Department Of Health And Human Services
National Institutes Of Health
National Institute Of Environmental Health Sciences

Minutes Of The National Advisory Environmental Health Sciences Council
May 20, 2002

The National Advisory Environmental Health Sciences Council was convened for its one hundred sixth regular meeting on May 20, 2002, at 8:30 a.m., in Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. The meeting was open to the public from 8:30 a.m. until 2:00 p.m. The meeting was closed for consideration of grant applications on May 20 from 2:00 p.m. until 4:15 p.m. Dr. Kenneth Olden presided as Chair on May 20, 2002.

Members Present:

Daniel Baden, Ph.D.
Noreen Clark, Ph.D. R.
Joan Cranmer, Ph.D.
Dale Eastman
Deeohn Ferris, J.D.
Michael Gallo, Ph.D.
Frederick P. Guengerich, Ph.D.
Daniel W. Nebert, M.D.
Martyn T. Smith, Ph.D.
Hon. Harriett M. Wieder

Members Absent:

Michael Karin, Ph.D.
Michael McClain, Ph.D.

Ex Officio Members Present:

Kelley Brix, Ph.D.
Eric L. Stephens

Liaison Members Present:

Michael Galvin, Ph.D.
Robert Spengler, Ph.D.
Hal Zenick, Ph.D.

Members of the Public Present:

Karalyn Colopy - Analytical Sciences, Inc.

NIEHS Staff:

Cindy Afshari, Ph.D.
Kathy Ahlmark
Beth Anderson
Lisa Archer
Trevor Archer, Ph.D.
Martha Barnes
Linda Bass, Ph.D.
Sharon Beard
PJ Blachshear, M.D.
David Brown
Gwen Collman, Ph.D.
Allen Dearry, Ph.D.
Dwight Dolby
Dorothy Duke
Lerlita Garcia
Kimberly Gray, Ph. D.
William Grigg
Janet Guthrie
Jerry Heindel, Ph.D.
Ethel Jackson, D.D.S.
Laurie Johnson
Marian Johnson-Thompson, Ph.D.
Annette Kirshner, Ph.D.
Cindy Lawler, Ph.D.
Charle League
Edith Lee
Carolyn Mason
Patrick Mastin, Ph.D.
Michael McClure, Ph.D.
Sheila Newton, Ph.D.
Liam O'Fallon
Joan Packenham, Ph.D.
Jerry Phelps
Chris Portier, Ph.D.
Susan Ricci
Jacqueline M. Russell
Anne Sassaman, Ph.D.
Carol Shreffler, Ph.D.
Shobha Srinivasan, Ph.D.
William Suk, Ph.D., M.P.H.
Claudia Thompson, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Jose Velazquez, Ph.D.

Charles Wells, Ph.D.
Brenda Weis, Ph.D.
Laura Williams-Boyd
Samuel Wilson, M.D.
Michelle A. Owens
Carolyn Winters
Mary Wolfe, Ph.D.
Geraldine Wolfle
Leroy Worth, Ph.D.

Other Federal Staff:

Robert Dyer, Ph.D. - EPA
Patricia Greenwel, Ph.D. - CSR, NIH
Peggy Jones - FDA
Rass M. Shayiq, Ph.D. - CSR, NIH
Anne Sowell - CDC
Michael D. Waters, Ph.D.- EPA
Paul M. Kuznesof - FDA

I. CALL TO ORDER AND OPENING REMARKS

The one hundred sixth regular meeting of the National Advisory Environmental Health Sciences Council was called to order by Dr. Olden.

II. REVIEW OF CONFIDENTIALITY AND CONFLICT OF INTEREST PROCEDURES - Dr. Kenneth Olden

Dr. Olden read the requirements of the Government in the Sunshine Act. All aspects of the meeting were open to the public except those concerned with review, discussion and evaluation of grant applications and related information. The Chairperson explained policies and procedures regarding confidentiality and avoidance of conflict of interest situations.

III. CONSIDERATION OF MINUTES OF FEBRUARY 11-12, 2002, MEETING

Council accepted the minutes without change.

IV. FUTURE COUNCIL MEETING DATES

September 9-10, 2002, (Monday and Tuesday) in Research Triangle Park.
February 10-11, 2003, Research Triangle Park.
May 19-21, 2003, Research Triangle Park.

V. REPORT OF THE DIRECTOR, NIEHS - Dr. Kenneth Olden

NIH Update: Dr. Olden began his report by commenting on the fact that Dr. Elias Zerhouni was sworn in this week as the new director of the National Institutes of Health.

With regard to other NIH activities of interest, Dr. Olden reported that the National Institute of Biomedical Imaging and Bioengineering (NIBIB) has a new director, Dr. Roderic Pettigrew, formerly at Emory University. There has been a $150 million dollar transfer from existing Institutes and Centers (IC's) to create NIBIB, which will now have its own appropriation.

The annual NIH budget retreat will be held on June 1. The discussion is driven by science, and NIEHS submitted three major research/resource-intensive areas for consideration: breast cancer and the environment, environmental medicine, and toxicogenomics. Resource-intensive programs also relate to the ability of NIH and NIEHS to fund increasing numbers of grants. With the complexity of these programs, the number of awards may decrease slightly, but the number of investigators involved will increase.

Legislative Update: The appropriation hearings are over and they went smoothly and were non-confrontational. It looks like there could be a 15% increase for NIH overall. The House hearings consisted of thematic panels. NIEHS testified with the National Heart, Lung and Blood Institute and the National Human Genome Research Institute around the theme of "prevention.

Senator Hillary Clinton and Senator Harry Reid of the Committee on Health, Education, Labor and Pensions held hearings on a bill they plan to introduce to create a national tracking system to monitor chronic diseases and their possible link to the environment. A paper by NIEHS grantees Arden Pope and George Thuston and colleagues on the health effects of air pollution was published at the time of the hearings, which was good publicity.

Congresswoman Louise Slaughter introduced a bill to fund studies on hormone disrupting chemicals. The bill authorizes up to $500 million dollars for NIEHS to conduct research on hormone disruption. It also requires an ongoing report on endocrine-disrupting chemicals and disease risks.

NIEHS Update: A recent paper on air pollution and lung cancer in the March 6 issues of The Journal of the American Medical Association (Pope/Thurston paper referenced above) showed new links between air pollution and lung cancer, demonstrating an 8% increase in lung cancer deaths annually for every 10 ug/mm3 of fine particulate matter. The authors also showed a strong correlation between fine particulates and death from cardiovascular disease. These findings will also be the subject of upcoming town meetings.

The Secretary announced that NIEHS has been awarded $10.5 million to support research and training related to the World Trade Center attack and its aftermath. Appropriation is in the process for $8 million to continue and expand the current projects.

An amount of $1.5 billion is expected to go to the National Institute of Allergy and Infectious Diseases (NIAID) as part of the bioterrorism/biodefense initiative. The major emphasis will be on vaccines and microorganisms. Toxicogenomics will also play an important role and there will be discussions with Dr.Tony Faucci about NIEHS participation in these bioterrorism initiatives.

Dr. Andrew Von Eschenbach, new director of the National Cancer Institute, recently visited the NIEHS for a day. This bodes well for new partnerships between our two Institutes.

There has been an evolution of the Environmental Health Perspectives (EHP) journal. We are close to selecting a new Editor-in-Chief, a non-NIEHS scientist to encourage submissions. We have also selected an Editor-in-Chief for EHP Toxicogenomics, a new journal, who is Dr. Ken Ramos. Pediatric environmental health will be emphasized in the current journal, with a separate section. Drs. Phil Landrigan and Brenda Eskenazi have agreed to serve as editors for this special section.

There was a recent article in EHP about our efforts in magnetic resonance microscopy (MRM). This is used to scan whole animals. Drs. Bob Maranpot and Robert Sills of the Division of Intramural Research are working with a group from Duke University to use this method to look at disease progression by studying the structure and chemical composition of the tissue. This allow for three-dimensional analysis, whereas traditional tools used by pathologists allows for two-dimensional analysis. MRM is performed on live animals, so each animal can serve as its own control since it can be analyzed for pre-existing disease before exposure. The number of animals used in each experiment can be greatly reduced. .

The April 2002 issue of EHP on Community Based Research and Environmental Justice was edited by Ms. Peggy Shepard, Dr. Mary Northridge and colleagues. The NIEHS pioneered this new model as a new paradigm for prevention. There is growing interest in informed consent for genomic-based research at the community level. Dr. Olden recently made a presentation on this to the NIH Council of Public Representatives.

Staff of the National Research Council have been meeting with senior NIEHS staff regarding monitoring developments in toxicogenomics and use of data in human risk assessments. NIEHS needs to take the lead by monitoring, communicating results and promoting their use in environmental decision-making.

Dr. Olden noted that the Institute had held a brainstorming session on breast cancer and the environment in April in anticipation of a new initiative on the subject. The report of this session is also available.

Dr. Anne Sassaman led a U.S. delegation to Hanoi to participate in an international conference and discuss the human health and environmental effects of Agent Orange/Dioxin in Vietnam in March. This conference was to begin the process of information sharing, determining the infrastructure for scientific collaboration and refining the research agenda. A Memorandum of Understanding was signed to by the U.S. and the Vietnamese at the end of this conference to begin this process.

The meeting of the NIEHS Public Interest Liaison Group will follow the upcoming NIEHS Leadership Retreat this week. The topic is "communication," and this is a time for valuable input for NIEHS programs.

The Report on Carcinogens, an activity of the National Toxicology Program, is a list of all substances known or believed to be carcinogens. The goal is to publish every two years, and NTP just published 9th Report. There are five levels of review: NIEHS and DHHS see the importance of the Report in terms of environmental health and economics.

DISCUSSION:

The Council discussion included the following:

Method of dissemination of the Report on Carcinogens and the fact that it is not intended to represent risk assessment.

The status of the US Environmental Protection Agency's continued support for the joint Children's Centers Program (unknown at this time) and its effects on the Program. Council members suggested that this might be a good opportunity to obtain additional funding through NIEHS.

The possibility of using existing registries in heavily-populated areas where there are high rates of breast cancer to look at possible environmental links.

Concern over the possibility that the total number of research project grants, especially R01s, will be lower this year and next and the implication for new investigators and demographics of the research community.

VI. Comparative Mouse Genomics Centers Consortium Update - Dr. Warren Ladiges

The Comparative Mouse Genomics Centers Consortium is investigating the concept that commonly occurring variations or SNP's in human genes contribute to commonly occurring diseases such as cancer, cardiovascular disease, neuromuscular disease, diabetes, and osteoporosis. The NIEHS established the consortium of five centers last year to develop new genetically engineered mouse models containing genes with priority polymorphisms for future studies. A summary of the progress in this Program is found at Attachment B.

VII. Toxicogenomics Research Consortium Update - Dr. Leona Samson

Dr. Samson was unable to attend the meeting, and the update was presented by Dr. Brenda Weis, Organ and Systems Toxicology Branch and staff coordinator for the Consortium. She presented background on the importance of the topic and the scientific opportunities inherent in the new field of toxicogenomics. The National Center for Toxicogenomics is an Institute-wide initiative, involving both intramural and extramural components, and combines toxicology with gene expression profiling, proteomics, and SNP analysis using a relational database. Dr. Weis described the Consortium which is the extramural component of the Center, and whose members are involved in both basic research using gene expression profiling and collaborative toxicology experiments. Her presentation focused on the goals of the collaborative experiments designed to identify toxicant signatures through cross-platform and trans-species comparisons with standardized dose and time protocols. Current efforts are centered on establishing harmonization

across laboratories and platforms by developing standard operating procedures and quality control of gene expression experiments. She described the experiments, the issues involved, and the timetable for completing this phase of the program. A summary of the update is found at Attachment C.

VIII. Chemical and Biological Terrorism Research in Environmental Health - Dr. William Suk, Ph.D.

Dr. Suk, Deputy Director for Program Development, Division of Extramural Research and Training, presented a concept for a research program on chemical and biological terrorism research that encompasses basic research, technology-driven exposure assessment tools, therapeutic/intervention strategies and surveillance measures in exposed populations. The concept document can be found at ATTACHMENT D.

The Council discussion was supportive, noting that NIEHS has to be visible and active. The focus on chemicals is important, but hasn't been very visible to date. Partnerships will be required, and a national network is a good concept, but will be difficult to implement. The intervention/surveillance studies should consider the NIEHS history of communication with communities. It was also noted that NIEHS is already engaged in a multidisciplinary approach to identifying toxic effects and that this existing work could be leveraged in future initiatives.

The Council voted unanimously to approve this concept.

IX. Report of the Director, DIR - Dr. Lutz Birnbaumer, Ph. D.

Dr. Birnbaumer referred to the written report from the Division of Intramural Research (ATTACHMENT E) and focused his comments on the Division's recruitments and priorities. He will be making decisions regarding resource allocations as priority recruitments are completed.

X. Report of the Director, DERT - Dr. Anne P. Sassaman, Ph. D.

Dr. Sassaman introduced new members of the Division present for the first time and referred Council to the document, Featured Activities of DERT found at ATTACHMENT F.

She gave a status report on the Extramural Loan Repayment Program. NIEHS was assigned four applications, three of which met the eligibility criteria. Of these three, a review committee of external consultants rated two as high priority. NIEHS will now engaged in negotiations with other Institutes in order to use all funds designated for this program.

A concept document was presented for Fiscal Year 2003 SBIR contract topics. Council unanimously approved this concept/topics found at ATTACHMENT G.

Closed Session: Dr. Sassaman continued her report in closed session in order to discuss specifics of the responses to RFAs that would be reviewed in a new expedited process.

Mr. Paul Jordan made a presentation on and demonstration of the Early Concurrence System of the Electronic Council Book and how this would be used in the upcoming Council review by subgroups of two RFAs over the summer. These RFAs are 1) Collaborative Centers for Parkinson's Disease Environmental Research and 2) Functional Proteomics: Applications to Environmental Health Research. The Council agreed with the process proposed and the assignment of members to the subgroups.

CLOSED PORTION OF THE MEETING

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

There was a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

XIX. REVIEW OF APPLICATIONS

The Council considered 126 applications requesting $32,171,382 in total cost. The Council recommended 126 applications with the total cost of $32,171,382.

XX. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 4:15 on May 20, 2002.

ATTACHMENTS:

A. Council Roster
B. Comparative Mouse Genomics Centers Consortium Update (Word Document)
C. Toxicogenomics Research Consortium Update (Word Document)
D. Chemical and Biological Terrorism Research in Environmental Health (Word Document)
E. Report of the Director, DIR In *Adobe Acrobat* Format
F. Report of the Director, DERT In *Adobe Acrobat* Format
G. Small Business Innovation Research Program Committee Concept Clearance (Word Document)

COMPARATIVE MOUSE GENOMICS CENTERS CONSORTIUM UPDATE

Warren Ladiges, University of Washington, Seattle, WA

The Comparative Mouse Genomics Centers Consortium is investigating the concept that commonly occurring variations (referred to as polymorphisms, more specifically as single nucleotide polymorphisms, or SNPs) in human genes contribute to commonly occurring diseases such as cancer, cardiovascular disease, neuromuscular disease, diabetes, and osteoporosis. The consortium is focusing on genes that help repair damaged DNA and/or regulate cell cycling in response to environmental influences such as cancer causing chemicals, toxic materials, UV light, diet, and oxidative stress. The goal of the program is to produce genetically modified mice with SNPs that mimic those found in the human population, and that may have clinical relevance, particularly after environmental challenge. Specifically, the intent is to make these new mouse models available to the scientific community so they can be analyzed as models of genetic susceptibility to disease as a consequent of environmental exposure. The Consortium consists of five centers located at Harvard University, University of Cincinnati, University of Texas MD Anderson Cancer Center, University of Washington in Seattle, and University of Texas in San Antonio. It functions through a steering committee consisting of the directors and co-directors of each center, coordination from NIEHS program administrators, and oversight from a Mouse Task Force. Three working groups within the consortium membership have been established and are now active: bioinformatics, mouse phenotyping, and intellectual property. Progress in the development of new genetically engineered mouse models is in the process of prioritizing specific genes, identifying promising SNPs, and making special preparations of the DNA from each gene containing the polymorphism(s) for insertion into laboratory mice. The five centers are now working with a total of 35 genes, with each center having unique but overlapping expertise with a specific set of genes. After less than one year in full operation, the consortium has one mouse line carrying two human SNPs in its DNA, while an additional seven lines are in the process of being generated.

Toxicogenomics Research Consortium Update

May 2002

Leona D. Samson

In September 2001 the NIEHS launched a large initiative by funding five academic research centers to further develop robust programs in the emerging field of Toxicogenomics. Each of the five groups will carry out genomics level research aimed at understanding the mechanistic basis of how environmental agents perturb biological systems, and thus aimed at understanding how environmental agents affect human health. In addition, these five centers will collaborate with the National Center for Toxicogenomcis at the NIEHS to develop practices and standards for transcriptional profiling, data generation and analysis, such that only high quality data is submitted to the extensive database that will emerge from these studies. In this presentation I will provide an update on how the Toxicogenomics Research Consortium has evolved in the last several months, and describe some of the research that will be undertaken by the academic centers and by the consortium.

National Institute of Environmental Health Sciences
Division of Extramural Research and Training
Office of Program Development

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL
May 20, 2002
Concept Clearance
for
Chemical and Biological Terrorism Research in Environmental Health

Introduction and Background

Public health professionals face many challenges, and now among those challenges is the possibility of an accidental or, more recently, a deliberate release of biological or chemical agents into the environment. Therefore, preparedness planning for biological and chemical threats needs to be carefully considered. This concept will focus primarily on the threats from chemical agents, which include bacterial toxins, and the role that the National Institute of Environmental Health Sciences (NIEHS) can play to increase the public health infrastructure within that arena. NIEHS=s mission is to reduce the burden of human illness and dysfunction from environmental exposures to chemical, physical and social stressors by understanding the interactions between environmental exposures and individual susceptibility over time. It is essential that NIEHS bring to bear its expertise and experience, individually, and in concert with its sister agencies, to assist with the nation's research infrastructure needs in preparedness planning, readiness assessment and surveillance. Furthermore, NIEHS needs to partner with other agencies in building laboratory capacity to improve methods of detection of toxins that could be used as agents of terror.

Vulnerability to chemical and biological toxicants exists because of our inability to detect their presence in real time. Rapid detection methods based on modern molecular techniques are being pursued, although their sensitivity and ability to report in a timely manner may not be adequate. Also, it is important to be able to detect certain agents at extremely low concentrations, which is proving problematic even with a variety of amplifying technologies. Screening tools for identifying people with special sensitivities are important, but inadequate at this time. In addition the development of individual biomarkers of exposure are also critical for determining exposed populations as certain sectors of our population (children, elderly, and genetically pre-disposed) maybe more susceptible to the harmful effects of chemical and biological agents.

To meet the challenges of developing a defense against chemical terrorism, NIEHS is proposing a plan that supports both basic and applied research on chemical and biological toxicants that could be released into the environment. The intent in establishing this Program is to provide a mechanism to support innovative research targeted at: 1) developing technology-driven advancement of real-time monitors of chemical and biological agents; 2) advancing the understanding of specific stress responses at the gene and protein level; 3) developing clinical

intervention strategies for prevention or treatment of diseases resulting from the exposure; and 4) tracking long term effects in exposed populations and environmental risk assessment modeling. This research strategy will help improve our readiness and capacity to respond to public health emergencies resulting from a deliberate or accidental release of a chemical or biological toxicant.

Research Areas

Basic Research

The remarkable progress that has been achieved through efforts to sequence the human genome and the genomes of other organisms has created unprecedented technological opportunities to advance the understanding of the origins of environmentally associated disease and toxicity. Primary among these technologies is the capability to utilize gene expression microarrays, proteomics and metabolomics analyses to characterize the consequences of chemical toxicant insults to humans and to surrogate organisms.

Research utilizing these advanced technologies will assist in understanding the disease-causing mechanisms of chemical toxins. This understanding will enhance the development of interventions and preventive measures against chemical warfare agents. Specifically, studies are needed to better understand the cellular and molecular mechanisms of these toxicants. Determination of specific gene expression and protein changes that reliably indicate toxic effects will allow for the development of gene expression-and protein based endpoints of toxicity

Information generated in these experiments and analyzed through robust bioinformatics will provide information on cellular networks of responding genes and proteins. In addition, this information will help define important target molecules for toxicity, as well as provide future biomarkers, and points of intervention in pathology. For example, current experiments suggest that is possible to establish signature profiles of altered gene or protein expression from exposure to single or a few acute doses of chemicals, indicating that this technology has the potential to lead to the development of potential biomarkers of exposure and toxic responses. Gene and protein expression analysis, reliable broad coverage technologies, and computer systems capable of manipulating large data sets are all necessary to gain a better understanding of the pathophysiology at the molecular level. This multidisciplinary approach will have direct application in clinical treatments to ameliorate specific effects of chemical and biological agents.

Technology-Driven Exposure Assessment Tools

Current advances in biotechnology and bioengineering have provided unique opportunities to infuse the disciplines of exposure assessment and analysis with new strategies and approaches in chemical measurements, bioimaging and biosensing, and miniaturization. The application of these methods will improve our ability to measure and monitor chemical warfare agents in the air, soil, water, and in human tissues and body fluids. Refinements in exposure assessment strategies using new technology will aid in the quantification of the disposition of these agents, including their metabolism and clearance in the body. Information from these new devices and products will provide more valid estimates of body burden and allow more precise pharmacokinetic models that are needed to make better predictions and aid in risk assessment. The integration of biotechnology with bioengineering, imaging techniques, advances in molecular biology and complex modeling of chemical fate within the body and environment, will

contribute to the risk assessment process for exposure to chemical warfare agents and on our ability to protect the public health

Nanoscale science and engineering are fields that are rapidly advancing to the point where they are able to provide tools for measuring individual molecules. This technology will be applied to develop small field deployable sensors worn by “first responders.” These "laboratories on a chip" could rapidly detect, quantify, and alert field personnel to a chemical threat. Thus, nanotechnology is emerging as a field critical for enabling such devices and has a tremendous potential for affecting environmental health science and exposure to chemical warfare agents.

Therapeutic/Intervention Strategies

A vital strategy in reducing the incidence of disease is through intervention. Interventions that take place at an early stage of disease, before the pathology is fully developed, provide the opportunity to reduce the severity of disease or possibly prevent mortality. By finding an early fundamental target that is the control point of a biochemical cascade of many subsequent events, a more effective and ubiquitous control of disease processes can be achieved.

Knowledge from basic research findings is crucial to the development of intervention and therapeutic strategies. An important basic research tool would be the ability to rapidly obtain genome sequence information and to understand the perturbations by chemical terrorism agents. Genomics research, coupled with other biochemical and exposure-related information, would be expected to facilitate the discovery of new target diagnostics, drugs, and therapeutics. In particular, comparative genomics (comparing the DNA sequences and gene expression profiles across different species) will be an important component of future research, helping us to understand what makes a particular chemical agent either harmful or benign. Finally, it is important to continue our efforts in the development of animal models that accurately recapitulate the disease process and can be used in developing intervention strategies and therapeutic regiments.

Surveillance Measures in Exposed Populations.

Beyond the acute effects of an accidental or intentional release of chemical and biological toxicants into the environment, there are also the dangers of chronic effects. It is important to develop good biomarkers of both exposure and affect that can be applied to potentially large numbers of individuals. Continued development of exposure models, development and validation of biomarkers of exposure, effect and susceptibility based on mechanistic data, and the application of these to epidemiological studies will be important for risk assessment. These strategies will lead to more effective preparedness, surveillance, and decontamination approaches.

Clinical studies contribute not just to the understanding of the end-stage pathology of disease and dysfunction, but also are essential to understanding the early events in pathogenesis. Studies on pregnant women and early embryonic development, specifically in the areas of cancer, teratology, and neuroendocrinology are of particular importance. The developing embryo is especially vulnerable due to increased cell division, differentiation, organ formation, growth and heart rate. In addition, studies of pregnant women and the developing embryo are necessary for understanding the liability to chemical warfare agent exposure on potential future generations.

Furthermore, like many environmental health issues, there is a clear genetic component in specific populations that put some individuals at higher risk for developing a disease. Thus we must continue NIEHS's efforts in the resequencing and characterization of single-nucleotide polymorphisms, which increase an individual's susceptibility to chemical and biological toxicants. These data integrated through robust bioinformatics with gene expression and proteome changes will help define at-risk populations who should receive more intensive intervention and follow-up after a chemical exposure. Efforts that increase our surveillance and epidemiological capacity will enhance our knowledge base of information and assist in our ability to conduct meaningful responses to public health disasters.

Program Strategy

This Program is envisioned as a multidisciplinary research program in the diverse areas of basic mechanistic research, diagnostics and exposure assessment, therapy and intervention/prevention, and population-based studies. As outlined above, it will provide for a national network of investigators poised to respond rapidly to release of a chemical or biological agent. Furthermore this Program will foster an interconnected research approach dedicated to understanding the complexities of diseases/dysfunctions caused by chemical and biological agents, which could be used as agents of terror.

Partnerships

NIEHS recognizes that this Program can only function effectively with proactive partnerships with other federal agencies. Through these partnerships, NIEHS will ensure programmatic efforts to secure up-to-date information systems and to be a part of integrated response team. Partnerships will take place at both scientific program management and fiscal levels, on a variety of research and prevention issues. Therefore, the NIEHS efforts will be fully integrated within the Centers for Disease Control and Prevention (CDC) Health Alert Network (HAN), a nationwide system that will distribute health advisories, prevention guidelines, distance learning, national disease prevention information, laboratory findings and other information relevant to state and local health departments, as well as other emergency response efforts. Other partnerships will also include: the National Institute of Allergy and Infectious Diseases (NIAID), the Agency for Toxic Substances and Disease Registry (ATSDR), US Geological Survey, the Department of Defense, and the Office of Homeland Security.

DIVISION OF INTRAMURAL RESEARCH

NAEHS COUNCIL UPDATE

MAY 2002

DIR Recruitments

Chief, Laboratory of Molecular Carcinogenesis
An international search is being conducted for a senior tenured investigator to serve as Chief of the Laboratory of Molecular Carcinogenesis. The candidate will be expected to:

- Develop and maintain strong personal research effort in the general area of molecular carcinogenesis, particularly as it relates to defining the critical target genes and cellular mechanisms in carcinogenesis and understanding how chemicals act upon these genes and cellular processes to influence cancer development.
- Provide overall leadership for the existing principle investigators within the Laboratory of Molecular Carcinogenesis, who study cell adhesion and migration, regulatory proteins, eicosanoid biochemistry, hormones and cancer, molecular and genetic epidemiology, metastasis, molecular toxicology and molecular mechanisms of gene regulation and metabolism.
- Recruit talented investigators to the Laboratory of Molecular Carcinogenesis and provide a focus for collaborations within the Institute.

The Candidate should have an international reputation in a specific area within the broad context of molecular carcinogenesis and it's relationship to the environment, an outstanding publication record, and a proven history of research leadership. A search committee has been formed with Dr. Thomas Kunkel, Chief of the Laboratory of Structural Biology, as Chair. The closing date for the search is June 14, 2002.

Chief, Laboratory of Molecular Toxicology
An international search is being conducted for a senior tenured investigator to serve as Chief of the Laboratory of Molecular Toxicology. The candidate will be expected to:

- Develop and maintain strong personal research effort in the general area of molecular toxicology, particularly as it relates to defining the critical target pathways, genes, and cellular mechanisms of target organ responses to environmental factors.
- Provide overall leadership for the existing principle investigators within the Laboratory of Molecular Toxicology, who study a diverse array of toxicological processes involving genetics, immunology, neurobiology, reproductive and developmental biology, as well as contribute to the efforts of the National Toxicology Program.
- Recruit talented investigators to the Laboratory of Molecular Toxicology and provide a focus for collaborations within the Institute.

The Candidate should have an international reputation in a specific area within the broad context of molecular toxicology and it's relationship to the environment, an outstanding publication record, and a proven history of research leadership. A search committee has been formed with Dr. John Pritchard, Chief of the Laboratory of Pharmacology and Chemistry, as Chair.

Chief, Laboratory of Computational Biology and Risk Analysis
An international search is being conducted for a senior tenured investigator to serve as Chief of the Laboratory of Computational Biology and Risk Analysis. The candidate will be expected to:

- Develop and maintain a strong personal research effort in the general area of bioinformatics, particularly as it relates to biological networks, proteomics and genomics.

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- Provide overall leadership for the existing principle investigators within the LCBRA who study the combined development of laboratory methods for humans and animals with computational, statistical and mathematical methods to further our understanding of the mechanisms underlying environmental disease.
- Recruit talented investigators to the LCBRA and provide a focus for collaborations within the NIEHS.

The Candidate should be a senior investigator with an international reputation in a specific area within the broad context of bioinformatics and its relationship to the environment. Possible research areas include but are not limited to mathematics, statistics, genetics, bioengineering and molecular biology. The successful candidate will also have an outstanding publication record and proven history of research leadership. A search committee is currently being formed.

Tenured or tenure-track Reproductive Epidemiologist
The Epidemiology Branch is conducting an international search for a reproductive epidemiologist who will develop an outstanding research program on reproductive or perinatal health and the effects of environmental factors, including fertility, pregnancy loss, diseases of pregnancy, fetal development, birth defects, and other problems of the neonatal period. The position will be filled at the tenured or tenure-track level, dependant upon the qualifications of the applicant. A search committee chaired by Dr. Mitch Eddy, Laboratory of Reproductive and Developmental Toxicology, has been formed. Evaluations of applicants will begin soon.

Tenure-Track Molecular Geneticist
The Laboratory of Molecular Genetics has conduced a nationwide search for a tenure-track molecular geneticist to conduct independent research preferably in the area of genomic stability. Dr. Marilyn Diaz, currently a Post-doctoral Fellow with Dr. Normal Klinman, Department of Immunology, Scripps Research Institute, was selected and she has agreed to come to the NIEHS in June 2002.

Tenure-track X-ray Crystallographer
The Laboratory of Structural Biology has conducted a nationwide search for a tenure-track X-ray crystallographer to conduct independent research on the structure of proteins, especially those involved in determining biological responses to stress. Dr. Jeffery Boyington, currently a post-doctoral fellow with Dr. Peter Sun in the Laboratory of Immunogenetics, National Institute of Allergy and Infectious Diseases, has been selected and he has agreed to come to the NIEHS in August, 2002.

Tenure-track Molecular Toxicologist
The Laboratory of Computational Biology and Risk Analysis has conducted a national search for a tenure-track researcher to develop an independent research program in molecular toxicology focusing on mechanisms of carcinogenicity and toxicity initiated through ligand-receptor interactions. A candidate has been proposed for this position and the final offer of appointment is pending approval by the NIH.

Tenure-track or tenured Biostatistician-Statistical Genetics

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The Biostatistics Branch is conducting an international search for a tenure-track or tenured statistician to conduct independent research on methods development in statistical genetics. The successful candidate will be expected to develop statistical methods for family-based studies aimed at identifying and mapping genes that influence risk modifying quantitative traits or diseases or that interact with the environmental agents that cause human disease. A search committee chaired by Dr. Michael Resnick, Laboratory of Molecular Genetics, has been formed and evaluations of candidates will start on July 1, 2002.

Staff Scientist Biostatistician
The Biostatistics Branch is conducting a national search for a statistician to collaborate closely with the National Toxicology Program. The successful candidate will provide statistical leadership and consulting support for the National Toxicology Program and will also develop methods related to design and analysis of toxicology studies. Applicants should have with experience in statistical consulting and a demonstrated ability with problems in applied statistics.

Staff Scientist-Head, Mass Spectrometry Protein Microcharacterization Core Facility

The Laboratory of Structural Biology is conducting a national search for a Staff Scientist to serve as Head of the Mass Spectrometry Protein Microcharacterization Core Facility in the Division of Intramural Research. The successful applicant will be a Staff Scientist in the Laboratory of Structural Biology under the supervision of Dr. K. Tomer and be responsible for the MALDI/MS and capillary HPLC/ESI/MS/MS identification of proteins isolated by 1-D and/or 2-D gel electrophoresis, in-gel digestion, determination of sites of post-translational protein modifications, identification of sites of interactions in protein complexes by limited proteolysis, protein purification by LC, and use of affinity techniques combined with mass spectrometry. Additional duties will include close interaction with DIR scientists, serving as a mass spectrometry expert during the planning and execution of experiments, and supervision of laboratory technicians.

Staff Scientist-Knockout Core Facility Manager
The Laboratory of Reproductive and Developmental Toxicology has conducted a national search for a Staff Scientist with expertise in mouse molecular genetics or a related discipline to serve as the Manager of the Transgenic Knockout Core Facility. Dr. Manus Ray, currently an Assistant Professor in the Department of Internal Medicine at Eastern Virginia Medical School, was selected and he has agreed to come to the NIEHS in July 2002.

Staff Clinician-Rheumatology
The Environmental Autoimmunity Group in the Office of Clinical Research has conducted a national search for a Staff Clinician to study the etiology, pathophysiology, and natural history of environmentally associated autoimmune diseases. A candidate has been proposed and the final offer of appointment is pending approval by NIH.

Staff Scientist-Veterinary Pathologist
The Laboratory of Experimental Pathology is seeking a toxicologic pathologist experienced in rodent toxicology and carcinogenicity studies to work within the National Toxicology Program (NTP). The successful candidate will be involved primarily in the management and oversight of the pathology peer review (evaluation), interpretation, and reporting of toxicology data. The candidate is also expected to identify and pursue special projects that will advance the understanding of

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various biological endpoints. A candidate has been proposed and the final offer of appointment is pending approval by NIH.

New DIR Recruit

Dr. Mariel Birnbaumer—Laboratory of Signal Transduction

The NIEHS welcomes Dr. Mariel Birnbaumer, who has recently been appointed as a senior tenured investigator in the Laboratory of Signal Transduction. Dr. Birnbaumer has a long track record of basic research accomplishments in the area of signal transduction. She worked first in association with Dr. Bert O'Malley on biochemical studies defining the components of the chicken progesterone receptor. She purified the chick progesterone receptor to homogeneity and obtained its amino acid sequence what resulted in the identification of the cDNA encoding the receptor protein. As an independent scientist, she developed a novel method to isolate the genes encoding G protein coupled receptors that stimulate adenylyl cyclase activity. This method, which relies on the acquisition of novel receptor responses by murine L cells stably transfected with human genomic DNA, was used to isolate the gene and the cDNA encoding the V2 vasopressin receptor. This was followed by the demonstration that mutations in the V2R gene, located in the q28-qter segment of the human X chromosome, are responsible for X-linked recessive nephrogenic diabetes insipidus. Her laboratory then characterized the biochemical consequences of several receptor mutations including alteration of ligand binding affinity, diminished coupling efficiency to the G protein, and profound reduction in the number of receptors transported to the cell surface due to protein misfolding. The latter mutation was found to be the cause of the disease for the majority of the 150 independent mutations identified up to now. Her laboratory has identified the post-translational modifications of the V2 receptor protein: glycosylation on asparagine 22, palmitoylation of cysteines 341 and 342, and O-glycosylation on the cluster of serines and threonines present in the extracellular amino-terminus. The V2R is the only G protein coupled receptor described to undergo this modification. Dr. Birnbaumer's laboratory also studied the effect of receptor occupancy by ligand: receptor phosphorylation and internalization, that regulates the extent of tissue response to AVP. Applying fluorescent imaging to study receptor traffic, her laboratory reported that the ligand-bound V2R is targeted to a perinuclear recycling compartment in its non-phosphorylated as well as phosphorylated states, suggesting that the interaction with the targeting proteins does not depend on the presence of phosphorylated serines and/or threonines. Internalized wild-type V2R does not recycle, but mutants lacking any one of a cluster of C-terminal serines and threonines do, suggesting that although targeting to this compartment is not determined by the extent of phosphorylation, exit from the compartment is prevented by full phosphorylation.

Future studies are designed to identify the molecular machinery that retains the desensitized V2 receptor in the cell using approaches such as mass-spectroscopic analysis of proteins that co-immunoprecipitate with the receptor naturally or after crosslinking. The observation that the V2 receptor exhibits constitutive internalization, i.e., enters the perinuclear compartment in the absence of vasopressin, indicates that cell surface receptor levels depend on the balance of internalization and recycling rates. Factors that affect internalization will be investigated and approaches will be designed to characterize their molecular basis. Dr. Birnbaumer also plans to examine the structural elements required for a productive receptor/G protein interaction applying fluorescence energy transfer techniques to examine the spatial arrangement of the intracellular loops of a G protein coupled receptor and reconstitution experiments with isolated G proteins.

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Selected Publications:

Birnbaumer, M., Seibold, A., Gilbert, S., Ishido, M., Barberis, C., Antaramian, A., Brabet, P., and Rosenthal, W. (1992) Molecular cloning of the receptor for human antidiuretic hormone. Nature 357: 333-335.

Rosenthal, W, Seibold, A., Antaramian, A., Lonergan. M., Arthus, M.F., Hendy, G.N., Birnbaumer, M., and Bichet, D.G. (1992) Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. Nature 359: 233-235.

Innamorati, G., Le Gouill, C., Balamotis, M., and Birnbaumer, M. (2001) The long and the short cycle. Alternative intracellular routes for trafficking of G-protein-coupled receptors. J. Biol. Chem. 276: 13096-13103.

Bowen-Pidgeon, D., Innamorati, G., Sadeghi, H., and Birnbaumer, M. (2001) Arrestin effects on internalization of vasopressin receptors. Mol. Pharm. 59: 1395-1401.

Klein, W., Mueller, C., Chu, P., Birnbaumer, M. and von Zastrow, M. (2001) Heterologous inhibition of G-protein coupled receptor endocytosis mediated by receptor-specific trafficking of beta-arrestins. J. Biol. Chem. 276: 17442-17447.

Birnbaumer, M. (2001) V2 Vasopressin Receptor Mutations and Water Homeostasis. Cardiovascular Res. 51: 409-415.

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Training and Mentoring

2002 NIEHS/NTA Science and Career Fair

The Fifth Annual NIEHS/NTA Science and Career Fair was held on May 10, 2002 in the Rodbell Conference Center, NIEHS. The keynote speaker was Dr. Alice Huang, Senior Councilor for External Relations and Faculty Associate in Biology at the California Institute of Technology. The panel discussion this year focused on "Exploring Career Opportunities in Science." It was moderated by Dr. Thomas Kunkel, Chief, Laboratory of Structural Biology, and Scientific Program Director, Environmental Biology Program, NIEHS. Panel participants included Dr. Huang; Dr. Marshall Brian, CEO and Founder, Howstuffworks.com; Dr. Robert Parker, Director of Developmental, Reproductive, and Neurobehavioral Toxicology, Dupont, Inc.; Dr. Karen Hopkins, a free-lance science journalist; and Dr. Claire Aldridge, Venture Development, UT Southwestern Medical Center. Other events at the Science and Career Fair included a poster session and four breakout sessions:

- Breakout Session #1: A Career in Academia
  Moderated by Dr. Shirley Chao (Fayetteville State University) and Dr. Dolores Grant (North Carolina Central University)
- Breakout Session #2: Career Alternatives in Non-Profit Organizations
  Moderated by Dr. Sherry Parker (Research Triangle Institute) and Ms. Louise Zeller (Blue Ridge Environmental Defense League)
- Breakout Session #3: Science Careers in Industry
  Moderated by Dr. Kimberly Cummings (Cato Research), Dr. Michael Santostefano (GlaxoSmithKline) and Dr. Vicki Tubbs (Cato Research)
- Breakout Session #4: Careers in Government
  Moderated by Dr. Joyce Royland (Environmental Protection Agency) and Ms. Letitia Williams (Centers for Disease Control and Prevention)

There were more than 300 registered attendees from universities and research institutions in the Triangle Area and the rest of North Carolina. More than 15 companies were represented. The NIEHS, the Chemical Industry Institute of Toxicology, the Burroughs Wellcome Fund, S & M Separation Technologies, Inc., and Taylor and Francis cosponsored this event.

DIVISION OF INTRAMURAL RESEARCH INTERNATIONAL ACTIVITIES IN 2001

Dr. Steven Akiyama (Laboratory of Molecular Carcinogenesis) reviewed grant applications for the Welcome Trust, United Kingdom; the Michael Smith Foundation for Health Research, Canada; and the Ministry for Universities and Research, Italy.

Dr. Trevor Archer (Laboratory of Reproductive and Developmental Toxicology) collaborated with Dr. David I. Rodenhiser, Child Health Research Institute, University of Western Ontario, Canada regarding the functional analysis of CpG methylation in the BRCA1 promoter region.

Dr. Perry Blackshear (Director, Office of Clinical Research) participates in numerous international collaborations, including those with: Dr. Nahum Sonenberg, McGill University, Montreal, Canada; Dr. George Kolias, Institute of Immunology, Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece; Dr. Matthias Gaestel, Institute of Clinical Biochemistry and Pathobiochemistry, Medical University Clinic, Wuerzburg, Germany; Dr. Brigitte Kaissling, University of Zurich, Switzerland; Dr. Georgia Panopoulous, University of Berlin, Germany; Dr. Willems Luc, Department of Applied Biochemistry and Biology, Faculty of Agronomy, Gembloux, Belgium; Dr. Marion V. Squiers, Dept. of Pathology, The Radcliffe Infirmary, Oxford, England; Dr. Orly Reiner, Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel; Dr. Henry Tabel, Dept. of Veterinary Microbiology, University of Saskatachewan, Saskatoon, Canada; Dr. Melitta Schachner, Zentrum für Molekulare Neurobiologie, Universitaet Hamburg, Hamburg, Germany; and Dr. Hoguen Kim, Dept. of Pathology, Yonsei University, College of Medicine, Seoul, Korea. Dr. Blackshear also has Cooperative Research and Development Agreements with AstraZeneca Pharmaceuticals and Oxford Glycosciences, both in the UK.

Dr. John Bucher (Toxicology Operations Branch) participated in the WHO IPCS meeting to prepare and review a document on the Safe Use of Fluorides, held in Beijing, China, May, 2001.

Dr. Glinda Cooper (Epidemiology Branch) is collaborating with Dr. Mats Lambe, of the Department of Medical Epidemiology of the Karolinska Institutet in Stockholm, Sweden, on an analysis of childbearing and the risk of scleroderma using national hospitalization and pregnancy data bases covering the population of Sweden.

Dr. William Copeland (Laboratory of Molecular Genetics) collaborated with Dr. Patrick Lestienne at the Université Victor Segalen, Bordeaux, France on the base composition at the boundaries of mitochondrial DNA deletions and duplications

Dr. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology) collaborated with: Dr. Kiyotaka Toshimori, Professor, Department of Anatomy and Reproductive Cell Biology, Miyazaki Medical College, Miyazaki, Japan, on cloning cDNAs for proteins involved in fertilization; Dr. Chunghee Cho, Department of Life Sciences, Kwangju Institute of Science and Technology (K-JIST), Kwangju, Korea to produce a conditional mutant for protamine; Dr. Chisato Mori, Professor, Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan, to develop targeting sequences for the spermatogenic cell-specific form of type 1 hexokinase; Dr. Ruth Shalgi, Department of Embryology, Sackler

Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, to isolate cDNAs for two ubiquitously expressed calpains and one spermatogenic cell-specific calpain; Dr. Patricia Cuasnicu, Instituto de Biologia y Medicina Experimental, Buenos Aires, Argentina, on the targeted mutation of the gene encoding epididymal protein DE. In addition, Dr. Eddy was a grant reviewer for the Michael Smith Foundation for Health Research, Canada; The Wellcome Trust, England; Comitato Telethon Fondazione ONLUS, Rome, Italy; and the National Health and Medical Research Council, Australia

Dr. David Dunson (Biostatistics Branch) is collaborating with Dr. Bernardo Colombo of the University of Padua, Department of Statistics, Padua, Italy on a large multinational European Study of Daily Fecundability.

Dr. Dori Germolec (Laboratory of Molecular Toxicology) organized a workshop on the assessment of the Allergenic Potential of Genetically Modified foods. Dr. Germolec is currently working on a collaborative project with two scientists from the Immunobiology group of the RIVM (Dutch National Institute for Health and the Environment) in Bilthoven, The Netherlands to evaluate hexachlorobenzene as a potential cause of autoimmune disease in humans, and she also serves on a recently formed WHO taskforce on the Epidemiology of Occupational and Environmental Factors Associated with Autoimmunity.

Dr. Beth Gladen (Epidemiology Branch) continues to collaborate with scientists from the Institute of Pediatrics, Obstetrics, and Gynecology in Kyiv, Ukraine and the University of Bristol, England. Dr. Gladen also continues to work with scientists at Health Canada, Ottawa, Canada to characterize patterns of PCB congeners.

Dr. Anton Jetten (Laboratory of Pulmonary Pathobiology) is collaborating with Dr. Jean-Pierre de Villartay Directeur dec Recherche, INSERM U429, Pavilon Kirmisson Hopital Necker-Enfants maladies, Paris; Dr. Hiroshi Kyono Chairman and Professor Department of Mucosal Immunology Research Institute for Microbial Diseases, Osaka University, Japan; and Dr. Bart Staels, UR. 545 INSERM, Universite de Lille, France. Dr. Jetten's collaborations are based on the generation of RORγ knockout mice performed at the NIEHS.

Dr. Matthew Longnecker (Epidemiology Branch) served as a World Health Organization, expert at meeting on non-dioxin-like PCBs. He also participated in a multinational comparison of polychlorinated biphenyl (PCB) levels across studies of human neurodevelopment involving scientists from the USA, Denmark, The Netherlands, Canada, and Germany.

Dr. David Miller (Laboratory of Pharmacology and Chemistry) participated in collaborative research projects with Dr. Gert Fricker, Institut fur Pharmazeutische Technologie und Biopharmazie, University of Heidelberg, Germany and with Drs. Rosalinde Masereeuw and Frans Russel, Dept. of Pharmacology and Toxicology University Medical Centre-Nijmegen, The Netherlands.

Dr. Yugi Mishina (Laboratory of Reproductive and Developmental Toxicology) collaborates with Drs. Masaharu Ogawa and Masahisa Ogawa at the Brain Science Institute, RIKEN, Japan.

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Ms. Retha Newbold (Laboratory of Molecular Toxicology) continues collaborations with Dr. Manfred Metzler and Dr. Sabina Kulling, Institute of Food Chemistry, University of Karlsruhe, Germany to investigate the long term effects of developmental exposure to several phytoestrogens including genistein and daidzein. She also continues providing scientific advice to DES Action, The Netherlands.

Dr. Chris Portier (Environmental Toxicology Program) met with US and Vietnamese scientists in Singapore met to develop a joint, collaborative research program to study the relationship between exposure to agent orange and dioxin and health and environmental effects in Vietnam. Dr. Portier also participated in the review of the Finland Academy of Sciences Centres of Excellence Programme; served as a member of the IARC Working Group to assess the strength of the evidence that extremely low frequency electric and magnetic fields could alter the incidence of cancer in humans; presented a plenary lecture on "Toxicogenomics, Toxicoproteomics, Mechanisms of Toxicity and Risk Assessment" at the Toxicology Symposium, Joint Meeting hosted by The Swiss Society of Pharmacology and Toxicology in cooperation with The German Society for Experimental and Clinical Pharmacology and Toxicology and The Austrian Pharmacological Society.

Dr. Ghanta Rao (Laboratory of Experimental Pathology) participated in international collaborative studies using the TG.NK breast cancer mouse model that are ongoing under the EU Phytoprevent Project. The National Institute of Public Health and Environment (RIVM) of The Netherlands and Danish Veterinary and Food Administration (VFA) of Denmark are the EU collaborators for these studies.

Dr. Walter Rogan (Epidemiology Branch) reported 10 years of follow-up of children poisoned transplacentally by PCBs in Taiwan, a collaborative study with the National Chang Kung University, Tainan, Taiwan.

Dr. Dale Sandler (Epidemiology Branch) continues to collaborate with researchers from the Czech Republic on a study of cancer incidence in Czech Uranium miners.

Dr. Roel M. Schaaper (Laboratory of Molecular Genetics) continued collaborations with Dr. Iwona J. Fijalkowska, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland, to study the precise mechanisms by which chromosomal DNA replication is achieved with high accuracy; with Dr. Kazuo Negishi, Gene Research Center, Okayama University, Japan, to study how base analogs interfer with the DNA replicational process to create mutations; with Dr. V. Alenin, Department of Genetics, St Petersburg State University, Russia, to study the mechanisms underlying mutagenesis by certain N-hydroxy derivatives of the natural nucleobases.

Dr. Stephen Shears (Laboratory of Signal Transduction) conducted collaborative research projects with scientists at the Department of Chemistry, Division of Molecular and Life Sciences, Pohang, University of Science and Technology, Korea; the Bergische Universitat Wuppertal, Fachbereich Chemie-Biochemie, Germany, and the Wolfson Laboratory for Medicinal Chemistry, Dept. of Pharmacy and Pharmacology, University of Bath, UK.

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Dr. Ken Tomer (Laboratory of Structural Biology) has a collaborative research project with Professor Michael Przybylski of the Konstanz University, Konstanz, Germany, focusing on mass spectrometric approaches for analysis of molecular recognition structures. Dr. Tomer also serves as a foreign expert for an EU microproteomics consortium coordinated by Professor Przybylski from Konstanz University, Germany and includes participants from Germany, France, Italy, Switzerland, and Hungary.

Dr. Clarice Weinberg (Biostatistics Branch) collaborated with a reproductive epidemiologist at McGill University in Montreal, Canada in a study of genetic and environmental factors related to intra-uterine growth retardation.

Dr. Roger Wiseman (Laboratory of Women's Health) collaborated with Drs. Peter Soderkvist and Shi-Mei Zhuang, Linköping University, Sweden, focusing on the characterization of molecular alterations of tumor suppressor genes and oncogenes in a variety of chemically induced tumors of mice.

Dr. Darryl Zeldin (Laboratory of Pulmonary Pathobiology) has collaborations with Dr. Martin Spiecker, Dep. of Medicine II/Cardiology St. Josef-Hospital Bochum Germany, to study CYP2J2 polymorphisms and cardiovascular disease; Dr. Dao Wen Wang, Tongji Medical University, Wuhan, PRC, to study interactions between nitric oxide synthase and endothelium-derived hyperpolarizing factors.

Highlights from the National Toxicology Program
May 2002

Agent Orange

Under the auspices of a joint U.S.-Vietnam cooperative research program, the conference, *United States-Vietnam Scientific Conference on Human Health Effects and Environmental Effects of Agent Orange/Dioxins*, was held March 3-6, 2002 in Hanoi, Vietnam. The conference brought together experts from around the world to discuss what is known about the health effects of Agent Orange and its major contaminants, the dioxins, and what is known about reducing the exposures of people to these chemicals. As a result of this conference and further discussions, Dr. Anne Sassaman, Director of the NIEHS Division of Extramural Research and Training, and Dr. Nguyen Ngoc Sinh, General Director of The National Environmental Agency of Vietnam, signed a document outlining the framework for research on human health and the environmental effects of Agent Orange/dioxin. The memorandum of understanding specifies activities that will guide future joint research collaborations between Vietnam and the United States. Joint discussions will continue to further establish the process and the guidelines that will facilitate the continuing exchange. Dr. Christopher Portier, Director of the Environmental Toxicology Program, chaired the U.S. organizing committee for this scientific conference. Additional details are available on the web at http://www.niehs.nih.gov/external/usvcrp/home.htm

Atlas of Mouse Liver Lesions

The Laboratory of Experimental Pathology of the Environmental Toxicology Program has prepared a digitized atlas of mouse liver lesions. The purpose of this atlas is to familiarize pathologists with the spontaneous and chemically induced lesions seen in livers of B6C3F1 mice. Persons interested in receiving a copy of this CD can contact Dr. Robert Maronpot (maronpot@niehs.nih.gov).

NTP Databases

The NIEHS' Environmental Toxicology Program has as one of its major scientific efforts, oversight of NTP toxicity and carcinogenesis studies. While some studies address general toxic effects on animal species, others focus on specific endpoints, such as the immune, reproductive, and neurological systems. The data for the general toxicity/carcinogenesis studies are collected off-site and transmitted to a central database at the NIEHS. However, most of the system-specific studies are conducted at contract labs and the data reside at those sites. The NTP is in the process of moving the data from these contract labs to an on-site database. Since the various study databases are not all in the same format, they are being converted into a single, easily searchable format (Oracle) that will permit running queries across the different study types. The NTP will develop applications that will allow the public and other interested groups to use the web to 1) query the data from all study types, 2) display tables of query results (html) on their computer screen, 3) provide options for graphical presentations, 4) obtain simple statistical manipulations of the data, and 5) export search results to their desktop computers.

Report on Carcinogens

The *Report on Carcinogens* (RoC) is an informational, scientific and public health document that identifies and discusses agents, substances, mixtures or exposure circumstances that may pose a carcinogenic hazard to human health. The NTP has responsibility for preparation of the RoC. It serves as a meaningful compilation of data on 1) the carcinogenicity, genotoxicity, and biologic mechanisms of the listings in humans and/or animals, 2) the potential for exposure to them, and 3) the regulations promulgated by federal agencies to limit exposures.

The scientific review of nominations to the 10th RoC is complete and publication is anticipated in 2002. The following table lists the nominations under consideration. The recommendations from the three scientific review peer review groups, the background documents on the nominations, and the public comments received are available on the NTP web site.

The review of talc (asbestiform and non-asbestiform) has been deferred pending an evaluation of concerns raised during the 2000 review.

Nominations under consideration for 10th RoC	Primary uses or exposures
Beryllium and beryllium compounds	Used in fiber optics and cellular network communications systems, aerospace, defense and other industry applications. Reviewed for possible upgrading to a known human carcinogen in the 10th Report.
2,2-bis-(Bromomethyl)-1,3-propanediol	Used as a fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam.
Broad-spectrum UV radiation, UVA, UVB, and UVC	Solar and artificial sources of ultraviolet radiation.
Chloramphenicol	Used widely as an antibiotic since the 1950s. Veterinary use of chloramphenicol has resulted in the occurrence of residues in animal-derived food.
2,3-Dibromo-1-propanol	Used as a flame retardant, as an intermediate in the preparation of the flame-retardant tris (2,3-dibromopropyl) phosphate, and as an intermediate in the manufacture of pesticides and pharmaceutical preparations.
Dyes metabolized to 3,3-dimethoxybenzidine (dimethoxybenzidine dyes as a class)	Dyes formerly widely used for leather, paper, plastics, rubber, and textile industries.
Dyes metabolized to 3,3-dimethylbenzidine (dimethylbenzidine dyes as a class)	Dyes formerly widely used for leather, paper, plastics, rubber, and textile industries.
Estrogens, Steroidal	Widely used in oral contraceptives and in post-menopausal therapy for women.
IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)	Found in cooked meat and fish.
Methyleugenol	Flavoring agent used in jellies, baked goods, nonalcoholic beverages, candy, and ice cream. Also used as a fragrance for many perfumes and soaps.
Nickel (metallic) and certain nickel alloys	Widely used in commercial applications for over 100 years.
Styrene-7,8-oxide	Used mainly in the preparation of fragrances and in some epoxy resin formulations.
Trichloroethylene	Widely used as a solvent with 80-90% used worldwide for degreasing metals.
Vinyl bromide	Used commercially since 1968, primarily in the manufacture of flame retardant synthetic fibers.
Vinyl fluoride	Used commercially since the 1960's, in the production of polyvinylfluoride that is used for plastics.
Wood dust	It is estimated that at least two million people are routinely exposed occupationally to wood dust worldwide. Non-

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Nominations under consideration for 10th RoC	Primary uses or exposures
	occupational exposure also occurs. The highest exposures have generally been reported in wood furniture and cabinet manufacture, especially during machine sanding and similar operations.

The NTP has initiated scientific review of nominations being considered for inclusion in the 11th RoC, scheduled for publication in 2004. The following table lists the nominations.

Nominations under consideration for 11th RoC	Primary uses or exposures
1-Amino-2,4-dibromoanthraquinone	A vat dye used in the textile industry.
2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ)	A heterocyclic amine formed in food during heating or cooking and found in cooked meat and fish
2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)	A heterocyclic amine formed during heating or cooking of meat and fish and found in cooked meat and fish.
Cobalt Sulfate	Used in electroplating and electrochemical industries, as a coloring agent for ceramics, a mineral supplement in animal feed, and a drying agent in inks, paints, varnishes and linoleum.
Diazoaminobenzene	Used to promote adhesion of natural rubber to steel, as a polymer additive, and as an intermediate in the production of a number of pesticides, dyes and other industrial chemicals.
Diethanolamine	Used in machine oils and metal cutting fluids, in textile processing and industrial gas purification, as an anticorrosion agent, and in the preparation of liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners.
Hepatitis B Virus	A small DNA-enveloped virus transmitted through contact with blood and blood products or other body fluids.
Hepatitis C Virus	An RNA-enveloped virus mainly transmitted in blood.
High Risk Human Papillomaviruses	Small non-enveloped viruses that infect genital mucous membranes; these infections are common globally.
X-radiation and gamma radiation	Used in medical diagnosis and treatment and produced in the use of atomic weapons.
Neutrons	May affect patients getting neutron radiotherapy and the passengers and crew of aircraft that are naturally bombarded by these particles.
Naphthalene	Used in making many industrial chemicals and as an ingredient in some mothballs and toilet bowl deodorants.
Nitrobenzene	Used in the production of aniline, a major chemical intermediate in the production of dyes.
Nitromethane	A stabilizer added to many halogenated solvents and aerosol propellants.
Occupational exposure to lead or lead compounds	Major occupational exposures are in the lead smelting and refining industries, battery-manufacturing plants, steel welding or cutting operations, construction, and firing ranges.
Phenylimidazopyridine (PhIP)	A heterocyclic amine formed in food during heating and cooking and found in cooked meat and fish.
4,4'-Thiodianiline	An intermediate in the manufacture of several diazo dyes.

NTP Centers

Center for the Evaluation of Risks to Human Reproduction (CERHR)

The CERHR serves as an environmental health resource to the public and health, research and regulatory agencies for scientifically based, uniform assessments of the potential for adverse effects on reproduction and development caused by agents to which humans are exposed. The following is an update of scientific peer review activities of the CERHR. All expert reports from these reviews and other CERHR information are posted on its web site.

Methanol Expert Panel Report

- Publicly available - April 26, 2002
- Federal Register notice announcing availability of the report and soliciting public comment published - Vol. 67. No, 89/ Wednesday, May 8, 2002
- Public comments due - July 8, 2002

Bromopropanes Expert Panel Report

- Publicly available - March 8, 2002
- Federal Register notice announcing availability of the report and soliciting public comment published - Vol. 67. No. 46/ Friday, March 8, 2002
- Public comments due - May 7, 2002

Ethylene Glycol/Propylene Glycol Evaluation (expert panel will meet in fall 2002)

- Federal Register soliciting public input on study information for these chemicals and suggestions of scientific experts to serve on the expert panel published -Vol. 67, No. 43/ Tuesday, March 5, 2002
- Public comments due – May 6, 2002

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

The NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) facilitate the development, scientific review, and validation of new and revised toxicological test methods that may predict human health risks better than currently used methods and may improve toxicity characterization, increase savings in time and cost, and even refine, reduce, or replace animal use. The NICEATM also promotes information sharing and communication among stakeholders.

NICEATM in collaboration with the ICCVAM is sponsoring an expert panel meeting to assess the current validation status of *in vitro* endocrine disruptor screening methods, including estrogen receptor and androgen receptor binding and transcriptional activation assays, and to develop recommendations for their further validation. The meeting will take place on May 21-22, 2002, from 8:30 a.m. to 5 p.m., at the Sheraton Imperial Hotel and Convention Center, 4700 Emperor Boulevard, Durham, NC 27703. Details about the meeting are available on the NICEATM/ICCVAM web site (http://iccvam.niehs.nih.gov).

International Conference on the Environmental Threats to the Health of Children: Hazards and Vulnerability

March 3-7, 2002
Bangkok, Thailand

Introduction
Incountries ofSoutheastAsiaandtheWesternPacific,as intherest oftheworld, environmental contamination results in serious and significant effects on the health ofchildren. The goal ofthe conference was to highlight the specific environmental conditions existing in Southeast Asia and the Western Pacific that affect the health ofthese populations, with particular emphasis on children. Participants at the conference hoped to raise awareness ofthe special vulnerability of children to degrading environmental conditions and to glean recommendations from experts and policy-makers in various environmental fields regarding these issues from both an immediate and a long-term perspective.

- Children are highly vulnerable to environmental toxicants. This susceptibility was recognized inthecreation ofthediscipline ofpediatricsandarisesfromthefollowing factors (National Academy ofSciences 1993):
- Children have greater exposures to environmental toxicants than adults.
- Children's metabolic pathways, especially in the first months after birth, are immature compared with those ofadults.
- Children's growth and development occur very rapidly and their delicate developmental processes are easily disrupted.

Because children have more future years oflife than most adults, they have more time to develop chronic diseases that may be triggered by early exposures.

Meeting Outcomes
This meeting was attended by scientists, public health professionals, educators, environmental health engineers, community workers and representatives from a number ofinternational organizations representing governmental and non-governmental organizations in South East Asian and Western Pacific countries. Participants committed to work jointly towards the promotion and protection ofchildren's health against environmental threats. The Bangkok Statement is the definitive outcome from this meeting. Highlights from that statement are excerpted below.

"WE COMMIT OURSELVES

To developing active and innovative national and international networks with colleagues, in partnership with governmental, nongovernmental and international organizations for the promotion and protection ofchildren's environmental health, and urge WHO to support our efforts in all areas, especially in the following four:

1 PROTECTION AND PREVENTION -To strengthen existing programmes and initiate new mechanisms to provide all children with access to clean water and air, adequate sanitation, safe food and appropriate shelter.
2 HEALTH CARE AND RESEARCH -To promote the recognition, assessment and study of environmental factors that have an impact on the health and development ofchildren.
3 EMPOWERMENT AND EDUCATION -To promote the education ofchildren and parents about the importance oftheir physical environment and their participation in decisions that affect their lives, and to inform parents, teachers and care givers and the community in general on the need and means to provide a safe, healthy and supportive environment to all children.
4 ADVOCACY -To advocate and take action on the protection and promotion ofchildren's environmental health at all levels, including political, administrative and community levels."

Bill Suk, Deputy Director for Program Development, DERT, was invited by the World Health Organization to be the honorary chair ofthe conference and gave the opening keynote address. The conference was opened by HRH Princess Chulabhorn and hosted at the Chulabhorn Research Institute. More than 400 researchers, public health investigators, and policy makers from 48 countries participated in the meeting. The Bangkok Statement can be found at: http://www.who.intlpehlcehlBangkoklbangkstatement.htm.

Vietnam -United States Scientific Conference on Human Health and Environmental Effects of Agent OrangelDioxin

March 3-6, 2002
Hanoi, Vietnam

Introduction
This conference was organized under the auspices ofa joint U.S.-Vietnam cooperative research program on the health and environmental effects ofAgent OrangelDioxin. In July 2001 the governments ofVietnam and the United States agreed to organize a conference that would bring together experts throughout the world to provide a broad assessment ofthe data available on the health and environmental effects ofAgent Orange/dioxin and the needs for future research. This

conference was used to identify future research directions and provide a foundation for future cooperative research projects and funding.

The goals ofthe conference were:
1 The exchange ofcurrent scientific information on the health and environmental effects of Agent Orange/dioxins,
2 The exchange ofcurrent scientific information on remediation measures to reduce exposures to Agent Orange/dioxins in humans and the environment, and
3 Examinationofthecurrentstate ofknowledgeandidentification offutureresearchneeds.

OnMarch 7 a panel ofinternational scientists identified gaps in the understanding ofthe health and environmental effects ofdioxin and recommended general areas ofresearch in Vietnam that would help fill these gaps. On Friday, March 8, senior scientists from the Vietnamese Ministry ofScience, Technology and the Environment, the Vietnamese Ministry ofHealth, the US National Institute ofEnvironmental Health Sciences, the US Environmental Protection Agency and the US Centers for Disease Control and Prevention met in Hanoi to establish an agreement for future research activities using findings from the three-day conference and one-day workshop as a guide. On March 10, Dr. Anne Sassaman, Director ofthe NIEHS' Division ofExtramural Research and Training, and Nguyen Ngoc Sinh, Director ofthe National Environmental Agency and Ministry ofScience Technology and Environment in Vietnam signed the Memorandum of Understanding, which can be found at http://www.niehs.nih.gov/external/usvcrp/mou31002.pdf. Dr. Christopher Portier (Director, Environmental Toxicology Program) chaired the U.S. Organizing Committee and Drs. Newton (OPPE), Rogan (Senior Investigator in the Epidemiology Branch) and Suk (Deputy Director for Program Development, DERT) also participated in the meetings.

Joint Meeting of the Toxicogenomics Research Consortium (TRC) Steering Committee and Cooperative Research Program (CRP) of the TRC

April 16, 2002 Radisson Inn Research
Triangle Park, North Carolina

Introduction

The Toxicogenomics Research Consortium (TRC) was established in November 2001 when the NIEHS Division ofExtramural Research and Training (DERT) awarded grants totaling $37 million over five years to five institutions to participate in the TRC as Cooperative Research Members (CRMs). The five institutions include: MIT, Duke University, UNC Chapel Hill, Oregon Health & Sciences University (OHSU), and the Fred Hutchinson Cancer Research Center/University ofWashington (FHCRC/uwA). A sixth CRM, the NIEHS Microarray Center (NMC), was added.

The CRMs provide specialized expertise in gene expression profiling, bioinfonnatics and proteomics and will conduct both cooperative (dependent) and independent research on different aspects oftoxicogenomics. The dependent research collectively fonns the Cooperative Research Program (CRP). The initial goal ofthe CRP is to conduct a series of cooperative gene expression experiments using shared and complementary microarray platfonns. The collaborative experiments will be used to develop standard procedures and quality control standards for gene expression experiments and to develop bioinfonnatics standards and tools for data comparison across the CRMs. This will be a unique contribution to the field oftoxicogenomics and will lay the foundation for additional experiments to detennine molecular responses to environmental stressors.

Thepurpose ofthemeetingwastwo-fold: (1)toconveneabrief(one-halfhour)meeting ofthe TRC Steering Committee to vote on the TRC Handbook and elect a chair for the next fiscal year; and (2) to discuss and finalize the proposed standardization experiments in gene expression profiling and data analysis to be conducted by the CRMs. Drs. VanHouten, *OPDIP*AB, Weis, OPD, and McClure, *OPD/OSTB,* organized the meeting. There were breakout sessions in Microarray Technology, Bioinfonnatics and Toxicology, as well as presentations the mtemational Life Sciences mstitute (ILSD Consortium and the NIDDK Consortium, both of which focus on gene expression profiling.

CRP participants included the principal investigators, microarray and bioinfonnatics core leaders, and toxicology project leaders from each ofthe six CRMs. Dr. Sassaman, Director DERT, gave the opening remarks. Dr. Suk, Deputy Director, OPD, provided programmatic guidance and input during the meeting. Participating DIRstaff included Drs. Tennant, Selkirk, Paules and Cunningham.

Meeting Highlights

The proposed standardization experiments, which systematically address sources ofvariation in gene expression experiments, data quality standards, and analysis tools (bioinfonnatics) for gene expression data, were developed by Drs. VanHouten and Weis using input from the CRMs. A consensus was reached for implementing the standardization experiments, including the source ofstandardRNAs,typeandsource ofchips,dataqualitystandards,datawarehousing, and bioinfonnatics standards and tools. Issues related to the selection oftoxicants and animal husbandry were discussed in preparation for additional standardization experiments to be conducted by the CRP. An experimental plan, including time lines and responsibilities, was developed for the initial standardization experiments. The NIEHS NMC (with input from UNC, OHSU) will prepare and distribute the standard RNAs, Drs. Dressman and Nevins (Duke) will print and distribute the mouse oligo chips, Nagalla (OHSU) will provide data warehousing for the gene expression data, and Spearman (Duke) and Nagalla will lead the meta-analysis ofdata across CRMs. Additional guidance will be sought from an outside statistician with expertise in gene expression data. A full meeting report is being prepared, and a final experimental plan developed, for consideration by the TRC Steering Committee.

Small Animal Neuroimaging: Defining Strategies to Illuminate Environment-Disease Linkages

March 17, 2002 National Institute ofEnvironmental Health Sciences Research Triangle Park, North Carolina

Introduction

Recent technological innovations now make it possible to apply many *in vivo* neuroimaging technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI) to small animals, including nonhuman primates, rats and mice. The availability ofthese new technologies coincides with progress in developing animal models ofvarious neurodevelopmental and neurodegenerative dysfunctions and improvements in assessment protocols for identifying deficits in animals that correlate well with human deficits. The integration ofneuroimaging techniques with traditional neurotoxicological assessments has the potential to enhance greatly the ability to relate behavioral, cognitive or motor dysfunction induced by a toxicant to structural and functional brain pathology.

The National Institute ofEnvironmental Health Sciences (NIEHS) held a workshop on April!7 that brought together neurotoxicologists with interest in neuroimaging approaches with experts in various imaging modalities to identify the best strategies for supporting use ofthese approaches by neurotoxicologists. Drs. Lawler (NIEHS) and Kirshner (NIEHS) organized the meeting. A panel often invited extramural scientists participated in the workshop, together with NIEHS intramural scientists and representatives from the National Center for Research Resources (NCRR) and the National Institute for Biomedical Imaging and Bioengineering (NIBffi).

Meeting Highlights

A series ofshortpresentationsshowcasedthecapabilities ofavariety ofneuroimagingmodalities for monitoring physiological, genetic, structural and functional status ofthe brain and provided examples ofthe successful application ofneuroimaging to address fundamental questions in toxicology and related disciplines.

The following recommendations emerged from the workshop discussions and will be used to plan future initiatives and program activities in this area.

- Increase awareness ofneuroimaging approaches within the neurotoxicology research community through sponsorship ofspecial topics sessions and educational short courses at national meetings
- Support multidisciplinary training at all levels (e.g., postdoctoral, midcareer) to facilitate partnerships between imagers and toxicologists
- Enhance use ofexisting imaging resources (e.g., NCRR Centers)
- Provide support for small scale pilot neuroimaging studies to determine feasibility
- Provide targeted support for professional imaging project scientists trained to serve as an interface between users and developers ofimaging technologies

Developmental Toxicology in the 21st Century: Multidisciplinary Approaches using Model Organisms and Genomics

April 22-24, 2002 NIEHS and the Radisson
Governor's Inn Research Triangle Park,
North Carolina

Introduction

The conference, which was aimed at both state-of-the-science and forward vision perspectives, brought together experts in three areas: GenomicslProteomics in Developmental Biology and Toxicology, Integration of Signaling Pathways in Development (comparative inter-species aspects), and Models ofGenetically Sensitized Organisms (genetic susceptibility aspects).

This conference brought together a multidisciplinary group ofresearch scientists using mouse, zebrafish, *Drosophila*, C. *elegans* and other relevant animal models, in a joint forum to discuss the current state ofemerging multidisciplinary knowledge relevant to evolutionarily conserved and shared developmental biology and toxicology mechanisms. The conference explored the potential for expandingthe understanding ofthe relationship ofdevelopmental biologyand toxicology mechanisms and environmental agent exposure(s) in originating functional and/or structural developmental defects in animal models relevant to the human condition. The meeting was sponsored by the NIEHS, U.S. EPA, American Chemical Council (ACC) and the NIH Office ofRare Diseases. It was co-organized by Drs. McClure (OPD/OSTB) and Philip Mirkes (University ofWashington) with the assistance ofan outstanding organizing committee having members from the 10M Committee on Developmental Toxicology (Board of Environmental Studies and Toxicology), academia and industry. The meeting drew over 130 participants and sponsored 26 poster presentations in addition to the primary sessions.

Meeting Outcomes Participants were introduced to the fact that this is a new day with regard to the study ofthe role ofenvironmental agents in developmental toxicity. Several principles were put forward throughout the meeting as the new approach for research in the area ofdevelopmental toxicology. These include:

1 The best approach is a multidisciplinary one where developmental biologists and toxicologists work together with molecular biologists and bioinformatic experts.
2 The study oftoxicant actions in the mouse or rat, traditional animals for developmental toxicology, may not be the best approach as there are other animal models that can be used that are amenable to genetic analysis and that are faster, cheaper and more sensitive to toxicant action.
3 There is a great conservation of signal transduction pathways across species that increases the usefulness ofmodel organisms as the results can be easily extrapolated to humans from these models.
4 It is no longer practical to study one gene or protein at a time. The candidate gene approach to studying mechanisms is no longer considered to be a valid approach in this era ofgenomics, proteomics, metabonomics and bioinformatics.

This new focus was evident throughout the meeting in such presentations as the use ofdrosphila for understanding Alzheimer's disease and developmental disorders, the comparisons ofsignal transduction pathways across species during development, the use of C. *elegans* to determine protein-protein interactions, and the use ofmouse, *Drosophila* and zebrafish mutagenesis studies to define signal transduction pathways during development and their perturbation by environmental agents. The power ofintegrating genomics and proteomics approaches was also highlighted as was the use of*Xenopus tropicalis* as the best model for studying eye development.

Participants had an opportunity to express their ideas for future directions and problems. They identified a need for increased use mechanisms to stimulate multidisciplinary training, the need for a more active role and societies in developing short courses on the new technologies and the development ofdatabases and bioinformatics as priority areas. A summary ofthe full meeting proceedings will be posted on the NIEHS Toxicogenomics web-site, provided to each participant and published in the newly restructured journal "Birth Defects Research" (formerly Teratology).

DERTPAPERS OFNOTE

George D. Thurston, ScD. NYU
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and P30ES00260

Lung Cancer and Cardiopulmonary Mortality in Response to Long-Term Exposure to Fine Particulate Matter.

Background: Over the past 30 years, many research studies have shown links between cardiopulmonary mortality and periods ofhigh particulate matter and sulfur oxide pollution. Later epidemiologic studies reported health effects at lower particulate matter concentrations. While not without controversy, new air pollution standards were set in 1997 for particulate matter measuring less than 2.5 :M in diameter. Though challenged by industry groups, these standards were later upheld by the Supreme Court.

Most ofthese studies focused on short-term health effects; however, long-term exposures may be more important in terms ofoverall public health. Previous long-term studies have been less conclusive. The current study was designed to assess the relationship between long-term exposure to fine particulate matter and all-cause, lung cancer, and cardiopulmonary mortality.

Advance: This study linked risk factor data for approximately 500,000 persons with air pollution data for U.S. metropolitan areas. These data were combined with cause ofdeath data. Fine particulate matter and sulfur dioxide pollution were associated with 4%, 6%, and 8% increases respectively in all-cause, cardiopulmonary, and lung cancer mortality.

Implication: This report shows that long-term exposure to combustion-related air pollution is an important environmental risk factor for cardiopulmonary and lung cancer mortality. This exposure is common in many metropolitan areas in the U.S. This study provides the strongest evidence yet for these effects which are observed after controlling for cigarette smoking, diet, occupational exposures, and other risk factors.

Citation: Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002 Mar 6;287(9):1132-41.

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James I. Morgan, Ph.D. St. Jude
Children's Research Hospital
ROIESI0772

Mutant Mouse Gene Discovered-Possible Link Between Nerve Degeneration and Regeneration

Background: A classic recessive mouse mutant model, known as Purkinje cell degeneration (PCD), is characterized by adult-onset degeneration ofPurkinje neurons in the cerebellum, photoreceptors in the retina, other neural cells, and defective spermatogenesis. Previously the gene responsible for this defect had not been identified.

Advance: This team ofinvestigators have identified mutations in the axotomy-induced gene, Nnal, as the cause ofthis condition. Their research shows that Nnal encodes a putative nuclear protein containing a zinc carboxypeptidase domain initially identified by its induction in spinal motor neurons after injury and during axonal regeneration.

Implication: The discovery ofthe defective gene in these mice could shed light on the pathology ofneurological diseases such as Alzheimer's and Parkinson's. It also has implications on the causeofretinitispigmentosaandpossiblymaleinfertility. Thediscovery ofthegene mayhelp develop treatment for repairing nerve damage and protecting nerves against damage. The discovery may lead to a better treatments for nerve degenerating accidents, such as head injuries, and radiation-induced nerve damage in cancer treatment.

Citation: Fernandez-Gonzalez A, La Spada AR, Treadaway J, Higdon JC, Harris BS, Sidman RL, Morgan JI, Zuo J. Purkinje cell degeneration (pcd) phenotypes caused by mutations in the axotomy-induced gene, Nna1. Science. 2002 Mar 8;295(5561):1904-6.

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P30ES06676

Discovery of a Repair Enzyme for Oxidatively Damaged DNA.

Background: Reactive oxygen species (ROS) are produced as byproducts ofrespiration and in response to infection or inflammation. Oxygen radicals are responsible for or have been implicated in a number ofdiseases as varied as cancer, arthritis, heart disease, Alzheimer's disease, and other sorts ofdegenerative neurological diseases. DNA is damaged when it comes into contact with ROS. Normally, this damage is repaired by enzymes that cleave out the damaged section and others that insert the correct genetic sequence; however, ifthe damage accumulates or overwhelms the repair mechanisms, disease will result.

Advance: These investigators have identified an enzyme they named NEHI which is similar to a DNA repair enzyme found in E. coli. NEHI appears to specialize in repairing oxidatively damaged DNA. The investigators postulate that once NEHI recognizes a damaged section of DNA, it binds to other proteins that may already be in the damaged area. They also found that the cellular levels ofthe enzyme are highest, perhaps 5-10 times higher, when replication is occurring and thus errors are most likely to happen.

Implication: The discovery ofthis enzyme suggests the possibility that many other similar enzymes exist than were previously known. This knowledge could lead to better more targeted drugs for to improve DNA repair. The team is now engaged in creating a transgenic mouse strain lacking the NEHI enzyme which could provide a clearer indication ofits function and involvement in disease prevention. Measuring levels ofthe enzyme in various disease states, like cancer cells, may have implications for improved chemotherapeutic strategies.

Citation: Hazra TK, Izumi T, Boldogh I, ImhoffB, Kow YW, Jaruga P, Dizdaroglu M, Mitra S. Identification and characterization ofa human DNA glycosylase for repair ofmodified bases in oxidatively damaged DNA. Proc Nat! Acad Sci USA. 2002 Mar 19;99(6):3523-8.

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Rachel B. Cervantes and Peter J. Stambrook, Ph.D.
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and T32ES07250

Differences in Frequency of Occurrence and Type of Mutation in Embryonic Stem Cells and Somatic Cells.

Background: The impact of environmental chemicals upon human health and well being is well documented, especially in the areas ofcarcinogenesis and mutagenesis. However, the effects of these chemicals and agents and their potential to cause mutagenicity in embryonic stem cells are not well known. Stem cells have been used to create a number ofgenetically modified species as experimental models ofhuman genetic diseases. They are increasingly being considered for their potential in the treatment ofhuman injury and disease. The types ofmutations and their frequency ofoccurrence may have impacts on the future clinical uses ofstem cells. These researchers have examined the spontaneous and induced mutagenic events in stem cells using a mouse model that is heterozygous for a marker encoding the enzyme adenine phosphoribosyltransferase (APRT).

Advance: These studies show that stem cells have significantly fewer mutations than mouse embryonic fibroblasts which is similar to adults cells *in vivo.* The distribution ofspontaneous mutagenic events is very different between the two cell types. Loss ofthe functional allele is the major mutation type in both cell types; however, mitotic recombination accounted for all loss of heterozygosity detected in somatic cells. Mitotic recombination in stem cells was suppressed and chromosome loss/reduplicationrepresented more that halfofthe lossofheterozygosity events. Long-term culture ofthe stem cells led to accumulation ofcells with adenine phosphoribosyltransferase deficiency and uniparental disomy (UPD).

Implication: Because UPD allows all recessive genes on a given chromosome to be expressed, possibly leading to increased incidences ofharmful recessive traits, the accumulation ofUPD in cultured stem cells raises concerns regarding the clinical use of stem cells maintained in continuous culture. This concern does not necessarily argue against the therapeutic use of embryonic stem cells but indicates the need for screening such cultures to ensure the absence of UPD.

Citation: Cervantes RB, Stringer JR, Shao C, Tischfield JA, Stambrook PJ. Embryonic stem cells and somaticcells differ in mutation frequency and type. Proc Nat! Acad Sci USA. 2002 Mar 19;99(6):3586-90.

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Patrick L. Kinney, Sc.D. Department ofEnvironmental Health Sciences, Columbia University, New York R21ES09142 and P30ES09089

Asthma Intervention in New York City: A Community Based Participatory Research Project

Background: The Community Based Participatory Research Program was started by NIEHS in 1995. The purpose ofawards in this program is to develop community-based public health research approaches to diseases and health conditions having an environmentally related etiology and detennine the impact ofthese methods. Awards are intended to stimulate further advances in the design and implementation ofprevention and intervention methods that are appropriately applied to environmental health; accumulate and evaluate data, making assignments of environmental etiologies ofdiseases more plausible; and develop, implement, and evaluate community-based exposure assessment protocols.

One grant in this program was awarded to researchers at Columbia University in northern Manhattan to study the effects ofallergens and air pollutants on asthma incidence in inner-city children. The main effort ofthis grant is to detennine whether a comprehensive integrated pest management intervention, including use ofpesticides, repairing cracks and leaks, and educating participants in maintaining pest-free environments, will reduce the severity of asthma symptoms and improve the clinical management ofasthma in the study participating children. In designing and initiating the study, the researchers have learned several important lessons that may help similar research projects carry on more smoothly.

Advance: Participant recruitment through infonnal community contacts proved to be insufficient. The researchers turned to the local medical center to find asthma patients interested in participating. This proved that multiple community organizations are necessary to enroll adequate numbers of study participants. Having good communication skills, education, and getting the participants involved have all been reinforced as essential components ofa successful intervention. The researchers have also detennined that poor housing quality is a severe detriment in keeping pest infestations down. Poor enforcement of standards has led to the fonnation ofcitizens groups whose goal is to lobby city officials for better enforcement of housing ordinances.

Implication: While not complete, this study highlights the challenges encountered in community-based research activities. It has shown that community involvement on many levels isessential ifinterventionsaretosucceed. Thisprogramcanserveasanexample ofhow research protocols need to be flexible and global in scope and will be beneficial for other community-based researchers in designing future experiments.

Citation: Kinney PL, Northridge ME, Chew GL, Gronning E, Joseph E, Correa JC, Prakash S, Goldstein I. On the front lines: an environmental asthma intervention in New York City. Am J Public Health. 2002 an;92(1):24-6.

Jeffrey A. Johnson, Ph.D. Environmental Toxicology Center, University of Wisconsin, Madison NIEHS Grants ROIES08089, ROlES 10042, and P30ES09090

Discovery of "Programmed Cell Life" Genes

Background: Oxidative stress is associated with neuronal cell death following acute insults such as epilepsy, ischemia, hypoxia, and hypoglycemia. It is also believed to be involved in a number ofchronic neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. The mechanism by which the cells die is apoptosis or programmed cell death. The central nervous system (CNS) is particularly susceptible to oxidative stress because ofits high metabolic rate which results in high rates ofoxidant formation which overwhelms anti-oxidant mechanisms such as glutathione (GSH) formation.

Other researchers have shown that treating cells in culture with *tert-butylhydroquinone* (tBHQ), which induces detoxification enzymes via the antioxidant responsive element (ARE), can protect cells from oxidative stress. In these experiments GSH was depleted, leading to increased oxidative stress followed by apoptosis suggesting that the protective effect oftBHQ may be due to the coordinated up-regulation of several genes. The current study investigated whether the tBHQ-mediated activation ofARE is a principal component generating this protective effect.

Advance: Using a neural cell line, these investigators determined that pretreatment with tBHQ reduced hydrogen peroxide-induced cell death. Introduction ofa selective inhibitor ofa particular enzyme in this pathway completely reversed the protective effect oftBHQ. Microarray analysis ofgene expression profiles associated with tBHQ were performed in the presence and absence ofthe inhibitor. Expression increased for a total of63 genes following tBHQ treatment. The inhibitor blocked the enhanced expression in 49 ofthe 63 genes.

Implication: These experiments are the first to demonstrate a set of"programmed cell life" genes involved in providing protection against oxidative stress-induced programmed cell death. Disturbance in the equilibrium ofthis system in such a way that increase programmed cell death must be counterbalanced by increases in the expression ofthis set of genes.

Citation: Li J, Lee JM, Johnson JA. Microarray analysis reveals an antioxidant responsive element-driven gene set involved in conferring protection from an oxidative stress-induced apoptosis in IMR-32 cells. J BioI Chern. 2002 Jan 4;277(1):388-94.

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P30ES00002

Gene-Environment Interactions in the Development of Skin Cancer

Background: The incidence ofnon-melanoma skin cancer (NMSC) has been increasing at an alarming rate over the past 50 years. This trend indicates that NMSC is increasingly becoming a public health problem. NMSC primarily results from exposure to UV radiation from the sun; however, there are other factors involved such as ionizing radiation, arsenic exposure, tendency to burn, and DNA repair capacity.

Recent studies have shown that a single nucleotide base difference, or polymorphism, in the code for a specific gene may alter DNA repair capability. Further research has identified three polymorphisms ofthe gene, known *asXRCC1*. The polymorphism results in a substitution at the 399th amino acid ofthe protein. The arg399gly polymorphism has been associated with cancers ofthe head and neck, breast, lung, bladder, stomach, and the colorectal region. The role ofthe gly399gly *XRCCl* is unclear because in some studies it has had a protective effect, increased risk in some studies, and shown no association in others. To address this inconsistency, these investigators performed a case-control study ofNMSC.

Advance: NMSC cases were derived from a survey of all newly diagnosed cases ofNMSC in New Hampshire. Environmental exposure history was obtained through a questionnaire which included information on sunburn and exposure to therapeutic ionizing radiation. In summary, the data show that the homozygous gln399glnXRCCl variant is associated with lower risk ofNMSC and suggests that the etiology ofsunburn-related squamous cell carcinoma may be significantly different by *XRCCl* genotype.

Implication: This study ofa classic skin cancer model, provides new insights into the role ofthe *XRCCl* 399 polymorphism and may help to explain the conflicting results relating this polymorphism to various types ofcancer. The function ofthe polymorphism is likely to vary by disease, ethnicity, and geography. Additional laboratory-based and larger population-based studies are needed to confirm these findings both in skin cancer and other environmentallyinduced cancers.

Citation: Nelson HH, Kelsey KT, Mott LA, Karagas MR. The XRCCI Arg399Gln polymorphism, sunburn, and non-melanoma skin cancer:evidence ofgene-environment interaction.Cancer Res. 2002 Jan 1;62(1):152-5.

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Daniel C. Liebler, Ph.D. Southwest Environmental Health Sciences Center,
University ofArizona R01ES10056 and P30ES06694

Salsa: A Hot New Tool for Protein Adduct Detection

Background: Proteins are known to be targets ofchemicals that induce toxicity and cancer. Recent developments in laboratory techniques and equipment have driven the growth ofa new fieldofproteinstudyknownasproteomics. Proteomicsisdefinedasthestudy oftheentire protein complement encoded by a genome or the study of every protein produced by the genes of an organism. The integration ofmodem protein separation methods with mass spectrometry techniques provides powerful tools to analyze modifications ofthe proteome. The focus ofthese investigator's efforts are applying proteomics methods to studies ofmolecular toxicology and carcinogenesis.

Advance: The researchers have developed methods to identify protein targets ofenvironmental chemicalsbysequenceanalysis ofpeptidesfrom damagedproteins.Theanalysis ofadducted peptides reveals specific adduct-dependent features, which serve as indicators for modified peptides. These characteristics permit the identification of adducted peptides in the presence of unmodified peptides. They have developed a data analysis algorithm called SALSA (Scoring ALgorithm for Spectral Analysis), which identifies specific characteristics ofmodified peptides.

Implication: SALSA can automate the evaluation ofthousands ofprotein spectra typically acquired in these analyses. The long-term objective oftheir research is to identify major protein targets ofenvironmental chemicals to direct new research at understanding mechanisms of chemical toxicity. The greatest utility of SALSA will be in mining proteomic diversity and predicting toxicity ofclosely related and structurally similar chemicals.

Citation: Liebler DC, Hansen BT, Davey SW, Tiscareno L, Mason DE. Peptide sequence motif analysis oftandem MS data with the SALSA algorithm. Anal Chern. 2002 Jan 1;74(1):203-10.

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Scott Ballinger, Ph.D.
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111 72 and ES09318

Cigarette Smoke and High Cholesterol Increase Mitochondrial Damage in Cardiovascular Tissues

Background: A growing body ofscientific evidence indicates that atherosclerotic lesions, the plaques that lead to hardening ofthe arteries and cardiac artery blockages, result from oxidative stress caused by metabolic defects and environmental exposures. Exposure to secondhand smoke (SHS) is considered a risk factor for heart disease and it has been linked to decreased blood

levels of antioxidants such as vitamins E and C, increased lipid peroxidation, and increased rates ofplaque fonnation.

The generation ofreactive oxygen and nitrogen species causes mitochondrial injury ranging from mitochondrialDNA (mtDNA) damage, decreased adenine nucleotide translocator (ANT) activity, to changes in mitochondrial proteins. While the mtDNA encodes genes necessary for oxidative phosphorylation, the ANT enzyme moves adenine nucleotides across the inner mitochondrial membrane, and thus, both processes are essential for energy production by the mitochondrion, its principal job in the cell. Therefore, oxidative stress may cause mitochondrial damage that could impact a variety ofcellular functions including energy production and cell signaling.

Advance: These investigators used a mouse model of SHS exposure and a transgenic mouse model ofhigh cholesterol to detennine whether SHS and high cholesterol can cause mitochondrial damage in cardiovascular tissues. The results show that both SHS and elevated cholesterol were associated with significantly increased mtDNA damage and protein nitration. Tobacco smoke exposure also caused decreased activities ofcertain mitochondrial enzymes. SHS and high cholesterol together resulted in increased plaque fonnation and even greater levels ofmitochondrial damage.

Implication: The finding reported by these investigators coincide with present theories that oxidative stress mediates cardiovascular disease by causing mitochondrial damage and dysfunction. These changes ultimately lead to decreased cellular energy production and cellular dysfunction which are important early events in cardiovascular disease.

Citation: Knight-Lozano CA, Young CG, Burow DL, Hu ZY, Uyeminami D, Pinkerton KE, Ischiropoulos H, Ballinger SW. Cigarette smoke exposure and hypercholesterolemia increase mitochondrial damage in cardiovascular tissues. Circulation. 2002 Feb 19;105(7):849-54.

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California School ofMedicine ES09581 and ES07048

Asthma Development in Athletic Children Exposed to Ozone

Background: Asthma among children has been on the rise in the U.S. and other developed countries for the past 20-30 years and has become the most common chronic disease among children in this country. Approximately 9 million children in the U.S. suffer from asthma, which is one ofthe leading causes ofschool absenteeism and causes millions oflost work hours for parents who must stay home to look after sick children. Poor air quality has been recognized for some time as a trigger for asthma attacks. Pollutants such as ozone, nitrogen dioxides, and particulate matter have been suggested as possible culprits

for these attacks, but little has been known regarding their effects on causing asthma to develop in children.

Advance: Researchers at the University of Southern California have shown for the first time that ozone may actually cause asthma. In a study of 3500 children with no history ofasthma from 12 southern California communities, 265 new diagnoses ofasthma were reported during a 5-year period. Children who played three or more sports in areas with high ozone concentrations were over three times as likely to develop asthma as children who did not play any sports. Time spent outdoors was also associated with the development ofasthma. There was no increased risk for asthma development in areas of low ozone concentration. Exposure to other air pollutants was not associated with increased risk ofdeveloping asthma.

Implication: These findings indicate that high exposure to ozone through time spent outdoors in contaminated air and increased breathing rates from physical activity might affect the development of asthma in previously health children. These findings could have policy implications as nations try to tackle the problem ofbalancing the economiccosts ofclean air with protecting the health oftheir citizens.

Citation: McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. Lancet. 2002 Feb 2;359(9304):386-91.

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Raymond Monnat, MD and David Eaton, Ph.D.
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The Varied and Surprising Spectrum of Mutations in Epithelial Cells

Background: Epithelial cells, such as skin cells, cells that line the intestinal and respiratory tracts, etc., comprise about 60% ofthe cells in the human body and are the source ofabout 85% ofhuman cancers. Despite these numbers and the importance ofepithelial cells in normal biology and physiology and disease development, very few studies have been performed on the frequency or breadth ofmutations in epithelial cell lines. To better understand the rate of mutation and the different mutations that occur in epithelial cells as a function ofage, these investigators used epithelial cell cloning and DNA sequencing experiments to characterize mutations ofthe hypoxanthine-guanine phosphoribosyltransferase *(HPR1)* gene in kidney epithelial cells.

Advance: The researchers found a high frequency and unusual spectrum ofkidney *HPRT* gene mutations suggesting that DNA damage or mutagenesis may be substantially different in kidney epithelium than in other epithelial cell types. Kidney epithelial cells contain abundant mitochondria and consume large amounts ofoxygen to produce the energy necessary to function

properly. Surprisingly these experiments show that kidney epithelial cells do not contain high numbers ofoxidative damage induced *HPRT* mutations. This suggests that reactive nitrogen species or circulating mutagens that are concentrated or metabolized in kidney tissue may be more important sources ofkidney epithelial cell mutations.

Implication: These findings suggest that the high-frequency, age-dependent increase and unusual mutations in kidney epithelial cells may play an important role in human kidney disease development. For example, mutation accumulation could cause decreases in kidney tubule function or functional cell numbers that accompany aging. The mutations could also increase the likelihood ofkidney tubule diseases. These studies show that epithelial mutations may be more important in epithelial cell disease development that previously realized.

Citation: Colgin LM, Hackmann AF, Emond MJ, Monnat RJ Jr. The unexpected landscape ofin vivo somatic mutation in a human epithelial cell lineage. Proc Nat! Acad Sci USA. 2002 Feb 5;99(3):1437-42.

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Northwestern University Medical School
ESI0549

Microarray Technology Used to Identify Altered Expression of Thirty **Genes in Response to *GLIl* Expression**

Background: Theprotein GUl isamember ofthefamily ofzincfingertranscriptionfactors. The GU family mediates the expression ofSonic hedgehog, an intercellular signaling molecule, and is critical in regulating cell cycle and differentiation in mammalian development. GLIl transforms cells in culture and is also expressed in several human cancers such as basal cell carcinoma, sarcomas, and medulloblastomas, which account for 20% childhood brain tumors. To identify genes specific to the *GLIl* transformation process, these investigators examined the expression profiles ofcells transformed with *GLIl* and compared them to profiles from cells transformed with *Ha-ras* in a cell line. Microarray technology was used for these comparisons becauseitallows forthestudy oftheexpression ofthousandsofgenesinasingleexperiment.

Advance: The profiling experiments identified 30 genes that were altered by *GLIl* expression. In the *Ha-ras* transformed cells, 124 genes were changed. Seven genes had altered expression levels in both types oftransformed cells. *GLIl* expression altered the expression of genes involved in cell cycle control, cell adhesion, signal transduction, and the regulation ofapoptosis or programmed cell death. Many ofthe *GLIl* targets identified in this study increase cell proliferation which indicates that GLIl-induced cell transformation occurs through multiple targets.

Implication: The number and breadth offunction ofthe genes whose expression was altered by *GLIl* demonstrates its importance as an important player in the control ofnormal developmental processesaswellasthedevelopment ofavariety ofcancers. Thecascade ofeventsresulting from *GLIl* expression provides many opportunities for further research and possible sites of attack for new cancer therapies.

Citation: Yoon JW, Kita Y, Frank DJ, Majewski RR, Konicek BA, Nobrega MA, Jacob H, Walterhouse D, Iannaccone P. Gene expression profiling leads to identification ofGU1-binding elements in target genes and a role for multiple downstream pathways in GLIl-induced cell transformation. J BioI Chern. 2002 Feb 15;277(7):5548-55.

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STAFF HONORS and AWARDS

Dr. Anne Sassaman, Director, DERT, was among the newly elected Fellows honored at the Fellows Award Breakfast at the annual meeting ofthe American Association for the Advancement ofScience in Boston in February. Dr. Sassaman was recognized for her creative direction and management extramural programs.

Dr. Sassaman was honored by being selected to present the first "Spirit Lecture" as part ofthe NIEHS Diversity Council's celebration ofWomen's History Month. This lecture, which will be presented each March, is recognition ofthe role women scientists play in not only laboratory or science administration, but also their contributions to the broader communities ofwhich they are a part. Dr. Sassaman's lecture was entitiled "Life! In Science," and she focused on the balance between professional and personal goals and the unique perspectives ofwomen's leadership style. She was presented with a plaque and honored at a reception.

Ms. Beth Anderson, OPD, received an "EMS" Service Award from the Environmental Mutagen Society (EMS) for her contribution as a co-editor ofthe EMS Newsletter. The award was presented at the annual meeting ofthe EMS held in Anchorage, Alaska on Tuesday, April 30.

The following DERT *OPO/GMB* staff received awards at the Grants Management Awards Ceremony:

Ms. Dorothy Duke, OPOIGMB, received several awards at the Grants Management Awards Ceremony. She was awarded the Excellence in Leadership Award for her service as the co-chair for the Vision Steering Committee, assisting in the development ofnew Vision Steering Committee initiatives and the implementation ofthe recommendations that were a result of the Vision Retreat held in April 2001. Dorothy has provided leadership and guidance to the various subcommittees through out the past year. She is actively involved in various subcommittees reviewing guidance that will be presented to the GMAC community.

Ms. Duke, OPOIGMB, also received an Excellence in Leadership Award for her work with the Grants Management Advisory Committee (GMAC) and Office ofExtramural Research staff, to resolve many issues surrounding the Just-In-Time (JlT) letter. This letter is sent to all applicants that receive scores of30 percentile or better on competing applications. Under her leadership, a resolution was found for the many questions related to the content ofthe letter, its transmittal, and instructions to potential grantees and a new letter for NUl was developed.

As part ofGMAC activities, *Ms. Duke, OPOIGMB,* received a Special Recognition Award for contributions as a Compliance Education and Review Team (CERT) representative to the NUl Proactive Compliance Site Visit (PCSV) Team during FY 2001. The PCSV initiative is a critical part ofNUl's commitment to fulfilling the congressional mandate ofproviding effective oversight ofthe administrative management of sponsored projects research. The purpose ofthe site visits is to assess institutional understanding ofFederal policies and regulations, to minimize or eliminate noncompliance, and to nurture a productive partnership between the NUl and its grantee institutions.

Ms. Duke, OPOIGMB, received a Letter ofAppreciation for participation on Proactive Compliance Site Visits as a member ofthe Compliance Education & Review Team (CERT) committee, serving on the FSR subcommittee, and for significant contributions to Subcommittee activities and participation in the majority ofsubcommittee meetings during the past year.

Ms. Carolyn Mason, OPOIGMB, received two Letters ofAppreciation from the Vision Steering Committee. The first was made "For significant contributions to IMPAC II GM Lead Users Group activities and participation in the majority ofsubcommittee meetings during the past year." The second was "For significant contributions to Grant Guidance Subcommittee activities and participation in the majority ofsubcommittee meetings during the past year."

Ms. Jacqueline Russell, OPOIGMB, received a Letter ofAppreciation "For significant contributions to Compliance Education & Review Team (CERT) activities and participation in the majority of subcommittee meetings during the past year."

Ms. Laura Williams-Boyd, OPOIGMB, received a letter ofAppreciation "For significant contributions to GMAC Subcommittee on Training activities and participation in the majority of subcommittee meetings during the past year."

STAFF ACTIVITIES

Dr. Van Houten and Mr. Phelps, OPDIPAB, gave a demonstration ofthe Scientific Publication Information Retrieval and Evaluation System (SPIRES) to the Planning and Evaluation Officers at their meeting on May 15. SPIRES was developed byNIEHS/CTB as a tool to track publications that have resulted from grants funded by NIEHS.

NIEHS (through the Worker Education and Training Program) sponsored a Technical Workshop entitled "Learning From Disasters: Weapons ofMass Destruction (WMD) Preparedness Through Worker Training." The workshop assisted trainers in creating the curricula necessary to train WMD remediation workers and emergency responders dealing with biological/chemical agents, in addition to helping trainers update existing curricula to incorporate lessons learned from workers responding to and working at the World Trade Center site. The workshop was held in Nashville, Tennessee on April 25-26. Staff attending the workshop and participating in various activities included *Mr. Hughes, Ms. Beard, and Ms. Thompson, OD/WETP.* On April 24, the semi-annual WETP Awardee Meeting was held. *Ms. Mason, OPDIGMB,* and *Dr. Sassaman* also participated in the meeting.

Dr. Sassaman gave a presentation and participated in a panel on grantsmanship and NIEHS programs at the annual meeting ofthe Society ofToxicology. This session, organized annually by the Education Committee ofthe Society, is an opportunity for members, especially young researchers, to learn about the process, how to get assistance in developing their applications or career plans, and the priorities ofthe NIEHS.

Dr. Collman, OPDICEMBB, organized participated in a brainstorming session on Breast Cancer and the Environment in Charlotte, North Carolina on April 20. More that 40 participants, including scientists and breast cancer advocates, discussed new scientific opportunities in this field. She will present a summary ofthis meeting at the NIEHS Leadership retreat in May. Other NIEHS staffparticipated in the meeting, among them, from DERT, *Drs. Sassaman and Dearry.*

Dr. Srinivasan, OPDICEMBB, was a participant at the meeting "RaciallEthnic Bias in RaciallEthnic Bias and Health: Scientific Evidence, Methods, and Research Implications" organized by Office ofBehavioral and Social Science Research in Vienna, Virginia, April 18-19. The purpose ofthe meeting was to develop a research agenda and identify future directions for incorporating the role ofracial/ethic bias in health both at the individual and structural levels.

Dr. Heindel, OPDIOSTB, gave an SBIR grantsmanship talk, including NIEHS SBIR interests, at the SBIR workshop held at East Carolina University, Greenville, North Carolina on April 16. Dr. Thompson, *OPD/CEMBB* and Ms. Anderson, OPD, also participated.

Dr. Gray, OPDICEMBB, gave a presentation entitled, "Cancer Research Opportunities at NIEHS" at the 2002 American Association for Cancer Research annual meeting held in San Francisco, April 6-10. She also served on an expert panel for a question and answer session sponsored by NCI regarding tips and recommendation for a successful grant proposal in cancer research.

Dr. Tyson and Mr. O'Fallon, OPDICEMBB, with support from Dr. Kenneth Olden and other senior NIEHS staff, organized the Interagency Working Group for Community-Based Participatory Research (IWG), a Federal interagency working group to strengthen communication among federal agencies with an interest in supporting community-based participatory research

(CBPR) methodologies in the conduct ofbiomedical research, education, health care delivery, or policy. The IWG is comprised ofrepresentatives from 25 Federal agencies/institutes/offices. The IWG met on February 22, 2002 and again on April 26, 2002. It is anticipated that this group will continue to meet on a quarterly basis.

Mr. Hughes, ODIWETP, presented on the safety and health training responses to the World Trade Center terrorist attack on September 11,2001 at the NIOSH Resource Center Annual Meeting in San Diego, CA on February 5.

UPCOMING MEETINGS and WORKSHOPS

On May 23-25, *Dr. Collman, OPDICEMBB,* will participate in a CDC-sponsored conference on breast cancer and the environment where she will speak to the group about needs for future research in this area. The conference, which is being organized by the University ofCalifornia at Berkeley, will be held in Santa Cruz, California.

Mr. Hughes and Ms. Beard, ODIWETP, will present at the 12th Annual Construction Safety and Health Conference and Exposition scheduled for May 21-23 in Chicago, Illinois. The Worker Education and Training Program along with Center to Protect Workers' Rights, NIOSH, the Construction Safety Council and many other organizations are sponsoring this conference. The conference will share information and ideas about effective safety and health interventions and how to move "best practices" from inception to practical implementation.

The NIEHS Superfund Basic Research Program is sponsoring a two-and-a-half day conference entitled "Arsenic in New England: A Multidisciplinary Scientific Conference," to be held in Manchester, New Hampshire on May 29-31. Exposure to arsenic in drinking water represents a significant health problem for people around the world. Though exposure to arsenic has been linked to increased risk ofcancer, heart disease, diabetes and reproductive disorders in humans, most studies have involved people exposed to elevated levels in the workplace or in parts ofthe world where drinking water contamination is exceptionally high. Scientists have little direct information about the effects ofarsenic at levels found commonly in the United States. In addition, the way arsenic interacts with other substances in biological systems is poorly understood. This two-and-a-half day, multidisciplinary scientific conference will focus on arsenic's natural occurrence; patterns of anthropogenic use and disposal in New England; mechanisms ofaction as a toxin; effects on human health; environmental impact and movement through ecosystems; and regulation and remediation strategies.

The Superfund Basic Research Program is sponsoring a conference, Bioremediation and Biodegradation: Current Advances in Reducing Toxicity, Exposure and Environmental Consequences, June 9 -12 at the Asilomar Conference Center in Pacific Grove, California. Research in the areas ofbiodegradative processes and bioremediation solutions forms a significant component ofthe SBRP. The objective is to bring together SBRP investigators, others who are leaders in the field along with younger investigators who are beginning to make a mark to discuss the exciting and cutting-edge advances that have been made in the last several years. The overall focus ofthe conference is on the research interface areas oftoxicity reduction, exposure assessment, and evaluation ofenvironmental consequences. In addition the conference will highlight the latest in technological advances and translational research.

Drs. Srinivasan and Tyson and Mr. 0 *'Fallon, OPDICEMBB,* are organizing a meeting on "Built Environment -Healthy Communities, Healthy Homes. Healthy People: Multilevel Interdisciplinary Research Approaches" in Research Triangle Park, North Carolina, July 15-16. This event is cosponsored by the Office ofBehavioral and Social Science Research and the Office ofRare Diseases. The purpose ofthis meeting, which will be held in conjunction with the

Health Disparities annual grantee meeting, will be to discuss the state ofthe science and explore future directions in conducting research on built environment and health. It will build upon the past workshops convened by NIEHS and the knowledge it has garnered from Health Disparities projects it has supported.

Drs. Gray and Collman, OPDICEMBB, are organizing a workshop entitled *"In Utero* and Prenatal Exposure Assessment Workshop" on September 24-25 at NIEHS, Research Triangle Park, North Carolina. With the public health emphasis on early life risk factors as a key marker for the onset ofadult-disease, more research in the area of*in utero* and prenatal exposure assessment is warranted. To understand the relationship between the *in utero* and prenatal environment and adult disease, scientists will have to focus on ways to assess early life exposures through non-invasive biological and non-biological measurements. These may include but are not limited to, identifying biomarkers ofthe *in utero* environment using various biological samples such as meconium, placenta, chorion villi, amniotic fluid, umbilical cord blood as well as the development ofcomplimentary questionnaires to assess relevant correlate information such as timing ofexposure, sources ofexposure, and other pertinent cofactors. A panel ofexperts will be brought together to discuss the best methods to ascertain early life exposures by identifying specimen-specific exposures, comparing various sampling techniques, and other types of supplemental data required to ascertain the true effects ofearly life exposures.

STAFF CHANGES

Recruitments:
Dr. Sally Eckert-Tilotta, has recently joined the Scientific Review Branch as a Scientific Review Administrator. She has a Ph.D. in analytical chemistry, and most recently was on the faculty of theUniversity ofNorthDakota. ImmediatelypriortohercomingtoNIEHS,shewasservingas interim director ofthe Office ofResearch and ProgramDevelopment there.

Dr. Leroy Worth Jr., is a new Scientific Review Administrator in the Scientific Review Branch. Dr. Worth is also trained in chemistry, and received his Ph.D. in biochemistry from the University ofMaryland, College Park. Before joining the Scientific Review Branch he was an investigatorinthe NIEHS Laboratory ofMolecular Genetics where he examinedmolecular mechanisms ofDNA mismatch repair in *E. coli.*

Mr. Ted Outwater has joined the Worker Education and Training Program as a Public Health Educator. He is the former Associate Director ofthe Hunter College Center for Occupational and Environmental Health, City University ofNY, and has had direct experience in health and safety training programs, as well as with non-profit foundations

Ms. Margarita Roque has joined OD as an Administrative Officer. Ms. Roque comes to NIEHS from the U.S. Census Monitoring Board, Presidential Members, where she served as Executive Director. She has also served as Associate Vice President for Institutional Advancement at the

University ofTexas Brownsville and Texas Southmost College, and worked for the Organization ofAmerican States/Inter-American Commission on Women.

Ms. Susan Ricci has joined the Grants Management Branch as a Grants Management Specialist. She has extensive experience in Federal grants and cooperative agreements administration as well as inter/intragency agreements. Most recently she was the Grants and Agreements Specialist for the Eastern Region, USDA Animal, Plant, Health Inspection Services, and previously worked for the Social Security Administration and the Department ofthe Interior.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
Division of Extramural Research and Training
Organs and Systems Toxicology Branch

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL
Small Business Innovation Research Program Committee
May 20, 2001

Concept Clearance
For
Small Business Innovation Research Program: Contract Topics FY 2003 Solicitation

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. This Small Business Innovation Research Program (SBIR) uses a combination of research and technology transfer in order to develop new products that will aid the mission of NIEHS. A portion of the SBIR funds ($1.5 M) are allocated for contract solicitations that will improve the productivity of the Intramural scientists at NIEHS and the larger scientific community by providing specific reagents and technologies and instruments needed to further research. This concept is for approval of the contract portion of the SBIR program for FY 2003.

Topics under Consideration for the FY 2003 SBIR Contract Solicitation

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1. **Development of software to associate haplotype populations with disease pathways.**
   Dr. James Selkirk

Software is needed to develop comparative species analysis of single nucleotide polymorphisms (SNPs) that can be uniquely associated with alleles of genes that result in increased susceptibility toward disease and adverse or no-effect response for environmental toxicants, e.g. styrene, butadiene, acrylamide, or medicinals such as chemotherapy agents. Algorithms need to be developed that can locate SNPs via BLAST type searches of human and non-human databases and that can make associations with known disease genes and sub-populations of susceptible individuals via literature data mining search strategies. This in silico approach will locate SNPs in various systems and develop disease gene lists for human as well as surrogate model systems such as rat, mouse and yeast. It will also help locate special populations with regard to susceptibility to diseases and/or environmental exposures.

2. **Development of antibody arrays for toxicoproteomics.**
   Dr. Alex Merrick

Toxicoproteomics is the global response of proteins to a toxicant from a cellular genome. A major technical challenge for toxicoproteomics is to be able to rapidly provide a level of information density comparable to gene expression arrays. The goal of this solicitation is the development, characterization and validation of either a complete protein array or sub arrays directed to determine the level of, for example, transcription factors, signaling pathway proteins, xenobiotic metabolism proteins, phosphorylated proteins etc. based on antibodies. Detection of low abundance proteins or protein modifications can theoretically be accomplished by antibody array chips as antibodies can be densely arrayed in a similar fashion to gene array chips. The development of antibody arrays for the detection of proteins or classes of proteins would have a major stimulatory effect on the field of toxicoproteomics as it would allow the detection of protein changes without expensive equipment or time-consuming analyses.

3. **Use of metabonomics to develop biomarkers of CNS and or liver toxicity.**
Dr. Gary Boorman

Metabonomics combines the techniques of high resolution NMR with pattern recognition technology to rapidly evaluate the metabolic status of an animal (or human) such that the onset, duration, severity and target organ localization can be distinguished. In this context, there is an urgent need to develop and establish the role of metabonomics for predicting the potential of environmental agents to cause or enhance disease and dysfunctions. The NIEHS is interested in supporting the development, characterization and validation of new biomarkers of central nervous system (CNS) and liver toxicity due to exposure to environmental agents. We are specifically looking for non-or minimally invasive metabonomic approaches using blood or urine to detect chemical perturbations indicative of the CNS and liver toxicity in general or to specific brain areas. The metabonomic biomarkers should be anchored in physiology or pathology such that they would be indicative not only of site of toxicity but also suggest mode or mechanism of toxicity. Eventually the study of metabolic changes in biofluids in response to pathophysiological insult can highlight key pathways and place transcriptome and proteome data in perspective.

4. **Development of software "virtual organs" to be used for interpretive toxicogenomics**
Dr. Michael Waters

In order to position scientific investigators for interpretation of toxicogenomic, proteomic, metabonomic and pathologic datasets it is highly desirable to develop a series of "virtual" target organ software packages. In this software, state-of-the-art understanding of normal cell structure-function, physiology, biochemistry, etc. for major target organs would be assembled in a series of "views" or graphic user interfaces. In addition, current knowledge about clinically useful diagnostic measures of target organ function would be incorporated in order to represent a stressed or malfunctioning organ. The initial target organs of interest are the liver and kidney. This virtual organ software should be setup so that toxicogenomic datasets that would represent perturbation of these organs could be added. Attendant changes in gene and protein expression, metabonomics, toxicology, and pathology would then be represented in the context of changes in normal cell structure-function, physiology, biochemistry etc. These integrated "views" of target

organ stress/toxicity would assist in properly interpreting the combined datasets and would aid in functional pathway and network discovery.

5. **Automated scoring of chromosome damage in sperm using FISH biomarkers**
   Dr. Jack Bishop

New molecular methodologies have been and continue to be developed for fluorescence *in situ* hybridizations (FISH) with chromosome specific DNA probes for use in examining mammalian sperm cells. This new methodology improves the power of detection of chromosome damage in male germ cells but the speed with which the various evaluations are made would be greatly enhanced if the scoring would be automated. The components needed for automating this process, such as computer controlled microscope stages, laser image analysis, and brightly labeled chromosome specific DNA probes are available. The purpose of this solicitation is to develop the appropriate software and hardware to automate the detection of chromosomally abnormal sperm using FISH technologies. The product developed should clearly demonstrate the ability to capture, store, review and analyze information with high sensitivity, specificity and throughput.

6. **Development of microarray profiles for microbial toxicity.**
   Dr. Ray Tennant

The demonstration that exposure of animals to specific chemical classes can be characterized through microarray analysis of altered gene expression provides the basis for development of similar expression profiles of animals exposed to microbes (bacteria, viruses, and other agents). The development of such profiles could lead to the identification of new biomarkers of specific microbial exposure and ultimately possibly yield important diagnostic tools. This project requests proof-of-principal experiments to determine if microarray data from blood cells could be used to distinguish an individuals expose to specific classes of pathogenic agents. A good example would be to compare gene expression data for animals exposed to B. anthracis vs B. subtillis. If gene expression data could distinguish between individuals exposed to these closely related bacteria that would constitute proof-of- principle that this approach may be useful for the development of diagnostic tools that would have applications in the area of "bioterrorism" as well as the detection and intervention of disease.