MIT CEHS NEWSLETTER
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Massachusetts Institute of Technology
CENTER FOR ENVIRONMENTAL HEALTH SCIENCES
FALL 2010

Emeritus: On the trail of aflatoxin

Toxicologist Gerald Wogan has dedicated his career to understanding—and fighting—a deadly carcinogen.

An article by Anne Trafton, MIT News Office (December 6, 2010)

IN THIS ISSUE

Editor's note: This is part of a series of articles linking the work of MIT's emeritus faculty members with the current state of research in their given fields.

In the spring of 1960, a mysterious liver disease killed hundreds of thousands of turkeys in the United Kingdom. The outbreak was soon traced to ground peanut meal, shipped from Brazil and contaminated with mold that produces a poison known as aflatoxin.

At the time, little was known about aflatoxin, but some scientists suspected it could be linked to liver cancer in humans. Soon after the U.K. outbreak, a young MIT toxicologist named Gerald Wogan launched a thorough, decades-long investigation into the toxin, eventually exposing it as one of the most potent carcinogens humans can encounter.

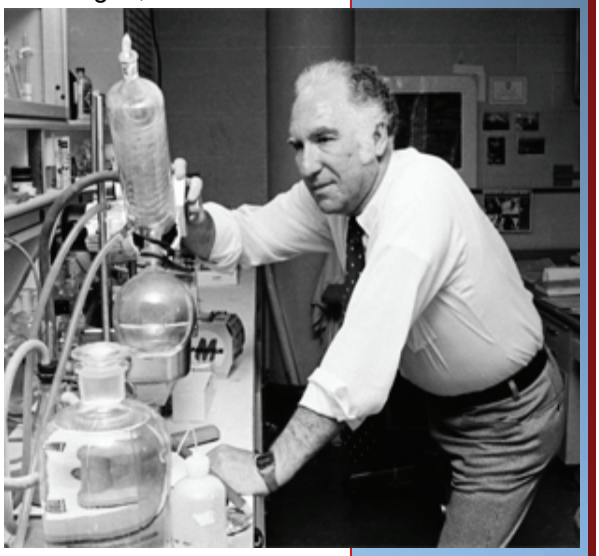
Throughout his career, Wogan not only made discoveries illuminating aflatoxin's role in liver cancer, which kills about 600,000 people per year, but he also used his knowledge to shape food-safety regulations in the United States and Europe, and helped develop new measures that could fight liver cancer in developing countries, where aflatoxin exposure is still common.

"A lot of people are content to do basic science, but he picked up that mantle of responsibility and went right into the regulatory arena," says John Essigmann, MIT professor of toxicology and chemistry and a former student of Wogan's.

A new toxin

Though he has become one of the world's foremost experts in toxicology, Wogan started his career as a physiologist. He came to MIT in the summer of 1961 to join a new program in food safety, which was part of the Department of Nutrition, Food Science and Technology.

At the time, food safety was a hot topic. "It was right after Rachel Carson published *Silent Spring*, and there was a lot of concern about pesticide residues and chemical residues and contaminants," recalls Wogan, who turned 80 this summer.



Upon arrival at MIT, he planned to study a puzzling toxic agent known as chick edema factor (later shown to be dioxin), which causes the sack around the heart to fill with fluid. However, shortly after the liver-disease outbreak in British turkeys, a UNICEF scientist urged him to look into the pressing problem of aflatoxin.

By then, British scientists had isolated and named the poison, but hadn't determined its chemical structure or figured out why it was so toxic. In 1962, Wogan attended a conference on aflatoxin in London, where a British pathologist offered him a sample of the fungus. Wogan slipped two Petri dishes containing the fungal colonies into his coat pocket and carried them onto the plane and across the Atlantic, back to MIT.

When Wogan got the fungus (known as Aspergillus flavus) back to his lab, "we started growing the mold on everything we could think of" — not just peanuts, but also wheat, corn and rice. Wogan and George Buchi, a natural-products chemist in MIT's Department of Chemistry, be-

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POSTER SESSION

February 4th, 2011

CEHS Annual Poster Session to be held at Morss Hall, Walker Memorial (Bldg. 50)

Abstract application form due January 14th, 2011 to Julie Coiro (julieh@mit.edu).

A form can be obtained at http://cehs.mit.edu/Events.html

CEHS NEWS

CEHS meets with Congressman Capuano to discuss environmental issues

In December 2010, the CEHS leadership, Director. Leona D. Samson and Deputy Director Peter C. Dedon, along with the COEC Director, Kathleen Vandiver and Administrative Officer, Amanda Tat (both not pictured), met with Congressman Michael Capuano of the 8th district to discuss environmental health issues concerning his district. The meeting was held in his office at 110 First St. in Cambridge, MA.

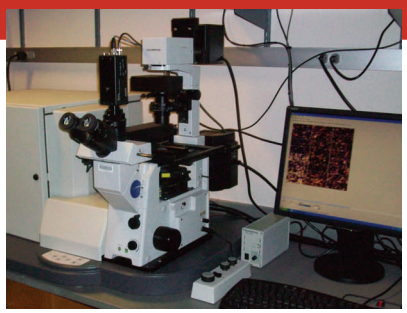
Clockwise: Peter C. Dedon, Congressman Michael Capuano, and Leona D. Samson

WELCOME

We are pleased to announce that **Mark Bathe**, Assistant Professor of Biological Engineering, has joined the Center. A major challenge in cell biology is how regulated interactions between single molecules can lead to the emergence of specific coordinated function on cellular length-scales. To better understand this challenge, Prof. Bathe has developed advanced computational techniques which integrate high resolution fluorescence light microscopy data with mechanistic, molecular-based models of fundamental cellular processes. The cellular processes include contractile ring assembly, constriction during cytokinesis, and chromosome transport during early spindle assembly.

FACILITIES CORES UPDATE

Genomics and Imaging Facilities Core—Imaging Core



The CEHS Imaging Core contains multiple imaging systems to assist CEHS members in their imaging needs. To assist in high-throughput imaging needs, we have multiple options including the Metasystems Imaging System and the Compucyte iCys Laser Scanning Cytometer (LSC). We have recently upgraded the LSC to include a 60X objective and the high resolution scanning option to enhance imaging capabilities. This system contains three lasers (405nm Violet, 488nm Argon Ion, and 633nm HeNe gas) and four fluorescence and brightfield detectors, to accommodate numerous experimental strategies. This system is being utilized for an increasing number of applications and formats including standard slides, 96-well plates, chamber slides and, most recently, microwells internally fabricated. Another option for high-throughput imaging is the Metasystems Imaging System, which is capable of automated image acquisition, event determination, and quantification of data. It is routinely used to measure DNA damage and chromosomal abnormalities in a high-throughput manner with the use of an automated slide feeder (80 slides). Accompanying software packages assist in performing numerous assays including automated metaphase spread searches, comet assays, sister-chromatid exchange assays, and allows the option to train the program to identify novel events. Another new addition to the core is an Accuri C6 Flow Cytometer which was partially supported by the Center. The system provides two lasers, four color detectors and both forward and side scatter detectors, as well as a user-friendly interface to simplify your flow cytometry experiments. For more information on the capabilities or training on these systems, please contact Jennifer Calvo (jcalvo@mit.edu, x3-8836).

COEC Update

COEC—Bi-directional Communication

Previously, NIEHS funded Community Outreach and Education Core (COEC) programs only interacted with the public to present their findings. Now COEC programs should actively seek public engagement and participation to create an open two-way dialogue. Below are some examples of bi-directional communication from the MIT COEC's program.

In June 2010, MIT received a NASA Innovation Grant to work with the Boston Public Schools. This award was the direct result of a community member's request. Ms. Pam Pelletier, Boston Public Schools' (BPS) Senior Program Dir. for Science, asked Dr. Kathy Vandiver, the COEC Director, to find a way to bring our unique hands-on LEGO DNA lesson materials to all the public high school students in Boston. She was looking for greater equity in science education. Thus COEC designed the student materials and delivered Saturday professional development programs to teachers this October. Recently 300,000 LEGO components arrived and we are organizing teams of MIT CEHS and community volunteers to assemble the LEGO DNA and Proteins kits to be delivered to 20 participating biology classrooms in March 2011. We plan to leverage this pilot project which is helping teachers make connections about DNA and environmental health to greater numbers of classrooms in the future.

In May 2008 a Boston-based team of nurses, which the MIT COEC convened in partnership with the MIT Clinical Research Center (now the Harvard Catalyst MIT Clinical Research Center) led by nurse manager, Catherine Ricciardi, RN, BSN, helped COEC crystallize its plans for a two-day molecular biology and genetics workshop for nurses. We heard that nursing coursework is deficient in genetics and molecular biology and that this knowledge is essential for nursing today. Nurses acknowledged they wanted more participatory learning opportunities, not just more lectures in their continuing education programs. In addition, nurses suggested we provide 15 Continuing Education Units (CEUs) with our workshop, to meet the annual requirement in one course. Our COEC workshop now offers hands-on LEGO molecular biology and genetics lessons as well as lectures and fieldtrips that apply those concepts to environmental health and other topics. Ricciardi presented a poster on the effectiveness of the LEGO models in teaching molecular biology and genetics to nurses at the International Association of Clinical Research Nurses (IACRN) at NIH in Bethesda, MD in October 2010, including the outstanding pre and post-test data we had collected so far.

A stakeholder-style meeting is held annually which is another representation of bi-directional communication. Our Community Advisory Board (CAB) provides our partners an opportunity to network with each other as well as to review and comment on the MIT COEC projects. It's actually more multi-directional than bi-directional communication. MIT COEC held its most recent CAB meeting in October 2010 with 24 members in attendance. The CAB meetings help remind the members about the NIEHS COEC core mission, MIT's COEC projects, raise awareness and understanding of the impact of the environment on health, and build knowledge about healthy behaviors. We used the Centers for Disease Control's (CDC's) discussion toolkit, CDC and Agency for Toxic Substances and Disease Registry (ATSDR) "National Conversation on Public Health and Chemical Exposures", and invited our partners to discuss what chemical exposures were of greatest concern in their lives and in the lives of their community members. As a result, the top concerns were cosmetics and personal care products, BPA, plastics as hormone disrupters, government standards for organic foods, and water quality. The discussion was very engaging and members bonded over common interests. At the close of the meeting, members were eager to continue learning from each other and finding more ways to collaborate in the future.

Upcoming COEC Activities

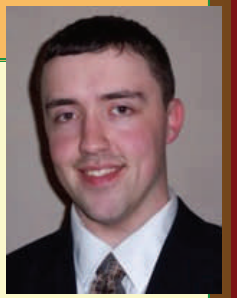
January 25-26, 2011—Nurses Workshop

April 30, 2011—MIT/CEHS Open House

May 7, 2011—Cambridge Science Festival-COEC exhibit

For more information, please visit our website http://cehs.mit.edu/COEP/outreachprograms.html

WELCOME



We are delighted to introduce a new member of the Center HQ staff, **Ryan Flanagan,** System Administrator, who joins us with extensive IT experience. Ryan is located in room 56-205 and can be reached via email ryanf@mit.edu or by phone 617-452-2072.

CEHS Featured Article continued

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came the first to figure out aflatoxin's structure and synthesize the two major forms of aflatoxin, in 1963 — just beating out a European team that was racing the MIT group to the structure.

Human health

Wogan and veterinary pathologist Paul Newberne then started measuring aflatoxin's effects in rats. Wogan used those results to persuade the FDA to establish guidelines, still in use, for the maximum allowable amount of aflatoxin in foods such as peanut butter.

"From the beginning, the goal was not only to understand the mechanisms of action and try to characterize it as completely as we could, but to try to understand what impact it had on human health," says Wogan. "The only reason I was interested in aflatoxin is because it was clear there was a large potential human risk."

To strengthen the link between aflatoxin and liver cancer in humans, Wogan set up an epidemiological study in Thailand in the late 1960s. Researchers from MIT and Thailand, in a collaboration dubbed MITHAI, measured aflatoxin levels in people's food and compared them with their liver-cancer rates.

After collecting data for five years, the researchers found a strong correlation between aflatoxin consumption and liver cancer. However, they needed more evidence to convince virologists, who already believed that the hepatitis-B virus was the most important contributor to liver cancer.

Essigmann, then a graduate student in Wogan's lab, made a key discovery that allowed the team to precisely measure aflatoxin exposure in humans, allowing them to prove the connection to liver cancer. Essigmann discovered that aflatoxin binds tightly to DNA, creating mutations that can lead to cancer. He and a graduate student, Richard Bennett, then developed a test that could detect the DNA-aflatoxin compound in urine.

Using that test, plus a blood test developed by Steven Tannenbaum, an MIT professor of biological engineering, the Wogan team could definitively track aflatoxin exposure. In 1992, two of his former graduate students, John Groopman and Thomas Kensler, now professors at Johns Hopkins University, published a study that conclusively linked liver cancer to the toxin. "It really did drive the nail home in the argument. Even the virologists started to refer to aflatoxin as a risk factor," says Wogan.

Wogan later showed that exposure to both aflatoxin and hepatitis B dramatically boosts the risk of liver cancer by 60 to 100 times that of being exposed to either agent on its own. That synergistic effect is still unexplained.

Fighting cancer with broccoli

While working out the mechanism of aflatoxin's toxicity, Wogan kept his eye on his overarching goal: reducing the risk of liver cancer, especially in developing countries, where aflatoxin is more frequently found in the food supply. His former students have carried on that legacy. In the late 1990s, Kensler found that a drug called oltipraz activates an enzyme that blocks aflatoxin's effects. A study he conducted in China, where aflatoxin exposure is common, found that giving the drug as a preventive measure dramatically reduced aflatoxin levels in the urine and blood.

However, oltipraz is prohibitively expensive, so the researchers looked for a dietary supplement that would do the same thing. It turns out that broccoli sprouts activate the same enzyme as oltipraz, so Kensler and colleagues are now studying the effects of a tea made from the sprouts. This has also reduced the amount of aflatoxin found in people who drink it.

Wogan, who founded MIT's Center for Environmental Health Sciences in 1978, still maintains a research lab at MIT, where he now focuses primarily on the cellular signaling molecule nitric oxide. However, three years ago, he, Essigmann and Tannenbaum resurrected their aflatoxin studies. This time, they're looking into a discovery Wogan made in the 1970s, that mice younger than 10 days old are very susceptible to aflatoxin exposure, but start to become resistant after 10 days.

By using the new tools of genomics and proteomics, the trio hopes to figure out what happens between the first and second weeks of life that makes the animals become resistant. "We can get lessons out of that that will teach us how to protect infants, and protect adults — it's a pure Wogan message," says Essigmann.