The Center provides infrastructure for existing research and training programs, support for core activities, funding for pilot projects, and unique opportunities for collaborative interaction.

The overall mission of the Environmental Health Sciences Core Center in Molecular Toxicology is to pursue outstanding basic biochemical and chemical research in environmental health and to translate this research to human disease and clinical outcomes. Programs range from basic chemistry to clinical medicine, focusing on important areas where research can improve human health.

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The Center in Molecular Toxicology

The Environmental Health Sciences Core Center in Molecular Toxicology at Vanderbilt University is an interdepartmental program funded by the National Institute of Environmental Health Sciences (NIEHS) since 1967. The Center provides an environment for research efforts by Center Investigators and affiliated researchers in the departments of Biochemistry, Biological Sciences, Chemistry, Medicine, Neurology, Obstetrics and Gynecology, Pathology, Pediatrics, and Pharmacology. Overall goals include 1) understanding phenomena related to toxic effects of environmental agents at the chemical and biochemical levels, 2) applying basic chemical and biochemical knowledge to situations involving human disease processes, and 3) establishing translational approaches to marry basic and clinical research efforts into a cohesive public health program. The 24 Investigators in the Center have international reputations in their fields and are heavily engaged in collaborations with multiple scientists. Investigators are involved in a wide range of basic and clinical research efforts related to the chemical and biological aspects of environmental toxicology, including oxidative damage, enzymatic biotransformation and reactions of electrophiles, DNA damage and genetic instability, maintenance of genomic integrity, and neurotoxicity. The Center is structured to focus resources in critical research areas, including four Facility Cores (Mass Spectrometry, Proteomics, Structural Biology, and Integrative Health Sciences), a Pilot Project Core, a Community Outreach and Engagement Core, and an Administrative Core that coordinates all program activities. The Center also functions to foster interaction through seminar programs, symposia, and affiliated training programs. The Center in Molecular Toxicology maintains a continued commitment to research, training, and community engagement programs that enhance collaborative opportunities in the environmental health sciences and serve to further establish this Center as a valuable resource in public health.

Oxidative Damage occurs in human cells when lipids in the body are bombarded by free radicals, rogue atoms that are highly reactive and destructive to delicate lipid-based cell membranes due to an odd number of electrons. This damage at the cellular level (a process known as lipid peroxidation) figures significantly in aspects of nutrition, various inflammatory diseases, and even cancer. Research involves the study of this process and how the body is able to defend itself against oxidative insult. Studies have led to discoveries about the effectiveness of antioxidants and certain trace elements in the diet.

Enzymatic Biotransformation and Reactions of Electrophiles. Certain proteins known as enzymes are responsible for metabolizing toxins, enabling the body to process harmful chemicals. Research focuses on issues related to metabolism and toxicity of xenobiotic chemicals (synthetic chemicals that do not occur naturally), as well as the role of enzymes in processing endogenous chemicals (chemicals produced by the body itself).

DNA Damage and Genetic Instability. A carcinogen is any damaging chemical (a toxin) or physical agent that causes the DNA within a cell to mutate: the primary step in the chain of events leading to cancer. In a botched attempt at repair, a DNA molecule may reconfigure itself such that normal cells are no longer created from the genetic “blueprint” the DNA provides. Center research is focused on identifying the processes leading to DNA damage and the resulting mutations that may occur.

Maintenance of Genomic Integrity. Researchers are studying the processes of cell damage, cell signaling, and cellular repair. In response to environmental stresses (such as toxic exposure), the way that cells respond dictates the extent of the damage to the organism as a whole. A damaged cell will signal a coordinated chain of events to stop the cell cycle long enough to repair itself and destroy any compromised cells that cannot be repaired (a process known as "apoptosis"). If there are miscues in this signaling process, irregular cells with damaged DNA (i.e., cancer) may be allowed to form.

Neurotoxicity. A number of toxic metals and other substances commonly found in the environment are implicated in adverse neurological health effects. Research efforts focus on the toxicity of metals including mercury, manganese, and uranium and other neurotoxic substances such as polycyclic aromatic hydrocarbons and dithiocarbamates (a class of compounds used widely in industry, medicine, and agriculture).

Center Director

In October 2011, Dr. Michael Aschner became the new Director for the Center in Molecular Toxicology when Dr. F. Peter Guengerich stepped down after having served in this role since 1981. The Center has since moved from the Department of Biochemistry into Dr. Aschner’s home department of Pediatrics. Administrative offices have been secured in the new space in Medical Research Building IV.
The Community Outreach and Engagement Core

The Center has been developing a new Community Outreach and Engagement Core (COEC) with the guidance and input of NIEHS staff and a number of other advisors, both internal and external. Jennifer Dix joined the Center as COEC Program Coordinator in April 2011, and in July 2012 Barbara Clinton (Director of the Vanderbilt Center for Health Services) became a member of the COEC team. These new Center staff members will play a critical role in the continued development of COEC programs and initiatives aimed at interfacing with Middle Tennessee community groups.

Community Forum

The first COEC Community Forum was held on January 16, 2012, 6:30-8:30 PM, at the Vanderbilt University Medical Center 100 Oaks facility. The subject was "Parkinson’s Disease: Environmental Factors and Risk." Speakers included two Center Investigators, Drs. Michael Aschner, Ph.D., and Aaron Bowman, Ph.D., as well as clinician/scientist Dr. Peter Hedera, M.D. Collectively, the three speakers presented information on current research efforts in both basic and clinical areas related to Parkinson’s. There were over 40 individuals in attendance, with a vigorous Q&A session at the end of the presentations. Based on assessment surveys obtained from attendees the event was highly successful and informative. Participants gave suggestions for future events, and topics will be chosen based on their feedback as well as feedback from the first focus group held last year. The next forum will focus on common toxicological myths and misconceptions and will be held in August 2012.

Over 40 attendees participated in the Center’s first Community Forum, “Parkinson’s Disease: Environmental Factors and Risk.”

COEC External Advisory Board

Five individuals from the community were invited to serve on the COEC External Advisory Board:

- **David Borowski**  
  Assistant Director of Environmental Epidemiology, Tennessee Department of Health
- **Terri Crutcher**  
  Assistant Dean, Clinical Community Partnerships and Clinical Director, West End Women’s Health Center
- **Mitzi Fawley**  
  Registered Nurse, Nashville Public School System
- **Stacy Jervis**  
  Registered Nurse, Vanderbilt Children’s Hospital
- **Yvonne Joosten**  
  Executive Director, Vanderbilt Office for Community Engagement and Associate Staff Member, Vine Hill Community Clinic

The next meeting of the COEC Advisory Board is tentatively planned for August 2012.
Pilot Project Awards

Congratulations to the pilot project awardees for 2012-2013:

1) Scott Baldwin, M.D., Professor of Pediatrics/Division of Pediatric Cardiology and Chris Brown, Ph.D., Assistant Professor of Pediatrics/Division of Pediatric Cardiology
\textit{NFATc1, a Potential Mediator of TCDD-induced Developmental Vascular Defects}

2) Swati Biswas, Ph.D.
Research Assistant Professor of Radiation Oncology
\textit{Mechanism of Oxidative Stress-mediated Bone Loss}

3) Erica Carrier, Ph.D., Research Instructor of Pharmacology and John Oates, M.D., Professor of Medicine/Division of Clinical Pharmacology
\textit{Levuglandin Modification of Histones}

4) Sean Davies, Ph.D. **SPECIAL SOLICITATION**
Assistant Professor of Pharmacology
\textit{Bioactive Aldehyde-modified Phosphatidylethanolamines}

5) Diana Neely, Ph.D., Research Assistant Professor of Neurology **SPECIAL SOLICITATION** and Aaron Bowman, Ph.D., Assistant Professor of Neurology
\textit{Translational Model for Neurotoxicological Risk Using Patient-specific Neurons}

6) Kevin Osteen, Ph.D.
Professor of Obstetrics & Gynecology
\textit{Nutritional Prevention of Toxicant-mediated Adverse Pregnancy Outcomes}

7) Qi Zhang, Ph.D.
Assistant Professor of Pharmacology
\textit{Mitigate Neural Excitotoxicity by Controlling the Turnover of Excitatory Amino Acid Transporters}

Pilot projects are preliminary investigations that can be carried out within one year or (at most) two years. The goal of the pilot project program is to enhance the competitiveness of external grant applications by providing resources for Vanderbilt investigators to conduct key preliminary studies. Pilot research projects are designed to develop into independently supported projects.
DNA: From modification to mutation

Our DNA is under continuous attack by physical or chemical agents produced by or introduced into the body. These agents can modify DNA, forming DNA adducts, which if not properly repaired can cause mutations that contribute to deregulated gene expression and cancer. Linlin Zhao, F. Peter Guengerich, the Harry Pearson Broquist Professorship in Biochemistry, and colleagues (laboratories of Martin Egli and Carmelo Rizzo) sought to understand how an unstable DNA adduct (N2,3-ethenoguanine), which is produced by exposure to the occupational carcinogen vinyl chloride, causes mutations. They used a chemical strategy to stabilize the adduct for detailed biochemical, kinetic and structural studies. The results, reported in the journal *Angewandte Chemie*, revealed the miscoding tendencies of this DNA lesion and highlighted the diversity of biological effects that can result from DNA adducts. Structural insights suggested that this adduct may be relevant to vinyl chloride-induced tumors, and its presence in unexposed humans (where it is a product of oxidative stress) may be an issue in disease.

This research was supported in part by grants from the National Institute of Environmental Health Sciences (ES010546, ES010375, ES005355, ES007028, ES000267) of the National Institutes of Health.

Neuronal clues to cholesterol-defect disorder

Smith-Lemli-Opitz syndrome (SLOS) is a developmental disorder caused by mutations in the gene encoding the last enzyme in the cholesterol biosynthetic pathway. The mutations result in reduced levels of cholesterol and accumulation of the precursor 7-DHC, which can be oxidized in free radical-mediated reactions to oxysterols such as DHCEO. Zeljka Korade, Ph.D., Ned Porter, Ph.D., and colleagues explored the consequences of 7-DHC and DHCEO accumulation in the brain tissue of a mouse model for SLOS. They found that cholesterol, 7-DHC and DHCEO have region-specific distributions in the brain, suggesting that the midbrain and cortex are the primary sites of vulnerability. They also showed that an oxysterol mixture is toxic to neurons and that DHCEO alone accelerates differentiation and changes the growth pattern of cortical neurons. The findings, reported in the March issue of *Neurobiology of Disease*, suggest that 7-DHC oxidative metabolites contribute to altered neural development in SLOS. The results imply that using antioxidants to reduce oxidative stress may be a beneficial treatment for SLOS.

This research was supported by grants from the National Institute of Mental Health, the National Institute of Environmental Health Sciences, and the National Institute of Child Health and Human Development of the National Institutes of Health.
**Structural Biology**

The laboratories included in the Structural Biology Facility Core are operated by the Vanderbilt campus-wide program in structural biology. These operate jointly as a Facility Core in the Center and provide access to shared NMR and crystallographic instrumentation. This Core plays a prominent role in the Center, operating to service both routine analytical needs and more complex studies in structural biology.

**Mass Spectrometry**

The objectives of the Mass Spectrometry Facility Core are to provide cost effective, state-of-the-art instrumentation to members of the Center for structural analysis of biological molecules and for qualitative and quantitative assays of xenobiotic agents and metabolites in tissues and physiologic fluids. Skilled personnel support sophisticated instrumentation and techniques in a modern, professionally managed facility and assist investigators in methods development, assay validation, and data interpretation.

**Proteomics**

The goal of the Proteomics Facility Core is to provide analytical proteomics capabilities to investigators in the Center. Proteomics is the study of proteomes, which are the functional complements to genomes consisting of diverse structural and catalytically functional multiprotein machines. Because proteins are principal targets of many chemical and physical agents, proteomics approaches are essential to defining the molecular mechanisms by which environmental agents affect living systems.

**Integrative Health Sciences**

The overall goal of the Integrative Health Sciences Facility Core is to facilitate both patient-oriented and population-based research directed at studies of the etiology, pathogenesis, and prognosis of disease in patient populations, and to integrate this work with the strong basic science programs within the Center in Molecular Toxicology. Core units provide services such as biomarker assays, biostatistical support, study design, and translational resources.
Center Location

The Center in Molecular Toxicology is located on the 11th floor of Medical Research Building IV in the Department of Pediatrics, Division of Pediatric Toxicology, Vanderbilt University Medical Center, Nashville, Tennessee.

Administrative Core

Prof. Michael Aschner
Center Director

Kathryn (Kakie) Mashburn
Center Manager

Wil Comstock
Administrative Assistant

Ellen Rochelle
Systems Administrator

Community Outreach and Engagement Core

Barbara Clinton
COEC Director

Jennifer Dix
COEC Program Coordinator

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(web site under construction!)

Upcoming Events

Community Forum
August 2012, TBA

COEC Advisory Board Meeting
August 2012, TBA

External Seminar Series
Mondays 12:00 PM - 1:00 PM
Beginning September 10, 2012

Open House for Undergraduates
Saturday, October 6, 2012
8:45 AM - 2:45 PM

The Center in Molecular Toxicology is supported by a grant (P30 ES000267) from the National Institute of Environmental Health Sciences, one of the National Institutes of Health.

Page 1 graphic: courtesy of Anne Rayner of the Vanderbilt Medical Arts Group (photos) and the Labs of Richard Caprioli, Walter Chazin, David Cortez, Fred Guengerich, Bill Valentine, and Mike Waterman, Vanderbilt University School of Medicine

Photo by Joe Howell/Vanderbilt