MIT CEHS NEWSLETTER

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Massachusetts Institute of Technology
CENTER FOR ENVIRONMENTAL HEALTH SCIENCES

Spring 2008

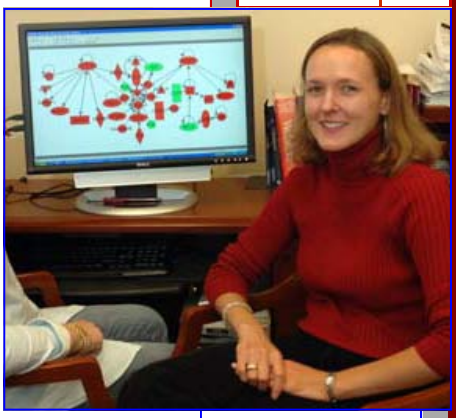
Taking on Global Health Issues: CEHS and Thailand Researchers Identify the Genome-wide Impact of Prenatal Arsenic Exposure in Newborns

Long term exposure to arsenic-contaminated drinking water is linked to the development of many types of cancer. As a result, the World Health Organization (WHO) has established a guideline of an arsenic level of 10 parts per billion (ppb) in drinking water. Even with this limit in place, millions of people are experiencing chronic arsenic poisoning around the world (including in the United States). In spite of this global crisis, little research has been done to examine the impact of this environmental contaminant on one of the most vulnerable populations, the unborn. Researchers from the MIT Center for Environmental Health Sciences (CEHS) and the Chulabhorn Research Institute (CRI) in Thailand have studied the effects of prenatal arsenic exposure on gene expression in the newborn. The babies of the study were born to pregnant women in Thailand who were exposed to varying levels of arsenic.

The research was led by Mathuros Ruchirawat, Director of the Lab. of Environmental Toxicology of the CRI in Thailand, and Leona D. Samson, Director of MIT's CEHS and the American Cancer Society Research Professor in the Departments of Biological Engineering and Biology at MIT. The first author of the study was Rebecca C. Fry, a research scientist at CEHS. Co-authors included Panida Navasumrit of the CRI and Chandni Valiathan, graduate student at MIT's Computational and Systems Biology Initiative. Together the CEHS/CRI team focused on the Ron Pibul district of Thailand. The groundwater in Ron Pibul is contaminated with arsenic resulting from tin mining activities that occurred from the 1960s to the 1980s. The arsenic levels in Ron Pibul are up to 50 times the WHO limit. To assess arsenic exposure, the CRI team took blood and fingernail clippings from 32 newborns and their mothers in the region.

In this study, the researchers applied various genomics tools to the data obtained from samples from the newborn population. The technologies applied in this study include transcriptional profiling, machine learning-based two-class prediction algorithms, and computational pathway mapping. This study is the first to use these approaches to distinguish between exposed and unexposed individuals in the general population. Blood from the babies born to arsenic unexposed and exposed mothers (based on WHO limits) was used for global gene expression profiling and molecular pathway analysis. RNA was extracted from the cord blood of the babies and hybridized onto the ~55,000 feature Affymetrix full genome arrays in the Genomics and Bioinformatics Facilities Core of CEHS. The gene expression data were further queried to identify differences in gene expression levels between babies born to mothers unexposed or exposed to arsenic.

One of the aims of the study was to establish the biological impact of prenatal arsenic exposure. To identify genes that were turned on or turned off as a result of prenatal arsenic exposure, the researchers divided the newborn population into two groups (e.g. arsenic unexposed or exposed). Using classic approaches for differential expression testing, the authors found that the genome-wide impact of prenatal exposure to arsenic is remarkable; there is a massive reprogramming of gene expression in the newborn with almost ~450 genes showing altered levels of expression in response to prenatal arsenic exposure. The researchers also identified that many of these genes are linked to a systemic inflammatory response and to cancer progression. Importantly, the research also shows that the expression level of just 11 of the identified genes could be used to classify which newborns had been exposed to arsenic. These 11 genes were identified using two-class prediction across the population of the study.



Rebecca Fry, Ph.D.
Director of CEHS Genomics and Bioinformatics Facilities Core, MIT

First, the researchers established a subset of newborns to serve as a "training population" composed of two classes (e.g. newborns born to mothers unexposed or exposed to arsenic). Those genes with expression that was significantly associated with arsenic exposure were identified from the training population. The identified genes were then used to "predict" or classify the samples of the newborn test population as having come from arsenic unexposed or exposed mothers. The prediction was carried out in a blinded fashion, where the analyst had no knowledge of the exposure levels of the babies in the test population. The researchers show that gene expression can be used as a classifier of environmental exposure in a population. Furthermore, the researchers managed to reduce the total number of genes from 170 (which predicted with 79% accuracy) to the subset of just 11 genes (predicting with 83% accu-

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IN THIS ISSUE

UPCOMING EVENTS

April 3, 2008
Samuel Wilson presents the Robert S. Harris Lecture

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SAVE THE DATE:
May 22, 2008
CEHS Annual Poster Session

AWARDS AND HONORS

Leona D. Samson Named AAAS Fellow

Professor **Leona D. Samson**, the American Cancer Society Research Professor, was cited for "distinguished contributions to cancer prevention and treatment, particularly for elucidating ways in which cells, tissues and animals respond to carcinogenic and chemotherapeutic agents." Samson is also a professor of toxicology and biological engineering in the Department of Biological Engineering, and is Director of the Center for Environmental Health Sciences.

Steven R. Tannenbaum Wins AACR Chemistry

Steven R. Tannenbaum, Professor of Toxicology, Biological Engineering Department; and Professor of Chemistry at the Massachusetts Institute of Technology, is the recipient of the Second Annual AACR-CICR Award for Outstanding Achievement in Chemistry in Cancer Research. The award was established in 2007 by the AACR's Chemistry in Cancer Research Working Group, through the support of GlaxoSmithKline, and honors novel and significant chemistry research which has led to important contributions to the field of cancer research. Professor Tannenbaum's study of chemistry as related to cancer has advanced our knowledge of chemical carcinogenesis, the molecular epidemiology of cancer, and more recently, anti-cancer drug development and evaluation.

Douglas Lauffenburger Wins '07 Galletti Award

Professor **Douglas Lauffenburger**, Head of the Department of Biological Engineering, has won the 2007 Pierre Galletti Award from the American Institute for Medical and Biological Engineering. The Galletti award, AIMBE's highest honor, recognizes an individual's "contributions to public awareness of medical and biological engineering, and to the promotion of the national interest in science, engineering and education." Professor Lauffenburger was cited "for training a generation of bio-engineering faculty, establishing an innovative biological engineering program at MIT, writing a seminal text on receptors and exemplary service to bioengineering societies." Professor Lauffenburger received the award in late February at the President's Dinner at the National Academy of Science.

James Fox Named President-Elect of AAVMC

Professor **James Fox**, Director of the Division of Comparative Medicine and Professor in the Department of Biological Engineering at the Massachusetts Institute of Technology, was named president-elect. of The Association of American Veterinary Colleges (AAVMC). Dr. Fox is a diplomat and a past president of the American College of Laboratory Animal Medicine and past chairman of the NIH/NCRR Comparative Medicine Study Section. Dr. Fox was recently elected to the Institute of Medicine of the National Academy of Sciences, and is a member of ILAR Council of the National Academy of Sciences.

BIOANALYTICAL FACILITIES CORE

Are you troubled by a molecule that you need to quantify in a cell or tissue? Then you should discuss your problem with the Directors of the CEHS Bioanalytical Facilities Core: Pete Wishnok, Koli Taghizadeh and Paul Skipper. This Facilities Core provides CEHS members with state-of-the-art equipment, technologies and expertise for analysis of virtually any type of biological molecule, from individual damage products or physiological chemicals to systems-level analyses such as proteomics and metabolomics. The Bioanalytical Facilities Core operates at three levels: as a service lab for analysis of your samples; as a training facility for supervised analyses; or as facility for fully trained users. The range of equipment includes more than a dozen different mass spectrometers of all types (GC/MS, LC/MS. LC/MS-MS, QTOF, ESI-TOF, MALDI-TOF, AMS) and chromatographic systems.

Several recent acquisitions have enhanced the capabilities of the Bioanalytical Facilities Core:

- ~ Agilent Chip-Cube: this microfluidic chromatography system interfaces with several mass spectrometers to greatly improve the sensitivity and throughput of chromatography runs, (e.g., 30 minute reversed phase separation reduced to 5 minutes).
- ~ Two new Agilent triple quadruple mass spectrometer systems that provide the highest sensitivity for quantitative mass spectrometry of small molecules, lipids, proteins, carbohydrates and nucleic acids.
- ~ A new Agilent quadruple time-of-flight instrument that combines high mass-accuracy (nearly exact mass for small molecules) with the sensitivity of tandem mass spectrometry.
- ~ An expanded collection of software packages that includes internet-based open-source database-searching packages such as X!Tandem and X!Hunter, in-house developed data-conversion routines, and an in-house license for the software package GeneSpringMS, which will notably enhance the ability to handle complex MS/MS data sets for biomarker discovery or for new metabolomics studies.

Core staff continue to develop new 'omic technologies and expand the application of these technologies more broadly to accommodate diverse Center research activities. CEHS investigators are encouraged to contact Dr. Pete Wishnok (wishnok@mit.edu) or Dr. Koli Taghizadeh (kolit@mit.edu) to discuss their research project and the ways in which these valuable services and tools can enhance their research.

CEHS NEWS

CEHS 2007 Poster Session

The CEHS Poster Session, a tradition started in 2004 continues to draw interest from a wide range of CEHS affiliated member labs. This year the poster session was held in May and there were approximately 53 posters presented from several different disciplines. It is the goal of the Center to bring together CEHS members/ affiliates labs to highlight their ongoing research projects as well as providing an opportunity for interaction with others and possibly leading to future collaborative, multidisciplinary approaches to research in the area of environmental health science.

This year the Center offered prizes to poster participants which were selected by our secret panel of judges.

CEHS 2007 Poster Session Prize winners for the Graduate Student Awards are:

1st Place (3 way tie):
Paul Huang from the White Lab
Alexandria V. Sams from the Griffith Lab, and
Dominika Wiktor-Brown from the Engelward Lab.
**Prize - $500 cash award.*
2nd Place: Lauren Frick from the Essigmann Lab.
**Prize - $100 cash award.*
3rd Place: Marcos from the Stocker Lab.
**Prize: - CEHS T-Shirt and Coffee Mug.*

CEHS 2007 Poster Session Prize winners for the Postdoc Awards are:

1st Place: Michelle V. Williams from the Tannenbaum Lab.
**Prize - $500 cash award.*
2nd Place: Shivashankar Kalinga from the Dedon Lab.
**Prize - $100 cash award.*
3rd Place: Diana Borenshtein from the Schauer Lab.
**Prize: - CEHS T-Shirt and Coffee Mug.*

1st and 2nd prizes were made possible by the Myriam Marcelle Znaty Fund.

2007-2008 Pilot Projects Awarded

CEHS allocates a significant portion of its NIEHS ES002109 funding to support pilot projects that: provide initial support for investigators to establish new lines of research in environmental health; allow exploration of innovative new directions representing a significant departure from ongoing research for established investigators in environmental health sciences; and stimulate investigators from other fields to apply their expertise to environmental health research.

Current award recipients and their project titles are:

- Sangeeta Bhatia, Associate Professor, Division of Health Sciences and Technology, “Microscale Engineered Liver Tissues for Evaluating Chronic Toxicity of Environmental Toxicants”
- Bevin Engelward, Associate Professor, Department of Biological Engineering, "Development of a High-Throughput DNA Damage Sensor for Environmental Health Studies"
- Jongyoon Han, Associate Professor, Department of Electrical Engineering and Computer Science, "Monitoring Low-Abundance Enzyme Activity by Preconcentration and Reaction in Micro/Nanofluidic Device"
- Douglas Lauffenburger, Department Head, Department of Biological Engineering, “Systems Biology Analysis of Nuclear and Membrane-Initiated Signaling by Endocrine Disrupting Chemicals”
- Lisiane Meira, Research Scientist, Center for Environmental Health Sciences "A Clinical Study of a Base Excision-Repair Activity, Genetic Polymorhisms, and Chronic Inflammation"

WELCOME

We are delighted to announce the new Center Members:

Sangeeta Bhatia, Associate Professor, HST/EECS

Ernest Fraenkel, Assistant Professor, BE

Jongyoon (Jay) Han, Associate Professor, EECS/BE

Scott Manalis, Associate Professor, BE/MechE

Jacquin Niles, Assistant Professor, BE

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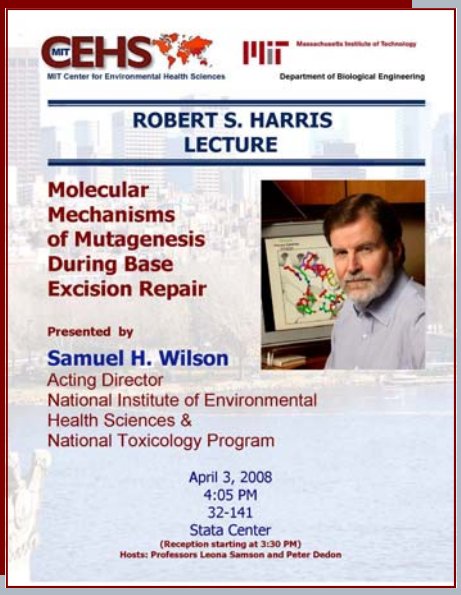
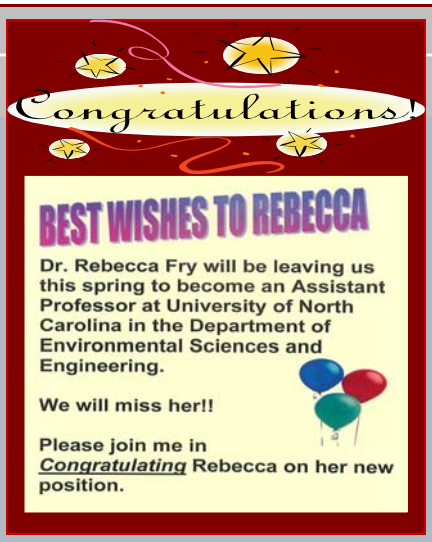
CEHS NEWS (CONTINUED)





COVER ART!

Diana Borenshtein, Prashant R. Nambiar, Elizabeth B. Groff, **James G. Fox**, and **David B. Schauer**.

Development of Fatal Colitis in FVB Mice Infected with *Citrobacter rodentium.*

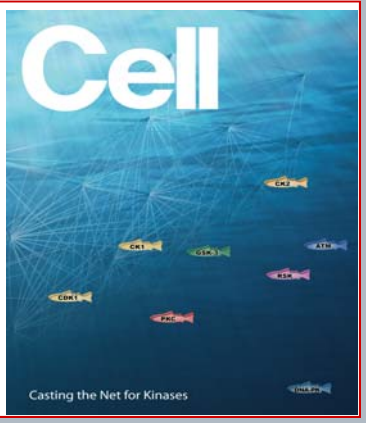
Infection and Immunity, July 2007, p. 3271-3281, Vol. 75, No. 7.

COVER ART!

Rune Linding, Lars Juhl Jensen, Gerard J. Ostheimer, Marcel A.T.M. van Vugt, Claus Jorgensen, Ioana M. Miron, Francesca Diella, Karen Colwill, Lorne Taylor, Kelly Elder, Pavel Metalnikov, Vivian Nguyen, Adrian Pasculescu, Jing Jin, Jin Gyoon Park, **Leona D. Samson**, James R. Woodgett, Robert B. Russell, Peer Bork, **Michael B. Yaffe**, et al.

Systematic Discovery of In Vivo Phosphorylation Networks.

Cell, Volume 129, Issue 7, 29 June 2007, Pages 1415-1426.



COVER ART!

VOL. 21, ISSUE 01 JANUARY 21, 2008 COVER

In celebration of its 20th anniversary, *CRT* invited all communicating authors who have published in the journal since its inception to contribute a photo.

Several CEHS members are featured on this journal cover, they are: **John Essigmann, Pete Dedon, Steve Tannenbaum, Gerald Wogan**, and **Leona Samson.**

Continued from page 1

racy) by varying the exposure levels of the training population. These genes may have the potential to be used as biomarkers of prenatal arsenic exposure in human populations.

Future research will include follow-up studies in different locations and with larger groups of subjects to confirm the potential of the 11 biomarker genes as a reliable indicator of prenatal arsenic exposure. In addition, the researchers are interested in identifying whether or not the gene expression changes will persist as these babies (now toddlers) get older. The study was published in the November issue of PLoS Genetics and received both National and International press coverage. Among others, the findings of the study were featured in the Boston Globe, the Washington Post, *Science*NOW Daily News and the Environmental Factor News Release of the National Institutes of Environmental Health Sciences (NIEHS). This study is an example of the CEHS's efforts to promote collaborative interdisciplinary research into global environmental health issues, specifically in the developing world. This research was funded by the NIEHS and the CRI.

The full reference for the manuscript is:
Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, Bhattacharya S, Kandjanapa K, Soontararuks S, Nookabkaew S, Mahidol C, Ruchirawat M, Samson LD. kappaB Signaling in Infants Born to Arsenic-Exposed Mothers. PLoS Genet. 2007 Nov 23;3(11):e207