MIT CEHS NEWSLETTER

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Massachusetts Institute of Technology
CENTER FOR ENVIRONMENTAL HEALTH SCIENCES

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CHASING COMETS – Engineers and Toxicologists working together

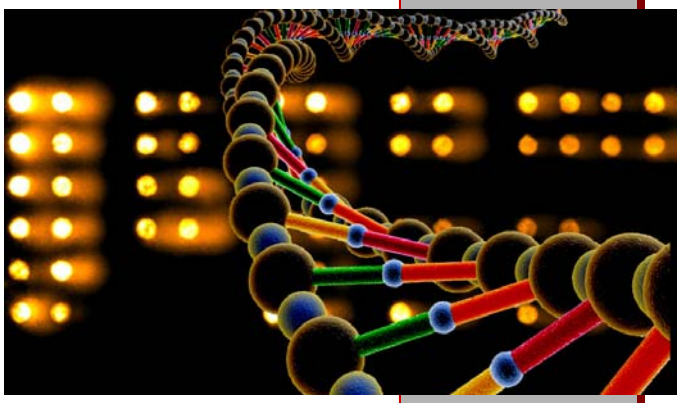
DNA damage promotes cancer, aging and heritable diseases. Fortunately, most of us have robust DNA repair systems that keep our sequences intact, but some of us are better at repairing our DNA than others. Differences in repair capacity predict both cancer susceptibility, and, since most cancer chemotherapeutics are DNA damaging agents, the efficacy of chemotherapeutics. Furthermore, increased knowledge about DNA damage and repair can be pivotal for environmental health decisions, since increased levels of DNA damage in people's cells can reveal environmental genotoxic agents, and thus promote policies that reduce dangerous exposures.

Despite the importance of DNA damage and repair, DNA damage is not measured in the clinic. Furthermore, DNA damage that is present in people's cells is rarely assessed as a means for evaluating genotoxic exposures from our environment.

During a trip to Singapore in 2006, sponsored by CEHS, Bevin Engelward had the good fortune to be part of a discussion among MIT, Harvard and Singaporean faculty with an interest in the design of future epidemiological studies. Through discussions about the end points that could be measured, it became clear that cell-based assays were notably absent. With the idea that a repair assay reveals the integrated effect of multiple polymorphisms, Bevin Engelward came back to MIT hoping to find a way to deliver a high-throughput "repair-o-meter" that would reveal multiple repair activities in parallel.

The key to a solution was a collaboration with Sangeeta Bhatia (Professor of Health Sciences and Technology (HST) and Electrical Engineering and Computer Science (EECS), and also member of the Center for Environmental Health Sciences, the Broad Institute, the Howard Hughes Medical Institute (HHMI), and the Koch Institute for Integrative Cancer Research). It was over a cup of coffee at Peet's in Lexington that ideas started to develop. Prof. Bhatia is a world leader in lab-on-a-chip technology, and together, Engelward and Bhatia started drawing out possible solutions. David Wood (currently a post-doc in the Bhatia lab) and David Weingeist (a graduate student in the Engelward lab), brought ideas, energy, determination, and skills that were necessary for finding a solution.

The team has now completely revamped the decades-old comet assay. The comet assay is a well known assay in which cells are lysed in agarose and subjected to electrophoresis. Damaged DNA migrates farther than undamaged DNA, yielding quantitative data on the extent of DNA damage. The comet assay hadn't changed much since the 1980s, and thus was extremely low throughput and not very useful for epidemiology or in the clinic. Each condition required a separate slide, so a researcher could only process about 10 samples per day. For an epidemiological study with 130,000 subjects, like the one planned in Singapore, it would take over a decade to collect the data.



After several iterations performed by James Mutamba, Sukant Mittal, and David Weingeist, discussions among Wood, Bhatia, and Engelward, eventually led to the idea of microwells in agarose. Bhatia and Wood devised a way to create an array of microwells the size of single cells in agarose. Ultimately, the microarray was combined with a 96 well plate design, making it compatible with high throughput screening technology. With support from a UROP student Margaret Wangeline, David Wood and David Weingeist demonstrated that

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HOLD THE DATE

February 4th, 2011

CEHS Annual Poster Session to be held at Walker Memorial

AWARDS AND HONORS

CEHS was awarded the 2009 EHS-MS Award, two years in a row!!

This past Fall, the MIT Center for Environmental Health Sciences was awarded the Environmental Health and Safety Award in recognition of demonstrating outstanding performance related to environmental health and safety issues in the EHS Management System and maintaining an exemplary EHS program throughout the year in a small Department, Center, or Laboratory category. The CEHS has won this award two years in a row!

Picture taken from the 2008 award ceremony

Professor **Bruce Tidor** was named the AAAS fellow as a result of his significant scientific contributions in the "use of computational modeling in understanding the structure and functions of proteins and in designing molecules".

Kathleen Vandiver received the 2009 Science Educator of the Year Award

Dr. **Kathleen Vandiver**, Director of CEHS Community Outreach and Education Core, is the recipient of the 2009 Science Educator of the Year Award for Middlesex County by the Massachusetts Association of Science Teachers (MAST) in honor of her exemplary leadership in promoting and advancing science education for students and teachers.

FACILITIES CORES UPDATES

Genomics and Imaging Facilities Core—BioMicro Center

The BioMicro Center has made a number of major upgrades over the last year in order to provide cutting edge equipment for genomics research. We have significantly increased on sequencing capacity with the addition of multiple Illumina sequencers, including the new HiSeq 2000, which was purchased by Dr. Penny Chisholm and Dr. Chris Burge with funding from the Moore Foundation and ARRA. In addition, we have increased our RT-PCR capacity with the purchase of two Roche LightCycler 480s and the addition of a Fluidigm BioMark dynamic array system. The BioMark system is able to process almost 10,000 qPCR reactions in a single plate. The BioMicro Center also has significantly increased our handling of high-throughput sample handling with the reactivation of a Tecan EVO 150, the purchase of a second EVO 150, and the acquisition of a Thermo Fisher Varioskan plate reader. These systems are designed to handle screening large libraries and to help with high-throughput analyses. The BioMicro Center is also hosting a Nanostring nCounter system on a trial basis. This system allows for counting individual nucleic acid molecules in a reaction using fluorescent barcodes in a highly multiplex manner (several hundred per reaction). More information about all of these systems can be found on our website: http://web.mit.edu/biomicro.

In addition to new instrumentation, the BioMicro Center has expanded our service portfolio. Sample preparation services are now available for microRNA arrays and array CGH. In addition, we will begin offering sample preparation for some types of Illumina sequencing over the summer. All of this has been made possible by a fantastic and growing staff of technicians. If you have any questions or wish to discuss a project, our email is biomicro@mit.edu or stop by and visit us in Room 68-316.

CEHS NEWS

COEC Nurse Workshop held January 2010

On January 12 and 13, 2010, the CEHS Community Outreach and Education Core (COEC) sponsored a Two-Day Nurse Workshop in Cell Biology and Environmental Health. Why a workshop on cell biology for nurses? Medicine has become more molecular with time. Today's nurses are finding it is necessary to update their knowledge of cellular processes to understand the etiology of human disease and to assess strategies for treatment and prevention.

The CEHS COEC Director, Dr. Kathy Vandiver working in partnership with Catherine Ricciardi, Nurse Manager of the MIT Clinical Translational and Science Center, convened a nurse focus group three years ago that helped us create this popular workshop. This nurse focus group encouraged the workshop theme of cell biology, recommended we offer 15 continuing education units (CEUs) and they endorsed the MIT CEHS COEC's active teaching practices which is non-standard in nurse CEU programs. Thus the COEC workshop featured the novel molecular models created from LEGO components by Dr. Vandiver.

Sophisticated simulations of cell processes (cell division, DNA damage and repair, protein synthesis) scheduled in the morning with the LEGO molecules were followed by lectures and translational activities, which applied these concepts to environmental health topics in the afternoon. On-line resources were employed as well. For example, the participating nurses explored a DNA repair protein (a glycosylase) with STAR BioChem, a 3-D protein viewer.

Speakers included Professor David Hunter, Harvard School of Public Health, presenting on the Nurses' Health Study, and Dr. Megan Rokop from the Broad Institute of Harvard and MIT. At the end of each day, participants enjoyed a short fieldtrip --- to the Broad Institute's DNA sequencing facility to learn more about the impact of the human genome project on medicine, and to Novartis Institutes for BioMedical Research (NIBR) for a lecture on drug development and a tour of their Cambridge facility. The workshop evaluations were very positive, and the MIT CEHS COEC has had inquiries from other NIEHS P30 Center COECs about this highly successful translational workshop.

WELCOME

We are delighted to announce the new Center Members: **Katharina Ribbeck**, Assistant Professor.

She joined the BE faculty in March 2010. Dr. Ribbeck holds expertise in biological transport barriers (including the nuclear pore and the epithelial mucosal matrices), and is pursuing application of basic mechanistic understanding of these barriers to problems such as viral infection and bacterial colonization in diseases such as AIDS and cystic fibrosis. Dr. Ribbeck's research interests will synergistically span our microbial and mammalian biological areas, with emphasis on quantitative analysis of biomolecular and cellular processes.

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the platform could be used to screen for DNA repair inhibitors, which have potential utility in the clinic. Finally, with the help of another MIT undergraduate, Drew Regitsky, custom in-house programs were developed for high throughput image analysis. Together, these technologies make it possible to process hundreds of samples per day, thus enabling population-wide studies of environmental exposures, as well as genotoxicity testing and drug screening.

Professors Bhatia and Engelward are co-senior authors on a manuscript entitled "Single cell trapping and DNA damage analysis using microwell arrays" that is coming out in the Proceedings of the National Academy of Sciences on the week of May 18th, 2010. David Wood is the lead author on this work, and he worked very closely with David Weingeist to complete this project.

One important aspect of the technology is that it can be readily disseminated at a low cost. This means that with only basic laboratory equipment, it is now possible to measure the levels of DNA damage in human cells with throughput that is compatible with epidemiological studies. Based on the important observations of Dr. Rebecca Fry when she was in the laboratory of Professor Leona Samson, it is now clear that babies *in utero* can be significantly affected by arsenic present in the drinking water of their mothers. In an effort to extend this work, the team is now collaborating with researchers at the Chulabhorn Research Institute in Thailand to measure the levels of DNA damage in the cord blood cells of babies born to mothers who were exposed to arsenic during pregnancy.

It is hoped that this new technology will open doors to studies that impact human health by providing rigorous quantitative data on the levels of DNA damage in human cells.

Left to right: B. Engelward, D. Weingeist, D. Wood, and S. Bhatia.

HIGHLIGHT PAPER

Blood Type and Pancreatic Cancer Linked (paper from at least 2 different NIEHS P30 Core Centers)

A new study funded in part by NIEHS reports novel findings related to the basic biology of pancreatic cancer, confirming that blood type is related to pancreatic cancer. More specifically, people with any blood type other than O are at a slightly increased risk for pancreatic cancer, a relatively rare, but usually fatal cancer. The team determined ABO genotypes in about 1500 cases and controls from twelve cohorts of participants enrolled in the Pancreatic Cancer Cohort Consortium (PanScan).

These findings are important because they provide some insights into the biology of the disease. Previous research found that normal pancreas cells carry a different pattern of the blood-type antigens on their surface than do pancreatic cancer cells. This suggests that changes in the ABO gene activity may occur as the cells become cancerous, possibly by interfering with the cells' ability to signal and adhere to one another and with the immune system's ability to recognize them as abnormal cells. The researchers point out that the ABO gene could also merely be a marker for other nearby genes that are more directly involved in cancer development. The association between blood type and pancreatic cancer risk provides a new line of investigation for understanding the mechanisms involved in pancreatic cancer development.

Citation: Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, Stolzenberg-Solomon RZ, Arslan AA, Jacobs EJ, Lacroix A, Petersen G, Zheng W, Albanes D, Allen NE, Amundadottir L, Anderson G, Boutron-Ruault MC, Buring JE, Canzian F, Chanock SJ, Clipp S, Gaziano JM, Giovannucci EL, Hallmans G, Hankinson SE, Hoover RN, Hunter DJ, Hutchinson A, Jacobs K, Kooperberg C, Lynch SM, Mendelsohn JB, Michauds DS, Overvad K, Patel AV, Rajkovic A, Sanchez MJ, Shu XO, Slimani N, Thomas G, Tobias GS, Trichopoulos D, Vineis P, Virtamo J, Wactawski-Wende J, Yu K,Zeleniuch-Jacquotte A, Hartge P, Fuchs CS.. (http://www.ncbi.nlm.nih.gov/pubmed/20103627) 2010. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res 70(3):1015-1023.