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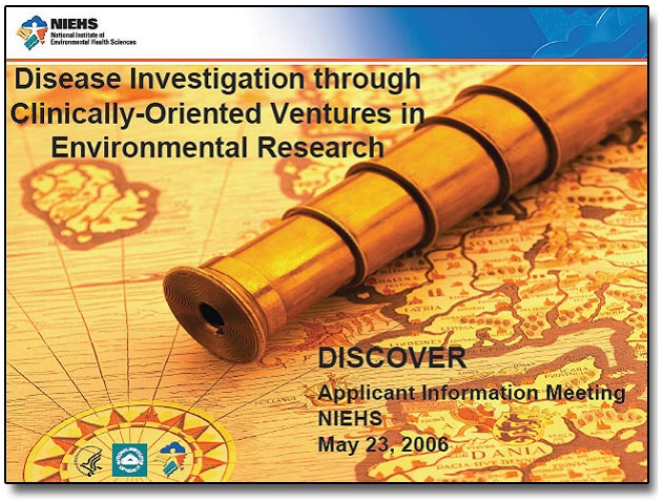
NIEHS Spotlight

DISCOVER—A New Research Opportunity

By Jerry Phelps



The Division of Extramural Research and Training (DERT) hosted a meeting in Rodbell Auditorium on May 23 for potential applicants to a new Centers program called DISCOVER (Disease Investigation through Specialized Clinically Oriented Ventures in Environmental Research). According to the Program's website, DISCOVER "will facilitate the integration of mechanistically driven and patient-oriented research to speed the translation of the environmental health sciences into clinical and public health applications."

About twenty potential applicants were present along with 13 more watching a webcast of the event. Claudia Thompson, chair of the Integrated Medicine Initiative Committee (IMIC), the DERT group that developed the Program, opened the meeting by welcoming both audiences and by introducing the members of IMIC. Next, Anne Sassaman, Director DERT discussed how DISCOVER will build on the strengths of NIEHS research in basic science, public health application, and translation and how it fits into the recently released NIEHS Strategic Plan. She outlined the goals of DISCOVER, which are to provide a focus on human diseases and pathogenesis, increase the number of physician-scientists in the environmental health sciences, develop improved measures of exposure, and to use exposure to environmental agents as a tool to understand biology. Sassaman also thanked the members of IMIC for developing the program on a tight timeline and for writing the request for applications that potential grantees will respond to with grant proposals.

The Program requires a Center Director and a lead Physician-Scientist each at a minimum of 15 percent level of effort. At least four research projects headed by Principal Investigators are required by each applicant institution; two must be public health or patient-oriented clinical research and two must be mechanistically-driven basic research projects. The role of the Physician-Scientist is to ensure the integration and translation of the basic findings into clinically-oriented outcomes such as new diagnostic tools, biomarkers, or new treatment or prevention strategies.

Various members of IMIC presented the scientific and administrative aspects of the Program and the granting process. Speakers included David Balshaw, Lisa Archer, Janice Allen and Jerry Heindel, and Jerry Phelps. Other members of IMIC in attendance included Kim Gray, Cindy Lawler, and Kim McAllister. The potential applicants were informed of the central themes of the program, fiscal and administrative matters related to the grant application, the specific review criteria for DISCOVER, how to put together a top notch application, and how success of the program will be evaluated to determine future directions.

Questions from the audience and those submitted by email from webcast viewers focused mostly on technical issues related to amount of effort by key members of the research team and clarification of their roles.

Four to six grants will be awarded for five years from the pool of applications. NIEHS set aside $9 million from the FY07 budget to begin the program. Applications are due on November 17 and awards are expected to be made on August 1, 2007. For more information, visit the web-site at http://www.niehs.nih.gov/dert/discover/home.htm.

NIH Exposure Biology Workshop Sets the Stage for the Genes and Environment Initiative

By Ernie Hood

A group of more than 100 participants from academia, government, and industry gathered May 16-17 in Greensboro to help the NIEHS develop a plan for the Exposure Biology Program (EBP), the environmental arm of the recently-announced Genes and Environment Initiative (GEI). EBP is an ambitious trans-NIH program designed to accelerate understanding of how genetic and environmental risk factors influence human health and disease.

NIEHS Director David Schwartz addresses the Exposure Biology Workshop participants (Photo by Steve McCaw, Image Associates)

The NIH Exposure Biology Workshop was co-sponsored by partner institutions in the GEI—the NIEHS and the National Human Genome Research Institute (NHGRI). NIEHS Director David Schwartz and NHGRI Director Francis Collins co-chaired, and Brenda Weis of the NIEHS and Phylliss Frosst of NHGRI co-organized the event. The workshop focused largely on identifying new technologies and approaches to measure diet and physical activity, personal exposures to chemical and biological agents, and the biological responses to these exposures.

"What we're doing is linking exposure to biology to disease in a very intimate way," said Schwartz, "so that we focus on the disease process, and can understand the genetics that underlie the susceptibility to these various exposures and environmental stressors."

Collins exhorted the diverse panel of experts to be creative and imaginative in their approach to the questions and issues at hand. "I want to ask you to step outside of your usual disciplinary boundaries, to think boldly with us about ways that we could capitalize on the opportunities that are here technologically to move this field forward at a more rapid pace," he said.

Scientific sessions designed to brief participants on the latest information in technology development, pathogenic mechanisms of exposure, and exposure applications took up much of the first day of the workshop. Later, attendees took part in break-out discussion sections intended to elicit specific recommendations for effective, efficient research initiatives and technology development in seven core arenas: Assessing Exposures, Biological Response to Exposures, Dietary Factors, Physical Activity, and Psychosocial Stressors, Efficient Approaches to Study Design and Biomarker Validation, and Intelligent Systems, Databases, and Computation. The detailed consensus reports from the groups will form the basis for tactical planning for the EBP, both to focus research investments in the short-term (next five years) and to establish a long-term research infrastructure. Such a wealth of information emerged from the groups' reports that Collins likened the experience to "drinking from a fire hydrant."

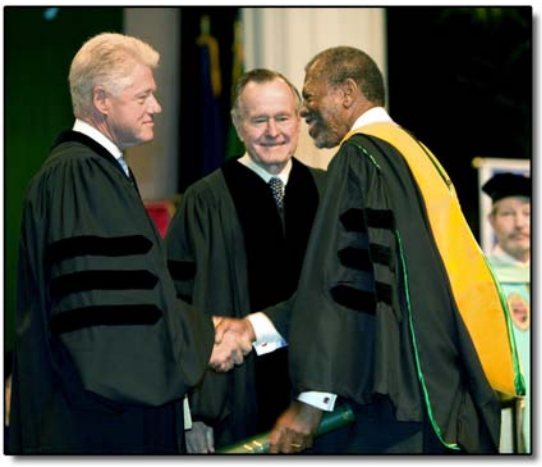
The near-term outlook for developing technologies to identify and measure exposures and their biological impacts appears to be excellent. Sensor technology is progressing rapidly at all levels, including applications to environmental and personal monitoring of exposures, dietary intake and physical activity. Sensors, probes, and imaging devices gather data on exposure and biological responses at the cellular and sub-cellular (molecular) levels. Experts reported that many of these technologies are either already available and can be used immediately, or can be readily adapted, for EBP applications. For example, commercially available devices for monitoring individual physical activity could be enhanced to provide additional data on location, ambient environmental conditions, or specified physiologic information.

Making the most of what's available now was also the theme of recommendations addressing data collection and reporting, and access to biological samples for analysis. Participants supported the idea of adapting existing cellular and wireless technologies to gather massive amounts of exposure data from sensors. Several groups recommended partnering with other agencies such as the Centers for Disease Control and Prevention to leverage biosample repositories like the National Health and Nutrition Examination Survey (NHANES) to more rapidly advance the development of exposure biomarkers.

The workshop also included a special discussion on *Training the Next Generation of Exposure Scientists* and a special presentation on the ethical and societal implications of the planned research activities within the EBP.

Olden Receives Honorary Doctorate from Tulane University — Stays Engaged in Cancer Research

By Jerry Phelps



Former Presidents Bill Clinton and George H. W. Bush congratulate Ken Olden (Photo courtesy of Tulane University)

Ken Olden, former NIEHS director, was awarded an Honorary Doctorate of Science from Tulane University on May 13. The honor was made even more special because Olden shared the podium with two former Presidents, George H. W. Bush and Bill Clinton. Olden was honored for his "extraordinary achievements in linking environmental health sciences with public health, and bringing attention to health disparities and environmental justice…". Olden's remarks focused on his career as a public servant and the privilege of serving the American public. He accepted the degree on behalf of all public servants and stated that by honoring him "all the efforts of public servants are honored as well."

Bush once appointed Olden to the National Cancer Advisory Board, and was sitting president when Olden was appointed NIEHS Director. Clinton was president during most of Olden's tenure as Director, and presented him with the Meritorious Executive and Distinguished Executive awards in 1996 and 1997, respectively. Bush and Clinton, the commencement speakers, were both awarded the Honorary Doctorate of Laws in recognition for their post-Katrina efforts in helping to restore the Gulf Coast area.

The pace of work has not decreased for Olden since he stepped down as Director of NIEHS last year. Neither has the complexity of the issues he is tackling. Olden says that when preparing for his lab's Board of Scientific Counselors review in 2003, he realized just how much he missed laboratory research. It was at that moment that he decided the time was right to turn over the reins of running NIEHS to someone else.

His laboratory research continues to focus on strategies to prevent metastasis of cancer by developing a greater understanding of the principles of cell adhesion. Olden's lab group, which includes Steve Akiyama and John Roberts along with a number of research assistants and post-doctoral fellows, is studying how carcinogenic cells are released from tumors and how they colonize cancer in other parts of the body. He is actively involved in the laboratory, as well as planning the lab's direction, and reviewing its output.

In addition to his efforts in the lab, Olden is using his new found "free-time" to focus on issues and challenges that always interested him. Olden is exploring new ways to address the issue of health disparities and wants to bring basic and clinical researchers into the arena along with sociologists. In framing the questions and debate on this topic, Olden thinks racial differences in the frequencies of gene polymorphisms are just as important as previously addressed issues such as behavioral differences. Olden cites BiDil®, a drug approved for heart failure in African Americans, as an example and suspects that genetic polymorphisms are at the root of why this drug is more effective in African Americans than Caucasians.

Another weighty task is the establishment of the Research Triangle Environmental Health Collaborative. Olden, acting as the group's Chair, and colleagues at Duke University, North Carolina State University, the University of North Carolina Chapel Hill, CIIT, and the Constella Group are establishing the Collaborative as a "think tank" on environmental health issues. The Collaborative, a non-profit organization, will host a summit in the autumn of 2006 to bring together "environmental and public health leaders to identify the 'grand challenges' facing environmental health and to plan a strategy for addressing these challenges." Olden's said, "One goal of the Collaborative is to increase the visibility and awareness of environmental health concerns and to highlight NIEHS and the other member organizations of the Collaborative as key players in solving them."

Olden serves without compensation on the board of the Michael J. Fox Foundation for Parkinson's Research. He also is guiding policy development on the social and ethical issues related to stem cell research as a member of a subcommittee of the California Stem Cell Advisory Committee. He is frequently asked to deliver invited lectures. He is currently writing a book chapter on gene-gene and gene-environment interactions and he was invited by Springer-Verlag to produce a textbook on health disparities. Stepping out of his "comfort zone," an editorial on the problems and solutions in the health care delivery system will soon be submitted to the New England Journal of Medicine. In September, he will begin a year-long teaching appointment in the Yerby Visiting Professorship at the Harvard School of Public Health.

Olden expressed gratitude to his many colleagues at NIEHS. Now with the time to focus on new priorities, Olden said he "is especially appreciative of NIH, NIEHS, and David Schwartz," current NIEHS Director for supporting his "continued laboratory research and the opportunity to pursue other endeavors."

Ramos Hitches a Ride on the "Prom Dress Express"

By Jerry Phelps

Rose Ramos holding a picture and a sketch of prom dresses she created for two high school girls in New Orleans, La. (Photo by Jerry Phelps)

Rose Ramos heard there was a shortage of prom dresses in the post-Katrina Gulf Coast region. The thought that there might be one young lady who was unable to attend her prom because she couldn't find a dress inspired Ramos to offer her expertise.

In March, Ramos read in the Washington Post about the Prom Dress Express, an effort organized by a high school student in Beltsville, Md. to collect and distribute used prom and pageant dresses to high school students along the Gulf who couldn't find or couldn't afford a dress. The discovery led Ramos to Cabrini High School, an all-girls Catholic school in New Orleans, La. and according to Ramos, one of a few high schools in New Orleans that will even have a prom this year. One-third of the students' families lost all their possessions during the aftermath of Hurricane Katrina. Ramos reached Judy Thompson the school's Guidance Counselor who connected her to Schwanna Eugene and Marilyn Carter; two students who were unable to find dresses that fit or conformed to the school's strict dress code. Working with a long list of measurements, a rough sketch for one dress, and a magazine cut-out for the other, she created two dresses in less than 10 hours and shipped them off to the girls in New Orleans.

Ramos is an experienced seamstress who ran her own custom prom and wedding dress business for 10 years in San Antonio, Texas. She has been carting around left-over material through several moves during the last five years. The business allowed her to quit a full time job, create dresses at night, care for her then-teenage children, and return to school to complete a Bachelor's degree at the University of Texas San Antonio. From there, she went to graduate school at the University of Pittsburgh where she received her Ph.D. She started a post-doctoral fellowship with Ken Olden in October 2005. Ramos' area of expertise is health disparities. During her stay at NIEHS, she will examine the risk of elevated pre-pregnancy body mass index for insulin resistance and the prevalence of pro-inflammatory mediators related to the risk of heart disease and Type 2 diabetes in the expectant mothers and the newborns.

Ramos said, "It took longer for the girls to decide what kind of dresses they wanted than it did for me to sew them." She had a little help from her daughter Michelle, who ironed the panels of fabric prior to Ramos stitching them together. Ramos learned to sew from her mother and grandmother at age ten. A friend who attended design school taught her how to create patterns from sketches and photographs. These days, she sews some for herself and for her four year-old granddaughter Makenzie.

The prom was May 12 and according to letters from Eugene and Carter, the dresses were a stunning success. Both girls expressed their sincere gratitude and Carter invited Ramos to "come to 'The Big Easy' when everything is settled down" to visit with her family. Ramos said, "Preparing for prom is always a crazy time for girls and their moms. I was thrilled to be able to offer relief from some of the craziness and provide some normalcy after the disruption experienced by these Katrina survivors over the last year."

NIEHS Family Day 2006

By Dick Sloane

Good fun, good people, good food! Yes, that's what you missed if you did not attend NIEHS's Family Day Festival held Thursday May 4th starting at 2:00 PM.

Activities included:

- A cake walk with David Schwartz
- Kids fishing
- Miniature golf
- Book exchange
- Disc jockey
- Karaoke
- Inflatable playground equipment
- Cookies and drinks for all
- Hula hoop contest and more
- Durham's Scrap Exchange (art projects for both kids and parents)
- Good will, satisfaction, and fun for all!

Antonio, son of Merit Reyes-Reyes, tries out the newest anti-bad hair day device and protective eye wear developed by the Health and Safety Branch. (Photos by Steve McCaw, Image Associates)

In addition to all of this, a picnic was prepared by the cafeteria staff and judged as delicious!

Many people contributed both directly and indirectly to the event, too many to list here, but they all deserve our copious thanks and praise!

If you weren't present, don't be discouraged! Planning for next year's Family day is already underway and you'll have another chance for an even bigger and better event!

Daughter Tziporah (left) and wife Louise (right) join Director David Schwartz for NIEHS Family Day.

Left to right, Nancy Powell, Diane Crawford and Vivi Shropshire perform karaoke. New careers blossoming?

Xiao-Ping Yang (right) and Olivia (left) (daughter of Yvette Rebolloso) enjoy the bubble machine. Who's having more fun?

Gwen Collman (left) and Dona McNeill (right) enjoy the festivities and renew their friendship.

Science Notebook

Of Mice and Men and Women: The Complex Trait Consortium Fifth Annual Meeting

By Ernie Hood

Many of the world's leading mouse geneticists gathered May 6-9 at the Friday Center in Chapel Hill, as the NIEHS, UNC-Chapel Hill, and Agilent Technologies sponsored the fifth annual meeting of the Complex Trait Consortium (CTC). The CTC is a loosely-organized but tightly-knit community of scientists who share a common goal of investigating the genetic underpinnings of complex diseases and behaviors in humans.

The human and mouse genomes are 98% identical, so the mouse makes an ideal model for efforts to link genotype, or an individual's specific genes, with phenotype, the characteristics that result from those genes, such as disease susceptibility, drug and chemical exposure metabolism, and even hair and eye color. Since most phenotypes are determined by the interactions of a multitude of genes, along with the influence of environmental factors, it's an enormously difficult—but hugely important—undertaking.

Conference co-organizer David Threadgill, professor of genetics at UNC-Chapel Hill explained that individualized medicine is the ultimate goal. Threadgill said individualized medicine means "being able to predict which individuals are going to be susceptible to certain environmental exposures, or to certain disease processes, so that interventions and preventive medicine can be applied where they are needed, rather than in a global fashion."

The meeting attracted 150 attendees, 30 percent more than last year's conference in the Netherlands. Co-organizer John (Jef) French, an NIEHS research physiologist in the Environmental Toxicology Program, attributes the significant increase in attendance to a great degree of interest in the field from scientists at NIEHS, and other area institutions such as UNC, Duke, and North Carolina State University. And, he says, it was a fortuitous time for the conference to be held here in the Triangle. "When we decided to host the meeting here, it was about the same time the selection of the new director at NIEHS was taking place. So we were very pleased that David Schwartz has an interest in mouse genetics. And this fits in very well with the new strategic plan at NIEHS, in terms of employing the genetic diversity in the mouse in such a way that it helps meet the research goals of the NIEHS."

Over the meeting's four days, oral and poster presentations reported results of 93 studies in a wide variety of mouse genetics applications, including obesity, cancer, drug and alcohol addiction, heart failure, and diabetes. Many other presentations imparted the latest advances in methodologies and bioinformatics in the field.

But perhaps the most important news to emerge from the conference was excellent progress in a major long-range project the CTC has undertaken. The Collaborative Cross is an ambitious effort to generate 1000 inbred, genetically diverse mouse lines—starting from 8 heterogeneous strains—which will model the genetic diversity of the human population. Upon its expected completion in approximately four years, the mouse genetics community will have a remarkably valuable new tool, and the field should spawn rapid advances in understanding of complex human traits.

Innovative new tools and methodologies are in development to take full advantage of the Collaborative Cross, and pilot studies have been encouraging. All raw data will be shared by the entire community, and will be fully integrated. According to Threadgill, it's expected to become the central resource for experimental mammalian biology. "It will be the resource for the next 20 or 30 years," he says, "that allows us to integrate biological information, and understand how that integrated biological system data creates individual differences that can be exploited to help human health."

NIEHS Well Represented at the EPA Science Forum

By Jerry Phelps

The EPA's Office of Research and Development (ORD) held its fifth Science Forum May 16-18 in Washington, DC at ORD's home in the Ronald Reagan Building. The meeting marked the first time NIEHS was invited to participate and the Institute sponsored an exhibit, speakers, and attendance by staff from the Superfund Basic Research Program (SBRP), the NIEHS Environmental Health Sciences Centers, and NIEHS DIR investigators.

The Forum attracted approximately one thousand participants. J. Craig Venter delivered the keynote address and focused his remarks on eco- and biodiversity. Venter is considered by many to be one of the leading genomic scientists of the 21st century. His presentation highlighted current efforts in advancing the science of genomics and in applying genomic advances to some of the world's most vexing public health and environmental challenges. This talk represented a new direction for Venter by highlighting his expansion into global ecology issues.

For the remainder of the first day, activities focused on the topic of individual susceptibility. Bill Suk, Director of the DERT Center for Risk and Integrative Sciences co-chaired the first session on Disease Susceptibility and the Environment, which featured a talk by Steven Kleeberger, Chief of the NIEHS Laboratory of Respiratory Biology. Kleeberger had the "honor" of following Venter to the podium. His talk, titled "The Genome and

Disease Susceptibility," described how epigenetics and gene-environment interactions act together in complex diseases such as asthma. Kleeberger's lasting impression from the meeting is that new genomics tools may "change the definition of the most vulnerable population," which EPA uses for regulatory purposes.

Elaine Faustman, from the NIEHS-supported Environmental Health Science Center at the University of Washington, was on the same panel with Kleeberger. She explored susceptibility during vulnerable life stages including susceptibilities of children and how childhood environmental exposures may lead to health problems throughout life and the involvement of anti-oxidant genes in the aging process.

Chris Portier, NIEHS Associate Director for Risk Assessment, co-chaired the second day plenary session on "Global Challenges." This session focused on how the changing environment may give rise to potential new public health risks, and also on actions that could be undertaken to ameliorate these risks. The third day highlighted the built environment, with a plenary session presentation by Howard Frumkin, ATSDR.

Lou Rozier in the Office of Communications served as the NIEHS publicity coordinator. Beth Anderson, also in CRIS, served as the NIEHS liaison with EPA in organizing the meeting. Anderson who works closely with the SBRP said, "I am particularly pleased that many SBRP investigators took advantage of this opportunity to showcase the Program's research before such a large audience of EPA research and regulatory staff."

Other NIEHS presenters and attendees included Douglas Bell, Donald Cook, Julia Gohlke, Jane Hoppin, and Claudia Thompson.

NIEHS Convenes Independent Expert Panel to Consider Use of CDC Vaccine Database to Investigate Thimerosal/Autism Connection

By Ernie Hood

The NIEHS convened a panel of scientific experts Thursday, May 4, at the Institute's Research Triangle Park, North Carolina campus to determine the feasibility of using a large database maintained by the Centers for Disease Control and Prevention (CDC) called the Vaccine Safety Datalink (VSD) to investigate the potential connection between exposure to the vaccine preservative thimerosal and autism. The panel was comprised of specialists in clinical and epidemiological research, biostatistics, neurotoxicology, and risk assessment.

NIEHS Director David Schwartz set the tone for the day's proceedings in his welcoming remarks. "We are very committed to this area of research," he said. "We believe it is essential that we identify the causes of autism…and that we explore all possibilities to try to decrease the risk of developing this disorder among the children in our country." Schwartz acknowledged the high level of expertise represented among the panel members and summarized the panel's mission. "We have assembled a group of individuals that we believe have a strong interest in getting to the roots of autism, but are independent and unbiased, and can look at the Vaccine Safety Datalink and identify the strengths, weaknesses, and utility of the VSD in terms of autism research. The charge to the committee is to evaluate the utility of the VSD as a resource to better identify risk factors related to autism, and to develop recommendations for the next steps."

The workshop's morning session was devoted to presentations that provided detailed background information to the panel members on the VSD—its technical aspects, considerations on research collaborations and data sharing, and current uses of the database, including past and ongoing research studies addressing thimerosal and autism. The balance of the day was taken up by discussion and brainstorming among the panel members.

Discussion initially focused on the feasibility and utility of the VSD for conducting a relatively straightforward "ecologic" study, looking at trends over time to determine whether changes in autism rates were correlated with the removal of thimerosal from most US vaccines in the late 1990s. Allowing for a lag time between thimerosal exposure by means of routine childhood immunizations and diagnosis of autism, an ecologic study should reveal an eventual concomitant drop in autism rates if thimerosal exposure was in fact a major causative factor. Most of the panelists agreed that given the limitations inherent to the VSD, it would not be the best source of data for such a study.

The panel also expressed concern that some of the limitations in the VSD must be addressed prior to further consideration and recommendation of any study. Panel members' concerns centered on limitations in the data's applicability to address specific questions regarding autism and vaccines, on variation in the quality of the VSD data, and on the need for an evaluation of the accuracy of the information in the VSD. For example, screening, developmental assessment, diagnostic and coding practices appear to vary from HMO to HMO, and the diagnosis of autism itself has changed over time. Panelists noted that the database appears to have less-than-complete information on referrals for outside evaluations and continuity of enrollment, both of which could result in underreporting of autism cases. Concern was also expressed about the ability to identify and access VSD records containing information on subjects' families, particularly data regarding maternal prenatal vaccinations and exposure to mercury-containing drugs, which could represent alternate or additional routes of exposure to mercury by newborn infants.

If these and several other questions about the VSD can be effectively resolved or circumvented, the panel recommended that a variety of potential future study designs should be considered. Several members agreed that it would be fruitful to consider a study in high-risk populations, such as the siblings of children diagnosed with autism or autism spectrum disorders. There also appeared to be consensus that data regarding prenatal exposure to thimerosal would be crucial to the validity of study conclusions, and that obtaining data from individual medical records would be necessary in order to reduce confounding.

Although the strengths and weaknesses of several potential study designs were discussed, panel members seemed particularly intrigued by a proposal to re-examine and expand upon a VSD-based thimerosal vaccine safety study previously conducted by the CDC (Verstraeten et al. Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases. Pediatrics. Volume 112, No. 5. November 2003.) It was suggested that updating this retrospective cohort study by adding data from more recent years and refining the methodologies employed will address some of the limitations of the previous study.

The panel was in broad agreement about the need for vigorous and transparent oversight of any eventual study, regardless of its final form. Members were particularly anxious to ensure public representatives of autism advocacy groups from the autism community be fully included in any entity empowered to develop and oversee the research initiative.

Several public advocacy groups were represented at the workshop, and were given the opportunity to address the expert panel on behalf of parents, families, caregivers, and children with autism. Many spoke movingly of their personal situations, and of the urgent need to aggressively deal with the autism epidemic facing the nation. They also expressed great frustration and skepticism about the objectivity of prior government-lead efforts to investigate the thimerosal/autism connection, as well as optimism that the convening of this expert panel by the NIEHS would result in a fresh, independent, and unbiased consideration of the issue.

A more detailed report of the panel meeting and deliberations will be completed within 90 days. The report will be made available to the public for comment, will be shared with the Autism Coordinating Committee for the National Institutes of Health (NIH). The actions eventually taken are likely to involve partnerships among NIH institutes and other federal agencies.

The Expert Panel was chaired by Irva Hertz-Picciotto, Ph.D. of the University of California, Davis. The other panel members were: Scott Bartell, Ph.D. of Emory University; Thomas Burbacher, Ph.D. of University of Washington; Julie Daniels, Ph.D. of University of North Carolina at Chapel Hill; Philip Davidson, M.D. of University of Rochester School of Medicine and Dentistry; Pamela Factor-Litvak, Ph.D. of Columbia University; Craig Newschaffer, Ph.D. of Johns Hopkins University; and Chirayath Suchindran, Ph.D. of University of North Carolina at Chapel Hill.

The Workshop's Planning Committee included: Cindy Lawler, Ph.D.; G. Jean Harry, Ph.D.; Christopher Portier, Ph. D.; and Sheila Newton, Ph.D.; of the NIEHS, and Frank DeStefano, M.D. of the CDC.

DERT Papers of the Month

By Jerry Phelps

Gene Variation Predicts Survival in Brain Cancer Patients

Researchers at the M.D. Anderson Cancer Center in Houston, Texas discovered a genetic variation that predicts survival in patients with an aggressive form of central nervous system tumor, glioblastoma multiforme (GBM). GBM and other gliomas arise from glial cells, which provide protection for neurons in the central nervous system and supply them with nutrients. The cause of GBM is unknown but it accounts for more than half of all primary brain tumor cases. The study appeared in the April 1 issue of the *Journal of Clinical Oncology*. It suggests that human telomerase (hTERT) is a possible target for therapeutic agents to combat cancer and it shows that molecular differences that relate to gene length can be predictive of treatment outcome. The researchers caution that larger studies are necessary to verify these findings.

hTERT is an enzyme that adds specific DNA sequence repeats to the ends of DNA strands in the telomere regions of the chromosomes. The level of hTERT expression has been shown to be a good outcome predictor for many cancers including cancer of the lung, breast, cervix, stomach, and colon. The development of biomarkers for GBM could be useful to modify treatments and improve outcomes of patients with GBM.

In previous research, the team found variations, or alleles, of the gene. These alleles were deemed either short (S) or long (L) based on the length of the DNA sequences. In the current study, median survival for patients with two short alleles (SS genotype) was about 11 months longer than those with either one or two long alleles (SL or LL genotypes).

Citation: Wang L, Wei Q, Wang LE, Aldape KD, Cao Y, Okcu MF, Hess KR, El-Zein R, Gilbert MR, Woo SY, Prabhu SS, Fuller GN, Bondy ML. Survival prediction in patients with glioblastoma multiforme by human telomerase genetic variation. J Clin Oncol. 2006 Apr 1;24(10):1627-32.

Genes Regulated by Estrogen Predict Survival in Hormone-Positive Breast Cancers

Charles Perou at the Lineberger Comprehensive Cancer Center at the University of North Carolina found that differential expression of estrogen-regulated genes is useful in predicting patient outcome in breast cancer.

This study shows that a selected set of estrogen-regulated genes may be useful in predicting the survival outcome and recurrence of cancer in hormone-receptor positive breast cancer patients treated with tamoxifen.

Breast cancers are classified as hormone receptor positive or negative depending upon whether cell surfaces contain significant levels of estrogen or progesterone receptors. Doctors use this information to determine whether women with breast cancer should be given anti-estrogen therapies such as tamoxifen or aromatase inhibitors.

The NIEHS-supported team first identified estrogen-regulated genes by treating an estrogen receptor-positive breast cancer cell line with estradiol and performing microarray analysis. The researchers then applied this gene-set to 65 primary breast cancer tumors. Further analyses refined the gene-set to 822 genes that optimally defined two groups based on the genes activated in the tumors. The poor-prognosis group showed high expression of cell proliferation and antiapoptosis genes, while the good-prognosis group showed high expression of estrogen and GATA3-regulated genes.

The researchers suggest additional studies are necessary focusing on whether the two groups gain similar benefits from chemotherapy and whether the poor-prognosis group might do better with alternative therapies.

Citation: Oh DS, Troester MA, Usary J, Hu Z, He X, Fan C, Wu J, Carey LA, Perou CM. Estrogen-regulated genes predict survival in hormone receptor-positive breast cancers. J Clin Oncol. 2006 Apr 10;24(11):1656-64.

A Mutation Linked with Autism Causes Cholinesterase Retention in the Endoplasmic Reticulum

NIEHS-supported investigators at the University of California San Diego determined that homologous arginine to cysteine mutations in butyrylcholinesterase and acetylcholinesterase result in endoplasmic reticulum (ER) retention. This mutation in butyrylcholinesterase is one that is found to give rise to succinylcholine apnea in patients with plasma butyrylcholinesterase deficiency.

The researchers propose that the mutation impairs processing through the ER and the Golgi apparatus of the cell because of misfolding of the proteins. Accumulation in the ER causes the protein to be more susceptible to proteosomal degradation. The authors speculate that altering intracellular oxidation/reduction parameters may assist in the proper folding of these proteins and their export. This finding could shed light on the molecular causes of autism and other neurological disorders associated with misfolding of proteins.

Neuroligin, butyrylcholinesterase, and acetylcholinesterase are members of the α, β-hydrolase fold family of proteins. Previous research has implicated a mutation in *neuroligin 3*, one of the five genes encoding the neuroligin family of proteins, in autism spectrum disorders. The mutation, an arginine to cysteine substitution, was identified in a set of twins and has been shown to result in the protein being retained within the ER with very little reaching the cell membrane. Misfolded proteins are known to cause ER stress, which has been implicated in a diverse group of human diseases including viral infections, diabetes, and neurodegeneration.

Citation: De Jaco A, Comoletti D, Kovarik Z, Gaietta G, Radic Z, Lockridge O, Ellisman MH, Taylor P. A mutation linked with autism reveals a common mechanism of endoplasmic reticulum retention for the alpha, beta-hydrolase fold protein family. J Biol Chem. 2006 Apr 7;281(14):9667-76.

Urine Biomarkers of Benzene Metabolism: An Example of "Exposure Biology"

Martyn Smith at the University of California Berkeley and Stephen Rappaport at the University of North Carolina Chapel Hill identified specific urinary metabolites of benzene as biomarkers of exposure in the April issue of the journal *Carcinogenesis*. They are conducting additional analyses to examine the dose-related metabolism of benzene and explore factors that might influence metabolism and risk of disease.

The researchers' goal was to see if differences in dose led to differences in the pattern of metabolite levels. In a population of occupationally exposed Chinese-workers and controls, they found that at lower exposures (less than 1 part per million [ppm]), the metabolism of benzene shifted towards its more toxic metabolites, hydroquinone and muconic acid.

Benzene is a highly used and important industrial solvent and precursor in the production of plastics, synthetic rubber, dyes, drugs, etc. It is a natural constituent of crude oil, is highly volatile and is a known carcinogen. Benzene is highly toxic to organs and systems involved in the production of blood and is a known cause of leukemia. Occupational exposures to benzene at air levels greater than 10 ppm have been linked to toxicity, but recent reports have raised concerns about the health effects at levels below 1 ppm.

The recently released strategic plan for NIEHS entitled "New Frontiers in Environmental Sciences and Human Health" describes the need for an initiative on Exposure Biology that will "Develop sensitive markers of environmental exposure, early (pre-clinical) biological response, and genetic susceptibility." This research is a clear example of work that may lead to the ability to quantify individual exposures and to identify features that account for differing responses to the same exposure.

Citation: Kim S, Vermeulen R, Waidyanatha S, Johnson BA, Lan Q, Rothman N, Smith MT, Zhang L, Li G, Shen M, Yin S, Rappaport SM. Using urinary biomarkers to elucidate dose-related patterns of human benzene metabolism. Carcinogenesis. 2006 Apr;27(4):772-81.

DIR Papers of the Month

By Jerry Phelps

Night Shift Work Protective for Parkinson's Disease?

Research results published in the April 15 edition of the *American Journal of Epidemiology* suggest that working night shifts may reduce a person's risk of developing Parkinson's disease. The study was conducted by Honglei Chen in the Epidemiology Branch at NIEHS along with colleagues at Brigham and Women's Hospital, the Massachusetts General Hospital, and Harvard School of Public Health.

The study looked at whether nurses working rotating night shifts were at a higher risk for developing Parkinson's disease compared with nurses who never worked night shifts. During 12 years of monitoring, the researchers documented 181 cases of Parkinson's disease in the 84,794 nurses who participated in the study. Nurses with 15 years or more of night shift work had 50 percent lower risk of Parkinson's disease.

The researchers also found that sleep duration was associated with Parkinson's disease risk. Nurses who reported nine or more hours of sleep per day were 84 percent more likely to develop Parkinson's disease than nurses who slept six hours or less.

Chen said "Working night shifts may be protective against Parkinson's disease or perhaps intolerance for night shift work is an early marker of Parkinson's disease." The authors warn that the novelty of these findings indicate that other studies are necessary to confirm or refute their results.

Previous research on this cohort of nurses from the U.S. Nurses' Health Study reported that night shift work was a risk factor for breast cancer development. These researchers postulated that nighttime exposure to bright lights interrupted the body's mainly nocturnal production of melatonin, a hormone produced by the pineal gland, and that this disruption somehow increased the risk of breast cancer. The current work was undertaken to further investigate the health effects of shift work.

Citation: Honglei Chen, Eva Schernhammer, Michael A. Schwarzschild, and Alberto Ascherio. A prospective study of night shift work, sleep duration, and risk of Parkinson's disease. Am. J. Epidemiol. 2006 163: 726-730.

New "Modifier Gene" Found that Affects the Severity of Cystic Fibrosis

Three researchers in the NIEHS Laboratory of Signal Transduction, Ling Yang, Jeff Reece and Stephen Shears, together with Sherif Gabriel at UNC, have discovered a "modifier gene" for cystic fibrosis (CF) known as inositol triphosphate kinase (ITPK1). The report appeared April 1 in the Journal of Cell Science.

CF is an inherited disease in which the composition of mucus changes dramatically. Although this disease affects several parts of the body, effects on the lungs provide the most serious clinical symptoms. Chronic obstruction of the airways is caused by an accumulation of thick sticky mucus in which pathogenic bacteria grow and thrive leading to progressive damage to the lungs.

CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. Yet, what has puzzled researchers is that even in individuals with exactly the same mutation, a broad spectrum of disease severity exists; some CF patients die early in childhood, whereas others live well as adults with only mild lung disease. These differences have led to a search for so-called "modifier genes" that might encode proteins that may either intensify or reduce the effects of the disease.

Shears and colleagues found that the main physiological function of ITPK1 is to synthesize an intracellular signaling molecule known as inositol (3,4,5,6)-tetrakisphosphate [Ins(3,4,5,6)P4]. Using tracheal epithelial cells in culture, they demonstrated that Ins(3,4,5,6)P4 inhibits secretion of chloride ions from the cells. This chloride movement would normally help the lungs secrete fluid and restore a more normal consistency to the mucus.

Other results show that variability in the degree of expression of ITPK1 alters the cellular levels of Ins(3,4,5,6)P4 and hence the degree of chloride secretion. These findings show that ITPK1 is a modifier gene for the CF condition. The authors argue that an improved ability to predict disease severity from analysis of genuine modifier genes "could offer new targets for more effective CF therapy earlier in life, before lung disease is irretrievably established." Work is continuing in an effort to improve understanding of how ITPK1 expression and cellular activity are regulated.

Citation: Yang L, Reece J, Gabriel SE, and Shears SB. Apical localization of ITPK1 enhances its ability to be a modifier gene product in a murine tracheal cell model of cystic fibrosis. J Cell Sci 2006 119: 1320-1328.

Cyclosporin Neurotoxicity and Timothy Syndrome Related to Aberrant Phosphorylation of the CaV1.2 Calcium Channel Protein

Investigators in the Laboratories of Neurobiology and Signal Transduction at NIEHS reported in the March 7 *Proceedings of the National Academy of Sciences* that two human conditions, cyclosporin neurotoxicity and Timothy syndrome, increase the activity of CaV1.2 calcium channels in the cell surface by stimulating their phosphorylation.

Enzymatically adding or removing phosphate on proteins is the most common form of molecular regulation, but only occurs at very specific recognition sequences in the protein. Cyclosporin selectively inhibits an enzyme that removes phosphate from proteins. Inhibiting this enzyme, calcineurin, in immune cells prevents their activation, so cyclosporin is used widely to prevent organ rejection following transplantation. When it must be used for long periods of time; however, cyclosporin often has neurotoxic side effects.

Timothy syndrome is a much rarer but more severe condition that involves disruption of several organ systems. Conditions may include congenital heart disease, webbing of fingers and toes, immune deficiency, intermittent hypoglycemia and cognitive abnormalities. Timothy syndrome is caused by mutations in the CaV1.2 calcium channel that is the primary link between electrical activity and heart muscle contraction, hormone release from endocrine glands, and learning in the brain.

Although calcium is required for all of these cellular processes, injecting too much calcium into cells rapidly kills them. Consequently calcium channels rarely open for more than a thousandth of a second at any one time. However, as Armstrong, Birnbaumer and their colleagues established, phosphorylation of the CaV1.2 calcium channel at one specific site on the protein dramatically increases the duration of each opening. Cyclosporin exaggerates this effect by preventing the phosphate from being removed by calcineurin. Similarly, the mutation responsible for Timothy syndrome adds a second recognition site for the enzyme that adds the phosphate, so the channel is again hyperphosphorylated, resulting in prolonged calcium entry.

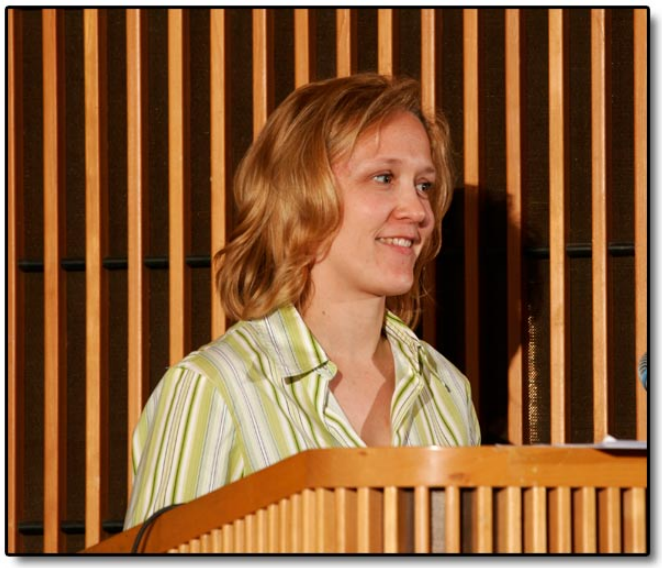
With the collaboration of Tom Darden in the Laboratory of Structural Biology, the NIEHS investigators also identified a potential structural mechanism for these effects which is similar to the mechanism of CaV1.2 channel regulation by dihydropyridines, drugs used clinically to treat human heart disease. Thus, there is now the potential to develop new drugs that selectively prevent the prolonged openings produced by hyperphosphorylation. These drugs could be used to prevent the neurotoxicity associated with chronic cyclosporin treatment or with Timothy syndrome.

Citation: Erxleben C, Liao Y, Gentile S, Chin D, Gomez-Alegria C, Mori Y, BirnbaumerL, Armstrong DL. Cyclosporin and Timothy syndrome increase mode 2 gating of CaV1.2 calcium channels through aberrant phosphorylation of S6 helices. Proc Natl Acad Sci U S A. 2006 Mar 7;103(10):3932-7.

Did You Know?

The NIEHS Diversity Council's Asian and Pacific Islanders Celebration

Xiaodong Wu of the Department of Economics at UNC delivers her lecture "The Growing Asian Economies: Will Tighter Regulation Mingles with Bribery Hurt Direct Foreign Investment?" (Photos by Steve McCaw, Image Associates)



Alyce Bradbury, Chair of the NIEHS Diversity Council, introduces the participants for the traditional Japanese tea ceremony.

Dressed in a beautiful silk kimono, Ayako Wilson explains the four governing principles of a traditional Japanese tea ceremony: harmony, respect, purity, and tranquility. Wilson said, "Silk kimonos start at $3,000 and the sky is the limit!"

The ceremony is made up of simple movements that together form an elaborate choreography as much art as tradition. Chika Koike (right) serves as "hostess" and performs the ritualistic service for "guest of honor" Hideko Tsurumi (left) and "second guest of honor" Chizuko Sueyoshi (middle).

Jennifer Chang performs traditional Chinese music on the Guzheng or "table harp." Chang, an accomplished musician, has played for the Japanese Emporer and President Bill Clinton.

NIEHS staff sample teas and cuisine from Asia and the Pacific Rim

Lucier Wins!

From Lucier Campaign Website

Retired Director of the Environmental Toxicology Program, George Lucier won a seat to the Chatham County Board of Commissioners in the May 2nd primary election. Lucier, who will be unopposed in the November general election, has been active in Chatham County politics since his retirement from NIEHS in 2000. He was a member of the County's Planning Board from 2001 to 2004 and served as Chair the last two years of his tenure. Lucier ran on a platform of better planning for the rapid growth in Northeast Chatham, expanding economic development in the county, and protection of the environment and quality of life. Lucier said, "I will represent all of Chatham County and will work hard to end the divisions between the Eastern and Western sections."

Peterson Honored At NIH Plain Language Ceremony

John Peterson in the Office of Communications and Public Liaison won an Honorable Mention at the April 19 NIH ceremony celebrating plain language held at Lipsett Amphitheater in Bethesda. The award was presented by Elias Zerhouni, NIH Director, for "Oceans of Discovery: How the Study of Oceans Can Improve Your Health," a fact sheet prepared by Peterson describing the joint NIEHS-NSF Centers for Oceans and Human Health program. The citation reads, "This fact sheet describes current research conducted by the NIEHS and other agencies on the health risks associated with exposure to marine toxins, as well as the medicinal benefits these toxins may provide. The colorful photographs and brief descriptions of research findings are presented in a way that is easily digested by a lay audience."

John Peterson, Public Affairs Specialist in the Office of Communications and Public Liaison (Photo by Jerry Phelps)

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