

# G<sub>x</sub>E News

A Newsletter of the

## Center for Environmental Genomics and Integrative Biology

*"An NIH-NIEHS Center of Excellence  
at the University Of Louisville"*

Kenneth S. Ramos, Ph. D., Director

J. Christopher States, Ph. D., Deputy Director

Jeannie Bowman, Center Administrator

*The Center for Environmental Genomics and Integrative Biology focuses on the elucidation of gene, protein and metabolic networks involved in cardiovascular disease, cancer and developmental origins of health and disease, and the role of environmental factors in these disorders.*

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### NIEHS Press

The current issue of *Environmental Factor* highlights activities of NIEHS grantees and intramural events and is available at <http://www.niehs.nih.gov/news/newsletter/index.cfm>. Among the highlights are an NIEHS-funded imaging tool, linkage between systemic DNA damage and intestinal inflammation, and an adaptive pathway that protects against oxidative stress.

## DIRECTOR'S CORNER

I want to thank each of you for your participation in the External Advisory Board review. A respectable audience was present throughout the day and our External Advisory Board members noted it as an excellent demonstration of support of the Center.

The Board was pleased with our responsiveness to the 2008 feedback and they indicated that the Center remains on track for the upcoming renewal. They were particularly impressed with the outcome of the Pilot Projects Program and the Director's Biomarkers Initiative.

It is now time for us to begin to compile data for our first competing renewal due February 1, 2010. The competition is expected to be formidable as NIEHS has decided to reduce the size of the Centers Program leading to increased number of resubmissions from 2007 and 2008. We will likely compete against twelve other Centers for only three awards. So, I urge you to respond to our requests for up-to-date information in a timely and thorough fashion. In November we will be asking for biographical sketches, updated grant information and publications. Career Development and Pilot Project recipients will be asked to provide a complete accounting of their progress and we will highlight several of the projects that have benefited from the services provided by CEGIB facility cores. If we pull together, I am confident that we can put UofL in the forefront of the competition.

Finally, a shortcoming of the membership for the past 2 years that must be corrected is our failure to cite CEGIB in our publications. NIEHS reviews publications for credit to their grant awards, and it is highly negative when there are hundreds of publications among the membership, with only ten acknowledging the Center. So, please add "**P30ES014443**" to your list of credits!

We look forward to a productive year ahead and the submission of a strong competing renewal application. I look forward to your feedback as we prepare for submission.

– Ken Ramos



Ken Ramos



## MEMBER ACCOLADES

Several of our members and their students recently received recognition for their research.

### Students

**Clarisse Muenyi**, also a graduate student in Chris States' laboratory received the Batelle Travel Award to Society of Toxicology for best presentation by a woman or minority student at the Ohio Valley Chapter Society of Toxicology in November for her poster "Augmentation of Cisplatin Cytotoxicity Associated with Altered DNA Damage Response and Cellular Platinum Accumulation".

### Center Members

**Mark Rothstein** published a commentary on [ethical implications of epigenetics research](#) in the April issue of *Nature Reviews Genetics*. This article raises important considerations to be considered regarding the new wave of epigenetics research.



## MEMBER HIGHLIGHT

Irene Litvan is the Raymond Lee Leiby endowed Professor of Parkinson Disease Research at the University of Louisville; Chief of the Division of Movement Disorders; and Director of the University of Louisville National Parkinson Foundation Center of Excellence at the Frazier Rehab Institute. She is an adjunct professor in the Anatomical Sciences and Neurobiology Department and in the Department of Pharmacology and Toxicology. Dr. Litvan came to University of Louisville in 2002 from Bethesda, MD, where she was Chief of the Neuropharmacology Unit at Suburban Hospital and Consultant at the Experimental Therapeutics Branch, NINDS. She was previously a Senior Staff Fellow at the NINDS until 1999. Dr. Litvan has published more than 190 peer-reviewed articles and chapters and is senior editor of 4 books on atypical parkinsonian disorders and dementias. She is an elected member of the American Neurological Association, Fellow of the American Academy of Neurology, and has received multiple awards including the NIH Merit Award. Dr. Litvan is an ad hoc reviewer for many US and European grant agencies and multiple journals and serves on many boards and committees including the Movement Disorders Society International Executive Committee, American Academy of Neurology Movement Disorder Section and World Federation Neurology Research Group on Dementia. She is the President of the local chapter of the Society for Neuroscience. Dr. Litvan's research is funded by multiple mechanisms including the National Institutes of Aging, Society for Progressive Supranuclear Palsy (CurePSP), CEGIB and the Parkinsons Support Center of Kentuckiana.

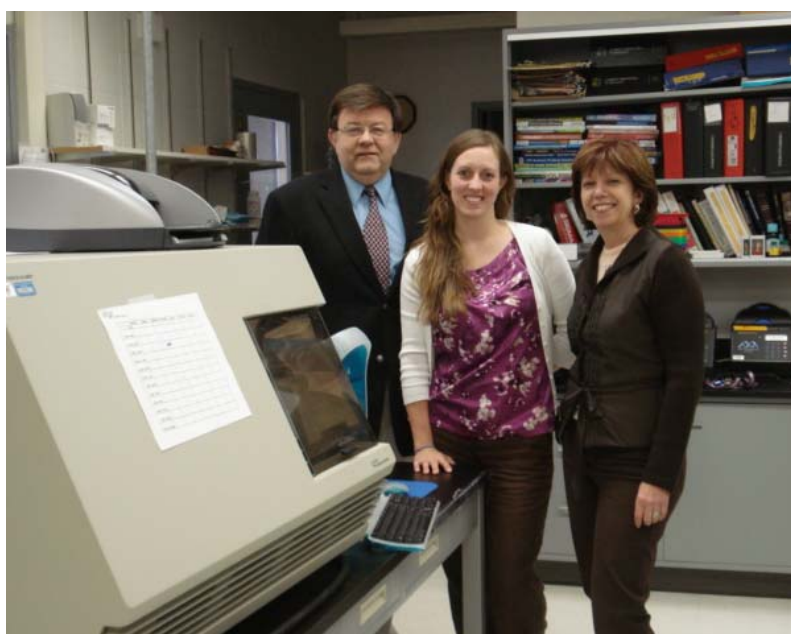


Dr. Irene Litvan

The overall interest of her research group is to better understand the nosology of various parkinsonian and dementia disorders, determination of genetic and environmental risk factors for these diseases and the advancement of symptomatic and biologic therapies. The current focus of her NIH grant is the

determination of genetic and environmental risk factors for PSP, an atypical parkinsonian disorder characterized by deposits of 4-repeat tau protein aggregates in neurons and glia. Dr. Litvan contributed to the body of work that determined the clinical and pathological diagnostic criteria for PSP as well as its association with the H1 haplotype of the

microtubule-associated protein tau (MAPt), which is associated with increased risk for PSP. Her current working hypothesis is that exposure to complex-1 inhibitors increases the risk of developing PSP when combined with genetic



Dr. Litvan with Dr. David Hein (left) and Lisa Potts (center)

abnormalities such as the H1 haplotype. Considering that oxidative stress and mitochondrial impairment is found in PSP pathology, Dr. Litvan is collaborating through a CEGIB grant with Drs. Hein (Pharmacology and Toxicology), Dr. Mathew Farrer (Neurology, Mayo Clinic, Jacksonville) and Lisa Potts, a PhD candidate in the Anatomical Sciences and Neurobiology department, to determine if PSP is associated with genes involved in protection from oxidative stress or responsible for the metabolism/detoxification of toxicants hypothesized to be involved in PSP. They are determining in autopsy-confirmed PSP cases and controls if polymorphisms in: *debrisoquine 4-hydroxylase (CYP2D6)*, *paraoxonase (PON) 1 and 2*, *N-acetyltransferase (NAT) 1 and 2*, *superoxide dismutase (SOD) 1 and 2*, *catalase (CAT)*, *glutathione peroxidase 1 (GPX-1)*, *heme oxygenase (decycling)-1 (HMOX-1)*, *DJ-1 (PARK7)*, *PTEN-induced kinase (PINK1)*, *parkin (PARK2)*, and *saitohin (StH)*, are associated with PSP. Lisa Potts is currently analyzing these data, while Dr. Litvan continues to lead a multicenter study that is recruiting 500 PSP patients and 1000 controls to determine if interactions of genetic and environmental factors are associated with the development of this mysterious and devastating disease. Findings of this study may help us understand the pathogenesis of more common tauopathies such as Alzheimer's disease. Her group is heavily involved in phase II and III symptomatic and neuroprotective clinical trials.



## CAREER DEVELOPMENT

-Russ Prough

In their own words, our past Career Development Awardees describe how they have achieved several hallmarks of their support from CEGIB:

Ming Ouyang, CEGIB Career Development Awardee has an accepted paper addressing computing hierarchical clustering using graphics processing units (GPU). Hierarchical clustering is commonly used in analysis of DNA microarray data.

This paper was accepted by a peer-reviewed conference for oral presentation and publication. The review process involved 3 reviewers to recommend acceptance of the work. The conference, 10th ACIS

International Conference on Software Engineering, Artificial Intelligence, Networking and Parallel/Distributed Computing (SNPD 2009) will be held in Korea. The webpage for the Conference can be located at <http://acis.cps.cmich.edu:8080/SNPD2009/index.html>. Ming is contributing his bioinformatics expertise to a CEGIB Biomarker Pilot Project with Dr. C. William Helm as PI. This project will be identifying plasma microRNA biomarkers for ovarian cancer. The team, which also includes Dr. Robert Jacobs and CEGIB Deputy Director, Chris States, plans to use these biomarkers to uncover potential environmental exposures that may contribute to formation of ovarian cancer.



Dr. Ming Ouyang

David Samuelson, our other CEGIB Career Development Awardee has also had a productive year. He has successfully received a fundable score on an R01 proposal to NIH/NCI to start 1, 2009. He has also recruited a graduate student two postdoctoral fellows. He currently has two undergraduate researchers contributing to work in the He has also submitted grant proposals to American Cancer Society (October) UofL's Center for Environmental Genomics



Dr. David Samuelson: "My desk due to grant writing."

Integrative Biology (November and February). As part of the CEGIB proposal, he has established an active collaboration with Dr. Jun Yan, Associate Professor in the James Graham Brown Cancer Center, to study immune system regulation of rat mammary cancer susceptibility. He has also initiated collaborations with Drs. Russell Prough, Professor, Department of Biochemistry &

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Molecular Biology, and Wolfgang Zacharias, Professor, James Graham Brown Cancer Center, to study genotype-environment interactions and gene-networks involved in breast cancer susceptibility. The goal for this collaboration will be a grant submission in October 2009 or February 2010 after preliminary results are obtained. A book chapter is in revision from David's work. He has also become involved in service activities, including service on a DOD Breast Cancer Research Program grant review panel and membership on the School of Medicine Research Committee, in addition to several teaching assignments in Biochemistry and Molecular Biology courses.



## PILOT PROJECTS PROGRAM

-Doug Darling

The CEGIB Pilot Project Program continues to provide support for developing new research directions in the field of environmental genomics and integrative biology. Pilot Project applications submitted in February were each sent to 3 - 5 outside reviewers and were reviewed by a panel of 8 U. of L. faculty. This committee spent hours discussing the applications. Many thanks to these reviewers for their thoughtful effort. The proposals which received the best overall scores were also the top ranked proposals by the external reviewers. Congratulations are due to Drs. Samuelson and Albert Cunningham, each of whom was awarded a \$30,000 CEGIB Pilot grant. Brief abstracts from their projects are below.

PI: Dr. David Samuelson

Title: Toward Breast Cancer Susceptibility Gene-Networks Genotype-Environment Interaction.

Breast cancer is an environmental disease. The risk of developing it is controlled by mostly uncharacterized genetic, epigenetic, and environmental components. Many identified polymorphisms that associate with breast cancer susceptibility are in non-protein coding DNA. Some associated polymorphisms are hypothesized to affect expression of a gene or genes that act to modify risk to breast cancer. Our research plan is to integrate comparative genetics, environmental toxicology, and gene expression studies to study mechanisms by which common genetic variation and modifier genes alter breast cancer susceptibility. We will investigate common genetic variation that exists naturally in humans and rats, and has been shown to associate with female breast and rat mammary cancer susceptibility in population-based genetic studies. This study is designed to identify potential candidate breast cancer susceptibility gene-networks, genotype-environment interactions, and environmental and endogenous compounds that alter expression of strong candidate breast cancer susceptibility genes.

PI: Dr. Albert Cunningham.

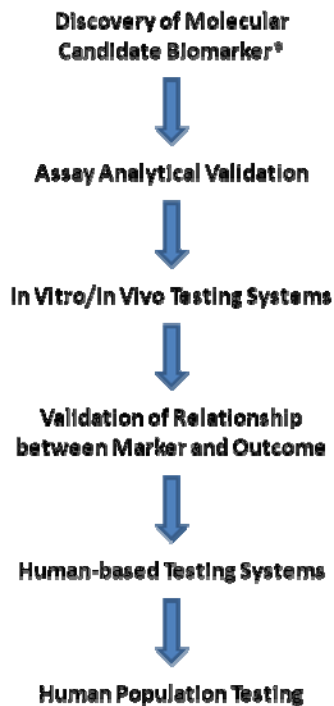
Title: Rational selection of chemical probes to identify breast cancer microRNA biomarkers.

Current breast cancer therapies have clear drawbacks and in the search for new agents, many compounds have been found to have antiestrogenic activity in experimental settings but very few are potential drugs for a multitude of reasons. The overall goal of the proposed research is to identify miRNAs and their gene targets that may provide novel biomarkers for drug development and new insights into the mechanisms involved in human breast tumorigenesis. The specific hypothesis for this project is that mammary carcinogens, aside from mostly being genotoxic, disrupt the normal proteome of breast cells by regulating the expression of microRNAs (miRNA). We plan to identify alterations in miRNA and target gene expression in primary human mammary epithelial cells (HMECs) and ER $\alpha$ -positive MCF-7 human breast cancer cells. Three structurally similar mammary carcinogens will be tested: PhIP, 2-acetylamino-fluorene (2-AAF) and 4-aminobiphenyl (4-ABP). These carcinogens were selected based on results from our computational structure-activity relationship (SAR) model of mammary carcinogens which indicated that they share a common structure(s) that differentiated them from both noncarcinogens and nonmammary carcinogens. Hence, it is our hope that data generated in this study may provide further evidence of a unifying mechanism (e.g., alteration of certain miRNA master gene regulators) for chemically-induced breast cancer.



## DIRECTOR'S BIOMARKER DISCOVERY AWARD

CEGIB unveiled the Director's Biomarker Discovery grants in late 2008. The NIEHS grant that supports CEGIB is focused on enhancing our understanding of environmental diseases. The discovery of biomarkers for environmental diseases can have a strong impact on both the basic understanding of disease and the practical treatment or intervention to ameliorate disease. Therefore, CEGIB has provided the means to accelerate the discovery and development of biomarkers by U.ofL. researchers.



\* Adapted from NCI TOC, version 4/2007

Biomarkers are defined as indicators of exposure, disease susceptibility, diagnosis, or response to therapy or intervention. This includes physiological, cellular or molecular biomarkers. The process of defining and development of biomarkers is summarized in the figure.

Projects were requested in August to identify or develop a biomarker of environmental disease. Each project was required to be designed to move a biomarker through at least 2 steps in the *Stages of Development in Biomarker Translation* figure. Applications were due in November for proposals for \$60,000 for one year. In addition to receiving support from CEGIB, each of these investigators received a match of \$20,000 from the School of Medicine Collaborative Matching Grant Program.

Congratulations are due to the four awardees;

Matthew Cave, MD; Biomarkers for hemangiosarcoma and toxicant associated steatohepatitis (TASH).

C. William Helm, MD; Plasma microRNA biomarkers of ovarian cancer.

Yong Li, PhD; MicroRNAs as Biomarkers for Multiple Myeloma.

Sumanth D. Prabhu, MD; MicroRNA as Biomarkers in Human Heart Failure.

## FACILITY CORE ACTIVITIES

### INTEGRATED HEALTH SCIENCE FACILITY CORE (IHSFC)

The IHSFC continued its activities to support the development and translational application of promising biomarkers. The Core planned and sponsored a symposium "[Translational Biomarkers Symposia / Workshop Discovery-to-Application](#)" that was attended by 104 faculty and staff. The morning session included a stimulating keynote presentation by Dr. Henry Rodriguez, Director of the National Cancer Institute Proteomics program. Dr. Rodriguez provided useful insights into the NCI/NIH vision for biomarker development and application. This was followed by three panel sessions focusing on specific aspects of biomarker development and applications. "The Science: Advancing the Technology of Biomarkers" included university and pharmaceutical researchers providing their perspective on development of new or better biomarkers including pharmaceutical, diagnostic and basic research applications. "Translating the Technology: Research, Clinical Application and Commercialization" included perspectives from the regulatory, intellectual property and commercialization arenas. The final session, "Sources of Funding for Translational Research" provided a discussion of federal small business grants (SBIR and STTR), state sources of funding and matching programs, and private and internal UofL funding sources available for translational research.

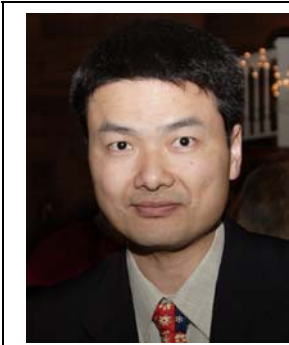
The afternoon consisted of two simultaneous Workshop Sessions for CEGIB Members and Staff that included case studies and discussion of common questions related to Science and Technology Transfer and Funding Sources and Strategies. These two sessions, attended in rotation by all attendees, provided an opportunity for vigorous discussions and questions from the audience. Specific case studies were presented to provide "real world" examples of hurdles and achievements common in translational biomarker research. A number of common themes were identified that will be summarized in a workshop report.

The Core is proceeding with its multi-pronged strategy to assist researchers in moving biomarker applications along the developmental pathway from molecule discovery to human population testing as illustrated in the previous [GxE News](#). Research groups are being invited to give a brief presentation of their biomarker development and application work followed by questions and discussion. The first such session was held in early March and provided a very productive and vigorous discussion ranging from assay and reagent refinement to human population applications to ethical/legal ramifications of the work. The meeting was viewed by all parties as highly successful. A follow-up meeting with the same researchers is planned in 3 to 6 months to discuss progress and hurdles encountered by the team. An invitation will be extended to researchers who attended the symposium/workshop for similar presentations and discussion.

Other activities of the IHSFC include review of CEGIB internal grant submissions that were not funded, to identify areas where intellectual input and resources could be applied to strengthen the proposals, making them more competitive for local and federal funding. We are developing a brochure describing the biomarker program and the supports offered by the Core, for distribution to the CEGIB community and other UofL environmental health researchers. Holly Clark, from the Office of Technology Transfer, has joined the Core and will provide a link to researchers submitting new intellectual property disclosures who will be provided the IHSFC brochure and an invitation to contact Core members to discuss their research.



## NEW GRANTS RECENTLY AWARDED TO CEGIB MEMBERS



**Yong Li**

PI: **Yong Li**  
Title: MicroRNAs Target p53 in Lung Cancer  
Funding Agency: Kentucky Lung Cancer Research  
Project Period: 11/01/08 to 10/31/10  
Project Award: \$150,000

PI: **Wolfgang Zacharias**  
Title: The lysosomal pathway of apoptosis as target for lung cancer therapy  
Funding Agency: Kentucky Lung Cancer Research  
Project Period: 11/01/08 to 10/31/10  
Project Award: \$68,182 direct cost/year



**Wolfgang Zacharias**



**Lori Millner**

PI: Lori Millner; **David W. Hein**, Mentor  
Title: N-acetyltransferase 1 polymorphism and breast cancer risk  
Funding Agency: BC083107 Department of Defense Breast Cancer Research Program  
Project Period: 09/29/2008- 09/28/2011  
Project Award: \$92,442 (total)



**David Hein**