywhere in the country: “If these enzymes are so bad, why would Mother Nature keep them around for 500 million years?” Indeed, if drug companies—when studying a candidate drug—find out that the chemical induces the CYP1 enzymes, the drug is usually shelved due to fear of its causing cancer.

In the Gonzalez lab (Bethesda, MD) in 1995 the mouse *Ahr* gene was ablated (“knocked out”), and in 1999 the mouse *Cyp1b1* gene was ablated. In these knockout mouse lines it was expected that absence of the AHR, or absence of the CYP1B1 enzyme, would protect the mice against undesirable environmental chemicals (dioxin, BaP, dimethylbenzo[a]anthracene, benzene) and this was indeed what was found.

In the Nebert lab in 1996 and 2000, the mouse *Cyp1a2* and *Cyp1a1* genes, respectively, were ablated. ABP was painted on the *Cyp1a2*(-/-) knockout mouse skin, and it was expected this mouse, also, would be protected against ABP-induced toxicity or cancer. Unexpectedly, it was found that the *Cyp1a2*(-/-) mouse was far MORE SENSITIVE to ABP...!! Similar findings occurred with IQ- and PhIP-exposed *Cyp1a2*(-/-) mice and the development of toxicity or cancer. Similarly, when *Cyp1a1*(-/-) mice received oral BaP, it was found that the *Cyp1a1*(-/-) mouse was far MORE SENSITIVE to BaP—in terms of immunosuppression, wasting, and even causing cancer of the small intestine...!!

These findings from the Nebert lab dispel a myth that has been around for more than three decades. Oral BaP-inducible CYP1A1 (in intestine and perhaps liver) is far more beneficial than it is detrimental. For 25 years the Centers for Disease Control and Prevention (CDC; Atlanta) have had a large program to assess the risk of children eating playground dirt containing BaP. Work from the Nebert lab suggests that kids need not worry about eating small amounts of BaP; in fact, it is probably good for them. Similarly, liver CYP1A2, in handling topical ABP, is far more beneficial than it is detrimental.



Daniel W. Nebert, MD,
CEG Associate Director
and Director of the Pilot
Project Program, pro-
duced issues 1 to 32 of the
CEG Interface.

Role of the CYP1 enzymes (continued)

The Nebert lab has also found that *Cyp1a1/1b1(-/-)* double-knockout mice are “rescued” from the undesirable effects of BaP seen in the spleen and bone marrow. These findings are interpreted that “the absence of BaP-inducible CYP1A1 in the intestine and liver leads to a much larger bolus of BaP circulating to the spleen and bone marrow, where CYP1B1 metabolically activates BaP to reactive intermediates that cause toxicity (immunosuppression).” In the absence of CYP1B1 and CYP1A1, metabolic activation of BaP in the spleen and bone marrow does not occur. Therefore, although the total body burden of BaP is about three times higher in *Cyp1a1/1b1(-/-)* mice than in *Cyp1a1(-/-)* mice, the former group shows much less toxicity than the latter group. This is an excellent example of clinical pharmacology: “the total body burden or the rate of clearance of a drug need not reflect the amount of toxicity in a particular tissue or organ.”

These studies (showing that CYP1A1 and CYP1A2 in the intestine are more good than bad, that CYP1B1 in immune cells is more bad than good) are true in the mouse. It is likely that these conclusions can also be made in humans, but (obviously), ethically, one cannot perform studies of such carcinogens in patients or volunteer populations. This is where the Nebert lab’s development of “humanized” mouse lines can be pivotal: by ablating both the *Cyp1a1* and *Cyp1a2* genes in the mouse, and then inserting the human *CYP1A1* and *CYP1A2* genes into that mouse, such a humanized mouse line has been created. These two human enzymes were first proven in 2005 to function normally (in terms of metabolic specificity and regulation) in all eight organs that were examined in the intact mouse.

This humanized mouse line is now commercially available (through The Jackson Laboratories, Bar Harbor, Maine) to all scientists worldwide who wish to carry out “human risk assessment studies” in mice. Any normal compound in the body as well as any dangerous foreign chemical—including dioxin, BaP and about two dozen drugs such as caffeine, Tylenol or the anti-asthma medicine theophylline—that are substrates for CYP1A1 or CYP1A2 (*i.e.* metabolism of these chemicals occurs by way of these enzymes) can be studied in this valuable humanized *bCYP1A1_1A2_Cyp1a1/1a2(-/-)* mouse line. The long-range goal is to assess the function of these human enzymes in the intact mouse, with regard to various environmental diseases including cancer.

—Contributed by Daniel W. Nebert, MD

Novel cytochrome P450 enzymes from fungal systems with high potential for use in oxidation and detoxification of environmental toxicants

Remediation of recalcitrant toxicants, including carcinogens occurring in the environment, is a continuing challenge. CEG researchers are harnessing the capability of Fungi, particularly those involved in wood rotting in nature, to tackle this problem. Fungi are the key players in recycling of the biomass-locked carbon in the environment. The enzymatic machinery evolved in these lower eukaryotic organisms for unlocking the aromatic carbon in the biomass can be harnessed to disrupt similar chemical bonds in synthetic toxic chemicals occurring in the environment.

The laboratory of Jagjit S. Yadav, a CEG member and Associate Professor at the Department of Environmental Health, has been researching this area, with funding from the NIEHS. Overall goals of this

The CEG-supported Genomics and Microarray Core assisted with the custom-designed microarrays. The Bioinformatics Core assisted with microarray data management and interpretation

research are genomic and functional genomic identification and characterization of fungal P450 proteins and development of novel P450 enzyme biocatalysts capable of biodegrading and detoxifying environmentally persistent hazardous chemicals, with a focus on **polycyclic aromatic hydrocarbons (PAHs)** and **endocrine disruptors** such as **nonylphenol**. Wood rotting fungi are the subject of current focus, mainly the white rots such as *Phanerochaete chrysosporium* (Pc) and brown rots such as *Postia placenta*. Genomic and functional genomic efforts by Yadav’s group led to the first genome-wide identification

and characterization of physiological regulation of expression of an extraordinarily diverse repertoire of 150 cytochrome P450 genes in the model white rot fungus *Phanerochaete chrysosporium*, using custom-designed microarrays (BMC Genomics 2005, 6:92; Mol. Genet. Genomics 2005, 274:454-66). Subsequently, subsets of candidate P450 enzymes for oxidation of recalcitrant PAHs and nonylphenol have been identified [Appl. Environ. Microbiol 2009, 75(17):5570-5580].

Lately, the group has unveiled an even larger, more diverse repertoire of P450 genes indicating novel mechanisms of xenobiotic degradation in the brown rot fungus *Postia placenta*, the work published in the Proceedings of the National Academy of Sciences [PNAS 2009, 106(6):1954-1959]. Efforts are continued to understand mechanistic aspects of the identified xenobiotic class-specific P450 enzymes, and development of novel P450 biocatalysts based on engineered microbes and/ or enzymes for pollutant detoxification applications.

—Contributed by Jagjit Yadav, PhD



Bisphenol A Linked to Metabolic Syndrome in Humans

New research from the University of Cincinnati (UC) implicates the primary chemical used to produce hard plastics—**bisphenol A (BPA)**—as a risk factor for the metabolic syndrome and its consequences.

In a laboratory study, using fresh human fat tissues, the UC team found that BPA suppresses a key hormone, adiponectin, which is responsible for regulating insulin sensitivity in the body and puts people at a substantially higher risk for metabolic syndrome. Metabolic syndrome is a combination of risk factors that include lower responsiveness to insulin and higher blood levels of sugar and lipids. According to the American Heart Association, about 25 percent of Americans have metabolic syndrome. Left untreated, the disorder can lead to life-threatening health problems such as coronary artery disease, stroke and type 2 diabetes.

Nira Ben-Jonathan, PhD, and her team are the first to report scientific evidence on the health effects of BPA at environmentally relevant doses equal to “average” human exposure. Previous studies have primarily focused on animal studies and high doses of BPA.

They reported their findings in the journal *Environmental Health Perspectives*. This scientific data came just before a key Federal Drug Administration meeting about the safety of the chemical in consumer products.

“People have serious concerns about the potential health effects of BPA. As the scientific evidence continues to mount against the chemical, it should be given serious attention to minimize future harm,” says Ben-Jonathan, a professor of cancer and cell biology at UC who has studied BPA for more than 10 years.

“Experimenting with human tissue is the closest we can come to testing the effects of BPA in humans. It’s a very exciting breakthrough because epidemiological studies looking at BPA effects on humans are difficult since most people have already been exposed to it,” she adds.

Scientists estimate that over 80 percent of people tested have measurable BPA in their bloodstream. The UC study was designed to mimic a realistic human exposure (between 0.1 and 10 nanomolar) so that a more direct correlation between human exposure and health effects could be drawn. To conduct this study, the UC team collected fresh fat tissue from Cincinnati patients undergoing several types of breast or abdominal surgery. These samples included three types of fat tissue: breast, subcutaneous and visceral (around the organs). Tissue was immediately taken to the laboratory and incubated with different concentrations of BPA or estrogen for six hours to observe how the varied amounts of BPA affected adiponectin levels. The effects of BPA were then compared to those of estradiol, a natural form of human estrogen.

They found that exposing human tissues to BPA levels within the range of common human exposure resulted in suppression of a hormone that protects people from metabolic syndrome.

“These results are especially powerful because we didn’t use a single patient, a single tissue source or a single occurrence,” she adds. “We used different fat tissues from multiple patients and got the same negative response to BPA.”

UC’s Eric Hugo, PhD, Terry Brandebourg, PhD, **Jessica Woo, PhD**, J. Wesley Alexander, MD, and Christ Hospital surgeon Jean Loftus, MD, participated in this study. The study was funded by grants from the National Institute of Environmental Health Sciences.



Nira Ben-Jonathan, PhD, recently received an ARRA supplement to her NIEHS R21 Exposure to Bisphenol A: Inhibition of Adiponectin Release by Human Adipocytes

This project received CEG support from the Director’s Discretionary Funds and a CEG Pilot Project Grant to Dr. Jessica Woo

Articles on page 4, 5, 7 and 8 were contributed by Amanda Harper and the University of Cincinnati Academic Health Center Public Relations & Communications, which also supplied many of the photographs.

CEG now accepting applications for 2010 Pilot Project Program

The CEG provides Pilot Project Program funds to support synergistic, innovative, high-risk/high-reward research with a multidisciplinary foundation plus the use of CEG Facilities and Services Cores. Every year the Center supports research projects that are centered on the gene-environment interaction. This seed money supports new initiatives in basic research, attracts investigators to research in Environmental Health Sciences, and enables our Center members to use the Facilities and Services Cores that would otherwise be unavailable to them. NIEHS-awarded funds are supplemented by \$50,000 per year from the Dean's Office of the College of Medicine.

The CEG has seen a return on investment of over \$18 for each dollar of pilot project grant money awarded.

Applications must be received by Monday, February 8, 2010. Details and instructions are available on the CEG website: <http://www.ch.uc.edu/ceg/> or by contacting Elizabeth Kopras.

Bisphenol A Linked to Chemotherapy Resistance

Exposure to **bisphenol A (BPA)** may reduce the effectiveness of chemotherapy treatments, say University of Cincinnati (UC) scientists. The research study, led by UC's **Nira Ben-Jonathan, PhD**, says that BPA—a man-made chemical found in a number of plastic products, including drinking bottles and the lining of food cans—actually induces a group of proteins that protect cancer cells from the toxic effects of chemotherapy. The findings are reported in the journal *Environmental Health Perspectives*.

Elizabeth LaPensee and Traci Tuttle have been supported by the NIEHS T32 Environmental Carcinogenesis and Mutagenesis—Peter J. Stambrook, PI

“Resistance to chemotherapy is a major problem for cancer patients, especially those with advanced or metastatic disease,” says Ben-Jonathan, a professor of cancer and cell biology at UC who has studied BPA for more than 10 years. “Finding out what contributes to that resistance can give us an idea of what to target in order to make chemotherapy as effective as possible.”

Researchers have suspected that BPA could play a role in cancer because of the chemical's structural similarities to a cancer-promoting compound called **diethylstilbestrol (DES)**.

But Ben-Jonathan's team found that BPA isn't exactly mimicking the action of DES.

“BPA does not increase cancer cell proliferation like DES does,” she says. “It's actually acting by protecting existing cancer cells from dying in response to anti-cancer drugs, making chemotherapy significantly less effective.”

Ben-Jonathan's team studied human breast cancer cells, subjecting them to low levels of BPA consistent with levels found in the blood of human adults. The team found that BPA is acting in cancer cells similar to the way estrogen does—by inducing proteins that protect the cells from chemotherapy agents. Estrogen's protein-inducing action has been previously linked to chemotherapy resistance, but researchers have been unable to explain why such resistance still occurs in certain patients with less estrogen. Ben-Jonathan says her team's research has important implications for this subgroup of patients.

“Patients with less circulating estrogen—post-menopausal women, for example—can also suffer from chemotherapy resistance,” she says. “Linking BPA to this problem gives us one more avenue to explore in terms of preventing chemotherapy resistance.”

“These data,” study authors write, “provide considerable support to the accumulating evidence that BPA is hazardous to human health.”

Coauthors include **Elizabeth LaPensee**, Sejal Fox and **Traci Tuttle**. The study was funded by grants from the National Institutes of Health, the Department of Defense and the Susan G. Komen Breast Cancer Foundation.

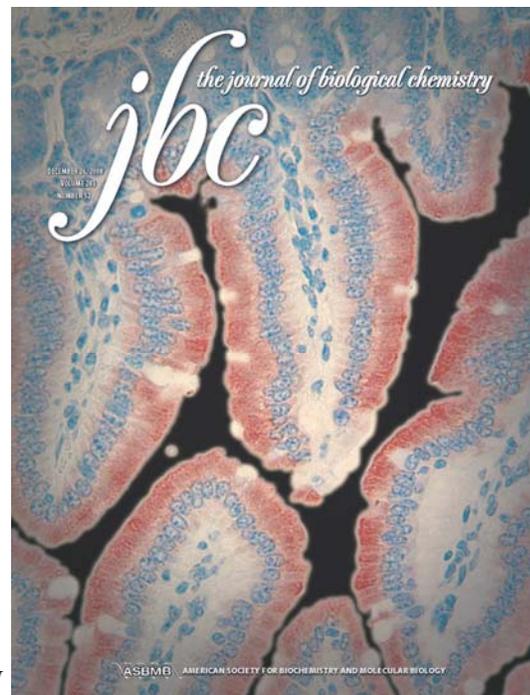
The cancer and cell biology department at UC is part of a joint cancer program involving the UC College of Medicine, Cincinnati Children's Hospital Medical Center and University Hospital. The collaborative initiative brings together interdisciplinary research teams of caring scientists and health professionals to research and develop new cures, while providing a continuum of care for children, adults and families with cancer.

Dr. Marian L. Miller's Work is Art

The "scientific artistic" cover for each of the weekly issues of *Journal of Biological Chemistry* is always a competition, usually among the scientists who are coauthors of articles that appear in that particular issue. For the 26 December 2008 issue, this award-winning cover was designed by **Dr. Marian L. Miller** from the Department of Environmental Health. The picture is an immunohistochemical photograph of duodenum (the segment of intestine just beyond the stomach) stained with an antibody to detect CYP1A1 protein. This picture is relevant to the accompanying invited mini-Review in this issue written by **Professors Daniel W. Nebert** and **Christopher L. Karp**, titled "Endogenous functions of the aryl hydrocarbon receptor (AHR): intersection of cytochrome P450 1 (CYP1)-metabolized eicosanoids and AHR biology".

The duodenum is most appropriate when considering synthesis and degradation of eicosanoids (which can be considered a distinct class of more than 150 "secondary signaling molecules"), because digestion of food elicits a continuous response of chronic pro-inflammatory and inflammation-resolution events, eicosanoid release, and eicosanoid actions. Award-winning scientific artistic covers that have been designed and submitted by Dr. Miller during her entire career have appeared in more than a dozen journals.

Dr. Miller has served as the Assistant Editor of *Interface*, and has supplied many of the logos and photographs throughout the department, including the CEG logo and graphics in this newsletter. She has been a vital collaborator of this Center, as evidenced by her more than thirty co-authored publications that cite the CEG.



Dr. Marian Miller's work has graced the covers of many journals over the course of her career.

Obesity Researcher Honored With Scientific Achievement Award

Randy Seeley, PhD, University of Cincinnati (UC) professor of psychiatry and associate director of the Obesity Research Center, has been given the **Outstanding Scientific Achievement Award** by the **American Diabetes Association (ADA)**.

The award recognizes outstanding scientific achievement in the field of diabetes, "taking into consideration independence of thought and originality," and is being presented this week at the ADA's 69th Annual Scientific Sessions in New Orleans.

Seeley's work is focused on peripheral hormones in the central nervous system that regulate food intake and body weight. In particular, he has focused on the numerous hypothalamic and gastrointestinal peptides and their associated receptors that influence both energy intake and energy expenditure.

He leads a partnership with Cincinnati's Ethicon Endo-Surgery aimed at better understanding of the basic biology behind obesity and finding new solutions for treating obesity and related conditions, including diabetes. The main focus of this research is to gain insight into the hows and whys behind bariatric surgery—such as the Roux-en-Y gastric bypass procedure.

Seeley is the **Donald C. Harrison Endowed Chair** and past winner of the **Lilly Scientific Achievement Award (2003)** and the **Ernst Oppenheimer Award from the Endocrine Society (2008)**. In 2006 he was invited to present at the Nobel Symposium.

**All publications and presentations resulting from CEG support must acknowledge
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Newest CEG member studies diet and cancer

Research has shown vitamin D is an essential part of building healthy bones, but could it also help prevent breast cancer? That's the question the newest CEG member, **Glendon Zinser**, PhD, hopes to answer in a translational science study currently under way. Zinser was awarded a pilot grant from Ride Cincinnati in 2008 to investigate the role of **vitamin D and fat tissue in breast cancer development**, hypothesizing that the active form of the vitamin could help prevent or treat the disease.

Geographical studies have shown that people who live in areas where they are exposed to more sunlight have lower incidence rates of cancer. Sunlight causes the body to produce an active form of vitamin D that promotes good bone health, but Zinser says it also appears to have cancer-preventing characteristics. Studies have shown the active form of vitamin D can be an effective treatment option for breast cancer cells in the laboratory.

"The real challenge is to figure out how to deliver the active form of vitamin D directly to the human breast cancer cells without disrupting the delicate calcium balance in the body," explains Zinser, research assistant professor in the Department of Environmental Health.

"Our findings suggest that adipose (fat) tissue may play an important role in allowing the body to convert the inactive form of vitamin D to the active form that helps control cell growth. If this is proven true in preclinical and cellular models, we will have a promising new approach to breast cancer prevention at our disposal," he adds.

Ride Cincinnati provided pilot grant funding for this study, which allowed Zinser to collect the initial data needed to justify more extensive studies. He has confirmed that adipose tissue is able to convert the inactive form of vitamin D to the active form. The next step is to determine if this active form will alter the growth of normal epithelial cells. If so, he will test whether it can also alter the onset of breast disease.

Zinser was awarded a two year R21 from NCI in September to continue this research.



Join us in welcoming Dr. Glendon Zinser to the Department of Environmental Health.

CEG Director Appointed to National Women's Leadership Program

Shuk-mei Ho, PhD, has been selected to be part of the 2009-2010 **Executive Leadership in Academic Medicine (ELAM)** Program for Women. Ho is one of 53 women leaders from academic health centers across the United States selected to participate in this elite program, offered at the Drexel University College of Medicine in Philadelphia. ELAM is the only national program dedicated to preparing senior female faculty for leadership at academic health centers—which include schools of medicine, dentistry and public health. Ho is the tenth University of Cincinnati (UC) College of Medicine faculty member selected for this program since its inception in 1994.

The year-long ELAM program focuses on exercises to strengthen executive management and strategic leadership initiatives—such as strategic finance, organizational dynamics and personal/professional effectiveness—as applicable to the academic health center environment. It includes three week-long in-residence sessions, plus use of new information technologies for distance learning and community building.

Grinshpun study chosen for David L. Swift Memorial Award

The recent study on respiratory protection against ultrafine particles led by **Dr. Sergey A. Grinshpun**, Professor of Environmental Health, University of Cincinnati, was chosen for the **David L. Swift Memorial Award**. This award is given once a year for an outstanding publication in the field of aerosol science and technology. The winner publication is selected by the AIHA's Aerosol Technology Committee. The ceremony will be held during the AIHCE-2009 in Toronto, Canada. This study was also awarded the John M. White Award for Respiratory Protection Studies, earlier this year.

The co-authors of this study include: Robert Eninger (who received his PhD from the University of Cincinnati Department of Environmental Health in 2008; presently continues his service with the US Air Force); Takeshi Honda (visiting scholar in UC DEH, 2006-2007; presently with Koken Ltd., Tokyo, Japan), **Tiina Reponen** (Professor, UC DEH); and **Roy McKay** (Assistant Professor, UC DEH)

Environmental Health Grants Focus on Lead in Toys, Lead-Safe Remodeling

University of Cincinnati (UC) environmental health researchers have received more than \$700,000 in new grants from the U.S. Department of Housing and Urban Development (HUD) for separate studies aimed at protecting people from the ill health effects of lead. The first study, led by **Scott Clark, PhD**, will investigate whether field portable X-ray fluorescence analyzers can accurately identify painted wood toys that fail to meet the Consumer Product Safety Commission's new limit for lead content in new paint: 90 parts per million, effective in August 2009. The current limit is 600 parts per million. Portable X-ray fluorescence analyzers are a standard tool used by home inspectors to test interior and exterior painted surfaces for lead. The device measures the amount of lead on the surface of a material—known as “lead loading.” Clark's team will use the same technology to estimate the lead content of painted toys in parts per million.

“Recent recalls of hundreds of thousands of toys imported from China have greatly increased public concern about lead-based paint exposure from environmental sources other than the home,” explains Clark, a professor of environmental health at UC. “Parents are rightly worried about whether the toys their children play with are safe and need guidance on how to detect potential problems.”

For this study, Clark and his team will test wooden toys made overseas in countries that do not have effective restrictions on lead-based paint. He says these are the most likely products to slip into the United States undetected by current import screening guidelines. The goal, says Clark, is to develop a more accurate method for directly testing—within a couple of minutes and without having to test the toys in a laboratory—whether toys made outside the United States contain unacceptable levels of lead-based paint. Clark says there is currently no scientifically proven method for such a “direct and virtually instantaneous” determination of the lead content of paint on toys.

The correlation of lead concentration and lead loading for a single layer of paint is only possible if the thickness of the paint is uniform. Clark and his colleagues have obtained over three hundred single layer samples of paint, many containing very high lead levels. The samples came from nearly a dozen countries on three continents.

“We believe by measuring the exact thickness of the paint on these samples, and on painted wood toys, we can use X-ray fluorescence to draw a more direct correlation between lead loading and lead concentration,” explains Clark. “Having this information will allow us to more accurately and rapidly determine if the toys meet U.S. guidelines for lead content.”

Research has shown that early-childhood exposure to lead from environmental sources such as consumer paint causes serious cognitive and physical delays.

“Health risks from toys will most likely be lower than that from lead-based paint hazards in housing, but the risk is still real. Lead poisoning prevention programs still need to address the public's concerns over contaminated toys,” Clark says. “The methods currently available for examining toys have not been adequately evaluated and could very well be inadequate.”

The second study, led by **Judy Jarrell, EdD**, will include a comprehensive review of the Ohio Department of Health's interactive training techniques and online tools for lead-safe work practices in an effort to synergize existing training opportunities and improve effectiveness.

“In the past, there has been limited oversight on lead-safe renovation training practices, so it has been up to the contracting company or independent contractor to ensure that their workers complete the proper training,” explains Jarrell, a professor of environmental health and director of the NIOSH (National Institute of Occupational Safety and Health) Education and Research Center continuing education program and the Great Lakes Regional OSHA (Occupational Safety and Health Administration) Training Institute Education Center.

“We want to offer as many training formats as appropriate to allow more people to learn and retain their knowledge about lead-safe renovation practices,” she adds. “In the end, good training protects both the workers and homeowners who employ them.”

To develop appropriate recommendations for a comprehensive training curriculum, Jarrell's team will partner with other approved training centers in Ohio to observe, compare and evaluate the effectiveness of various training formats, including group seminars, interactive training and online learning modules. Jarrell says all contractors who work on homes built prior to 1978 are required by the State of Ohio to complete lead-safe renovator training. According to the Environmental Protection Agency (EPA), common renovation activities like sanding, cutting, and demolition can create hazardous lead dust and chips by disturbing lead-based paint, which can be harmful to adults and children. Starting in March 2008, the organization began the phasing in of required certification in lead-safe remodeling. Environmental health researchers will seek to create a standard training curriculum that meets both the EPA and HUD's training and certification requirements.

The UC occupational health research team developed the EPA model lead abatement contractor and project designer training courses currently used by the EPA. Bill Menrath, senior research associate, is a key investigator on each of these studies.



Scott Clark, PhD, has been focusing his efforts on exposure pathways and intervention evaluation for environmental lead.

Center for Environmental Genetics Faculty Happenings

— UC Professor Elected in NCRP Scientific Committee —

Dr. Ranajit Chakraborty has been elected as a member of the US National Council on Radiation Protection (NCRP) Scientific Committee. In this capacity, Dr. Chakraborty will help NCRP in a NIOSH-funded project to develop new risk estimates of radiation exposure for disease causation. For the past four years he is also serving the Committee-1 of the International Commission of Radiological Protection (ICRP) as a geneticist, in which his tenure is now extended until 2011. These accolades are recognition of Dr. Chakraborty's pioneering work on modeling genotype dependency of radiation sensitivity, which forms the basis of inter-individual variation of risk of radiation exposures on disease causation.



— Joseph Caruso on editorial board of new journal —



Launched in January 2009, *Metallomics: Integrated biometal science* is a peer-reviewed journal covering the research fields related to metals in biological, clinical and environmental systems. The journal has published six issues in the first year, will increase to 12 issues in 2010, and welcomes submissions of primary articles, communications and reviews.

The scientific field of metallomics is receiving great attention as a new frontier in the investigation of trace elements in biology. In responding to the need for a dedicated subject journal for the emerging research community, RSC Publishing anticipates that *Metallomics* will be a key voice and presence within the field, helping to support and shape its identity.

The RSC is a leading learned society publisher, with a strong reputation for technical innovation and fast publication. Articles published in *Metallomics* will benefit from wide exposure, with free access to all content published during 2009 and 2010 giving maximum visibility to your research. The journal will maintain a strong conference presence, and receive extensive promotion to the wider scientific press.

You can read more about the journal scope at <http://www.rsc.org/Publishing/Journals/MT/About.asp>.

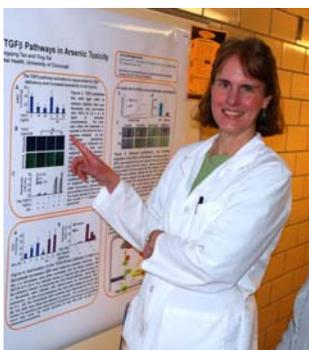


— Litsa Kranias Receives Honorary Doctorate —

Litsa Kranias, PhD, Chair and Professor of Pharmacology and Cell Biophysics, was presented with an honorary doctorate degree from the University of Athens in Greece during a special ceremony held March 5. Kranias presented the highlights of her research during the event. She was formally recognized by the university president and dean of the Medical School at the Aula of the University of Athens. The ceremony was broadcasted on the Greek national news.



— Mary Beth Genter named Editor-in-Chief —



Dr. Mary Beth Genter, Associate Professor in the Department of Environmental Health, has been named the new Editor-in-Chief of the *International Journal of Toxicology*. The International Journal of Toxicology publishes timely, peer-reviewed papers on current topics important to toxicologists. Six bi-monthly issues cover a wide range of topics, including contemporary issues in toxicology, safety assessments, novel approaches to toxicological testing, mechanisms of toxicity, biomarkers, and risk assessment. The Journal also publishes invited reviews on contemporary topics, and features articles based on symposia. In addition, supplemental issues are routinely published on various special topics, including three supplements devoted to contributions from the Cosmetic Review Expert Panel.

Congratulations to the 2009 CEG Next-Generation Biomedical Investigators

Two main mechanisms are used to recruit young researchers to environmental health sciences research. The **Next-Generation Biomedical Investigators (NGBIs)** are junior faculty in the very early stages of their careers. The 2009 Next-Generation Biomedical Investigators have received CEG funds to assist them with salary support, software updates, professional meeting attendance, and use of the ITS core to produce preliminary data.

The 2009 Next-Generation Biomedical Investigators:

Opeolu Adeoye, MD, Assistant Professor, Department of Emergency Medicine

Yuet-Kin (Ricky) Leung, PhD, Research Assistant Professor, Department of Environmental Health.

Alexey Porollo, PhD, Research Assistant Professor, Department of Environmental Health.

Ge Zhang, PhD, Research Assistant Professor, Department of Family Medicine

Guo-Chang Fan, PhD, Research Assistant Professor, Department of Pharmacology and Cell Biophysics

John Reichard, PharmD, PhD, Research Scientist, Department of Environmental Health

Congratulations to the 2009 New Investigator Scholars

The other mechanism for increasing human capital in environmental health sciences research is aimed at clinicians who have already demonstrated a desire to become researchers. Originally entitled the Masters of Science in Clinical Research mechanism, the name has been changed to **New Investigator Scholars** award. Many of the clinicians are enrolled in a PhD program in epidemiology and biostatistics, rather than a master's program, or they are working as post-doctoral fellows post MD. The new name better reflects the nature of this mechanism. The 2009 NIS awardees are:

Christopher Codispoti, MD, Clinical Fellow, Division of Allergy and Immunology

Tolly Epstein, MD, Clinical Fellow, Division of Allergy and Immunology

Nicholas Newman, DO, FAAP, Clinical Fellow, Molecular Epidemiology in Children's Environmental Health, Department of Environmental Health

Haejin Kim, MD, Fellow, Division of Allergy and Immunology

Career Development Core workshop—K awards/career development grants

Join us on Tuesday, January 12, 2010 at 12:00 am in 121 Kettering lab to discuss K awards and other career development grants.

Fernald Medical Monitoring Program lauded for design and outcomes

What is the appropriate remedy for a population of thousands of people exposed unwillingly to potentially dangerous environmental hazards with health effects that can take a long time to appear?

Dr. Susan Pinney and her co-authors present the results of the **Fernald Medical Monitoring Program**, one of the largest medical monitoring programs to conduct health screening as a result of exposure to environmental hazards in the December issue of the *Journal of Occupational and Environmental Medicine*. They show that a comprehensive medical monitoring program (MMP) is a beneficial and appropriate course of action, providing both general and exposure-specific health benefits to balance potential harm that might come to a population as a result of exposure.

The accompanying editorial argues that the current requirement in some states to limit medical monitoring solely to markers or endpoints of the specific exposure is "medically unsound, statistically invalid, and ethically indefensible." Instead, future MMPs should "address all common and correctable risk factors," not just those currently known to be associated with a given exposure. The Fernald MMP is described as a "pioneering example of how such a program can operate and how it should be evaluated."

UC's Robert Wones, MD, Susan M. Pinney, PhD, Jeanette M. Buckholz, MSN, Colleen Deck-Tebbe, PharmD, Ronald Freyberg, MS and Amadeo Pesce, PhD, provided the leadership for the Fernald MMP. The study was funded by the Fernald Settlement Fund and the Center for Environmental Genetics—NIEHS P30-ES06096. The FMMP database and samples are available for research use.