Volume 1 Issue 3

GxE NEWS

Center for Environmental Genomics and Integrative Biology

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

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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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, 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 September 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
Chairman & Professor
Biochemistry

UNIVERSITY OF LOUISVILLE®
SCHOOL OF MEDICINE

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 Assoicated with Altered DNA Damage Response and Cellular Platinum Accumulation".

IvoTeneng received his Ph.D. in Biochemistry and Molecular Biology from the University of Louisville in May 2009. His primary research in the **Ramos** laboratory focused on the regulation of Long Interspersed Nuclear Element-1 (Line 1) in mammalian cells'. Ivo and his family will be moving to Albuquerque, New Mexico where he will begin a career in industry.

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

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.

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:

Dr. Ming Ouyang

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

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 July 1, 2009. He has also recruited a graduate student and two postdoctoral fellows. He currently has two undergraduate researchers contributing to work in the lab. He has also submitted grant proposals to American Cancer Society (October) and UofL's Center for Environmental Genomics and 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 & 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.

MEMBER HIGHLIGHT

When asked how her father influenced her life, Dr. Irene Litvan's eyes glow warmly and her sophisticated demeanor softens perceptibly. It is apparent that Marcos Litvan watched over his daughter's journey from tiny Uruguay on the far southeastern corner of the South American continent to her life today as a neurological researcher at the University of Louisville. Yet, Dr. Litvan tells a story of how her father, a creative industrialist who had a burning desire to be a physician, took his medical books out of their home and stored them at a cousin's house because he was concerned that his love of medicine would unduly influence the important choices his three children would make about their own futures. His effort to create a clear and fertile slate for their minds was not entirely successful, because two of his three children and three of his five grandchildren are doctors. In another story Dr. Litvan speaks of the time her older brother was nearing the completion of his degree in economics and, upon reconsidering his career, thought of changing to medicine. Her father's simple advice: "Finish this one first".

The concept that "whatever you learn - you are going to love it" is a truism left to his children by Mr. Litvan. "The more you learn about something, the more you love it" explains Dr. Litvan. "And that is what I felt about research and about everything that brings emotions into one's life. It is so important that whatever we do, we don't lose our humanity, who we are as human beings, and how we can improve ourselves. There was a time when research was done and people forgot about human beings and I think it is a sad part of the human story."

Dr. Litvan's own story begins when her adventuresome grandparents married in Russia and moved to Argentina in the nineteenth century. They brought furnishings and parts of their old home with them, along with many of the customs of their native Russia. As the family grew, they stayed close and they shared traditional values and an expanded sense of community service that included humanity as a whole. "My family had a lot of important feelings about human beings and freedom. Those values were extremely important to us", she says.

The brain has always fascinated Dr. Litvan; how we learn to talk, how our memory works, how the brain functions. She was undecided between a career in medicine or psychology, so she started both, and in the end, medicine won out. She also speaks five languages: Spanish, English, Italian, Portuguese and Catalon, the language of Barcelona, Spain.

When Dr. Litvan was at the NIH her research interest was in human memory and it gradually expanded to include movement disorders. "I wanted to know, why the failures? I began systematically studying, one by one; am I making the right diagnosis, is the drug getting absorbed, are we giving enough, is it getting in the brain? That brought multiple research areas that have expanded with time."

But, more important to Dr. Litvan was the need for answers that she saw in her patients and their families. As soon as she finished a study, they were asking her about the next one. She sensed how important it was to have hope, to know that someone was trying to find the causes and cures for these diseases. "They didn't have anybody to give them hope and I felt that hope was so important." Dr. Litvan felt that if she would study it, perhaps she could do something about it. She worked on developing criteria for the diagnosis clinically and pathologically. "It is not a question of treating symptoms", she says, "It is a question of curing a disease and there is no other way to cure a disease than to find what causes it. And that is really what this is all about. Trying to understand what are the genes that may be influencing or what are the environmental factors that may lead some person to have the disease verses another one that doesn't get the disease."


Dr. Litvan

"There was a time when research was done and people forgot about human beings and I think it is a sad part of the human story."

That Dr. Litvan has great passion for her work and humanity, is without question though. One needs only to log onto the Litvan Neurological Research Foundation's website and read the tribute to Marcos Litvan to know where this passion came from: "This foundation was created in memoriam of my dad and all those who always fought for advances in medicine, peace and justice without losing their human essence".

Perhaps children do not follow their parent's footsteps. They follow their dreams.

Dr. Litvan's research group wants to better understand the nosology of various parkinsonian and dementia disorders. They are working to determine genetic and environmental risk factors for these diseases and to advance symptomatic and biologic therapies. Her NIH grant focuses on the determination of genetic and environmental risk factors for Progressive Supranuclear Palsy or PSP, an atypical parkinsonian disorder.


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

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 send 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.

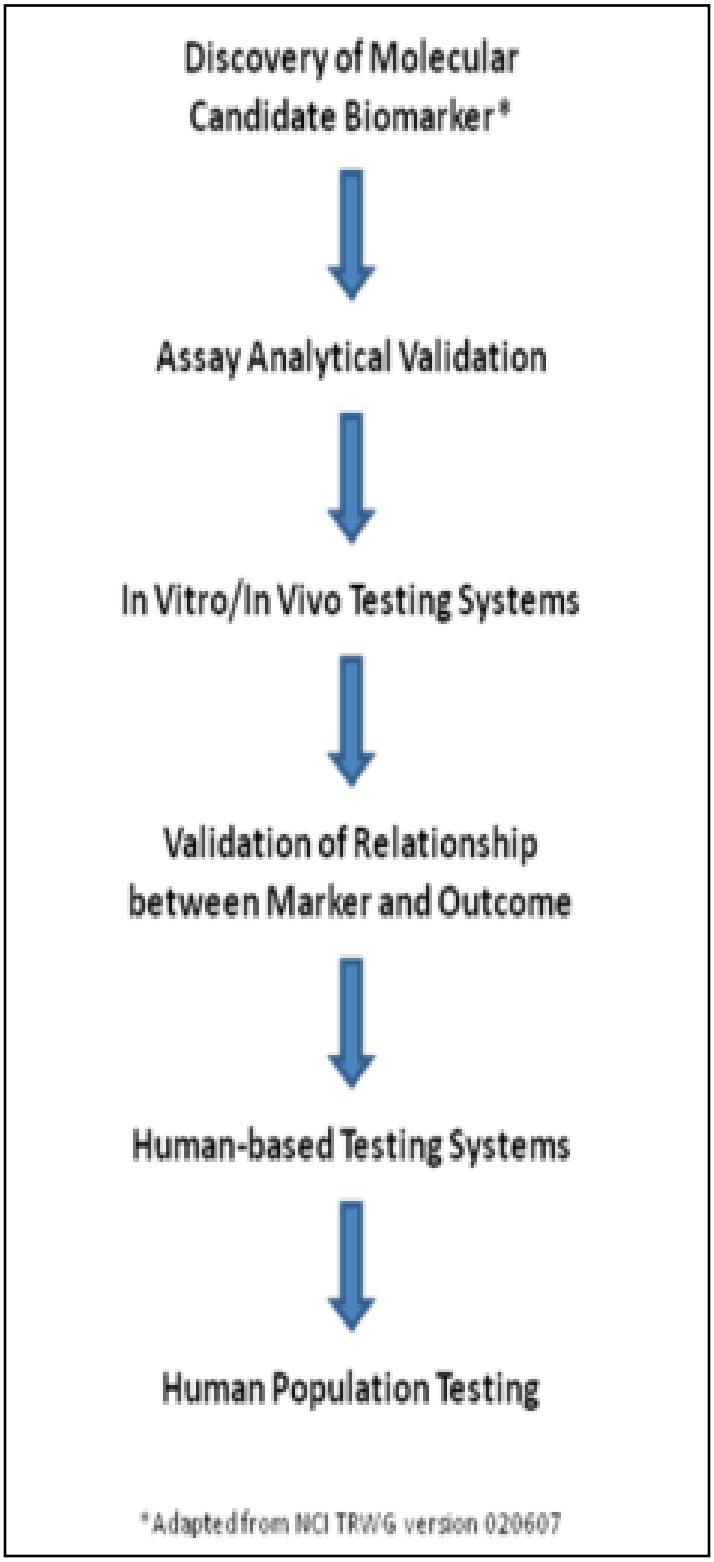
PI: Dr. Albert Cunningham.

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 ERα-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.



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

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FACILITY CORE ACTIVITIES continued

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

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

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)