



**Texas A&M University**

# CERH Highlights

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**Remember to add the CERH Membership Retreat scheduled for October 7th-8th to your Calendar!**

## FROM THE DIRECTOR

by Philip E. Mirkes, Ph.D.

Greetings to all CERH members:

As the new Director of the CERH, I wanted to let you know about some upcoming events. As part of the process leading to the renewal of the CERH grant in 2006, I initiated an evaluation of all the CERH Facility Cores to determine what, if any, changes need to be made to maximize service to CERH investigators. To date we have received responses from 41 of 60 Center members. If you have not yet returned your needs assessment, please do so. Results from this questionnaire will be shared at the upcoming CERH retreat (see below).



Together with the CERH Scientific Advisory Group, I am in the early stages of planning a CERH retreat, the purpose of which is to update CERH members on Center activities and to develop a shared vision for the Center that will carry us into the renewal, now less than 2 years away. The retreat, to be held at Del Lago Resort and Conference Center (near Conroe, TX) will begin mid-afternoon October 7<sup>th</sup> and conclude around 4 p.m. on the 8<sup>th</sup>. Please reserve these dates on your calendar. An agenda is currently being developed and will be emailed to all Center members as soon as it is completed. I know we all have busy schedules; however, I encourage all CERH members to attend this retreat.

Developments from the retreat will begin the process of preparing for our next External Advisory Board Meeting tentatively scheduled for early December. Feedback from this group will then be used to formulate a strategic plan for the next 2 years.

Finally, plans are also underway for the annual CERH symposium to be held in early December, perhaps in conjunction with the External Advisory Board Meeting (details to follow soon). Robb Chapkin has agreed to organize this year's symposium.

During the past 9 months, I have met many of you and I hope to meet all Center members by the end of this year, and I look forward to working with all of you as we move forward toward our competitive renewal in 2006.

**Be sure to cite Center support (P30-ES09106) on all relevant publications.**

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# MOLECULAR MECHANISMS THAT UNDERLIE BIRTH DEFECTS

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Philip E. Mirkes, Ph.D.

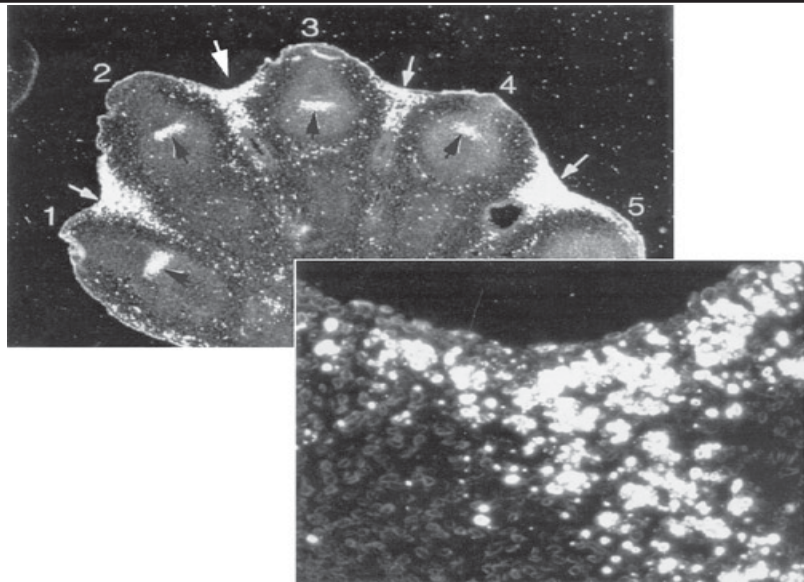
Birth defects caused by exposure to environmental agents are preventable, provided the substances or conditions that disrupt embryo/fetal development are identified. If a pregnant woman avoids exposure to teratogens (environmental agents that cause congenital malformations), she eliminates the associated risks to her fetus' development. Although only a small percentage of environmental agents have been shown to cause birth defects in humans, all new drugs and a limited number of chemicals are tested in animals to assess teratogenic risk. These studies are expensive, and the large number of agents that require testing creates a demand for less expensive methods.

Less expensive tests have been proposed, but they are unlikely to be useful predictors of developmental toxicity until science has a better understanding of how teratogens actually interfere with the process of prenatal development, argues CERH Director Dr. Philip Mirkes. "We don't know enough about the biology of normal development to really know the appropriate questions to be asking of these tests," he says. Most human teratogens have been identified based on population studies that look back in time and correlate prenatal exposures to particular environmental agents with patterns of congenital malformations. For example, on the basis of data from the population prenatally exposed to thalidomide, we know it is a potent human teratogen. Yet, Dr. Mirkes notes, poor understanding of mechanisms of teratogenesis means we still don't know why.

For the past 25 years, Dr. Mirkes has been investigating fundamental cellular processes with the goal of uncovering how the basic mechanisms of development are disrupted by exposure to developmentally toxic environmental agents. Answers to the questions he is asking will provide a foundation for improved methods for screening potentially teratogenic agents. They will also pave the way for strategies that could protect against effects of harmful exposures. "Even though what I do is very basic, I think there is a real possibility that it could strengthen our ability to prevent birth defects. That's the goal—what motivates us to do what we do," says Dr. Mirkes.

Cell death, one of the processes Mirkes is investigating, is an important part of normal development. Cell death is associated with the development of most tissues and organs, he explains. "For example, we don't have webs between our fingers because all those cells die away during development and we end up with digits." A limited amount of cell death is critical to normal development, but the process of teratogenesis involves cell death beyond what is typical. Researchers have found evidence of large amounts of cell death in animals exposed to agents known to cause various tissues to develop abnormally. "The process of cell death is actually controlled by very specific molecules and genes," says Dr. Mirkes. "Over the past several years we've been looking at some of these key genes—how they regulate cell death in the embryo and how they might be affected by agents that cause birth defects."

Currently Dr. Mirkes is focusing on a protein called Bcl-2, known to be a key factor in controlling whether a cell lives or dies. To learn more about the specific role of this gene in response to teratogenic agents, Dr. Mirkes' lab is developing a transgenic mouse model, in which the Bcl-2 gene can be overexpressed. With this model, they can test the hypothesis that an embryo with an excess of this gene and its protein product will be protected from the adverse effects of developmental toxicants.



These dark-field images from one of Mirkes' studies depict a tissue section through a rat embryo limb bud at day 15. The section has been stained using the TUNEL method, which detects DNA fragmentation associated with a form of cell death called apoptosis. The images reveal that apoptosis is associated with this stage of normal limb development. Numbers refer to the individual digits of the developing limb. The white arrows indicate apoptosis occurring in the tissue between the digits. The black arrows point to apoptosis at the interphalangeal spaces, which give rise to joints. The image at the lower right is a greater magnification of the area between digits 2 and 3.

Another major focus of Dr. Mirkes' research is to elucidate the mechanisms that an embryo can call upon to protect itself from agents that can cause cell death and, subsequently, abnormal development. For the past several years, he has been investigating a group of cellular proteins known as heat-shock proteins. Dr. Mirkes has found that these proteins can protect an embryo from the stress related to the very thing that induces their production—elevated maternal body temperature, also called hyperthermia, caused by high fever. In humans, hyperthermia that occurs during embryonic brain development has been linked with malformations of the central nervous system. Dr. Mirkes and his colleagues

have shown that while acute exposures to elevated temperatures result in abnormal development, less severe exposures can actually protect embryos from a subsequent acute exposure. It seems that production of a certain amount of heat-shock proteins induces protection, so-called thermotolerance. Other research suggests that heat-shock proteins may also protect against the effects of other teratogenic agents.

To learn more about how a particular heat-shock protein provides protection, Dr. Mirkes has turned again to a transgenic mouse model. His investigation is focusing on Hsp-70, the gene whose protein has been most clearly implicated in the protection process. Hsp-70 is normally silent. It only “turns on” and begins protein synthesis in response to stress, such as exposure to elevated temperature or other specific teratogenic agents. By studying an animal model in which Hsp-70 can be turned on in a controlled fashion, Dr. Mirkes hopes to answer basic questions that may someday lead to therapeutic interventions for use after a teratogenic exposure. “If, for example, a woman has a very high fever, we might be able to give her a therapeutic agent that very quickly stimulates production of Hsp-70 in her embryo,” suggests Dr. Mirkes.

In addition to his own research, Dr. Mirkes takes an active role in fostering communication among researchers, clinicians and policy-makers. He is a past president of the Teratology Society, a national organization composed of members from four professional areas: clinicians, mostly pediatricians and obstetricians; basic scientists; individuals who work in the pharmaceutical and chemical industries, and members of government agencies. The Teratology Society publishes a tri-partite journal, shares scientific findings at its annual meeting, and, with assembled expertise from its various areas of membership, prepares position papers on issues related to teratogens. Currently, Dr. Mirkes is editor of one of the society's journals, *Birth Defects Research: Clinical and Molecular Teratology*.

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## IMAGE ANALYSIS FACILITY CORE

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Robert C. Burghardt, Ph.D.

The CERH continues to sponsor workshops in optical microscopy offered by the Image Analysis Core. The one-day workshops were initially developed to assist CERH investigators and trainees with basic information needed to optimize use of optical instruments in the core including: 1) Introduction to Optics; 2) Procedures to Achieve Theoretical Limit of Resolution in Microscopy; 3) Theory and Principles of Image Formation; 4) Contrast Methods in the Optical Microscope; and 5) Introduction to Digital Imaging and Image Processing. Recent workshops for CERH investigators and trainees were held on May 28, and July 16, 2004, and another is planned for August 20, 2004. CERH personnel interested in attending the August or future workshops should contact Bob Burghardt ([rburghardt@cvm.tamu.edu](mailto:rburghardt@cvm.tamu.edu)).

These workshops were recently expanded with funding from the American Association of Anatomists (AAA) awarded in December 2003 to Drs. Laurie Jaeger (Reproductive and Developmental Biology Research Core) and Bob Burghardt (Reproductive and Developmental Biology Research Core and Image Analysis Facility Core) in order to contribute to CERH outreach activities directed by Ms. Carmen Sumaya (Outreach Core). The goal is to expose under represented minorities to fundamentals of analytical microscopy as well as to recruit young investigators with interests in environmental health research. The first outreach module was held on January 6, 2004 for a group of five Prairie View A&M graduate students plus professional research staff in the laboratory of Dr. Gary R. Newton of the Agricultural Research Center. One of the participants who has earned a M.S. under Dr. Newton's direction has been recruited to join the laboratory of Dr. Thomas E. Spencer (Reproductive and Developmental Biology Research Core) this fall. The second AAA-CERH jointly sponsored workshop planned for the Fall 2004 is targeting upper level undergraduate graduate students at Texas A&M University at Kingsville, who are interested in pursuing graduate studies.

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## CERH FALL MEMBERSHIP RETREAT - OCTOBER 7TH-8TH

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Don't forget to mark your calendars for this very important special event! We encourage each of you as members to participate, as many items will be discussed at this retreat. Please review your possible and email reserve your space. All for by the CERH so all there!

calendars as soon as Amber Robinson to expenses will be paid you need to do is be

**Be watching your email for more information!**



**This will be an event you won't want to miss!**

**DEL LAGO WATERFRONT CONFERENCE CENTER AND RESORT**

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# PROTEIN TECHNOLOGIES FACILITY CORE

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Larry Dangott, Ph.D.

Larry Dangott and the staff of the Protein Technologies Facility Core have completed the fourth offering of their 5-day training course on 2D gel electrophoresis and Proteomics approaches to protein identification. The course was presented in the PTFC in Biochemistry & Biophysics and was attended by 13 students from throughout TAMU as well as Trinity College in San Antonio. The workshop was subsidized by funding from the CERH and several Center scientists were in attendance.

Originally begun as a three-day workshop two years ago, the PTFC expanded the course to include hands-on training in sample preparation as well as real-time Isoelectric focusing with Immobilized pH gradient strips. The students chose between bacterial cells, tissue culture cells or bovine muscle samples for their experiments. Several students provided their own samples.

The 2D gels worked great. Next, the class learned the Proteomics procedure of in-gel digestion to use in a protein identification experiment using MALDI-TOF mass spectrometry. Drs. Shane Tichy and Bill Russell of the Laboratory led the mass spectrometry portion of the course for Biological Mass Spectrometry in the Department of Chemistry. Shane presented a lecture on the general principles of mass spectrometry and demonstrated to the students how to prepare digested samples for MALDI-TOF analysis using micro-C18 reverse phase pipet tips. After mass spectra were acquired, Bill took the students to the computer lab and led them in exercises to help them learn how to use public database search engines to perform the last step of protein identification using the increasingly popular method of mass spectrometry.



The course will be offered again in the fall. Please keep checking our website ([pcl.tamu.edu](http://pcl.tamu.edu)) for the dates and times. CERH members receive a tuition-waiver for the course (\$350 value). We hope to see you there.

The PTFC has increased its capabilities to identify proteins and characterize post-translational modifications using Electrospray mass spectrometry. After a slow start, the PTFC is bringing protein identification services on-line. This has been made possible by several changes in the PTFC as well as some additions. Most important is the addition of a new staff member, Sabrina Schmidtke, who will spend 50% effort on mass spectrometry-related service work. Sabrina has been on-board since September and has already gotten the machine tuned-up, validated and running samples on a daily basis.

Although we anticipate that the instrumentation will offer greater sensitivity in the future, we currently are soliciting samples of proteins in gels that are stained with Coomassie. We are not accepting samples stained with silver but hope to push our sensitivity lower over the summer months. You should check our website for latest developments ([pcl.tamu.edu](http://pcl.tamu.edu)).

The ThermoFinnegan LCQ DecaXP electrospray ion trap instrument we have purchased with funds from the Life Sciences Task Force and placed in the PTFC specifically to bring these new techniques to TAMU scientists at the service level. The success of this project was due in no small part to the activities and support of the CERH administration and its members. We hope you will avail yourselves to these recent upgrades and improvements and consider ways that the Protein Technologies Facility Core can help contribute to your research program.

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## COMMUNITY OUTREACH AND EDUCATION PROGRAM

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Carmen G. Sumaya, MPH

The Hispanic community in Bryan/College Station includes a population of at least 27,000. Many of these families could be classified as belonging to an under-served population. With a large portion of the Hispanic population being uninsured and thereby with decreased access to health care services, an important avenue to maintain and improve health is through *health education and outreach*. In addition, many Hispanics have a language obstacle, speaking only Spanish or having an insufficient understanding and use of the English language.



The Community Outreach and Education Program (COEP) is now addressing this need in the community through a Promotora Program. *Promotora* is a Spanish term for lay community educator, also known as community worker. A promotora is a trusted member of the community who wants to improve the well being of their community. Promotoras often focus on health and health-related issues.

The COEP with Texas A&M Center for Environmental and Rural Health has established a partnership with health care providers and community-based organizations to develop a promotora program for the Brazos Valley. The organizations involved in the program include the Bryan/College Station Community Health Center (Lori Bui), the Brazos County Health Department (Sara Mendez), *Better Living for Texans* (Dee Dee Matthews), and St. Joseph Regional Health Center (Alyssa Locklear), Bryan Independent School District (Marlyn Milton), and Fiestas Patrias (Alma Villarreal). The

primary goal of the program is to improve the health of the under-served populations in the Brazos Valley through education and facilitating access and utilization of the health care system. The program has the following objectives:

- identify trusted members of the under-served Hispanic populations (followed by other minority, under-served groups) who could serve as promotoras;
- identify and prioritize 4 to 5 concerns in the selected community;
- train 4 to 6 promotora volunteers in different aspects of health promotion and how to facilitate access to medical care;.
- provide specific health education to the targeted, under-served populations of our community;
- assess the effectiveness of the health education efforts; and
- replicate the promotoras program to other communities in the Brazos Valley

This promotora program will develop a bilingual, culturally sensitive, health education curriculum adapted to the needs and characteristics of the community. The projected start date is September 1, 2004. A long-term goal of the COEP is to have this Promotora Program serve as a model for other communities in the Brazos Valley and across Texas.

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## PILOT PROJECTS 2004

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Robert S. Chapkin, Ph.D.

One of the major missions of the CERH is to fund pilot projects that will lead to NIH funding of research related to environmental health issues. Fourteen applications for pilot projects were received for 2004 and six were funded, each investigator was awarded \$25,000 over a 1 year period for these studies.

Dr. Deborah Bell-Pedersen, "A Circadian-Based Approach to Treating Aspergillus"  
Dr. Vincent Cassone, "In Vivo Interactions of Circadian and Toxic Responses"  
Dr. Mee Young Hong, "Dietary Fish Oil Protects Against Oxidative DNA Damage"  
Dr. Gregory A. Johnson, "Effects of Osteopontin on Conceptus Development and Implantation"  
Dr. Weston Porter, "Singleminded-2 in Breast Cancer"  
Dr. Coran Watanabe, "Probing Marine Natural Product Biosynthetic Pathways"

The CERH wishes to thank the members of the Pilot Project Committee for overseeing the external review of each of the applications. The committee members are Drs. Robert Chapkin (chair), Emily Wilson, Yanan Tian, Kirby C. Donnelly, Joseph Sharkey and Alan R. Parrish.

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## NEWS AND NOTES FROM THE CENTER

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Fuller W. Bazer - named Distinguished Professor and received an Honorary Doctorate from the University of Guelph. He will also receive the Carl G. Hartman Award from the Society for the Study of Reproduction in August at the annual meeting in Vancouver, BC.



Thomas E. Spencer - will receive the New Investigator Award from the Society for the Study of Reproduction in August. Was elected Vice Chair of the Gordon Research Conference on Reproductive Tract Biology for 2006 and will serve as Chair in 2008. Had a paper published in May in PNAS.



Dr. Joe Sharkey was named editor of the Journal of Nutrition for the Elderly. This highly regarded professional journal is focused on the growing elderly population from the standpoint of nutrition-the single most important environmental determinant of health. The quarterly journal, now headquartered in the Department of Social and Behavioral Health at SRPH, covers all essential aspects of nutrition, such as the clinical correlation between the pathophysiology of diseases and the role of nutrition, the psychosocial aspects of eating, and client education suggestions. The journal has recently been selected for inclusion in Index Medicus/MEDLINE.

**Be sure to check the weekly email announcements from the Director for current information on events of interest to CERH Investigators. Send items to be included in upcoming newsletters to [parrish@medicine.tamu.edu](mailto:parrish@medicine.tamu.edu)**

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