



May 2007



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NIEHS Spotlight

Institute Looks to Its Future Growth

By Eddy Ball

On March 30 at a town meeting in Rodbell Auditorium, NIEHS formally began the year-and-a-half process of developing a Master Plan for growth and change for the RTP campus. On hand to explain the steps involved were representatives of the NIH Office of Research Facilities (ORF). Approximately 200 NIEHS employees attended the meeting.

In his opening remarks, NIEHS Director David Schwartz, M.D., emphasized the role of employee involvement in the planning process. “I think it’s really important to involve everyone in this planning,” he said. The Institute has an opportunity to influence “what kind of research atmosphere” the campus will have over the next twenty years. “Your input is absolutely critical.”

In addition to infrastructure updates and architectural changes to add flexibility to the facilities, Schwartz said the Institute needs to make changes in the working environment of the campus. Admitting that his time on the Bethesda campus had spoiled him, Schwartz described his vision of a more university-like campus, unifying the workplace by bringing all NIEHS offices together and stimulating creative exchanges among employees. He also mentioned the addition of a conference center, short-term housing for visiting scientists and students, an expanded fitness facility and more options for dining as priorities.

ORF Division of Facilities Planning Acting Director Ron Wilson then outlined the purposes of the Master Plan. With input from employees, planners will compile long-range space and infrastructure requirements, define priorities, outline procedures to ensure community involvement and address environmental issues for a sustainable campus. ORF will develop three alternative scenarios by Summer 2007 as the basis for the final Master Plan/Environmental Impact Statement to be submitted in Fall 2008.

“You’re sitting almost in the middle of a preserve,” Wilson noted. “Our intent is to maintain the good features of this campus and build on them... [while incorporating] the good things we have in Bethesda.... We want the campus to reflect who you are.”



By 2028, NIEHS could be a much different place than it is today. NIH planners forecast a doubling of employment in RTP and increasingly dense development surrounding the campus. (Photo courtesy of Steve McCaw)



When he started to describe his personal vision of the future campus, Schwartz admitted that “my time in Bethesda spoiled me a little.” As he envisions the Institute in 2028, the campus should have the best of both worlds — the resources of a university nestled in the idyllic setting of the present RTP campus. (Photo courtesy of Steve McCaw)

As important as the Master Plan will be in getting improvements what Wilson called “some buy-in from officials at the highest levels of NIH,” the plan itself does not guarantee anything. In response to a question from the audience, Facility Planner Susan Cantilli explained that the Master Plan is a framework in which future development can be accommodated if and when budget and political priorities and mandates dictate.

Realization of any Master Plan depends on priorities of NIH and the Department of Health and Human Services (DHHS) priorities, Congressional and Presidential policy decisions, and federal budgetary realities.

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Scientific Counselors Review Two DIR Labs

By Eddy Ball

On March 25-27, the NIEHS Board of Scientific Counselors (BSC) conducted external reviews of research by nine investigators in the Laboratory of Molecular Carcinogenesis (LMC) and Laboratory of Molecular Toxicology (LMT). The process began with a closed session off-site on March 25 and continued in Rodbell Auditorium on March 26-27.

When the meeting opened on March 26, NIEHS Director David Schwartz, M.D., welcomed the reviewers and underscored the importance of periodic reviews to the overall mission of the Institute. “We rely on your critiques and take them very, very seriously,” he told the board. “Our scientists take this feedback as ways of helping them improve the work that they’re doing and improve the research opportunities that they pursue both in intramural research and in extramural collaborations.”

LMC scientists under review were Chief Trevor Archer, Ph.D., Kenneth Olden, Ph.D., Steve Akiyama, Ph.D., Karen Adelman, Ph.D., Paul Wade, Ph.D., Robert Langenbach, Ph.D., and Thomas Eling, Ph.D. LMT Investigators Ray Tennant, Ph.D., and Richard Paules, Ph.D., were also reviewed.

The BSC was comprised of its chair, John Hildebrandt, Ph.D., a professor at the Medical University of South Carolina, and a select group of scientists from universities and research centers with expertise relevant to the research under review. Acting Scientific Director Perry Blackshear, M.D., served as board secretary.

Each investigator made a 25-minute presentation that was followed by questions from the reviewers, with some also making suggestions. To ensure confidentiality, the BSC



Chair John Hildebrandt is a professor and chair of the Department of Cell and Molecular Pharmacology at the Medical University of South Carolina. Shown beside him is Perry Blackshear. (Photo courtesy of Steve McCaw)



NIEHS Director David A. Schwartz, M.D., ponders a point during Trevor Archer’s presentation. To his right are Hildebrandt and Blackshear. (Photo courtesy of Steve McCaw)

periodically went into closed session to discuss more candidly their evaluations of individual presenters and to meet with principal investigators or trainees from the labs.

Lab members displayed their data during a poster session in the lobby. Following the lab presentations, Darryl Zeldin, M.D., presented a proposed contract for knockout mouse development for Contract Concept review.

The BSC performs a rigorous external scientific review of each laboratory and branch in the Division of Intramural Research at least once every four years. The reviewers evaluate intramural scientists on their accomplishments since their last reviews and their future plans.

The process takes into consideration the overall direction of the research programs, their interactions within the laboratory and the Institute, including mentoring, and the relevance of research to the mission of NIEHS. As needed, the board also hears Contract Concept Review proposals.

Along with its review of branches and labs, the board reviews each tenure-track investigator approximately three years after the individual's original appointment. This review provides an evaluation of the candidate's progress toward tenure.

According to review guidelines, the BSC will submit an evaluation summary within two months of its meeting to the scientific director. Each investigator will receive a copy of the report dealing with the overall laboratory and his/her individual research. The scientific director will then make a written response to the BSC recommendations, which may include responses to the BSC review from individual investigators.

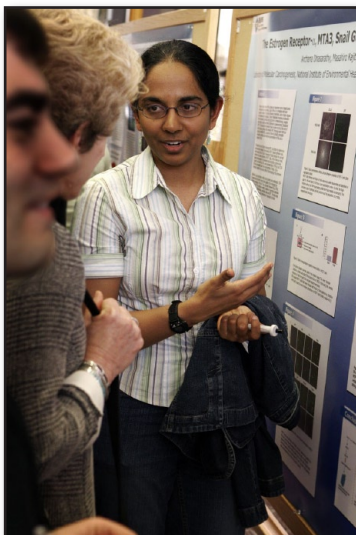
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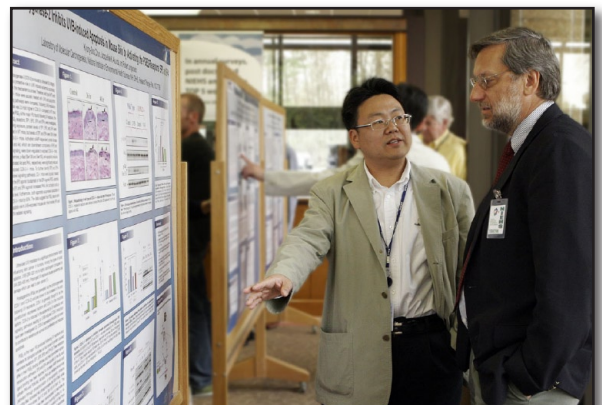
BSC member Susan Fischer, Ph.D., a professor at the University of Texas M. D. Anderson Cancer Center, questioned several of the presenters. (Photo courtesy of Steve McCaw)



Towering above his reviewers, Trevor Archer explained data to board members John DiGiovanni, Ph.D., (left) and Michael Stallcup, Ph.D. (right) as Ken Olden (at podium) prepares for his talk and Steve Akiyama looks on. DiGiovanni is a researcher at the University of Texas M. D. Anderson Cancer Center, and Stallcup is a professor at the University of Southern California Keck School of Medicine. (Photo courtesy of Steve McCaw)



LMC Fellow Archana Dhasarathy, Ph.D., discussed her work in Wade's lab with Susan Fischer. (Photo courtesy of Steve McCaw)



LMC Fellow Kyung-Soo Chun, Ph.D., talked with John DiGiovanni about his research in Langenbach's group. (Photo courtesy of Steve McCaw)

SEAD Researchers and Advisors Meet at NIEHS

By Eddy Ball

On April 12 and 13 the NIEHS Epidemiology Branch (EB) hosted a two-day meeting of Soy Estrogens and Development (SEAD) project researchers and advisors in Rodbell Auditorium. Researchers reported on the results of the project's three cross-sectional pilot studies and explored three potential new areas of study.

On the second day of the meeting, participants met in break-out sessions facilitated by Advisory Group members. The groups considered the feasibility of new endpoints, study designs and methodologies for future studies. The meeting also included a special presentation by Israeli Pediatric Endocrinologist Zvi Zadik, M.D., who reported on his work with the Soy Committee of the Israel Ministry of Health to develop guidelines for the use of soy with infants there.



Rogan queried advisor Mel Grumbach, M.D., several times about his critique of the endocrine assessment methodologies. (Photo courtesy of Steve McCaw)

SEAD – A Project at the Crossroads

As Walter Rogan put it in his opening remarks, “We’re at a junction now where we have developed these tools [for researching effects of soy formula] and used them in the field. The question now is ‘Where do we go from here?’” Later in the meeting, Rogan summarized the findings of the pilot studies with a presentation titled “High isoflavone exposure in soy fed children — should we care?”

Although researchers identified a slight trend toward feeding effect in the vaginal cytology data and some of the hormone results, ultrasound, physical exam and several of the biochemical assays uncovered no discernable impact of exogenous estrogen on results. The pilot studies resulted in a feasible and repeatable physical exam. The ultrasound exam for breasts, uterus, ovary and testes is usable now, but ultrasound of the thymus and prostate showed high variability that needs to be worked out in a larger sample. Except for questions about the estradiol methodology and physical problems with saliva collection in newborns, the microsample methods for sex hormones, gonadotropins, and sex-hormone binding globulin are usable.

Based on the results of the pilot studies, Rogan suggested further research to confirm vaginal cytology with a one-year follow up, to compare cytology results in vaginal cell and spun urine, to reconcile breast bud differences with ultrasound and physical exam and to re-assess hormone results.

Add-on studies considered during the meeting brought up the inescapable issues of cost, recruitment and consent, and study duration. Rogan and others mentioned several times the need to find out who else is performing similar work and look into the possibility of combining resources by “piggy-backing” SEAD endpoints onto existing studies with established cohorts. It may also be useful, Rogan added, to explore cohorts in other countries, such as Korea, where more parents use soy-based formulas with their newborns.

Looking even farther into the future beyond sex-typed behavior, bone and body composition, and immune function, Rogan speculated on what it might mean “for us to go out and not just be a soy formula study.” SEAD researchers could extend their work to include chemicals suspected of endocrine disrupting activity, such as phthalates, bisphenol A, DDE and some PCBs. Rogan also mentioned the possibility of using measures of anogenital distance and neonatal behavior as endpoints in studies of *in utero* exposures to endocrine disruptors.

EB Principal Investigator Walter Rogan, M.D., and Project Officer Beth Ragan organized the meeting. Full sessions were chaired by Laurence Finberg, M.D., a professor in the University of California at San Francisco (UCSF) School of Medicine. As participants met, they were surrounded by posters reporting data from recent studies. The poster display included a [new study by Rogan and SEAD collaborators](#) that will be presented at the Pediatric Academic Societies' meeting on May 8 in Toronto.

The SEAD project evolved from the 2004 study "[Isoflavones in Soy Infant Formula: A Review of Evidence for Endocrine and Other Activity in Infants](#)" by Rogan and then Postdoctoral Fellow Aimin Chen published in the *Annual Review of Nutrition*. The article surveyed the small body of existing human data and the substantial laboratory evidence of hormonal and other activity at doses in animals relevant to the soy-fed infant.

Rogan and Chen called for further clinical and epidemiological study in the face of a disparity between data from animal and human studies. Although obvious toxicity has not been observed in the large number of infants fed soy formula over the past 50 years, infants consuming the formulas showed serum/plasma concentrations of genistein that exceed the concentration seen in laboratory studies using doses that were pharmacologically or toxicologically active in animals.

This apparent paradox motivated researchers in the project to develop new research methodologies for more accurate measurements in newborns and infants. Investigators have looked for better evidence on whether the outcomes of animal experiments have any relationship to what actually happens to human infants on the formulas.

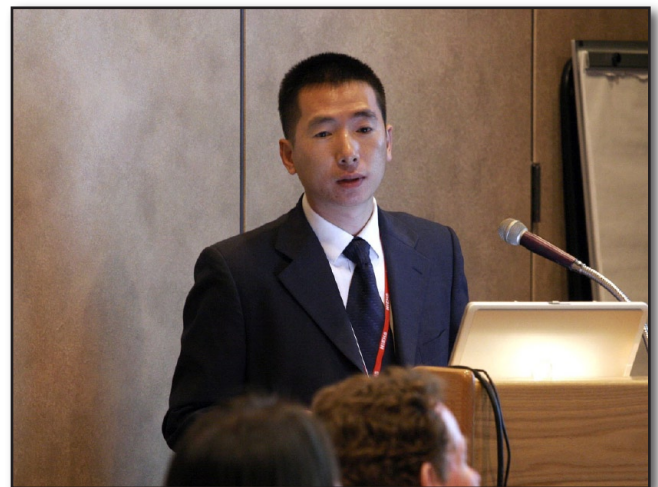
The initial three SEAD studies field-tested protocols for performing physical, sonography and biochemistry studies of infants. In many cases researchers were examining parameters that are not usually studied in this age group and had to adapt methodologies, both to fit the needs of the population and to satisfy parents asked to give informed consent for any testing performed.

In several cases, the investigators were forced to substitute less sensitive measures for "gold standard" methods validated with other populations. The number of infants tested ranged from 72 in the physical exam study to 372 in the biochemistry study.

Following reports on the three cross-sectional pilot studies, participants heard presentations on potential new directions for the next phase of SEAD from scientists who had not been involved in the project previously. These new directions included studying effects on psychological sex differences, bone and body composition and immune system development among infants consuming soy-based formula.



EB Postdoctoral IRTA Fellow Ruby Nguyen, Ph.D., presented results of the ultrasound exam. Children's Hospital Co-Director of Fetal Imaging Judy Estroff, M.D., followed Nguyen with a report on the methods used. (Photo courtesy of Steve McCaw)



EB Postdoctoral Fellow Yang Cao, Ph.D., presented the preliminary results of sex hormone and gonadotropin assessments. NIH Ultramicro Analytic Immunochemistry Resource Chief Terry Phillips, Ph.D., DSc., participated by phone from Bethesda. (Photo courtesy of Steve McCaw)

Reports by the break-out groups evaluated the feasibility of expanding SEAD into these new directions. As in the earlier pilot studies, researchers in any of the proposed study areas would face problems with using some methodologies and equipment designed for older children and adults to evaluate infants.

In addition, to undertake meaningful studies, researchers would need to recruit larger groups of infants, to include controls and be able to follow subjects prospectively over a longer time period. These kinds of studies can be very expensive and are plagued by a host of confounding factors, including patterns of soy consumption, the variability of isoflavone levels in soy products consumed by mothers and the distinctive smell of the soy-fed infant, which makes designing a double-blind control study almost impossible.



Advisors Laurie Moyer-Mileur, Ph.D., R.D., of the University of Utah, took notes during the physical exam report. Next to her sat Finberg (center) and Grumbach. (Photo courtesy of Steve McCaw)



Shown at the advisor's table were Estroff (left) and Abbott Laboratories' Research and Development Scientists Russell Merritt, M.D., Ph.D., (center) and Chris Cordel, Ph.D. (Photo courtesy of Steve McCaw)

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Epidemiologist Examines Nutritional Policies to Curb Obesity

By Eddy Ball

While economists are fond of warning that “there’s no free lunch,” Epidemiologist Ichiro Kawachi, M.D., Ph.D., offered his audience at NIEHS a little different caveat — there are no easy answers to curbing the epidemic of obesity. Speaking in Rodbell Auditorium on April 10, Kawachi discussed “‘Thinning Out’ the Obesity Epidemic: The Role of Nutritional Policies” in a regional event hosted by NIEHS Bioethicist David Resnik, Ph.D.

Kawachi is a professor of Social Epidemiology at Harvard University and the author of several studies on obesity, including a 2006 [review](#) of food taxation and pricing



Kawachi's wit and easy manner, as well as his delightful New Zealand accent, charmed an audience that included scientists, Environmental Diseases and Medicine Program fellows and a group of students from UNC-CH. (Photo courtesy of Steve McCaw)

strategies with colleague Daniel Kim. In his NIEHS talk, Kawachi surveyed frequently proposed strategies for influencing the food choices Americans make. He examined the extent of popular support for nutritional policies, their cost effectiveness and the advantages and drawbacks of various approaches.

Although he noted that “strong rationales do exist to intervene, especially to combat child obesity,” Kawachi was careful to analyze the potentially unforeseen consequences of the policies that have been proposed. “The more you think about that apparently simple question [of when government intervention is justified and what form it should take],” he noted, “the more difficult it is to have a straight answer.”

Looking at the issue from both the free market and public health perspectives, Kawachi proposed a rationale for regulation based on the economic view that a market failure can justify intervention. Obesity stems from a failure of information, it creates additional cost to taxpayers for treatment under the Medicaid and Medicare programs, and it endangers children and adolescences — vulnerable populations who make decisions irrationally and with little inclination to delay gratification.

Approaching nutritional policy with a commonly agreed upon rationale is important, Kawachi observed, because the 2003 Harvard Forums on Health Poll indicated that a people are evenly divided on the question of whether obesity is private concern or a legitimate public health issue. In addition, only 35% of people responding to the poll thought that government should have a role. A majority favored interventions by healthcare professionals and the schools instead.

As he evaluated strategies for curbing obesity through public health policies, Kawachi brought up the oft-invoked analogy between tobacco and obesity. “That analogy is useful up to a certain point,” he maintained, “but there are many problems with it.” Unlike junk food, tobacco is a single product with no nutritional value that creates easily understood health risks for smokers as well as for others exposed to smoke.

Trying to educate consumers, implement taxes or adopt restrictions on foods that promote obesity may not always produce the desired effects, Kawachi argued. Even if they actually pay attention to nutritional disclosures, some people will actually choose less nutritious foods because they equate nutritional value with bad taste. Taxes could end up hurting the very people they were designed to help, and it would be difficult to decide which foods to tax and how much tax to impose. “Taxing Coca Cola from a vending machine is an easy target,” Kawachi explained, “but even a cheese burger does provide some nutrients.”



The Harvard epidemiologist displayed a number of graphs during the lecture, including this one showing the percentages of poll respondents supporting various regulatory proposals. (Photo courtesy of Steve McCaw)



Not surprisingly, the lecture was well attended by young scientists in the NIEHS Epidemiology and Biostatistics Branches. Shown here were (from left) Postdoctoral Fellows Ronghen Lin, Ph.D., Haidong Kan, Ph.D., and Honglei Chen, Ph.D. The two women were visiting UNC students. Next to them was Laboratory of Molecular Carcinogenesis Principal Investigator Tom Eling, Ph.D.

Restrictions, such as zoning to keep fast food outlets away from schools and limiting use of food stamps, would create a nightmare for planners trying to define just what constitutes a junk food. Even restrictions that seem to be obvious winners, such as banning soft drink machines and junk food in schools, can cause problems. Poorer schools often rely on drink machine revenues to support extracurricular activities, and bans on junk food could lead to the kind of resistance that developed in Great Britain from “meat-pie moms” who opposed the bans instituted there.

“There are many barriers, I think, to even an apparently simple directive like making restaurants disclose nutritional content,” Kawachi concluded. “There are [still] many things we need to know before we can begin to suggest nutritional policies that are realistic or viable.”

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Epidemiology Branch Fellow Wins Poster Session Award

By Eddy Ball

Research Fellow Martha Montgomery won a top prize in poster session competition at the [Eighth Annual Women’s Health Research Day](#) held April 3 and 4 at the Friday Center in Chapel Hill. Montgomery received the Judge’s Award recognizing an emerging or unfunded area of women’s health research, an honor that carried with it a \$1,000 cash prize.

Montgomery was lead author on a study titled “Pesticide Use and Age-related Macular Degeneration in Female Spouses of Pesticide Applicators.” The study grew out of earlier work performed by several of her co-authors in Phase One of the [Agricultural Health Study \(AHS\)](#), which enrolled a cohort of 52,395 pesticide applicators and 32,347 of their spouses from 1993 to 1997.

In her prize-winning study, Montgomery looked at macular degeneration among 23,000 women in the cohort of spouses, using updated information from Phase Two of the study. She and her colleagues plan a follow-up study to validate the participants’ self-reported macular degeneration with medical records and collect saliva samples that can be used in gene expression studies.

In planning and conducting the study, Montgomery collaborated with her mentor in the Epidemiology Branch, Staff Scientist Freya Kamel, Ph.D. The two have worked closely together since Montgomery began her tenure as a Post-baccalaureate Intramural Research Training Award (IRTA) Fellow in June 2006.

Along with Kamel, Montgomery collaborated with five other scientists at NIEHS and the National Cancer Institute (NCI) who have been involved in the AHS. They included Staff Scientist Jane Hoppin, Sc.D., Biostatistician David Umbach, Ph.D., NCI Senior Investigators Michael Alavanja, Dr.P.H., and Aaron Blair, Ph.D., and Branch Chief Dale Sandler, Ph.D.



IRTA Fellow Martha Montgomery is weighing her options for the future. “I’m leaning toward an M.D.,” she said. “You can do research with an M.D., but you can’t do clinical practice with a Ph.D.” (Photo courtesy of Steve McCaw)



Staff Scientist Freya Kamel. “Freya’s been an incredible help,” Montgomery said. “I really feel that she has my interests in mind.” (Photo courtesy of Steve McCaw)

“It’s been great,” Montgomery said of her experience with colleagues in the Epidemiology Branch. “I’m getting more experience in how to think about designing a study. I’ll also be getting experience in data collection, the field aspect of epidemiology. That’s a valuable experience that I might not have been able to get elsewhere.”

The 24-year-old fellow holds a Bachelor of Arts in Chemistry from Carleton College and a Master of Health Science in International Health-Disease Prevention and Control from the Johns Hopkins School of Public Health. In addition to her prize-winning poster presentation, she displayed her work at the February meeting of the AHS National Advisory Panel.

She has also taken course work at UNC-CH while at NIEHS and attended Institute lectures that address epidemiological issues or appeal to more general audiences, such as talks in the Frontiers in Environmental Sciences series. In what spare time she has, Montgomery is completing two papers as lead author on her master’s work in southern India and as second author on iron absorption in Peruvian infants.

Abstract

Montgomery MP, Hoppin JA, Umbach DM, Alavanja MC, Blair A, Sandler DP, Kamel F. Pesticide use and age-related macular degeneration in female spouses of pesticide applicators.

BACKGROUND. Age-related macular degeneration (AMD) is the leading cause of blindness in white populations in industrialized countries, and women may have a higher risk of AMD than men. Previous cross-sectional analyses in a study of a large agricultural cohort found that prevalent retinal or macular degeneration was consistently associated with fungicide use among both licensed pesticide applicators and their wives.

OBJECTIVE. Estimate the risk of incident retinal degeneration (IRD) associated with the use of pesticides and other farm-related activities among farm women.

METHODS. We investigated wives of pesticide applicators in the Agricultural Health Study, a prospective cohort study involving 23,000 women from North Carolina and Iowa. Diagnosis of retinal or macular degeneration was self-reported in a self-administered questionnaire completed at enrollment and in a five year follow-up telephone interview. Details of lifetime use of pesticides and participation in farm-related activities were reported at enrollment. We used logistic regression analysis controlling for age, state, and years of smoking.

RESULTS. A total of 207 women reported a physician’s diagnosis of retinal or macular degeneration since enrollment, and 23,030 women served as controls. Ever use of fungicides was weakly associated with IRD (odds ratio (OR) 1.5, 95% confidence interval [0.9 – 2.7]). Three other functional groups (herbicides, insecticides, and fumigants) and three insecticide classes (organochlorines, organophosphates, and carbamates) were not associated with IRD. The association with fungicides was stronger in North Carolina (OR 2.2 [1.1 – 4.7]) than in Iowa (OR 1.0 [0.4 – 2.4]). Of the specific fungicides, women who had used captan had more than double the odds of IRD (OR 2.3 [1.2 – 4.4]) of women who had not.

CONCLUSIONS. Our results extend findings from previous studies indicating that fungicide use is associated with retinal degeneration. Although the etiology of AMD is not well understood, inflammation, which may occur as a consequence of exposure to fungicides, is believed to play an important role. The next step is to evaluate self-reported diagnosis of retinal or macular degeneration using medical records to identify cases with confirmed AMD or other forms of macular degeneration.

Montgomery expects to stay at the Institute for another two or three years and add several publications to her CV before deciding on the next step in her career. She is considering pursuing a Ph.D. in epidemiology or an M.D. with a concentration in epidemiology and public health.

Strongly influenced by her earlier public health work in Ghana, Thailand and India, Montgomery is leaning toward a career with an international health organization, such as the World Health Organization, UNICEF or Médecins Sans Frontières/ Doctors Without Borders. “There are a number of other global health organizations,” Montgomery noted. “But some have political biases that I would have to consider and decide whether I agree with them or not.”

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Prospective UNC Students Visit NIEHS

By Eddy Ball

Twenty young people visiting the University of North Carolina campus in their final weeks of high school got insight into what a career at NIEHS might hold for them during an afternoon visit to the Institute on April 12. Accompanied by University of North Carolina at Chapel Hill Admissions Officer Bob Patterson, the prospective students gathered in Rodbell Auditorium for a program organized by Marian Johnson-Thompson, Ph.D., NIEHS director of Education and Biomedical Research Development.

Johnson-Thompson designed the program to give the students, many of them undecided about their majors, an introduction to NIH, NIEHS and the broad range of career opportunities in a scientific research institution. An important theme in Johnson-Thompson’s welcome and opening comments was the inclusiveness of work at the Institute. Because of the wide variety of skills needed to pursue the NIEHS Strategic Plan, she explained, “We need people with every major you mentioned.”

The program featured a brief lecture on respiratory illnesses linked to environmental exposures by Epidemiologist Sam Arbes, Ph.D., a principal investigator in the Laboratory of Respiratory Biology (LRB). After Arbes had impressed his audience with the extent of the respiratory health problem posed by asthma and allergies, he outlined in broad strokes the kind of work scientists in the LRB perform.

“We seek to answer three important questions,” Arbes said. LRB investigators want to know how much allergen people are exposed to, if interventions can effectively lower allergen levels, and whether reducing levels can prevent asthma or improve symptoms.

The students then viewed a UNC-TV “North Carolina Now” report on the Sister Study, featuring an interview with Epidemiology Branch Chief Dale Sandler, Ph.D. The feature offered the students additional insight into the overarching theme of environmental science — exploration into the gene-environment interaction linked to a spectrum of human disease.



The students got a taste of epidemiology at NIEHS during Arbes’ talk. (Photo courtesy of Steve McCaw)

Following the group sessions, students broke into small groups for discussions led by NIEHS employees involved in the Institute's biomedical research and support activities. Three small groups were led by Health Scientist Administrator Joan Packenham, Ph.D., and by laboratory scientists Luranell Burch, Ph.D., and Ron Herbert, D.V.M., Ph.D., whose labs the students visited. The other discussion groups featured John Schelp in science policy, Eddy Ball, Ph.D., in communications and Jack Field in scientific computing.

As their final activity, the students came back together to report on their small-group talks. What they said reinforced for all of them Johnson-Thompson's theme of the day. "Everyone has a talent of some kind," she maintained, "and NIEHS can probably utilize whatever talent you decide to develop in your time at Carolina."

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The small group made for informal discussion as Johnson-Thompson provided transition between activities. (Photo courtesy of Steve McCaw)



Integrated Laboratory Systems Contract Technician Kimwa Walker (left) showed these aspiring scientists around the Laboratory of Experimental Pathology. Before they left, the students also spent some time with the lab's microscopes. (Photo courtesy of Steve McCaw)



Science Notebook

Rodbell Lecturer Reports on Progress in Deciphering the Histone Code

By Eddy Ball

The honored speaker at the ninth annual Dr. Martin Rodbell Lecture on April 10 was chromatin biology researcher C. David Allis, Ph.D. Allis is the Joy and Jack Fishman Professor and Head of the Laboratory of Chromatin Biology at The Rockefeller University.

Allis delivered a talk titled “Beyond the Double Helix: Reading and Writing the Histone Code” at the event hosted by Chief of the Laboratory of Molecular Carcinogenesis Trevor Archer, Ph.D., who has been a friend of Allis for more than 17 years. Allis has published a number of ground-breaking studies in the course of a career that has spanned more than 25 years.

“In the mid-1990s [he] initiated a series of incredibly important papers,” Archer noted, “that really redefined for us our appreciation of the contribution of chromatin structure and chromatin biology to understanding aspects of human health and disease.” Archer also remarked on the important contributions that this “complete scientist” has made to the careers of the young scientists who have worked with Allis over the years.

“Whether we like it or not,” Allis said as he moved into his explication of the histone code, “our genome, our blueprint, is really not naked DNA, and we’re stuck with the fact that it’s ultimately packaged in the higher order chromatin polymer.” Chromatin, the epigenetic template for gene signaling, is made up of protein-rich assemblies that collectively regulate how cells interpret their DNA.

Chromatin is subject to a wide array of histone amino-terminal or “tail” modifications by methyl marking of amino acid residues. Together these marks make up what is known as the “histone code.” This code, in essence, produces a “read-out” determining whether genes that are critical to cancer development and growth are turned off or on.



Rodbell Series Lecturer C. David Allis emphasized that “nature isn’t just playing games with histone sequences.” In fact, he said, “These are part of DNA damage response.” (Photo courtesy of Steve McCaw)



Host Trevor Archer welcomed his long-time friend and colleague. (Photo courtesy of Steve McCaw)

The Allis lab and the labs of collaborators have endeavored to identify the enzymes, especially such cancer-related ones as Ezh2 and MLL, that are the “writers” of the code at various places on the histone tail. After these methyl marks are written, Allis explained, they are read by downstream effectors, including nucleosome remodeling factor.

“Our histone 3 tail might be actually a biological repertoire for signals that then literally lead to these downstream on-or-off epigenetic states,” he said. As cells reproduce, the codes are passed on from one generation to the next.

“Every amino acid in histones may matter,” Allis noted. The next phase of Allis’ research agenda will involve expanding his research from what he called “a tail-centric view” into further investigation of the roles of bromodomains and nucleosomes, including the development of a “designer nucleosome” and exploration of cross-nucleosome modifications.

At the end of his lecture, Allis showed slides with dramatic evidence of the translational value of histone code research. The slides depicted tumors treated with epigenetic therapy utilizing a new class of targeted anticancer agents called histone deacetylase (HDAC) inhibitors to shrink treatment-resistant tumors.

Given orally, these inhibitors target the mechanism believed to be responsible for silencing some tumor suppressor genes and other genes involved in cell cycle progression, cell proliferation, programmed cell death (apoptosis) and differentiation (transformation of young cells into specialized cells).

Speaking at the Dr. Martin Rodbell Lecture Series is a special honor for a research scientist because the series honors the Nobel Prize-winning pioneer in G protein-mediated signal transduction. Rodbell served as scientific director at NIEHS from 1985 to 1988. Upon his retirement from NIEHS in 1994, he was honored with the title of Scientist Emeritus of the National Institutes of Health.

Later that year, Rodbell shared the Nobel Prize in Medicine or Physiology for his work with G proteins prior to coming to NIEHS. In 1998, he gave the first talk in the series, titled “Fifty Years in Science: Zigs and Zags with a Common Theme.” He died later that year.

Attending the lecture as honored guests were Rodbell’s widow, Barbara, and family friends Joyce Shaver Hitchings and Martin Klein, Ph.D. Following the lecture, Archer handed Mrs. Rodbell the famous Rodbell statue that she presented to Allis.



Honored guest Barbara Rodbell sat with family friends Joyce Shaver Hitchings (behind Rodbell) and Physicist Martin Klein. (Photo courtesy of Steve McCaw)



After presenting the statue to Allis, Rodbell embraced the lecturer as Archer clapped and look on. (Photo courtesy of Steve McCaw)

Biochemist Speaks on DNA Precursor Metabolism

By Eddy Ball

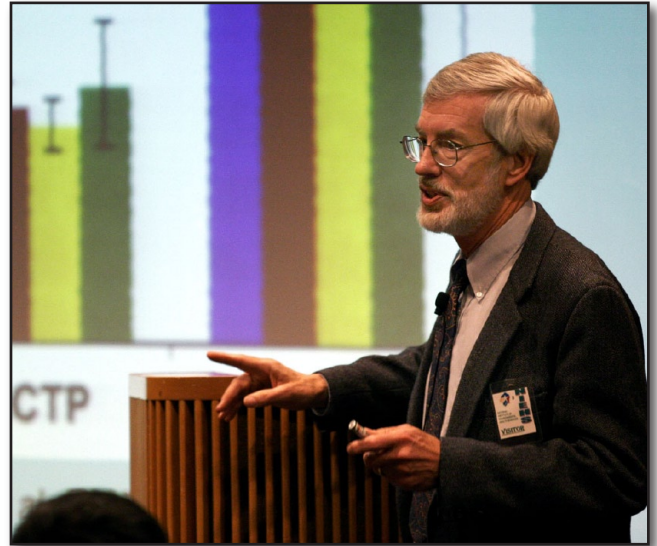
Christopher Mathews, Ph.D., gave the most recent talk in the Laboratory of Molecular Genetics (LMG) Fellows Invited Guest Lecture Series on April 2. Mathews is a Distinguished Professor Emeritus of the Department of Biochemistry and Biophysics and a member of the Environmental Mutagenesis and Carcinogenesis Research Core at Oregon State University. His lecture was titled “Maintaining Precursor Pools for Mitochondrial DNA Replication.”

Mathews’ talk focused on the imbalances in intracellular concentrations of the four deoxyribonucleoside triphosphates (dNTPs) that serve as the building blocks of DNA and their involvement in mutagenesis and, ultimately, cancer. His research suggests the intriguing possibility that alterations in the sizes of or ratios among these four precursor pools may be one of the earliest biochemical changes leading to mutations responsible for some mitochondria-linked diseases and cancer — that “pool size changes could be related to actual mutational pathways occurring *in vivo*,” he explained.

The term “pool” refers to the amount of each dNTP contained in a cell. Mathews has conducted laboratory experiments to determine the size and ratios of the four mitochondrial (mt) dNTP pools under normal conditions and conditions of induced imbalance. His lab has also explored the metabolic and genetic control and properties of the enzymes that generate dNTPs, ribonucleoside diphosphate (NDP) reductase and ribonucleotide reductase (RNR).

Mathews has found that normal cells have naturally unbalanced pool sizes and that deviation from this delicate balance can induce replication errors, stimulating genomic instability and mutagenesis. Specifically, Mathews has discovered that mitochondrial dNTP pools can vary dramatically from cytosolic pools. Because mtDNA replication is a continuous process in the cell, replication errors, including point mutations and deletions, can have a cumulative effect.

The high spontaneous mutation rate of mtDNA thus may help account for the large number of genetic differences between a tumor cell and the normal cell where it originated. A better understanding of nucleic acid enzymology could lead to identification of novel targets for antiviral and anticancer drugs.



LMG Fellows Invited Guest Lecturer Christopher Mathews. (Photo courtesy of Steve McCaw)



LMG Senior Investigator Ben Van Houten was intrigued by recent data from Mathew’s research. (Photo courtesy of Steve McCaw)

In the course of researching dNTP pools, Mathews' lab has developed methodologies for studying specific processes of DNA biosynthesis that were previously not well understood and has challenged some of the common wisdom about them. He has explored the hypothesis that damaged nucleotides may be pre-mutagenic lesions in part because of their oxidation by free radical species prior to incorporation into DNA.

The lab developed an HPLC assay to measure pool sizes of one of the oxidized nucleotides, 8-oxo-dGTP, in cell extracts. Although he found dGTP to be the least abundant dNTP in mammalian or bacterial cells, his data called into question the widespread assumption that dGTP oxidation is a significant contributor to mutagenesis induced by reactive oxygen species.

Several times during his lecture, Mathews acknowledged that many questions still need to be answered about the role of precursor pools in the cancer cascade.

"We obviously have a lot of work ahead of us," he said

at one point about the technical difficulties he has encountered. In addition, there is the fundamental question that Mathews and other researchers continue to face: is the mutagenic accumulation of dNTPs, as it seems, an important step in the process of carcinogenesis — or could it be an accidental by-product?

LMG Fellow Stephanie Nick- McElhinny was host for the lecture.

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Frontiers in Environmental Sciences Lecture Series Update

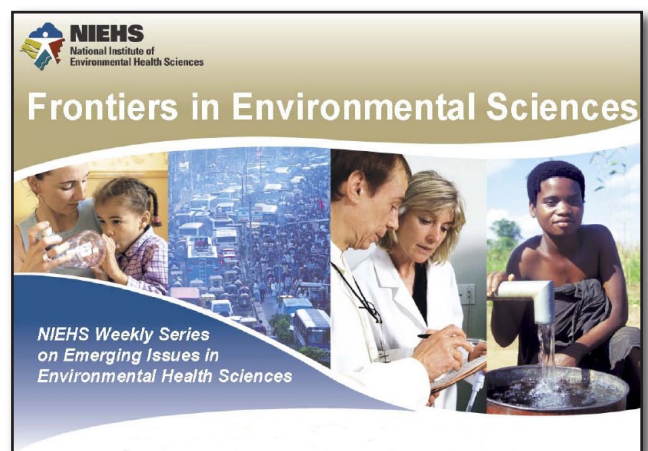
By Eddy Ball

The Frontiers in Environmental Science Lecture Series continued in April with RTP area scientists sharing results of their recent research with scientists at NIEHS. March closed with a lecture by Geneticist Fernando Pardo-Manuel de Villena, Ph.D. Lectures in April included talks on the mechanisms of carcinogenesis by Experimental Pathologist William K. Kaufmann, Ph.D., Neurophysiologist David Armstrong, Ph.D., and Pathologist James Swenberg, D.V.M., Ph.D.

As web casts of the lectures become available, they will be posted on the Frontiers in Environmental Science [website](#).



LMG Senior Investigator Bill Copeland (foreground) and Supervisory Research Geneticist Mike Resnick (at right, taking notes) joined fellows from their labs at the lecture. (Photo courtesy of Steve McCaw)



March 30: “On the Origin of the Laboratory Mouse: Lessons from the NIEHS Resequencing Project” by Fernando Pardo-Manuel de Villena, Ph.D. Hosted by William Schrader, Ph.D.

Fernando Pardo-Manuel de Villena is an assistant professor of cancer genetics at the UNC-CH Lineberger Comprehensive Cancer Center. His laboratory is interested in the study of nonrandom segregation of chromosomes during meiosis in mammals, and he is a pioneer in utilizing the results of the NIEHS Mouse Genome Resequencing Project.

Analysis of the project’s copious data revealed a significant degree of variation in the laboratory mouse, leading to the realization that different families of the genus *Mus* can be as different from each other as humans are from chimpanzees. His research, which has been submitted for publication, convinced Pardo-Manuel de Villena that researchers still do not have a good mouse population to use.

April 6: “Mechanisms of Human Environmental Carcinogenesis” by William Kaufmann, Ph.D. Hosted by Christopher Portier, Ph.D.

William Kaufmann is a researcher in the Laboratory of Human DNA Metabolism in the Department of Pathology at the University of North Carolina. His main interest relates to the manner in which cell cycle checkpoints suppress chromosomal instability.

Kaufmann used his findings in research on melanoma as the model for the ways human environmental carcinogenesis modifies checkpoints’ suppression of chromosomal instability. He has also been able to pinpoint markers of early stage carcinogenesis that may help clinicians intervene more successfully. Melanoma is an especially fruitful tumor to study, according to Kaufmann, because it is possibly the most prevalent and directly lethal of any of the recognized environmental diseases, killing some 7,000 individuals each year.

April 13: “Thyroid Hormone Signaling and the Implications of Its Disruption for Human Health” by David Armstrong, Ph.D. Hosted by Christopher Portier, Ph.D.

Principal Investigator David Armstrong serves as acting chief of the NIEHS Laboratory of Neurobiology. He and his colleagues in the [Membrane Signaling Group](#) investigate the signal transduction pathways that regulate the activity of voltage-gated calcium and potassium channels in the mammalian neuroendocrine system.

His lecture focused on thyroid hormone, which is essential for normal development and metabolism of many human tissues including the brain. When thyroid hormone production or signaling is disrupted during development, the implications can be severe, including deafness, growth retardation and reductions in cognitive ability. According to Armstrong, the basic molecular mechanisms responsible for thyroid hormone’s effects on brain development are not completely understood.



At his April 13 lecture, David Armstrong discussed the health effects of disruption in thyroid hormone signaling. (Photo courtesy of Steve McCaw)

April 20: “The Use of Biomarkers to Inform Mechanisms of Carcinogenesis and Risk Assessment” by James Swenberg, D.V.M., Ph.D. Hosted by John Pritchard, Ph.D.

James Swenberg is the Kenan Distinguished Professor of Environmental Sciences and Engineering and faculty director of the UNC-CH Lineberger Comprehensive Cancer Center. He is interested in the role of DNA damage and repair in toxicity, carcinogenesis and risk assessment, including damage arising from direct interaction of chemicals or their metabolites and indirect damage arising from oxidative stress.

His talk focused on results of experiments with ultra-sensitive and highly specific mass spectrometry methods for measuring the DNA and hemoglobin adducts of vinyl chloride and 1,3 butadiene. He has found that identical DNA adducts are caused by lipid peroxidation. Among other findings, he has determined that low exposures to vinyl chloride, such as are found in occupational settings (0.1 ppm), were associated with only a 5% increase over the endogenous levels.

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GEMS Showcases Systems Biology Approach at Spring Meeting

By Eddy Ball

The Genetics and Environmental Mutagenesis Society (GEMS) held its 2007 Spring Meeting April 16th at the Environmental Protection Agency (EPA) RTP headquarters. The meeting’s theme was “Integrative Bioinformatics: Systems Biology Approaches to Genetics, Metabolism and Disease.” In the absence of GEMS President-Elect Rose Anne McGee, President Greg Stuart, Ph.D., chaired the meeting.

Speaking at the half-day event were two NIEHS investigators, Ben Van Houten, Ph.D., and Chris Portier, Ph.D., and two Triangle-area biologists, William K. Kaufmann, Ph.D., of the University of North Carolina at Chapel Hill and Paul M. Magwene, Ph.D., of Duke University. A fifth speaker, Michael B. Yaffe, Ph.D., of Massachusetts Institute of Technology, was unable to attend the meeting due to flight cancellations in Boston.

The meeting opened with an introduction to the systems biology approach by Van Houten, who is a senior investigator and head of the DNA Repair and Mitochondrial Damage Group in the Laboratory of Molecular Genetics (LMG). Van Houten explained the difference between the characteristic reductionist approach in science and the emphasis on synthesis and integration that is the hallmark of systems biology.

“Systems biology is a complete description of how all of the components of a biological system work together,” Van Houten explained as he outlined the four basic steps of the approach. After describing the system as completely as possible, he continued, “then do something to that system, add a chemical, knock out a gene, perturb it in some way.”



Attendees at the Spring 2007 GEMS Meeting enjoyed lunch before the presentations began. (Photo courtesy of Steve McCaw)

With the system perturbed, the researcher then measures the changes in that system as globally as possible — typically using “omics” methodologies and taking advantages of databases, such as genome sequencing, RNAi libraries and mapping. Based on insight into the system gained by studying it under stress, he noted, “you can then describe the system much better because you understand how the system changes.”

Van Houten then demonstrated how a systems biology approach helped his group gain insight into accumulated mitochondrial DNA damage and common gene expression patterns unique to the pathogenesis of disease in patients with Friedreich’s Ataxia. Pathways analysis allowed the team to identify transcriptional changes associated with cell death, cardiovascular disease, neurological disease, and muscular and skeletal disorders.

In his presentation, Portier, NIEHS associate director and director of the Office of Risk Assessment Research, focused on applying the tools and principles of systems biology to evaluation of health risks from exposure to environmental agents. This kind of research can have important regulatory consequences, and researchers must take into consideration such factors as economic cost and society’s wants in an effort to formulate policies based on rigorous scientific investigation and sophisticated computer modeling.

Kaufmann, a researcher in the UNC Laboratory of Human DNA Metabolism, has applied systems biology to his investigations into the severe chromosomal instability that leads to development of malignant melanoma. He and his colleagues have used computational tools to create models of nucleotide excision repair and the G2 checkpoint. With these models they have simulated the cell’s response to DNA damage in order to discover new alleles that can protect against the ultra violet light-induced chromosomal damage that triggers this environmental cancer.

NIEHS and GEMS

Celebrating its twenty-fifth anniversary this year, GEMS is a regionally active group of scientists, toxicologists and others sharing a common interest in the interplay of genetics and the environment. The group holds two meetings each year, one in April and a larger, full-day event in November that features talks and poster session competitions for postdoctoral fellows.

Although the GEMS membership includes scientists with an interest in toxicology and mutagenesis from many of the Triangle’s government agencies, universities and private sector research groups, NIEHS scientists and fellows make up a significant part of the membership and board of directors:

President Greg Stuart, Ph.D. - Stuart works as a special volunteer in the Mitochondrial Replication Group with LMG Director William Copeland, Ph.D. He is supported by a National Research Council Research Associateship Award from the National Academies.

President-Elect Rose Anne McGee – McGee is a biologist working in the Division of Extramural Research and Training. She is an associate scientific review administrator with the Scientific Review Branch.

Secretary Gloria Jahnke, D.V.M. – Jahnke is a toxicologist employed by Sciences International who, until recently, worked as a contract scientist with the National Toxicology Program at NIEHS.

2005-2007 Councilor Janice Allen, Ph.D. – Allen is a molecular biologist working in the Division of Extramural Research and Training. She is a health scientist administrator in the Scientific Review Branch.

2006-2008 Councilor Cindy Innes – Innes is a biologist with the Environmental Toxicology Program. She is involved in research in the Laboratory of Molecular Toxicology.

2007-2009 Councilor Dan Shaughnessy, Ph.D. – Shaughnessy holds a doctoral degree in environmental health. He was a fellow in the Laboratory of Molecular Carcinogenesis before taking a position as a health program administrator in the Division of Extramural Research and Training Susceptibility and Population Health Branch.

2007-2009 Councilor Kristine L. Witt – Witt is a toxicologist in the Environmental Toxicology Program. She is involved with research in the Toxicology Operations Branch.

PostDoctoral Member Dario C. Ramirez, Ph.D. – Ramirez is a fellow in the Environmental Toxicology Program and works in the Laboratory of Pharmacology and Chemistry. When he won the Best Talk/Travel Award at the 2006 GEMS Fall Meeting, he was invited to join the board.

Closing out the program, Magwene, a professor of biology at Duke Institute for Genome Sciences and Policy, discussed the experimental and computational approaches his group has used in yeast to understand the phenomenon of pleiotropy, the ability of a gene to manifest itself in more than one way in different tissues. Magwene has taken a systems approach to explore the contributions of genetic architecture, genetic variation and evolutionary history to producing these effects.

To find out more about upcoming programs sponsored by GEMS or to join the group, visit the [GEMS website](#). GEMS actively promotes the involvement of students by offering memberships for \$5.00 and a reduced fee of \$10.00 for meeting registration and encourages participation by minority groups, women in science, and handicapped or other historically under-represented groups, according to Stuart.

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Van Houten was the keynote speaker at the meeting. (Photo courtesy of Steve McCaw)



When GEMS President Greg Stuart presented Portier with his honorary coffee mug, Portier joked that he'd need to list it on his annual NIEHS financial disclosure statement. (Photo courtesy of Steve McCaw)



A systems biology approach helped UNC Professor Kauffmann pinpoint where in the cell cycle that double strand breaks in DNA were more likely to evade DNA repair. (Photo courtesy of Steve McCaw)



A major research interest in the Magwene Lab at Duke is developing analytical and algorithmic approaches for addressing problems in systems biology and evolutionary biology. (Photo courtesy of Steve McCaw)

Upcoming: Distinguished Lecturer to Discuss Gene Transcription

By Eddy Ball

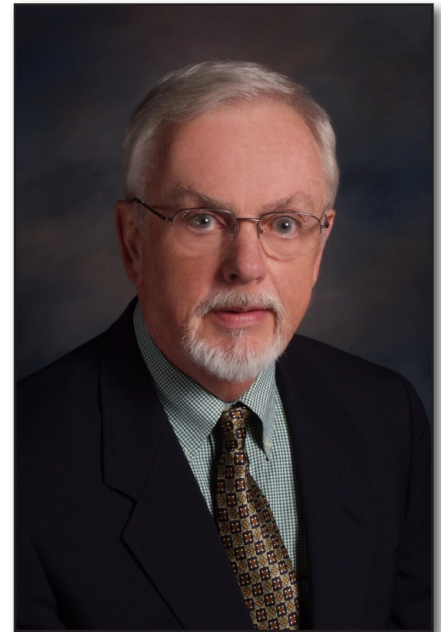
Bert. W. O'Malley, M.D. will deliver the final talk in the 2006-2007 NIEHS Distinguished Lecture Series on May 22 at 11:00 in Rodbell Auditorium. O'Malley is a professor and the chair of the Department of Molecular/Cell Biology at Baylor College of Medicine. He will address "The Expanding Roles of Nuclear Receptor Coactivators."

O'Malley's lab has cloned and studied a number of different subfamilies of nuclear receptor family coactivators and examined their role in enhancing gene transcription. He describes coactivators as the "boosters" or "amplifiers" of the transcriptional regulation exerted by nuclear receptors and has looked into their role in the epigenetic changes that are involved in tumor development. According to current thinking, steroid receptors/coactivators affect steps in gene expression that include initiation, re-initiation, mRNA processing and termination.

He and his associates recently described for the first time the pathway of a powerful promoter of tumor growth, steroid receptor coactivator 3, and the action of a tumor suppressor molecule REG-gamma — a development that may prove to have important clinical applications in the treatment of breast, prostate and similar cancers.

John Cidlowski, Ph.D., is the lecture host.

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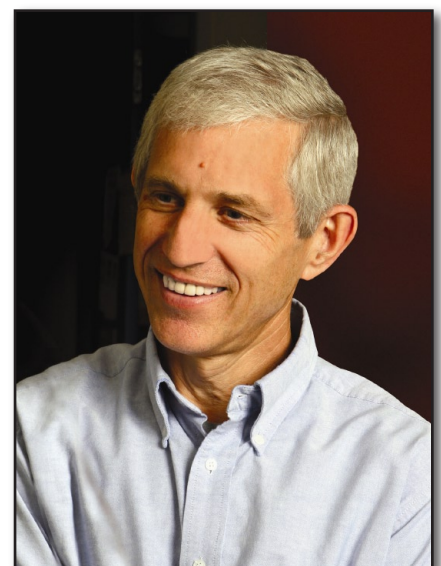


*Distinguished Lecturer Bert O'Malley
(Photo courtesy of Baylor College
of Medicine)*

Upcoming: Kunkel to Speak in Duke Seminar Series

Speaking at the Nanaline H. Duke Building on Research Drive in Durham on May 11, NIEHS Senior Investigator Tom Kunkel, Ph.D., will deliver the penultimate talk in the Spring 2007 Duke University Medical Center Biochemistry Seminar Series. Kunkel's lecture, titled "Structure-Function Studies of DNA Replication Fidelity," will begin at 12:00 in room 147. Kunkel is chief of the Laboratory of Structural Biology and a member of the Laboratory of Molecular Genetics.

As Kunkel will explain in his talk, replication of eukaryotic nuclear genomes requires DNA polymerase alpha to initiate synthesis at origins and of Okazaki fragments on the lagging strand, subsequently allowing DNA polymerases delta and epsilon to then perform the bulk of chain elongation. Amazingly, we still do not know with certainty which of the latter two polymerases replicates the leading strand and which replicates the lagging strand.



*Senior Investigator Tom Kunkel.
(Photo courtesy of Steve McCaw)*

In an attempt to identify the leading and lagging strand polymerase(s), Kunkel's group has used a structure-function approach to generate yeast pol alpha, delta and epsilon mutator derivatives with six characteristics that will help to assign where and when these enzymes operate in cells.

This seminar will describe biochemical and *in vivo* studies of one such mutator polymerase allele that support the interpretation that DNA polymerase epsilon has an important role in leading strand DNA replication.

No registration is required for this seminar, and the series is open to the public.

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Upcoming: Zeldin to Give Talk at UNC-CH Medical School

NIEHS Senior Scientist Darryl Zeldin, M.D., will lecture on "Cytochrome P450 Metabolites and Cardiovascular Disease" on May 14 in Chapel Hill. Zeldin is a principal investigator in the Laboratory of Respiratory Biology. He will speak at 12:00 p.m. in G202 in the Medical Biomolecular Research Building at the University of North Carolina, 103 Mason Farm Road.

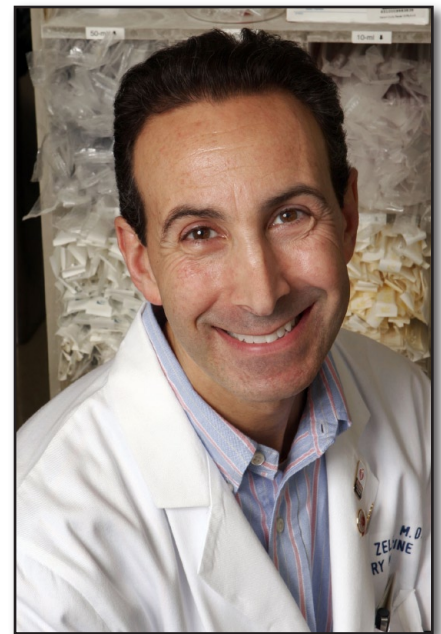
According to Zeldin, cytochrome P450 epoxygenases such as CYP2J2 metabolize arachidonic acid to epoxyeicosatrienoic acids (EETs) which are converted to dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (EPHX2). Previous work has shown that EETs possess a myriad of potent biological effects within the cardiovascular system.

Studies with CYP2J2 transgenic and Epx2 null mice confirm that this eicosanoid pathway is involved in maintenance of cardiovascular homeostasis. Recent studies have documented that genetic variation in both the *CYP2J2* and *EPHX2* genes influences cardiovascular disease risk in humans.

Genetic variation in the *EPHX2* gene is associated with increased risk of incident coronary heart disease in a large prospective cohort from the United States. The development of pharmaceuticals which enhance circulating EET levels, either by activating P450 epoxygenases or inhibiting EPHX2, may represent a novel approach to cardiovascular disease prevention and/or treatment.

Zeldin's lecture is sponsored by the UNC School of Medicine. No registration is required for this lecture, and the series is open to the public.

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Senior Scientist Darryl Zeldin
(Photo courtesy of Steve McCaw)

Upcoming: Frontiers in Environmental Sciences Lectures in May

By Eddy Ball

The NIEHS weekly lecture series on emerging issues in environmental sciences continues in May. Unless otherwise indicated, lectures take place at 9:00 a.m. on Fridays in Rodbell Auditorium.

- **May 4:** Mike Ehlers, M.D., Ph.D., Duke University, “Receptor Trafficking and Dynamic Nanoarchitecture of the Postsynaptic Membrane.” Hosted by Serena Dudek, Ph.D.
- **May 11:** Donald Lo, Ph.D., Duke, “New Brain Tissue-Based, High-Throughput Models for Neurodegenerative Diseases.” Hosted by David Armstrong, Ph.D.
- **May 18:** Yvonne Dragan, Ph.D. (tentative), Topic TBA. Hosted by Chris Portier, Ph.D.
- **May 25:** OPEN
- **June 1:** Vann Bennett, M.D., Ph.D., Duke, Topic TBA. Hosted by David Armstrong, Ph.D.

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DETR Papers of the Month

By Jerry Phelps

Birch-bark Extract, Betulinic Acid, Inhibits Prostate Cancer Growth

Betulinic acid is an oxidation product of betulin, a traditional medicine product of the triterpene family derived from birch tree bark. Previous research characterized it as an effective inhibitor of human melanoma tumor growth through the induction of apoptosis. Other triterpenoid compounds have the same anti-carcinogenic and anti-inflammatory effects and are currently being studied in clinical trials for their potential use in treating leukemia.

A group of NIEHS-supported researchers reports that betulinic acid might also be an effective treatment for prostate cancer. In a series of experiments using prostate cancer cell cultures and an animal model of prostate cancer, betulinic acid treatment decreased the growth of the cancer cells. The compound induced proteasome-dependent degradation of the specificity protein transcription factors Sp1, Sp3 and Sp4 in the prostate cancer cells. These factors are over-expressed in many tumor types.

These results indicate the anti-tumor effects of betulinic acid are associated with specific degradation of specificity protein transcription factors resulting in the inhibition of blood vessel formation and the activation of pro-apoptotic responses in tumors, but not in non-target tissues exhibiting low specificity protein expression. Ongoing studies with betulinic acid are investigating tumor-type similarities and more potent formulations for possible new chemotherapeutic agents.

Citation: [Chintharlapalli S, Papineni S, Ramaiah SK, Safe S.](#) 2007. Betulinic acid inhibits prostate cancer growth through inhibition of specificity protein transcription factors. *Cancer Res* 67(6):2816-2823.

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Remodeling Complex Activates Nucleosomes for Migration to Chromatin

Repair of double strand breaks (DSBs) in DNA protects organisms by maintaining the integrity of their genomic structures. The most serious type of DNA damage, DSBs occur in chromatin, the tightly wound complexes of DNA and associated proteins known as histones that enable DNA to fit into a smaller volume within the cellular nucleus. Previous research has implicated histone modification and chromatin remodeling in the recognition and repair of DSBs; however, the nature of the remodeling and how it affects DSBs are not fully understood.

NIEHS-funded researchers recently discovered a chromatin alteration caused by a single DSB generated by an enzyme known as Ho endonuclease. The experiments were carried out using *Saccharomyces cerevisiae*, a well-known yeast model. The break causes rapid migration to the damage site of nucleosomes, which form histone-free DNA 200-300 base pairs in length adjacent to the break. Additional experiments determined that blocking a key chromatin structure remodeling complex (RSC) or deleting *RSC2* severely reduced chromatin remodeling.

Ionizing radiation and oxidative free radicals, agents humans are exposed to every day, can cause breaks in both strands of DNA. The investigators conclude that RSC is vital for efficient DSB repair by mediating chromatin remodeling at the site of the break and allowing the repair machinery access.

Citation: [Shim EY, Hong SJ, Oum JH, Yanez Y, Zhang Y, Lee SE](#). 2007. RSC mobilizes nucleosomes to improve accessibility of repair machinery to the damaged chromatin. *Mol Cell Biol* 27(5):1602-1613.

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Dietary Antioxidant Flavonoids Protect Against Post-Menopausal Breast Cancer

Flavonoids, also called bioflavonoids, are a class of plant compounds most commonly known for their antioxidant properties. They are commonly found in citrus fruits, green tea and grape skins. Previous research suggests that flavonoids have anti-carcinogenic properties. Research conducted as a part of the Long Island Breast Cancer Study Project shows that dietary flavonoid intake is associated with a decreased risk of breast cancer in post-menopausal women.

The study examined a total of 1,434 cases of breast cancer along with 1,440 controls. Cases and controls were interviewed regarding known and suspected risk factors for breast cancer and were asked to complete a food frequency questionnaire. The researchers found a decrease in breast cancer risk associated with dietary flavonoid intake which was stronger for post-menopausal women. The reduced risk varied from about 25 percent to 50 percent based on the type of flavonoid consumed.

Numerous laboratory studies show that flavonoids are able to inhibit aromatase, a key enzyme in the production of estrogen, inhibit tumor cell proliferation and decrease the production of reactive oxygen compounds. All of these mechanisms are thought to influence breast cancer development. This study suggests that post-menopausal women could reduce their risk of developing breast cancer by eating foods or drinking beverages containing flavonoids.

Citation: [Fink BN, Steck SE, Wolff MS, Britton JA, Kabat GC, Schroeder JC, Teitelbaum SL, Neugut AI, Gammon MD](#). 2007. Dietary flavonoid intake and breast cancer risk among women on Long Island. *Am J Epidemiol* 165(5):514-523.

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Glutathione Gene Polymorphism Protects Against Pancreatic Cancer in Elderly

Each year in the United States, nearly 34,000 people are diagnosed with pancreatic cancer and some 32,000 of them will die within five years of diagnosis with about half dying within 6 months. The only known risk factor for the malignancy is smoking, and very little is known about how genetic and environmental factors interact to lead to the disease.

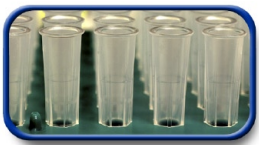
An NIEHS-funded team of investigators hypothesized that genetic variations in the detoxifying enzyme glutathione S-transferase (GST) affect the detoxification of carcinogenic agents and chemotherapeutic agents in the pancreas, thus impacting the risk and survival of pancreatic cancer. They studied 352 pancreatic cancer patients and matched them to 315 healthy control subjects.

The study results show that older individuals with the GST polymorphism known as *GSTP1**C had a reduced risk, and in 5-fluorouracil treated patients, those with the *GSTP1**C lived significantly longer, about six months. This study is believed to be the first to suggest a protective effect of *GSTP1* polymorphisms in pancreatic cancer.

The authors conclude that genetic polymorphisms of *GSTP1* could be one of several possible mechanisms that modify the risk of pancreatic cancer in older people and may affect the survival rate.

Citation: [Jiao L, Bondy ML, Hassan MM, Chang DZ, Abbruzzese JL, Evans DB, Smolensky MH, Li D. 2007. Glutathione S-transferase gene polymorphisms and risk and survival of pancreatic cancer. Cancer 109\(5\):840-848.](#)

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DIR Papers of the Month

By Eddy Ball

Receptor Signaling Key in Mouse Embryo Development

NIEHS-funded investigators have demonstrated *in vivo* the crucial role played by a bone morphogenetic protein (BMP) type I receptor known as ALK2 in early mouse embryogenesis. The scientists from the NIEHS Molecular Developmental Biology Group and the Knock Out Core, in collaboration with two University of Southern California researchers, reported their results in the February issue of the journal *Developmental Dynamics*.

The research team analyzed mutant mice embryos with deleted gene coding sequences, called exons, to determine the effects on development. A normal vertebrate embryo develops from a simple multi-cell state (blastocyst) into a complex, three-dimensional organism through an infolding process called gastrulation. The investigators found that mutation in *Alk2* by deletion of exon 5 or 7 interfered with BMP signaling and prevented gastrulation from taking place. The embryo died as a result of failing to undergo normal development. Expression analyses identified dramatic down-regulation of key genes for proper development, suggesting that *Alk2* is involved in their cascades.

While the downstream target genes of *Alk2* are as yet unknown, this study brings researchers closer to understanding the causes of developmental failure in the mouse embryo — and offers insight into developmental problems, such as cranial, cardiac and neuronal dysgenesis in human and other mammalian embryo.

Citation: [Komatsu Y, Scott G, Nagy A, Kaartinen V, Mishina Y](#). 2007. BMP type I receptor ALK2 is essential for proper patterning at late gastrulation during mouse embryogenesis. *Dev Dyn* 236(2):512-517.

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Receptor D6-Deficient Mice Show Lowered Airway Reactivity

In a recent NIEHS-funded study, a team of researchers led by investigators in the Laboratory of Respiratory Biology found an unexpected decrease in airway reactivity among allergen-challenged receptor D6-deficient mice. The researchers had set out to determine whether D6 has chemokine-binding and anti-inflammatory functions in the lung, as it does in the skin.

To do this, the researchers compared the responses of D6-deficient mice and genetically matched C57BL/6 mice that had been sensitized to ovalbumin and exposed to either a single-day acute or a 7-day challenge with this allergen. The investigators then analyzed airway inflammation and chemokine levels, leukocyte accumulation and airway responsiveness. They found that the D6-deficient mice had greater pulmonary inflammation than C57BL/6 mice following these challenges. Unexpectedly, however, they found that airway responses after the acute exposure were significantly higher in C57BL/6 mice than in the D6-deficient strain, despite the higher levels of inflammation in the altered strain. The same trend was also seen in naïve D6-deficient mice.

If it can be determined that D6 functions similarly in humans, the researchers concluded, “antagonists of D6 might provide a novel therapeutic avenue to reduce air hyper-reactivity in some clinical settings.”

Citation: [Whitehead GS, Wang T, DeGraff LM, Card JW, Lira SA, Graham GJ, Cook DN](#). 2007. The chemokine receptor D6 has opposing effects on allergic inflammation and airway reactivity. *Am J Respir Crit Care Med* 175(3):243-249.

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Inflammation Pathways and the Blood-Brain Barrier

Researchers at the NIEHS Laboratory of Pharmacology and Chemistry have described a novel signaling pathway that, when activated by chronic inflammation, can up-regulate a drug efflux transport protein that tightens the blood brain barrier protecting the central nervous system (CNS). For a significant number of patients, this tightening of the barrier effectively reduces the efficacy of pharmacological treatment for such CNS disorders as epilepsy and glioblastoma, a common primary tumor of the brain.

The researchers examined the long term consequences of inflammation by continuously exposing rat brain capillaries *in vitro* to one of two inflammatory mediators, tumor necrosis factor- α or endothelin-1, components of the brain’s innate immune response. Exposure triggered a rapid, initial decrease in P-glycoprotein activity, two- to three-hours at the low activity level and then a dramatic increase in activity. The initial weakening of

the barrier's selective defense may provide a therapeutic window for pharmaceuticals that normally enter the CNS poorly. The dramatic up-regulation of P-glycoprotein activity six hours following the brain's initial immune response then makes it harder for drugs to reach the CNS.

Results of the study, which appeared in the March 2007 issue of the journal *Molecular Pharmacology*, may point the way toward development of new interventions to treat CNS disorders, possibly by targeting inflammatory signaling pathway the authors were the first investigators to describe.

Citation: [Bauer B, Hartz AM, Miller DS](#). 2007. Tumor necrosis factor alpha and endothelin-1 increase P-glycoprotein expression and transport activity at the blood-brain barrier. *Mol Pharmacol* 71(3):667-675.

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Smoking Linked to Increased Telomerase Activity in Lung Cells

A multi-disciplinary research team has demonstrated a strong association between levels of telomerase activity and the number of pack-years of smoking in human cell culture analysis. Telomerase is an enzyme that regulates cell replication, and increases in telomerase activity may signal the development of cancerous cells.

The NIEHS-funded team included investigators from the Laboratory of Molecular Carcinogenesis, Epidemiology Branch and Biostatistics Branch working in collaboration with scientists from the Catholic University of Korea, Vanderbilt University and the University of North Carolina at Chapel Hill. The scientists obtained bronchial epithelial (HBE) cells from 26 subjects and determined the telomerase activity in the cultures using a telomeric repeat amplification protocol assay.

The study could not establish definitively a causative role of tobacco in the activation of telomerase. However, the research team did demonstrate an association between tobacco carcinogen exposure and telomerase activity in normal bronchial epithelium — suggesting that tobacco carcinogen exposure might reflect an early and specific molecular change that is associated with an increased potential lifespan of these cells.

This research is important because telomerase activation and other epigenetic alterations, such as K-ras activation, p16 promoter hyper-methylation and p53 mutation, can occur in normal human cells before any clinical evidence of the disease is manifest.

Citation: [Yim HW, Slebos RJ, Randell SH, Umbach DM, Parsons AM, Rivera MP, Detterbeck FC, Taylor JA](#). 2007. Smoking is associated with increased telomerase activity in short-term cultures of human bronchial epithelial cells. *Cancer Lett* 246(1-2):24-33.

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Inside the Institute

NIEHS Showcases Travel and Vacation Opportunities

By Eddy Ball

On April 4, Alma Britton, Dona McNeill and others in the Administrative Services and Analysis Branch did their part to help NIEHS employees and contractors learn more about why tourism is such a big deal in North Carolina. This was a brand new idea for NIEHS. Representatives from North Carolina tourist industry, companies, organizations and chambers of commerce set up booths to promote their destinations at the newly popular NIEHS Travel and Vacation Fair.

The North Carolina Tourism Division claims that tourism is one of the state's biggest industries, luring 45 million people and \$14 billion to the state each year. Looking at the Fair's sample of all the state has to offer, it's easy to see why. North Carolina offers visitors three distinctly different regions full of things to see and do. The Travel and Vacation Fair had booths with four of North Carolina's growing number of vineyards, several beach destinations and some mountain favorites. The Piedmont was represented by the North Carolina Zoo in Asheboro and the cities of Winston-Salem, Fayetteville and Durham.

As promised by Britton and McNeill, there were goodies for the taking, even some free food, and the event was a big hit with people touched with spring fever and wanderlust. The big disappointment, however, was that all the wine bottles in Rodbell Auditorium remained securely corked because of government policy.



By lunchtime, Rodbell Auditorium was crowded with the curious. (Photo by Eddy Ball)



Although the wine caught his eye, Scott Merkle had to be satisfied with water and soft drinks from the cafeteria. (Photo by Eddy Ball)



Ranger Martha Flanagan's photo display of state parks was a draw for outdoor enthusiasts. (Photo by Eddy Ball)



Welcome Center Specialist Buck West represented the Eastern Band of the Cherokee Indians. Two days each week he works at the Oconoluftee Indian Village, a re-creation of an early 18th-century Cherokee community. (Photo by Eddy Ball)



As folks soon found out, there's more to nearby Fayetteville than soldiers, pawn shops and bars. (Photo by Eddy Ball)



Wine, wine everywhere, but not a drop to drink. Connoisseurs will just have to visit Dupin Winery to find out if they like the line of North Carolina-produced wines. (Photo by Eddy Ball)

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Vendors Promote Products in Spring Show

By Eddy Ball

On April 5, sales representatives from 34 suppliers of laboratory and medical equipment lined the mall area in D and E modules to show off new products, give away trademarked merchandise and convince the Institute's scientists that their products and services would outperform what's now being used in the labs.

Like manufacturers of tennis shoes, i-pods and cell phones, laboratory equipment suppliers make good use of color and eye-catching design to set their products off from the competition. Whether the products on display are the old standard pipettes and plates or state-of-the-art benchtop homogenizers and digital microcentrifuges, iMac colors are the in thing — and a great way to bring out the inner child in a customer. Even when straight lines, impact-resistant white plastic and stainless steel can't be avoided in a product, manufacturers seem to find some way to make new products “cooler” and more desirable than what scientists now have on hand.

“Cutting-edge” and “integrated” were important adjectives for reps at the fair trying to market cell culture tools for stem cell research and detection reagents and antibodies for proteomics. Because many of the suppliers at the NIEHS Spring Vendor Show were North Carolina-based, often right here in the Triangle, service and quick turnaround were also popular themes.

Vendor shows are an important part of making NIEHS science better and more efficient. New products force scientists to re-think the familiar and expose themselves to new and improved ways of doing their important work. The shows also save time by bringing different suppliers together in one venue so buyers can compare the wares displayed side by side.



Two modules in length, the show featured colorful displays, such as this one from Sarstedt, tempting scientists to stop to look at new supplies for their labs. (Photo by Eddy Ball)



Just 30 minutes into the six-hour event, the show was already filling up, and most of the reps were staying busy with new prospects. (Photo by Eddy Ball)



VWR International Rep Carmen Costa clearly had the salesperson's winning combination — an inviting smile and boundless confidence in her product line. "We have everything you need," she proudly announced to potential customers. (Photo by Eddy Ball)



Appearing a bit skeptical, Laboratory Technician Trisha M. Castranio looked on as Biologist Greg Scott, center, checked out new products. The salesman stood by ready to answer questions, but he also was poised to make eye contact with new prospects. (Photo by Eddy Ball)

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Spring is Book Time at NIEHS

By Eddy Ball

Spring is a time to celebrate the outdoors, break out the summer clothes and begin to attack those extra winter pounds with a vengeance. At NIEHS, however, it's also a time for a little browsing and book buying at two events sponsored by the Institute's Fitness and Wellness Program to help employees and contractors exercise their minds as well as their bodies.

On March 27 and 28, NIEHS held the fourth annual Usborne Children's Book Fair in the D-Mall in the Rall Building. The colorful display of books, puzzles and games for children of all ages beckoned parents, relatives and the simply curious to see what was new this year — and possibly recapture the wonder they felt themselves as children exploring new worlds through the magic of reading.



Usborne Books Representative Shelley Morrisette (Photo by Eddy Ball)

Usborne Representative Shelley Morrisette was on hand to help customers find age-appropriate materials. Titles ranged from items in the *Your Baby Can Read* and *Fabulous Fiction* series, for younger learners, to *Energy, Forces and Motion* and *The Victorians*, for more advanced readers.

The books aren't just for kids, Morrissette noted. "I've seen grown-ups spend time browsing our more advanced books, especially the ones on World War II and sports." Along with its own authors, Usborne also publishes several classics for all ages, such as Mark Twain's *Tom Sawyer* and Mary Shelley's *Frankenstein*.

Along with its reputation for quality and colorful books for children, United Kingdom-based Usborne Publishing is recognized for its innovative line of internet-linked books. The company promotes this line as offering children "an invaluable aid for homework and an extra measure of safety in cyberspace." Usborne's linking saves time by cutting out search engines. Because young readers access the web indirectly through Usborne links, the books take readers safely and quickly to related content on the Internet, helping parents prevent children's accidental access to adult material or otherwise offensive content.



Parents of toddlers had a wide range of Usborne selections. (Photo by Eddy Ball)

On April 19, the D-module mall became a temporary bookstore again as Books Are Fun held its spring sale. While Usborne Publishing specializes in books for children and young adults, twice each year Books Are Fun brings a large selection of books for all ages and interests to NIEHS, priced as much as 70 percent less than retail. A division of Reader's Digest, Books Are Fun also offers a range of music CDs, DVDs, knick-knacks and book-related items.



Contractor Joyce Pulliam stopped by the Usborne Book Fair during her lunch break to browse the selection of books for very young children. (Photo by Eddy Ball)



Project Officer Jennie Foushee (left) asked Books Are Fun Representative Sharon Bobbitt for help finding a CD. (Photo by Eddy Ball)



The Books Are Fun rows stretched almost the entire length of D-module. (Photo by Eddy Ball)



Laboratory of Neurobiology Special Volunteer Chao Chuan Wang, Ph.D., browsed the cooking section at Books Are Fun. (Photo by Eddy Ball)

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EPA Fortress Gets New Look

By Eddy Ball

NIEHS veterans with at least seven years service will remember well the old headquarters of the EPA at the corner of Alexander and NC 54. Prior to the construction of the new facility across the lake from NIEHS, the EPA building, fondly known as the “Fortress,” was the RTP headquarters for the agency. When the new building opened, EPA employees at the Fortress and at the agency’s Durham offices relocated to the new facility.

Workers on-site weren’t certain about the ultimate fate of the property, but one thing is sure: the imposing edifice is undergoing some big changes.



Until mid-April, from some perspectives, the building looked almost the way it had for thirty years. (Photo by Eddy Ball)



A Case swing excavator can crawl over almost anything with its tank-like tracks and demolish steel-reinforced brick walls with ease. (Photo courtesy of Steve McCaw)



Everyone likes an office with a view, but this is not quite what most people have in mind. (Photo courtesy of Steve McCaw)



Construction dust rises as the excavator loads debris into dump trucks for removal. (Photo courtesy of Steve McCaw)

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Nature Awakens at NIEHS

By Eddy Ball

Photographer Steve McCaw rarely goes anywhere without his camera and gear, and the sight of spring's arrival on campus was too glorious for him to ignore. On his way to a recent photo shoot, McCaw paused to smell the flowers and take some pictures of the natural beauty that makes the campus such a unique place to work.



Suddenly, color seemed to be everywhere on campus. (Photo courtesy of Steve McCaw)



Almost overnight, the pedestrian underpass was transformed into a park. (Photo courtesy of Steve McCaw)



Vegetation of every kind could sense that it's time to awaken and explode with growth. (Photo courtesy of Steve McCaw)



Instead of the bare oaks of winter, lush vegetation surrounds the campus lake as twilight conceals the brown hues of its silted waters. (Photo courtesy of Steve McCaw)

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Calendar of Upcoming Events

- **May 3** in Rodbell, 10:30 - 11:30 — LPC/LMT Seminar Series featuring Jeffrey Trent, Ph.D., speaking on “Systems Medicine in Cancer Therapeutics.”
- **May 4** in Rodbell, 9:00 – 10:00 — Frontiers in Environmental Science Lecture Series with Mike Ehlers, M.D., Ph.D., speaking on “Receptor Trafficking and Dynamic Nanoarchitecture of the Postsynaptic Membrane.”
- **May 9 (off campus event)** in Schiano Auditorium, Fitzpatrick Center for Interdisciplinary Engineering, Medicine and Applied Sciences (CIEMAS), Duke University, 100/101 Science Drive at 4:00 — Annual McGinnis Lecture with Greg Hannon, Ph.D., speaking on “Evolutionary Conserved Roles for Small RNA pathways.”
- **May 11** in Rodbell, 9:00 – 10:00 — Frontiers in Environmental Science Lecture Series with Donald Lo, Ph.D., “New Brain Tissue-Based, High-Throughput Models for Neurodegenerative Diseases.”
- **May 11 (off campus event)** in Room 147, Nanaline Duke Building, Research Drive, at 12:00 — Duke University Medical Center Biochemistry Spring 2007 Lecture Series with Tom Kunkel, Ph.D., speaking on “Structure-Function Studies of DNA Replication Fidelity.”
- **May 14 (off campus event)** in G202 Medical Biomolecular Research Bldg UNC-CH, 103 Mason Farm Road, at 12:00 — Lecture by Darryl Zeldin, M.D., speaking on “Cytochrome P450 Metabolites and Cardiovascular Disease.”
- **May 16 - 17** in Rodbell, 8:30 – 5:00 — National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee Meeting.
- **May 18** in Rodbell, 9:00 – 10:00 — Frontiers in Environmental Science Lecture Series TBA.
- **May 18 (8:30 – 4:00) - 19 (8:00 – 12:15) (off campus event)** in Alumni Hall at the Carolina Club on the University of North Carolina at Chapel Hill campus — UNC’s Institute for Pharmacogenomics and Individualized Therapy Conference: “One of a Kind: The Search for Individualized Therapy.”
- **May 21 (8:30) – 23 (5:00) (off campus event)** in Washington, D.C. — Second Bisphenol A Expert Panel Meeting
- **May 22** in Rodbell, 11:00 – 12:30 — Distinguished Lecture Series featuring Bert O’Malley, M.D., speaking on “The Expanding Roles of Nuclear Receptor Coactivators.”
- **May 22** in Executive Conference Room (1:30 – 2:00) and Rodbell (2:00 – 3:30 — Asian-Pacific Islander Seminar.
- **May 25** in Rodbell, 9:00 – 10:00 — Frontiers in Environmental Science Lecture Series TBA.
- **May 25** in Rodbell, 10:30 – 11:30 — NIEHS Special Seminar featuring Michael Waalkes, Ph.D.

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