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
September 13-14, 2004

The National Advisory Environmental Health Sciences Council was convened for its one hundred thirteenth regular meeting on September 13, at 8:30 a.m., at the Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The meeting was open to the public from 8:30 a.m. until 5:00 p.m.. The meeting was closed for consideration of grant applications on September 14, 9:30 a.m. to 11:30 a.m.. Dr. Samuel Wilson presided as Chair on September 13 and 14, 2004.

Members Present:

Teresa Bowers, Ph.D.
Joan Cranmer, Ph.D.
Dale Eastman
Elaine Faustman, Ph.D.
George Friedman-Jimenez, M.D.
Bernard Goldstein, M.D., Ph.D.
Michael Gallo, Ph.D.
George Gray, Ph.D.
Frederick P. Guengerich, Ph.D.
David Losee, J.D.
Martin Philbert, Ph.D.
Peter Spencer, Ph.D.
Peter Thorne, Ph.D.
James G. Townsel, Ph.D.
Frank Talamantes, Ph.D

Members Absent:

Douglas Benevento, J.D.
Deborah Brooks

Ex Officio Members Present:

James Neville, COL

Ex Officio Members Absent:

Liaison Members Present:

Marion Ehrich, Ph.D.
Hal Zenick, Ph.D.

Members of the Public Present:

NIEHS Staff:

Kathy Ahlmark
Janice B. Allen, Ph.D.
Beth Anderson
David Balshaw, Ph.D.
Martha Barnes
Linda Bass, Ph.D.
Sharon Beard
Lutz Birnbaumer, Ph.D.
David Brown
Gwen Collman, Ph.D.
Allen Dearry, Ph.D.
Dorothy Duke
Sally Eckert-Tilotta, Ph.D
Pamela Evans
Rich Freed
Janet Guthrie
Kimberly Gray, Ph. D.
Jerry Heindel, Ph.D.
Mike Humble, Ph.D.
Ethel Jackson, D.D.S.
Laurie Johnson
Marian Johnson-Thompson, Ph.D.
Annette Kirshner, Ph.D.
Dennis Lang, Ph.D.
Cindy Lawler, Ph.D.
Charle League
Elizabeth Maull, Ph.D.
Carolyn Mason
Patrick Mastin, Ph.D.
RoseAnne McGee
Terry Nesbitt, Ph.D.
Liam O'Fallon
Michelle Owens
Joan Packenham, Ph.D.
Jerry Phelps

Chris Portier, Ph.D.
Les Reinlib, Ph.D.
Anne Sassaman, Ph.D.
Carol Shreffler, Ph.D.
Shobha Srinivasan, Ph.D.
William Suk, Ph.D., M.P.H.
Claudia Thompson, Ph.D.
Sally Tinkle, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Brenda Weis, Ph.D.
Samuel Wilson, M.D.
Mary Wolfe, Ph.D.
Leroy Worth, Ph.D.

Other Federal Staff:

Ross Shayiq, Ph.D. - CSR
Patricia Greenwel, Ph.D. - CSR
Caroline Dean - FDA

I. CALL TO ORDER AND OPENING REMARKS

The one hundred thirteenth regular meeting of the National Advisory Environmental Health Sciences Council was called to order by Dr. Wilson, Deputy Director, NIEHS. Dr. Wilson welcomed the members of the Council and introductions were made around the room.

II. REVIEW OF CONFIDENTIALITY AND CONFLICT OF INTEREST PROCEDURES - Dr. Samuel Wilson

Dr. Wilson 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 May 17, 2004, MEETING

Council accepted the minutes without change.

FUTURE COUNCIL MEETING DATES

February 14-15, 2005 NIH - Bethesda
May 23-25, 2005 NIEHS (with Leadership Retreat)
September 15-16, 2005 NIEHS

IV. REPORT OF THE DIRECTOR, NIEHS - Dr. Samuel Wilson

Dr. Olden provided written notes for Dr. Wilson to share with the Council. Dr. Olden extended a special welcome to Dr. Gallo after his absence from the previous two meetings. He then thanked the outgoing members for their service to the Institute and to the Council: Dr. Joan Cranmer, Ms. Dale Eastman, Dr. George Friedman-Jimenez, Dr. Michael Gallo and Dr. Fred Guengerich.

Dr. Olden offered his sincere apology for not being able to attend the Council meeting due to a previously scheduled activity that he could not get out of. He was hoping that his successor would be at NIEHS at this point, but pointed out that he believed that a decision for the new NIEHS director was eminent.

NIH received a Congressional directive to develop an "public access" policy and maintain a digital repository at the National Library of Medicine as part of PubMed Central. Advocacy groups have argued that open access is necessary if patient groups are to be well-informed about their health and disease management options. One proposal would allow public access via a summarized lay version, but not necessarily to the entire technical article. There is a concern that the number of publications will provide information that has not been vetted and peer reviewed. Such publications may provide information that is detrimental.

There is a fear that this public access could drive some journals out of business and could also bankrupt some scientific societies that serve a research and educational need. There is language in the House Appropriation Committee Report that requires that results be free and continuously available no later than six months after publication. There has not been any similar language in the Senate bill and although the language in not necessarily binding, NIH has responded.

Dr. Zerhouni has held meetings with scientists, publishers and patient advocates. Council member Dr. Gallo attended one of the meetings. The proposal calls for researchers to submit their paper to NIH after it has been accepted for publication and edited. The articles will not be made public before six months to give the journal time to profit from their work.

There are conflict of interest concerns with respect to the publishing and review of manuscripts. The Center for Science in the Public Interest has raised concerns that journals with financial conflicts of interest policies do not disclose this fact to the reader. While a few journals have conflict of interest policies, none impose sanctions against authors who fail to disclose conflict of interest.

There have been questions about priority setting at NIH. The House Oversight Panel has questioned the wisdom of allowing extramural scientists to propose their own research projects. They are concerned that NIH must be responsive to the public-that we not just fund what researchers want to study versus what needs to be studied.

The NIH Institute and Center Directors had a two-day retreat with Dr. Zerhouni and his senior staff to discuss priority setting and the development of metrics to assist in this that would include scientific excellence, burden of disease and scientific opportunity. The NIEHS SPIRES

bibliometric database was well-received as a useful tool. Issues related to mentoring of future leaders were also discussed.

The Obesity and the Built Environment Conference had over 600 in attendance and a lot of good press. Secretary Thompson and Dr. Zerhouni participated.

Dr. Olden mentioned the IOM Roundtable on Nanotechnology on May 27th. Although nanotechnology-derived products are already entering the marketplace, research to address the health implications represents only about the 1% of the investment in nanoscience.

A Swedish twins study, published in the July issue of Neurology, confirmed earlier studies in that they concluded that environmental factors play a major role in the development of Parkinson's Disease. The title of the article is "No Evidence for Heritability of Parkinson's Disease in Swedish Twins."

Dr. Olden commented on the presentations of Dr. Hall and Dr. Zeldin, being particularly proud that their recruitment was the result of strategic planning involving the Council and the senior leadership of NIEHS.

Dr. Olden's comments ended with a report that research at UCLA showed that air pollution can reduce children's lung function to less than 80% of the lung function expected at their age. The paper was published in the September 8 issue of the New England Journal of Medicine by John Peters. The study involved children between the ages of 10-18. They compared children in the most polluted communities versus those in the cleanest cities. It is unclear how air pollution retards lung development but it may be related to chronic inflammation. Almost 18,000 children were studied in 12 southern California communities.

Dr. Wilson proceeded to give his report as the Deputy Director. He discussed the NAS/IOM roundtable on Environmental Health Sciences, Research and Medicine Symposium - "Global Environmental Health in the 21st Century: From Government Regulation to Corporate Social Responsibility." The program covered a wide range of topics including new European Union initiatives regarding standards for releasing chemicals into the environment. There was also the Roundtable on Rural Environmental Health on 11/29-30. There is a NAS/NRC Committee on Emerging Issues and Data on Environmental Contaminants where the focus in on toxicogenomics. This committee also publishes a newsletter.

The proposed American Gene and Environment Study (AGES) is planned as an exercise with a large cohort study to look at effects of genetics and the environment on human health over the lifespan. The National Human Genome Research Institute (NHGRI) is taking the lead in assembling large planning committee. There will be three workshops over the spring and summer with seven subgroups to report recommendations in September. NIEHS is taking the lead in a subgroup on environmental exposure and technology development. Drs. Wilson, Suk, Thompson and Weis and Mr. Brown are the key players from the Institute.

Plans for the study assume 100 field centers with 0.5-1 million high through-put assays required, the cheaper the better and smaller the sample size the better. The cell lines will be available and

we can assume that research and development will be required to enhance the field of exposure assessment, to build the national exposure map, and to develop personalized exposure monitoring. The potential impact of AGES on exposure assessment is far-reaching and could revolutionize environmental health research on personal monitoring.

Council member Dr. Talamantes questioned the term "molecular profiling," asking if it may be a loaded term. Council member Dr. Goldstein stated that this was good for NIEHS but noted that there is not any EPA involvement. He also expressed a concern, stating that the US is so heterogeneous and the "environment" changes rapidly; the only potential pay-off for this project may be technology development.

Dr. Wilson commented the study must be focused with set priorities. Within AGES enterprise, many investigators can participate. Dr. Guengerich stated that some of these same issues came up in the initial discussions of the Environmental Genome Project. Dr. Wilson commented that the candidate gene/candidate exposure approach needs to be integrated into AGES. Dr. Spencer asked if a broader definition of the environment would change NIEHS priorities. The theme is that the environment is broader than historical factors and there is no special priority according, to Dr. Wilson. The question was asked by Dr. Thorne how this would be paid for and Dr. Wilson answered that there would have to be new money appropriated but it would be likely in the current climate to have to come from existing appropriation, if at all. Dr. Talamantes asked if there will be planning linked to existing international studies. So far they are not far enough along in the planning to know this.

V. Autism Report - Dr. Cindy Lawler (Attachment B)

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that emerge prior to the age of 3 years and are characterized by impairments in social and communicative skills and the presence of stereotyped and repetitive behaviors and interests. There is current evidence for environmental influences of autism which include examples of rare environmental agents that increase autism risk which are thalidomide and valproic acid. The available data are insufficient to determine an environmental contribution for most cases of autism because of the lack of data and the methodological problems with existing data.

The history of the NIEHS involvement began with brainstorming sessions in 2000 and 2001. NIEHS joined the NIH Autism Coordinating Committee in 2000 and cosponsored scientific sessions and meetings. University of California- Davis and University of Medicine and Dentistry of New Jersey are two Centers for Children's Environmental Health and Disease Prevention focused on autism that were funded in September 2001.

A study published by Hornig et al. (Molecular Psychiatry, 2004,9:933-45) reported a significant interaction between immunogenetic and environmental factors in mediating neurotoxicity during early development. Mice were administered the ethyl-mercury containing vaccine preservative thimerosal, in a dosing regimen that mimicked the routine childhood vaccination schedule, behavioral disturbances and striking morphological changes in brain were observed in auto-immune sensitive SJL/J but not the C57 or BALB mice.

These observations raised the questions of the reliability of the findings, the mechanism of effects in mice, the usefulness of paradigm as a new model of gene-environment interaction, and the translation of findings to public health. The NIEHS response is to support direct replication of study, which is in progress and to use the expertise at NIEHS UC-Davis Children's Center. There will also be a partnership established between the Division of Extramural Research and Training and the National Toxicology Program. Work will be done to improve study design by adding 10 times the dose, measuring mercury levels in blood and brain, examining social behaviors, using unbiased stereology and adding immunology measures.

The NIEHS accomplishments in autism include the support of rigorous new studies to examine the potential role of environmental factors in autism; the support of development of new tools and models of autism, including biomarker and models of gene-environment interaction; and the demonstrated responsivity to public health concerns.

Discussion among the Council included a comment that the SJL animal has a number of other lesions - are any of these autoimmune dysfunction seen in autistic children? Dr. Lawler responded that this had not been established and there were no appropriate control groups. Dr. Goldstein asked where we were going with this and the implications. This is a difficult issue and can we give credence to findings that may have negative public health implications.

VI. NAS/NRC Committee Update: Emerging Issues of Toxicogenomics - Dr. Shelton-Davenport and Dr. Roberta Wedge (Attachment C)

The National Research Council's (NRC) Committee on Emerging Issues and Data on Environmental Contaminants, sponsored by NIEHS, provides a public forum for communication among government, industry, environmental groups, and the academic community about emerging evidence and issues in environmental toxicology, risk assessment, exposure assessment, genomics, and other related fields, with an emphasis on toxicogenomics. The standing committee does not itself prepare reports. It has developed proposals for new studies, including the newly established Committee on the Application of Toxicogenomics Technologies to Predictive Toxicology. Other activities conducted by the standing committee include a newsletter, a website, and occasional webcasts of the workshops and open meetings.

The Committee has identified a number of topics for further consideration that will result in workshops or conferences and consensus reports. These will examine the impact of toxicogenomics on predictive toxicology and be a broad overview of the benefits potentially arising from these technologies and identification of the challenges to achieving them. The Committee will consider questions related to three subject areas: data collection, management and reporting; applications in toxicology research and regulation; and legal, social, ethical and communication issues. The report is due at the end of 2005.

Council discussion followed. The question was also raised whether there were any Council members serving and currently there are not, but they are looking at former Council members for the future. Dr. Gray asked about how NRC information is being fed back to guide research programs. Dr. Zenick responded that EPA is the beneficiary of these activities- both intramural and extramural.

Ms. Eastman asked about the public representation. The response was that in there is representation from groups such as the Natural Resources Defense Council and the Environmental Defense Fund, but not representation from health advocacy groups. This may be changing in the future as technology develops. However, meetings open and the audience is engaged in the discussion.

VII. Summary of Leadership Retreat/Discussion - Dr. Sheila Newton (Attachment D)

Dr. Newton's summary included the retreat topics which were:

- Translation of research to medicine and public health
- Nanotechnology: Risks and benefits
- Innovative approaches to exposure assessment

Translation and Improving Public Health included the re-engineering of the research enterprise to focus on the outcomes, stepping up the emphasis on prevention rather than treatment and giving consideration to revolutionary rather than marginal change in how the research establishment operates.

The Nanotechnology session included the overview and relevance to environmental health; nanobiosensors for use in environmental health research; use of nanotechnology for exposure assessment; industrial use and safety of nanotechnology, NTP activities and the NIEHS research directions involving nanotechnology.

In the session Innovative Approaches to Exposure Assessment topics included gene-environment interactions as key determinants of health and disease. Excellent tools and data are available on the "gene" side; exposure data are weaker and new approaches are needed. The question is how we best do this.

Dr. Newton requested feedback from the Council members on topics and future topics. There was discussion from the Council. Dr. Gray asked about the broad definition of the environment and if these factors could be brought better into the exposure picture, especially nutrition. This might best be done by collaborations with other ICs or agencies.

The involvement of the National Institute of General Medical Sciences and the "lessons learned" from the pharmaceutical industry pertaining to toxicity might be useful. There should be a focused methodology discussion in the future of specific issues related to translation and prevention.

VIII. RNA Interference: How a Viral Silencing Suppressor Inactivates siRNA - Dr. Traci Hall (Attachment E)

Dr. Hall presented her work on the siRNA, explaining that siRNA is a recently discovered "small interfering RNA," which is double-stranded and by binding to mRNAs can lead to their destruction and result in down regulation of the gene. Applications of RNA interference include studies of gene function and therapeutics, targeting viral genome or viral protein expression,

targeting oncogene expression in cancer, or targeting overexpressed genes in other diseases. Her own work involves a plant viral protein, p19, that binds to siRNAs suppressing RNA silencing. Structural studies provide information on its function and its usefulness as a tool for understanding RNA silencing in other systems, such as humans, mice, and fruit flies. She presented the results of n elegant X-ray crystallography studies of the interaction of p19 with siRNA and the specifics of the molecular binding. Her conclusions about its structure and its relationship to other homologous protein structures suggest that p19 apparently binds without sequence specificity to siRNAs, and it has been demonstrated to suppress RNAi in HeLa (cultured human) cells.

IX. Asthma, Allergy and the Indoor Environment - Dr. Darryl Zeldin

Dr. Zeldin presented the clinical characteristics of asthma which included:

- chronic lung disease
- reversible airflow obstruction
- airway inflammation and bronchial hyperresponsiveness
- intermittent bouts of wheezing, cough and shortness of breath association with allergy

There are 31.3 million people in the U.S affected by asthma. There has been an increase in emergency room use, hospital admission, school absences/work absences and a negative impact on the quality of life of individuals who suffer from asthma. The prior studies on indoor allergen and endotoxin exposure have been generally small in scope and homes have been localized to a defined geographic region. There also was poor representation of different SES groups, home characteristics, race/ethnicity and urbanicity.

The objectives of the National Survey of Lead and Allergens in Housing (NSLAH) are to conduct a scientifically valid study of indoor allergen types/levels in floor and bedding dust in the nation's housing to provide estimates of allergen exposure in the U.S. population; to identify housing characteristics and behavioral factors associated with high allergen exposure; and to examine the relationship between indoor allergen exposure and disease (allergy and asthma). Data collection for the study will consist of resident questionnaires, home observations and vacuumed dust samples will be taken.

The dust mite feeds on constituents of house dust and lives in bedding, carpeting and upholstered furniture. Sensitization to allergen is associated with increased risk of asthma. Exposure to mouse allergen is a known cause of asthma in certain occupational settings. Sensitization to mouse allergen has been proposed as a risk factor for asthma in inner-city environments. Half of U.S. households have either a dog or a cat living in the home. Sensitization to dog or cat allergens is an important risk factor for asthma and asthma symptoms.

The strengths of the NSLAH are that the study is large; nationally representative sample of homes; and a comprehensive indoor environmental exposure assessment. The limitations consist of cross-sectional study design and the health outcome assessment based on questionnaire data alone. (Vojta P.J., et al, First National Survey of Lead and Allergens in Housing: Survey Design and Methods for the Allergen and Endotoxin Components, Environmental Health Perspectives,

110:527-532 (2002). Arbes S.J., et al, House dust mite allergen in US beds: Results from the first National Survey of Lead and Allergens in Housing, J Allergy Clin Immunol, 111:408-414 (2003). Cohn et al, National prevalence and exposure risk for mouse allergen in US households, J Allergy Clin Immunol, 113:1167-1171 (2004). Arbes et al, Dog allergen (Can f 1) and cat allergen (Fel d 1) in US homes: Results from the National Survey of Lead and Allergens in Housing, J Allergy Clin Immunol, 114: 111-117 (2004))

The National Health and Nutrition Examination Survey is conducted annually by the National Center for Health Statistics and the CDC with 5000-6000 subjects surveyed per year. Components of the survey include questionnaires, medical examinations and medical laboratory testing. The overall program objectives are to monitor trends in the prevalence, awareness, treatment and control of selected diseases, monitor trends in risk behavior and environmental exposures, analyze risk factors for selected diseases and establish a national probability sample of genetic material for future genetic research. This will be a useful survey for future work on the impact of allergens and other environmental factors on asthma.

X. Follow-up Information from Retreat Discussion - Dr. Sheila Newton

This was a continuation of the information presented and discussion from Item VII.

XI. Report of the Director, DERT - Dr. Anne Sassaman

Dr. Sassaman began her report by referring to the report on staff activities and introducing new staff members. Her report included a status report on the 2004 Extramural Loan Repayment Program, which resulted in 16 applications assigned to NIEHS, of which 6 new ones were funded (4 clinical, 2 pediatric), and 5/5 renewals received support, all of which were clinical. She then summarized the Fiscal Year 2004 Roadmap initiatives that had NIEHS participation and described the involvement of the staff in these initiatives, none of which were led by the NIEHS.

In a move to provide some stability or continuity to programs in which NIEHS has made an investment in developing a cohort or special resource; to enable an applicant whose score falls just outside the funding cut-off but whose project needs only limited additional data for a revision; or to encourage early career stage applicants, the Institute plans to utilize a new mechanism, the NIH High Priority, Short-term Project Award (R56). Dr. Sassaman reviewed for Council the features of this new award, which will be considered only for domestic R01 awards and will be based on Institute review of the summary statement and relative ranking of priority score or percentile, not a separate application.

After calling attention to some recent findings from NIEHS-supported studies that have been in the national news, Dr. Sassaman turned the discussion to the new NIH administrative structure which will provide support to all grant-supported activities, the Division of Extramural Activities Support (DEAS) within the Office of Extramural Research. She explained how this grew out of NIH's response to requirements under the A-76 Competitive Sourcing policy and described the impact on the Division of Extramural Research and Training (DERT). NIEHS was required to transfer 15 FTEs and has been reallocated 12. However, the on-board strength of the support staff at the October 3 "stand-up" of the new organization is 6 current staff, 3 new hires, and no

task leader for assignment of tasks. She described the likely implications of this for Division operations and service to the community, and asked for understanding and patience during the transition.

Dr. Sassaman concluded her report with a review of the Early Council Concurrence process that was approved by the Council at its May meeting. Per the agreement, Dr. Olden has appointed three members to act on behalf of the Council for Fiscal Year 2005. These members are Dr. Martin Philbert, Dr. Peter Thorne, and Ms. Deborah Brooks. Mr. Paul Jordan then provided a brief demonstration of the process and answered questions from the members.

CLOSED PORTION OF THE MEETING

XII. Report of the Board of Scientific Counselors - Dr. John Hildebrandt

The Council met in closed executive session to hear a report of the Board of Scientific Counselors and the review of the Laboratory of Computational Biology and Risk Assessment and the Laboratory of Experimental Pathology. Dr. Hildebrandt reported on the recommendations of the Board and the Institute's response.

XIII. Consideration of Grant Applications - Dr. Anne Sassaman and DERT Staff

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.

The September 2004 Council considered 286 applications requesting $65,243,324 in direct cost. The Council recommended 155 applications with a total direct cost of $38,901,814.

XIV. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 12:00 p.m. on September 14, 2004.

Attachments:

A. Council Roster
B. Austism Report - Dr. Cindy Lawler
C. NAS/NRC Committee Update - Dr. Shelton-Davenport and Dr. Roberta Wedge
D. Summary of Leadership Retreat/Discussion - Dr. Sheila Newton
E. RNA Interference - Dr. Traci Hall

Environmental influences in autism: provocative clues and false leads

Cindy P. Lawler, Ph.D.
Scientific Program Administrator
National Institute of Environmental Health Sciences

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that emerge prior to the age of three years and are characterized by impairments in social and communicative skills and the presence of stereotyped and repetitive behaviors and interests. Compelling data have emerged to support the view of ASDs as biologically-based brain disorders with a strong genetic basis. Recently, there has been a growing interest in the potential contribution of chemical, biologic and infectious environmental agents to ASDs. A number of factors have contributed to this heightened interest, including the large apparent increase in ASDs prevalence, highly publicized concerns about possible links between ASDs and childhood vaccination and an increased awareness of the unique vulnerability of fetuses and children to adverse effects of environmental exposures.

There are few data available that bear directly on the contribution of environmental factors to ASD, as much of the existing data are subject to serious methodological flaws. To encourage and support more rigorous research in this area, the NIEHS has sponsored several brainstorming sessions and scientific meetings and, in partnership with the US EPA, has funded two Centers for Children's Environmental Health and Disease Prevention (UC-Davis and University of Medicine and Dentistry, NJ) that focus wholly or partly on the role of the environment and gene-environment interaction in ASDs.

One of the noteworthy areas under investigation is the role of immune system abnormalities in ASDs and the potential contribution of specific toxic agents in creating and/or exacerbating immune dysfunction. A provocative study published recently by Hornig et al. (*Molecular Psychiatry, 2004, 9:833-45*) bears directly on this issue. Hornig et al. reported a significant interaction between immunogenetic and environmental factors in mediating neurotoxicity during early development. When mice were administered the ethyl-mercury containing vaccine preservative thimerosal, in a dosing regimen that mimicked the routine childhood vaccination schedule, behavioral disturbances and striking morphological changes in brain were observed in auto-immune sensitive SJL/J, but not C57BL/6J or BALB/cJ mice. These findings support the idea that heritable variation in characteristics of the immune system can create vulnerabilities for the neurodevelopmental effects of specific toxicants. To enable rapid pursuit of this provocative finding, the NIEHS is supporting an independent replication of the Hornig et al. study and is considering strategies to encourage further research to establish the relevance of these findings to ASDs.

"NAS/NRC Committee Update: Emerging Issues of Toxicogenomics"
Dr. Shelton-Davenport and Dr. Roberta Wedge

The National Research Council's Committee on Emerging Issues and Data on Environmental Contaminants, sponsored by NIEHS, provides a public forum for communication among government, industry, environmental groups, and the academic community about emerging evidence and issues in environmental toxicology, risk assessment, exposure assessment, genomics, and other related fields, with an emphasis on toxicogenomics. Although the standing committee does not itself prepare reports, it has developed proposals for new studies, including the newly established Committee on the Application of Toxicogenomic Technologies to Predictive Toxicology. The standing committee has also provided oversight for the development of workshops on a variety of topics related to toxicogenomics, including the use of toxicogenomics in cancer risk assessment, how to communicate toxicogenomic information to non-experts, and the application of toxicogenomics to cross-species extrapolation. Each of these workshops will have summaries prepared and distributed. Other activities conducted by the standing committee include a newsletter, a website, and occasional webcasts of the workshops and open meetings.

NIEHS ANNUAL LEADERSHIP RETREAT
May 17-19, 2004
Greensboro, North Carolina

Executive Summary

The 2004 NIEHS Annual Leadership Retreat was held May 17-19, 2004, at the Grandover Resort Hotel in Greensboro, North Carolina. Held every year since 1992, the Retreat is designed to allow a variety of stakeholders the opportunity to candidly exchange information and ideas regarding the mission of the NIEHS, the Institute's strategic plans and priorities, and the nature of its current and future investments in the research enterprise. The event was attended by several NIEHS personnel, including staff members of the Office of the Director and managers of the Institute's intramural and extramural research programs. Also attending were invited members of the scientific community representing academia and industry, as well as officials from a cross-section of patient advocacy and environmental groups, many of whom are members of the National Advisory Environmental Health Sciences Council and the NIEHS Public Interest Liaison Group.

This year's Retreat included sessions examining three topics of vital current interest to the Institute:

- ***Translation****: Research investments and translation to medicine and public health*
- ***Nanotechnology****: Benefits to environmental health and risks to public health*
- ***Innovative Approaches to Exposure Assessment****: Current approaches versus a "disease-oriented" approach that takes advantage of the modern tools of biology*

Translation Session Highlights

The Retreat began with an evening session during which participants viewed an episode of *The Charlie Rose Show* that featured a panel discussion regarding the war on cancer, focusing on the points raised by author Clifton Leaf in his recent multi-part series in *Fortune* entitled "Why We're Losing the War on Cancer." Several of the issues discussed on the program were pertinent to consideration of the NIEHS' research enterprise, and the balance of the evening was devoted to a lively discussion that set the stage for the following morning's Translation Session.

NIEHS Director Dr. Kenneth Olden challenged attendees to consider the issues raised in the video in terms of how they applied to the challenges facing the Institute in translating its science into practice for the improvement of public health.

Several discussants mentioned the inherent conservatism of the peer-reviewed grant-making infrastructure, which tends to stifle creativity, or discourage bold initiatives or risk-taking, and promote working at the margins. Ms. Deborah Brooks (Michael J. Fox Foundation for Parkinson's Research) advocated a more directed, results-oriented approach to the research enterprise, which her organization practices successfully, achieving specific research milestones even with limited funding resources.

Discussants also responded favorably to Mr. Leaf's assertion that disease prevention should receive much more emphasis within the research enterprise, particularly within the NIH research portfolio. This is often the result of leaders in the scientific community being heavily invested in the search for cures, as opposed to a focus on better health care through prevention and outreach activities, which can often be achieved through relatively low-budget, primary prevention initiatives.

Along the same line, discussants found an argument put forth in the video by Andy Grove, chairman of Intel and a cancer survivor, to be compelling. Calling for revolutionary change in the cancer research infrastructure, he advocated a systems engineering approach to comprehensively attack the problem and devise solutions. Speakers agreed that this idea holds merit for reconfiguration of the NIH research enterprise to become more effective at translating the entire spectrum of research to improving health.

The following morning, the session on Translation began in earnest with a presentation by J. Michael McGinnis of the Robert Wood Johnson Foundation: "Public Health and Our Research Investments." Dr. McGinnis cited impressive returns on biomedical research over the past 30 years, including a five-year increase in life expectancy during that time frame, which has been worth an estimated $60 trillion to Americans, constituting a 3:1 return for each dollar invested. The question at this point, however, is "Can we do better?" Or, more specifically, can the NIEHS do better as it evaluates the public health effectiveness of its research investments? He suggested that the research portfolio be constantly evaluated for balance according to three tests: the encouragement of prevention research, the need for public health action, and the quest to elucidate determinants of health such as genetic predispositions, environmental

exposures, social circumstances, behavioral patterns, and medical care. The intersections of these domains, he maintained, is where research should be concentrating its efforts, in order to understand the dynamics of interactions among the domains, identify etiologic factors, and develop biomarkers.

Dr. Alex Ommaya, Director of the Institute of Medicine's Clinical Research Roundtable, spoke on "Challenges in Translation: Current Status and Proposed Solutions." He held that major opportunities for advances in the diagnosis, prevention and treatment of many of the major diseases have been impeded by challenges that persist in the process of translating research progress into clinically relevant, useful knowledge. Those challenges can be broadly characterized as blocks that inhibit the translation of basic science to human studies, and the translation of new knowledge into clinical practice. A number of factors contribute to that situation, including high costs, career disincentives, lack of qualified investigators, regulatory burdens, fragmented infrastructure, incompatible databases, lack of willing participants, and lack of funding in certain areas. Dr. Ommaya then presented data depicting an imbalance between the enormous funding of basic research and the comparatively modest funding of clinical trials, and said that the Clinical Roundtable has noted this, and suggests that investment in outcomes research should be increased.

He proposed that Community-Based Participatory Research would be a promising approach to improving translation. The major challenges to the effectiveness of translation, according to Dr. Ommaya, are enhancing public engagement, information systems, and an adequately trained workforce. He presented several ideas identified by the Clinical Roundtable for solutions within each of those areas. He concluded his remarks by presenting an overview of a proposal being put forward by the Roundtable to establish a Cooperative for Health Improvement Research, which would combine three existing research cooperatives into a single public/private cooperative involving a variety of stakeholders, based at the Institute of Medicine, and with a combined budget of $50 million.

The Discussion following the presentations was conducted in two sections. Session chairperson Deborah Brooks set the initial tone by asking attendees to consider whether the funding community has been too focused on supporting science for science's sake, and too little goal-oriented. Discussants agreed that the NIH Roadmap is a good first step in the right direction to encourage and facilitate translation, but that there are gaps that need to be filled, particularly in the areas of training and

the need for broader study of health problems related to environmental factors. Dr. Elaine Faustman (University of Washington) pointed out that the NIEHS has in fact been forward-thinking in its approach to studying gene-environment interactions, addressing the domain intersections alluded to by Dr. McGinnis.

Several speakers emphasized the need for more collaboration, particularly among the various federal agencies involved in public health research and regulation. Dr. George Friedman-Jimenez (New York University) noted that while reorganizing the NIH from the ground up would be too big a task, and probably unnecessary, increased collaboration would result in a more effective public health approach.

The balance of the initial discussion was devoted to consideration of the priorities and investments of the NIEHS, and how the portfolio is assessed. Dr. Olden stressed that one of the goals of the Retreat was to listen to the thoughts and ideas of the various attendees regarding those issues, to ensure that the right investments are being made. Responding to an inquiry from Dr. McGinnis, he also pointed out that there is very little flexibility in the Institute's ability to respond to short-term opportunities, but with long-term planning and strategic assessments, investments can be gradually shifted to react to changing priorities.

The second section of the translation discussion session concentrated on how well the Institute's investments match up to the priorities identified in one of Dr. McGinnis' slides:

Implications for Priorities

- Identification and characterization of etiologic factors within domains
- Understanding the dynamics of interaction at the domain intersections
- Developing markers to identify individual consequences of domain collisions
- Enhancing environment for population laboratories and community trials
- Giving strong focus to interdisciplinary initiative and cross-domain collaboration
- Moving greater attention to understanding the character and physiology of sense of well being and the environmental correlates

Discussants generally gave the Institute high marks in terms of its activities related to Dr. McGinnis' identified priorities. They initially focused on the question of biomarkers as an area in need of more basic research,

particularly in validation and application of biomarkers. Dr. Sheila Newton (NIEHS) observed that although the NIH Roadmap mainly addresses diagnostic biomarkers, NIEHS is also concerned with exposure markers and screening markers, which lead to different applications.

Responding to Dr. Olden's request to consider Dr. McGinnis' point addressing cross-domain interaction, several speakers returned to the issue of collaboration among different disciplines. There was some disagreement about the value of cross-training, but consensus that incentives to collaboration are necessary. It was noted that NIEHS has had some successful initiatives involving cross-discipline collaboration, most notably various centers and Superfund centers.

Regarding Dr. McGinnis' call for more population-based community trials, Dr. Olden noted that NIEHS is not presently making a huge investment in that area. Dr. Gwen Collman (NIEHS) pointed out that such studies are long term and require intensive investments, citing the NIEHS Centers as an example. Several speakers noted the difficulty of recruiting patient subjects or control subjects for clinical trials. Disease advocacy group attendees noted that they are an under-utilized resource for such recruitment.

Attendees were pleased to see Dr. McGinnis' call for more attention to well-being in the research enterprise. Several described it as a key priority that should receive more emphasis, particularly as an approach to prevention without automatically assuming the involvement of pharmaceutical treatment. Dr. Olden asked that the Advisory Council analyze the Institute's investment in this area at its next meeting.

Nanotechnology Session Highlights

Chairperson John Bucher (NIEHS) introduced the nanotechnology session by briefing attendees on some of the basic concepts in the field.

Nano-scale particles are extremely small – from 1 to 100 nanometers – and exhibit unusual and often highly desirable properties as a result. Their physical and chemical characteristics are often quite different from larger forms of the same compounds because of their enormous surface areas. Biological interaction of nanoparticles with organic systems will be an important issue, both in terms of potential toxicity and opportunities for beneficial medical applications. Toxicity questions will be explored by the National Toxicology Program (NTP), which has accepted nanomaterials

for study, in hopes of optimizing the technology's benefits to human health and the environment, while minimizing potential risks.

Dr. Vicki Colvin (Rice University) then presented an overview of nanotechnology, with an emphasis on its relevance to environmental health. She pointed out that research and development in nanotechnology are progressing rapidly, as are investment and commercial application, with the industry projected conservatively to be worth $1 billion in the US alone within the next ten years.

She noted that there are both naturally occurring nanoparticles, such as volcanic ash, and anthropogenic nanoparticles, which are both incidental, such as materials found in automobile exhaust, and engineered. Although there is much material in the literature regarding incidental nanoparticles, there has been very little study to date of the potential risks associated with engineered nanoparticles, which are often very different in composition from the incidental variety. Some studies have shown that engineered nanoparticles are capable of interacting with cells, and due to their often desirable reactivity, are unlikely to be inert in most biological systems.

Dr. Colvin emphasized three important lessons regarding engineered nanomaterials: 1.) they are different from solids or molecules in terms of their behavior when interacting with biological systems, 2.) surface is the most important characteristic, and 3.) particle surfaces can and will change. Each of these elements needs to be understood more thoroughly to enable the production of biocompatible nanomaterials.

Next, Dr. Martin Philbert (University of Michigan) updated attendees on his group's work on nanobiosensors known as PEBBLEs (Probes Encapsulated by Biologically Localized Embedding). PEBBLEs are real-time, reversible sensors that read out information on the environment either inside or outside the cell. They are capable of transmitting readings of a wide variety of biochemical variations, including the effects of perturbations. Due to their extremely small size, PEBBLEs are able to exist in cells without engendering a response. There are three classes of the probes, each with its own advantages and uses: hydrophilic, hydrophobic, and ampiphilic. They are biocompatible, calibratable, and can last for several days within cells. Dr. Philbert shared information regarding many potential applications of the sensors, including potential diagnostic and therapeutic uses.

Dr. David Walt (Tufts University) then presented his laboratory's work on nanoscale sensors used for exposure assessment. The fiber optic array

sensors his group is developing conduct all three levels of analysis simultaneously: sample acquisition, sample pretreatment, and the measurement itself. The fibers comprise a high-density array, with up to 60,000 individual features in a half-millimeter bundle, each capable of generating 2,000 genotypes, resulting in up to 3 million distinct measurements per experiment. The system, which relies on optical fluorescence, is also designed to perform cross-reactive pattern recognition, allowing the recognition and characterization of agents, without necessarily knowing their individual identities. Dr. Walt likened this capability to the human olfactory system.

Dr. Mark LaFranconi (The Proctor & Gamble Company) then contributed brief remarks about nanotechnology from the industrial perspective. He cited its tremendous potential, not only in high technology areas, but in our everyday lives as well, as products utilizing the advantageous properties of nanomaterials enter the consumer mainstream. He noted that there are presently barriers to rapid development, particularly within the health and safety area, in terms of hazard assessment and the ability to predict effects across a broad range of materials. Until such assessment can be conducted more globally, each material is being tested on a case-by-case basis, which is hampering innovation. Industry is moving forward slowly, he said, until the ability exists to make predictive, rapid, cost-effective decisions about materials. He also stressed that public perception would be critical to the ultimate acceptance of nanotechnologies.

Dr. Nigel Walker (NIEHS) then briefed attendees on the NTP's plans to evaluate the safety and toxicity of nanoscale materials. The research will initially focus on nanomaterials already in common use, such as titanium dioxide in cosmetics and fullerenes in semiconductors. Part of the effort will be to develop screening and hazard evaluation programs and pharmacokinetic models, enabling the analysis of materials according to class-wide parameters, rather than being restricted to evaluating each and every new nanomaterial that is developed, which would be impractical.

Dr. William Suk (NIEHS) followed with a presentation regarding the Institute's analysis of appropriate directions for extramural research involving nanotechnology, which began with a workshop conducted March 8-9, 2004. He pointed out that NIH currently funds approximately $80 million in nanotechnology research, as part of the government's National Nanotechnology Initiative, which coordinates the efforts of 17 governmental agencies in the field. NIEHS currently funds $1.6 million in nanotechnology-related research, most of which falls under the

Superfund Basic Research Program. That amount is expected to rise substantially in the near future under a new solicitation that has recently closed. Based upon the discussions at the workshop, the Institute is highly interested in supporting work developing two areas of nanotechnology with particular promise within the environmental arena: nano-scale optical sensors (such as those described by Drs. Philbert and Walt), and functional nanoprobes for use in therapy and remediation. Dr. Suk also stressed that since nanotechnology is an inherently interdisciplinary field, it will be vital to train more students specifically in the technologies to be able to take full advantage of the benefits they have to offer.

The discussion session on nanotechnology initially focused on the issue of interdisciplinary training. Drs. Colvin and Walt observed that interdisciplinary work should receive more emphasis at the post-doctoral level, after an individual is already well grounded in a particular discipline. Dr. LaFranconi added that nanotechnology is likely to become a specific discipline itself in the future.

The balance of the discussion centered on health and safety issues related to nanotechnology. Dr. Philbert advocated a proactive stance in personal protection in terms of industrial hygiene. Dr. Faustman said that while she is excited about the potential benefits of the technology, she is concerned that potential health and environmental effects should be fully investigated. She added that this constitutes a unique opportunity for NIEHS to take a leadership role in researching lung responses, testing approaches, and application of nanotechnology in fields such as pollution prevention. Dr. Colvin, noting that the industry is just now emerging, concurred that NIEHS is poised to contribute to the responsible evolution of the industry.

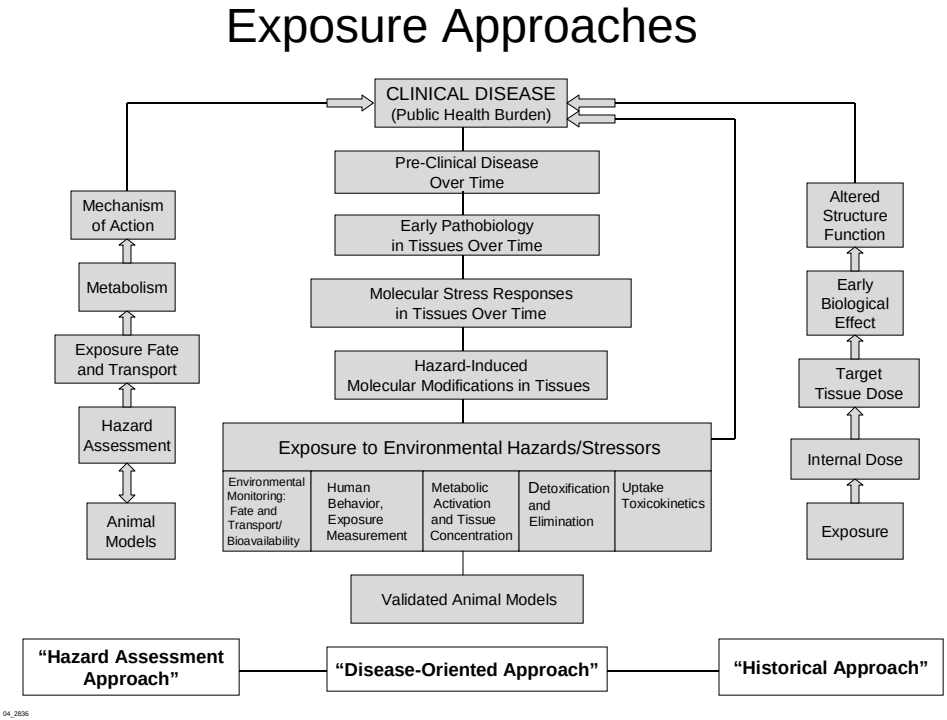
Dr. John Balbus (Environmental Defense) expressed his concern that there seems to be a lack of urgency in pursuing the research. Dr. Bucher responded that the regulatory agencies are vigorously working to learn more about nanotechnology in order to be able to effectively regulate practices in the industry. Dr. Walker also noted that due to the urgency of the issues, it was important to design studies correctly, so as not to inadvertently turn the public against a technology with so many potential benefits.

Discussing the potential pathophysiology of nanoparticles, Dr. Colvin observed that there has been some suspicion of autoimmune response, but that her center has mainly seen membrane interactions. Dr. Philbert noted that a dose index would need to be developed, particularly in the case of therapeutic agents. Dr. LaFranconi pointed out that route of

exposure must also be considered, with dermal and inhalation exposures the most likely in the case of nanomaterials. Responding to a question from Dr. Samuel Wilson (NIEHS), Dr. Colvin said that some of the nanoparticles can be expected to produce oxidative stress within cells, as several are designed to produce such reactions. However, coatings can offer some protection, and work is underway to be able to toggle oxidation reactions on and off within particles.

Exposure Assessment Session Highlights

Dr. Wilson, as session chairperson, opened the proceedings with a brief presentation of the issues to be addressed as participants considered the viability of adopting a "disease-oriented" approach to exposure assessment. He pointed out that the definition of environment has broadened considerably in recent years, and that the field today enjoys an improved toolbox, with new methods and technologies, the "-omics" revolution, and better cell and animal models. Also, due in large measure to advocacy by the NIEHS, the crucial role played by gene-environment interactions in the human disease burden is well recognized today. There are presently three approaches to exposure assessment: the Historical Approach, the Hazard Assessment Approach, and the Disease-Oriented Approach (see chart below). The rest of the presentations in the session were devoted to describing these approaches, and to discussing the need for more emphasis on the disease-oriented approach.



Dr. Faustman, describing the historical approach, began by discussing some of the scientific concepts underlying the exposure component of overall risk. Exposure information, in the linear progression from exposure and dose to clinical disease explored using the historical approach, can be obtained by direct measurement, predictive modeling, biological monitoring, or a combination of those approaches.

There are three methods of predictive exposure assessment: the scenario method, the microenvironment method, and the Monte Carlo method.

To illustrate the various uses of the historical method of exposure assessment, Dr. Faustman summarized three exposure case studies conducted at her facility, the Center for Child Environmental Health Risks Research at the University of Washington. She concluded by presenting a framework encompassing exposure, toxicokinetics, toxicodynamics and outcomes to describe assessment of the effects of a toxicant on development, spanning across exposure assessment, toxicity assessment, and risk characterization.

Next, Dr. William Greenlee (CIIT Centers for Health Research) briefed attendees on the hazard assessment approach, describing the modes by which hazards are identified. The overall purpose of the hazard assessment approach is to describe the dose-response curves related to exposures as precisely as possible, and to glean knowledge from their characteristics. Hazard assessment often begins with rodent bioassay data, in which exposures are far higher than typical human exposures. The challenge with that method is how to determine the relevance of an identified hazard to human health outcomes, by understanding the nature and shape of the dose-response curve at doses corresponding to relevant environmental exposures, and by avoiding specious extrapolations, accounting for differences in human population.

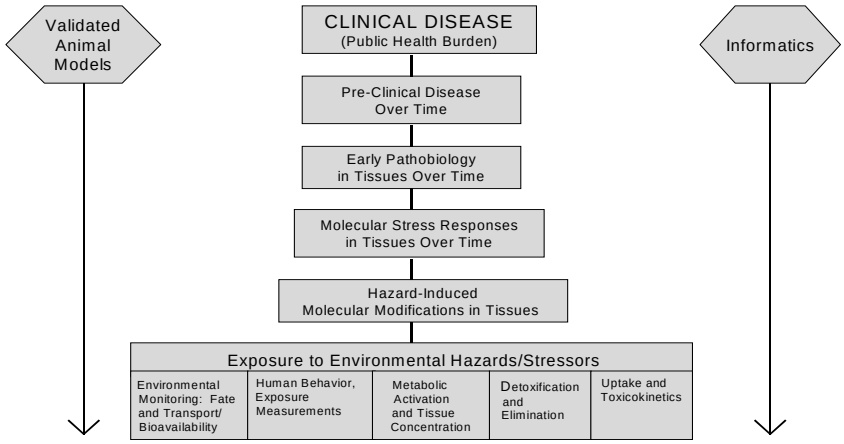
According to Dr. Greenlee, high throughput analytical equipment has enhanced this method by allowing the development of a systems biological approach, characterizing transcription processes and signaling networks in the flow from DNA to mRNA to proteins to systems.

With increasing recognition of intracellular and intercellular signaling cascades, it has become more challenging to characterize complex regulatory networks. This has spawned an approach known as modular biology, in which cellular functions are seen to be carried out by modules made up of many species and interacting molecules. This modular approach can lead to a more refined understanding of dose-response characteristics.

Dr. Wilson followed, and began his look at the disease-oriented approach by describing some of the limitations inherent in the historical approach: it cannot be used to get precise tissue measurements of dose beyond a very narrow laboratory situation, it is not optimal in population-based studies due to difficulties in measurement, and it is difficult to make exposure science either hypothesis-driven or disease-oriented. However, it is clear that "one size will not fit all" in exposure science, since there are several domains that must be integrated.

Dr. Wilson stressed that there is a need for accurate, consistent endpoints that can be measured precisely over many years, since exposure measurement is constantly evolving and changing. One of the hallmarks of the disease-oriented construct for exposure is that it will provide consistent comparisons over decades via general population health studies.

Indicators in Exposure Research



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Armed with the necessary informatics and validated animal models, the disease-first model starts with clinical disease and public health burden, by collecting – over time - the molecular indicators necessary to characterize a certain condition as a clinical disease. Ultimately, hazard-induced molecular modifications in tissues are identified, and exposure to environmental hazards or stressors can be characterized according to the five parameters depicted.

Dr. Wilson pointed out that the NIEHS already has several existing examples of initiatives using the disease-first approach, including the Parkinson's Disease Consortium, the Breast Cancer Centers, and the

autism focus in the Children's Health Centers at UMDNJ-Rutgers and UC-Davis.

The formal session concluded with remarks by two invited discussants: Dr. Paul Lioy (EOHSI) and Dr. Tina Balhadouri (American Chemistry Council). Dr Lioy, while endorsing the disease-oriented approach as a good way to more directly relate scientific information to people, pointed out some of the formidable challenges associated with the approach, including the risk of mistaken hypotheses, and its inherent difficulty. Dr. Bahadori described the current state of the field of exposure assessment, and stressed the need for improved methods of interpreting information gathered by biomonitoring.

Dr. Elaine Hubel (EPA) and Dr. Alex Merrick (NIEHS) joined the above presenters on the panel for the discussion session.

Several discussants noted that the disease-oriented approach has been part of the exposure assessment paradigm all along, in cases such as Legionnaire's disease, cancer, and other conditions in which exposures have been retrospectively linked to disease, as well as in historical epidemiological efforts to link locally high incidence of diseases to exposures.

Others mentioned that the disease-oriented approach would require the involvement of experts from a wide range of other fields, and that prioritization and goal-setting, with the incorporation of concepts from engineering, would be crucial to its effectiveness and efficiency.

Dr. Carol Henry (American Chemistry Council), echoing Dr. Lioy's concern, pointed out that with the disease-oriented approach there would be times when the results would be negative, and that people are often reluctant to accept the value of negative results. Dr. Olden stated that he did not see taking a phenotype as the endpoint and working backwards as a risk, given the current definition of the environment. Eliminating potential culprits would be just as valid and valuable as identifying them, allowing the search for culpable gene-environment interactions associated with a particular disease to move into other areas.

Several discussants expressed the opinion that it might be more fruitful to put more emphasis on wellness and the well cell, looking forward, as opposed to looking at a single disease and working backward.

Dr. Wilson, responding to queries, noted that the disease-oriented approach would require a long-term, detailed study involving a large

cohort. Noting that the logistics of such a study would be challenging, discussants, including Dr. Merrick and Dr. Gwen Collman (NIEHS) said that the –omics technologies would be of great use in identifying biomarkers. Dr. Collman suggested biomarkers might be identified in populations with known exposures, and then extrapolated out into epidemiological studies. Dr. Merrick suggested a tighter coupling of the discovery-based technologies with a disease-oriented approach, so that as new biomarkers or signatures are identified, new hypotheses could be quickly generated and disseminated to the academic community for testing.

As the discussion drew to a close, Dr. Olden noted that the American people are looking for big new ideas from science, that they are willing to make the necessary investments, and that the proposal of a disease-oriented approach to exposure assessment is an example of "big science" that has the potential to change the paradigm and have a major beneficial impact upon public health. Dr. Wilson added that the field of environmental health needs to be sure that the environment side of the gene-environment equation is adequately addressed in a way that makes sense, that is exciting, that links to the genes involved, and links to important public interest issues. Pointing to the many successes of the NIEHS in recent years, he stressed that the Institute, and the scientific community as a whole, have the opportunity to make major inroads in answering the fundamental questions about exposures and the role they play in disease and the public health burden.

Adjourning the Retreat, Dr. Olden thanked attendees for their thoughtful and provocative participation, and expressed optimism that the issues covered in the conference would be effectively addressed in the future.

siRNA measures up: Crystal structure and binding specificity of an RNA silencing suppressor

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RNA silencing in plants likely exists as a defense mechanism against molecular parasites such as RNA viruses, retrotransposons and transgenes. As a result, many plant viruses have adapted mechanisms to evade and suppress gene silencing. Tombusviruses express a 19 kDa protein (p19) that has been shown to suppress RNA silencing in vivo and bind silencing-generated and synthetic small, interfering RNAs (siRNAs) in vitro. It has been proposed that p19 sequesters siRNAs, thus depleting the RNA silencing signal. We have determined the 2.5 Å crystal structure of p19 from the *Carnation Italian ringspot virus* (CIRV) bound to a 21-nt siRNA and demonstrate in biochemical and in vivo assays that CIRV p19 protein acts as a molecular caliper to specifically select siRNAs based on the length of the duplex region of the siRNA. CIRV p19 binds tightly to siRNAs of 20–22-nt, but progressively weaker to siRNAs of 23–26-nt and poorly to a 19-nt siRNAs. Thus, since plants produce two size classes of siRNA, CIRV p19 likely inhibits the mRNA degradation that is correlated with short siRNAs and has lesser effects on the DNA methylation and retrotransposon silencing associated with longer siRNAs. Although amino acid sequence homologs have not been detected in proteins other than tombusvirus p19s, this mode of recognition may represent a prototype for other siRNA-binding proteins in the RNA silencing machinery.