



CHINESE ACADEMY OF SCIENCES AND
U.S. NATIONAL INSTITUTES OF HEALTH

Joint Workshop on Environmental Pollution and Cancer in China and the United States

Executive Summary

JANUARY 5-8, 2010
GUANGZHOU, CHINA



Introduction



Photograph of workshop participants taken at the Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences

On January 5-8, 2010, U.S. and Chinese scientists met in Guangzhou, China, to discuss environmental causes of cancer, including research goals and opportunities for collaboration in this area. Hosted by the Chinese Academy of Sciences (CAS), a prestigious research organization that includes more than 90 institutions across China, this *Joint Workshop on Environmental Pollution and Cancer in China and the United States* included a wide range of approximately 50 health and environmental scientists. Participants represented multiple agencies in China and the United States. Participants from China represented the CAS, the National Natural Science Foundation of China (NSFC), national and local centers for disease control, and several top universities. U.S. participants represented the National Cancer Institute

(NCI), National Institute of Environmental Health Sciences (NIEHS), John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC), and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) – all of which are part of the U.S. National Institutes of Health (NIH), and several academic institutions.

The main purpose of the workshop was to expand cooperation between Chinese and U.S. researchers in order to identify environmental factors that trigger the pathogenesis of lung cancer, elucidate the carcinogenic effects of pollutants, and develop novel therapeutic strategies for patients. Scientific presentations focused on the impact of environmental pollution on cancer in children and adults.

Opening Remarks

During opening remarks, speakers from the United States and China highlighted the uniqueness of the workshop in targeting critical environmental health issues of concern to both countries, and opportunities for collaboration to accelerate the development of interventions to eliminate suffering and death caused by environmental pollution. Dr. Donghai Wu, CAS, emphasized the importance of the workshop in increasing awareness of environmental pollution and cancer and the need to discuss opportunities for mutual cooperation to address this critical issue. Dr. Jinghua Cao, CAS, acknowledged the critical challenge that the environment and cancer present for both countries, the rapid economic development in China that is accompanied by environmental pollution and degradation, and the utility of international cooperation and cross-disciplinary approaches to better understand the complex environmental interactions and solutions to address the unprecedented effects on public health. Dr. Cao further noted that research efforts currently are underway between CAS and NIH, but stressed that much more can be done with regard to joint research funded and supported by both governments, and to develop joint applications for NIH research grants.

Dr. Robert Croyle, NCI, highlighted NIH's long-standing agreement with China to collaborate in the areas of biomedical research and basic sciences. He noted the significance of the workshop, given its targeted focus and multidisciplinary composition of basic, clinical, and population-based scientists, and emphasized that global health science and international collaboration are top priorities for NIH and are fully supported by U.S. President Barack Obama and Dr. Francis Collins, Director, NIH. Like Dr. Cao, Dr. Croyle underscored the need to develop a framework to leverage resources to further advance biomedical research and the technological capacity to support research and policies in the areas of health/public policy, environmental policy, and science policy that facilitate collaboration. He noted that now is an opportune time to engage in such collaboration with China, given its rapid technological advances and training of Chinese scientists. This workshop garnered the full support of Dr. Zhu Chen, Minister of Health, People's Republic of China, who addressed and congratulated the efforts of workshop participants by letter.

Keynote Addresses

The scientific context of the workshop was established by two keynote addresses delivered by Dr. Yan Sun, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, and Dr. Jonathan Samet, University of Southern California. Dr. Sun discussed “Incidence, Time Trends, Prevention, and Management of Lung Cancer During the Past 50 Years in China,” and noted that cancer has become the leading cause of death in China and of the dramatic 400 percent increase in lung cancer mortality during the past 40 years. He further noted that more research is needed to address the environmental and genetic etiology of cancer in China. Dr. Sun explained that China has 350 million smokers and, although smoking rates among women are low, lung cancer incidence is rising and possibly could be explained by cooking oil methods, radon, and secondhand smoke (SHS) exposure, as well as by genetic susceptibility.

Dr. Samet discussed “Challenges and Opportunities in Investigating Cancer and the Environment,” and emphasized several challenges and opportunities for research collaboration, including the: increasing public concern about the effects of the environment on health, increasing numbers of chemicals and toxicants in use, need to develop sensitive surveillance methodologies and tools, need to identify the role of genetic susceptibility on the effects of environmental exposures, and development and use of predictive models. Dr. Samet explained the need to define what we mean by “environment,” and noted that epidemiologic and exposure-assessment methods to identify the nature and scope of the problem are critical to addressing the issue of environmental pollution and cancer. He further noted that large sample sizes will be needed to detect and distinguish the effects of specific environmental contaminants, given the large number of potential interactions.

Plenary Sessions

The core of the workshop was six plenary sessions on important emerging areas for research cooperation between China and the United States, and potential new research projects that could be supported through NIH, CAS, or other funding mechanisms. Concluding sessions focused on funding opportunities that could be used to support U.S.-China research collaborations in the area of cancer and the environment. For each plenary session topic, moderators and participants were asked to discuss the state of the science, gaps in the science, methodological issues, ways to move the science forward, and opportunities for research collaboration.

Pollutants, Hazards, and Solutions

Dr. Xinming Wang, CAS, and Dr. Gary Ellison, NCI, chaired this plenary session, which sought to identify pollutants that trigger the pathogenesis of lung cancer, including pollutants that merit future investigation. The session also focused on strategies to reduce/eliminate the hazards caused by the pollutants. Chinese speakers discussed emerging environmental issues in China. Dr. Wang discussed the hazards of mainstream tobacco smoke, and focused on myriad carcinogenic chemicals present in popular brands of cigarettes sold in China. Dr. Thomas Novotny, San Diego State University, emphasized that toxic chemicals are not only present in

cigarette smoke, but other sources of environmental contamination include thirdhand smoke and the toxic chemicals left behind in non-biodegradable cigarette butts. Dr. Wang also discussed how hazardous toxicant guidelines differ by country, and noted that China's allowable levels for many toxicants are higher than those of many other countries; he suggested that new guidelines are needed in China. Dr. Xinhui Bi, CAS, gave an overview of e-waste ("end-of-life" electronic products) pollution. Dr. Bi noted that e-waste is a growing problem worldwide and particularly in China. E-waste contributes to environmental pollution and poses a significant threat to human health. Dr. Yize Xiao, Yunnan Centers for Disease Control and Prevention, discussed a study of lung cancer in Xuanwei, a key coal-producing city in China. The research suggests that removing coal furnaces can decrease lung cancer mortality, especially among women.

U.S. presenters discussed methodological issues associated with measuring environmental pollution and focused on the source and specific exposures that can contribute to the risk of cancer. Dr. Francine Laden, Harvard University, outlined several critical challenges for environmental epidemiology. For example, the chemical of interest and causative aspect of exposure provide challenges in exposure assessment. She presented research from a retrospective

occupational cohort of workers from unionized trucking companies exposed to diesel exhaust. A statistical model was developed to estimate exposure for each subject, and historical exposures also were considered. Lung cancer risk among drivers was significantly higher statistically than that for the general population. Dr. Michael Greenstone, Massachusetts Institute of Technology, commented on the “black box” challenge associated with measuring exposures and teasing apart the various compounds/pollutants, interactions, and effects. Dr. David Cocker, University of California at Riverside, noted that diesel exhaust is a complex mixture of chemicals that varies by source and vehicle. He described a mobile emission laboratory that allows for measurement of various chemicals in diesel exhaust and contributes to our understanding of how diesel emissions produce atmospheric changes that may lead to disease. Dr. Philip Hopke, Clarkson University, discussed an analytic approach to apportioning particulate matter and identifying the likely source of contaminants. These methods are increasingly being used in health effects studies recognizing that all particles are not equally toxic. Dr. Ellison highlighted the complexity of exposure assessment when contaminants can vary by source and emphasized the need to accurately measure exposures to minimize bias; this is critical when examining gene-environment interactions. Dr. Carol Kasten, NICHHD, noted that in terms of gene-environment interactions, new genetic research on copy number variants and regions of the genome that have chromosomal mutations associated with “environmental genes” (e.g., genes that detoxify) suggests that we may eventually

be able to identify a class of compounds if not specific species of contaminants.

There was general agreement that collaboration between U.S. and Chinese scientists will advance studies of the environment and cancer and that researchers could collaborate to identify biomarkers of chronic exposure to air pollution, study sources and effects of pollutants from e-waste dismantling sites, and conduct epidemiologic studies to better understand the etiology of lung cancer among Chinese women in Xuanwei.

Tobacco, Carcinogenesis, Prevention, and Control

Dr. Gonghuan Yang, Chinese Center for Disease Control and Prevention (China CDC), and Dr. Deirdre Lawrence, NCI, chaired this plenary session, which examined tobacco use, carcinogenesis, prevention, and control methods in China and the United States. Speakers noted that China is the world’s largest producer and consumer of cigarettes, and that cigarette smoking prevalence and cigarette consumption are increasing among men, women, and children in China. Dr. Yang gave an overview of lung cancer rates and cigarette smoking patterns in China and presented data that show about 350 million people in China smoke, including 66 percent of men and 3-4 percent of women. Children are starting to smoke at younger ages, smokers are smoking more cigarettes per day, and lung cancer rates are rising. A participant discussed the challenges of doing tobacco control in China and the impact it would have

on the stability of the country. Dr. Yang noted that China is implementing tobacco control efforts to reduce smoking prevalence and its associated morbidity and mortality.

Dr. C. Anderson Johnson, Claremont Graduate University, noted that providing an economic basis for discouraging production of tobacco products might be a viable strategy particularly if the proportion of tobacco revenue as part of China's gross domestic product drops low enough and lung cancer rates remain high. Dr. Kasten mentioned that Chinese tobacco control efforts may need to emphasize the role of tobacco and its negative health effects on children. Dr. Novotny discussed the changing patterns and risks for smoking initiation among young women in China and noted that China accounts for about 36 percent of the global cigarette market. Because of the low smoking prevalence and relatively low lung disease burden among women in China, few studies have focused on tobacco use in women there. Dr. Kasten noted that research efforts should include biomarkers and other measures of use/exposure given the cultural norms around the unacceptability of female smoking. Dr. Novotny noted that certain subgroups of Chinese women, including migrants and sex workers, have been found to have significantly higher rates (33%) of tobacco use. Dr. Johnson addressed adolescent smoking in the United States and China. He noted that effective smoking control strategies are similar in the United States and China; that smoking and drinking behaviors generally are initiated during adolescence and early adulthood, when the brain rapidly develops addictive patterns; and that smoking control programs and policies should address

biobehavioral characteristics that place youth at risk for lifelong substance abuse.

Dr. William Martin, NIEHS, commented that social and behavioral determinants of smoking among women and girls in China and the United States are similar, despite cultural and political differences. Interventions that address these determinants could prevent widespread tobacco use among Chinese women.

Dr. Biliang Zhang, CAS, discussed the potential role of microRNAs (miRNAs) in regulating gene response in lung cancer among smokers and nonsmokers. He noted that miRNA profiles might serve as biomarkers for smoking-related lung diseases and help to explain the regulatory mechanisms that mediate the body's response to tobacco smoke and other environmental agents.

Dr. Samet emphasized the importance of miRNA research and noted that smokers who have not developed lung cancer should be considered for inclusion in such studies. Dr. Neil Caporaso, NCI, commented that international collaboration would be particularly useful to mitigate the limitations imposed by small sample sizes, especially when there is a need to stratify on factors like smoking status and histology.

It was noted that collaborative international research should continue to contribute to the understanding of nicotine addiction and its prevention, and that funding for international research collaborations is essential and one source could be through the Bloomberg Initiative to Reduce Tobacco Use (<http://www.tobaccocontrolgrants.org>).

risks during the course of treatment. Genetic biomarkers that predict risk of toxicity and distant metastases are needed to inform personalized radiation treatment approaches. Dr. Wei presented Dr. Liao's research on the association of TGF β 1 SNPs with radiation toxicity (i.e., radiation pneumonitis) and/or disease outcomes independent of radiation dose and lung/tumor volume in NSCLC patients. Results indicated that TGF β 1 is a biomarker for toxicity risk and distant metastases that may inform treatment decisions. Larger, randomized clinical trials are needed to validate these findings.

Suggested areas for research collaboration between investigators from the United States and China in this area included developing data-sharing platforms and agreements, assessing dietary influences on cancer risk and treatment, and assessing traditional Chinese medicines that may be useful in preventing and treating lung cancer.

on the heterogeneity of risk factors for lung cancer between U.S. and China populations and suggested that it would be interesting to examine the role of diet and protective factors like green tea. Dr. Samet emphasized that these data provide a good opportunity to conduct cross-country studies in parallel using biomarker data given comparable cigarette exposure across countries. Dr. Cao agreed that more systematic, comparative studies that consider multiple factors, including outdoor air pollution and genetic susceptibility, are needed to explain these lung cancer rates.

Participants encouraged investigators from the United States and China to collaborate on developing data-sharing platforms and agreements, developing valid measures of SHS exposure, studying differences in smoking-related cancer risk in China and the United States, and conducting cross-country, parallel, case-control studies of environmental and genetic modifiers of smoking-related risks using biomarker data.

Environmental Exposures and Childhood Cancer

Dr. Zhu Li, Peking University, and Dr. Carol Kasten, NICHD, chaired the fourth plenary session, which focused on methodological challenges in investigating the genetic and environmental etiology of childhood cancer. Dr. Li noted that the etiology of childhood cancers is mostly unknown but has been related to physical environmental exposures (e.g., ionizing radiation), chemical and infectious exposures, and genetic risk factors. He highlighted the China Children and

Family Cohort Study II (CFCS) that will enroll participants across three generations and will serve as China's "sister study" to the National Children's Study (NCS) in the United States. Investigators from both studies will work together to test multiple hypotheses involving environmental exposures and disease, including cancer, at multiple life stages.

Dr. Kasten discussed the NCS (<http://www.NationalChildrensStudy.gov>), which investigates environmental, genetic, and psychosocial factors that affect children's health. The NCS will include a prospective sample of 100,000 women and their newborns followed through the child's 21st birthday, measure multiple pollutants at key developmental phases, confirm biomarker data, and analyze copy number variants believed to be essential to human adaptation to the environment. Dr. Kasten also discussed the International Childhood Cancer Cohort Consortium (I4C), which includes CFCS, NCS, and other prospective cohorts from the European Union and Australia, and will pool data from childhood cohorts to study cancer. Dr. Li noted that international collaboration with pooling of data from multiple birth cohorts has become the standard. Dr. Patricia Buffler, University of California at Berkeley, discussed the Northern California Childhood Leukemia Study (NCCLS), which was designed to examine the relationship between environmental exposures and childhood leukemia, explore modification of risks by metabolic polymorphisms and DNA methylation, and improve research methods such as disease classification and exposure assessment.

Dr. Sun noted that the incidence of childhood leukemia is rising especially in the cities of China, and it has been suggested that this is due to chemicals from new housing and furniture. Dr. Kasten noted that genetic factors may be more important than environmental factors because childhood leukemia occurs early in life, but also noted that there may be genetic susceptibility to environmental risks. Dr. Buffler noted that research shows multiple genetic events are associated with childhood leukemia, and it is likely that multiple exposures rather than a single exposure may be responsible. Approaches for using newborn screening bloodspots (NBS) to provide data on environmental exposures and other factors involved in the etiology of cancer are needed, and the controversy associated with use of NBS in the study of childhood cancer needs to be addressed.

Participants suggested that investigators from China and the United States could collaborate by organizing joint meetings regarding the NCS and CFCS, and in discovering new environmental biomarkers.

Lung Cancer Pathogenesis

The fifth plenary session was chaired by Dr. Hongbin Ji, CAS, and Dr. Peter Ujhazy, NCI. This session focused on the cellular and molecular/genetic changes that underlie lung cancer, with an emphasis on translation to early detection and chemoprevention. Dr. Ji discussed the ErbB pathway in relation to lung cancer. He emphasized that this pathway is important for normal epithelial cell function and genetic alteration of components in the ErbB pathway is associated with non-small

cell lung cancer (NSCLC). Dr. Ji and colleagues also are developing a lung cancer research database (<http://www.megabionet.org/bio/hlung>). Dr. Tao Zhu, University of Science and Technology of China, discussed his research on artemin (ARTN), which is expressed in human tissue and tumors. Research has shown that increases in ARTN gene expression are associated with NSCLC, and analyses using the Oncomine database (<http://www.oncomine.org>) show that increases in ARTN gene expression are correlated with lung cancer related to tobacco use, high tumor grade, distant metastasis, disease relapse, chemoresistance, and death in lung cancer patients.

Dr. Ujhazy highlighted NCI's Specialized Programs for Research Excellence (SPOREs), which was established to facilitate the development of new clinical tools and applications for decreasing cancer incidence, morbidity, and mortality based on laboratory, clinical, and population-based research. He highlighted research findings from the lung cancer SPOREs sites and made particular reference to the role of oncogenes like EGFR in NSCLC. Dr. Caporaso discussed several lung cancer research collaborations, including the Environment and Genetics in Lung Cancer Etiology (EAGLE) Study; the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; and the Gene Environment Association Studies (GENEVA) Lung Cancer GWAS, which conducts pooled analyses of data from the EAGLE and PLCO studies. EAGLE is a case-control study conducted in Northern Italy as part of a collaboration between U.S. and Italian researchers. The GENEVA Lung Cancer GWAS aims to identify genes associated with

lung cancer, determine tobacco phenotypes, and examine lung cancer survival. This GWAS recently confirmed the role of chromosome 15 in lung cancer risk, smoking intensity, and dependence in smokers. One participant inquired if the association of chromosome 15 and smoking or lung cancer was real. Dr. Caporaso mentioned that the association exists with smoking intensity and dependence and with lung cancer even after adjusting for smoking. It is not easy to tease out the effects of smoking, and the Asian studies may be helpful in that regard. Dr. Caporaso noted some benefits of consortia, including large sample sizes that allow for subgroup analyses, interdisciplinary expertise, and increased resources.

Dr. Reid commented on NCI's Cohort Consortium and suggested that investigators consider this source for potential collaborations. Investigators suggested that science may be moved forward if enhanced support for consortia that engage Asian/Western investigators was provided and incentives to share tissue and data were incorporated in such support.

Opportunities for collaboration between investigators from China and the United States in lung cancer pathogenesis cited by the group included developing biomarker-based targeted therapies, coordinating molecular epidemiology studies, developing appropriate animal models, performing deep sequencing of lung cancer cell lines, and characterizing lung cancer risk factors such as chronic obstructive pulmonary disease (COPD), diet, physical activity, and air pollution in Asian and Western countries.

Pathogenesis and Therapeutics

The sixth plenary session focused on developing novel therapeutic strategies for lung cancer, and was chaired by Dr. Zhihai Qin, CAS, and Dr. William Martin, NIEHS. Dr. Qin discussed chemical carcinogens and immunological reactions and noted that cancer is associated with cell inflammation, which can be caused by viral exposure (e.g., hepatitis), physical mutations, chemical mutagens, and inherent mutagens. Dr. Qin provided an overview of the extrinsic and intrinsic pathways that connect cellular inflammation and cancer and explained that tumor tissue is composed of neoplastic cells and different kinds of stromal cells, such as fibroblasts, endothelial cells, and other inflammatory cells. Cytokines can play an important role in tumor development by regulating the inflammatory response. His research focuses on the role of inflammatory cytokines produced by immune cells on stromal fibroblasts during chemical carcinogenesis. Dr. Qin noted that fibroblasts are important to study and discussed research from studies using mouse models that showed that the interactions between cytokines and fibroblasts can promote or inhibit tumor development. This research also suggested that the inflammation site (e.g., skin versus intramuscular) may play an important role in tumor promotion versus inhibition.

Dr. Zhili Li, Chinese Academy of Medical Sciences and Peking Union Medical College, focused on the importance of monitoring glycoproteins (e.g., haptoglobin) as a guide to prognosis in chemotherapy. Haptoglobin is a hemoglobin-binding protein in the plasma that functions to remove hemoglobin from blood. Dr. Li highlighted research

showing that haptoglobin concentrations in serum/plasma differ significantly in cancer patients compared to noncancer patients. Furthermore, haptoglobin concentration levels during chemotherapy may predict prognosis in NSCLC. Dr. Li also emphasized the potential role of monitoring glycoprotein levels in cancer and personalized medicine, translational medicine, and managing drug side effects.

Dr. Guangbiao Zhou, CAS, noted that the development of cancer is highly dependent on a balance between protein kinase and phosphatase activities. Specifically, phosphatase CIP2A expression is low in healthy cells (which inhibits cell proliferation) and high in cancerous cells (which increases cell proliferation and transformation). Dr. Zhou added that CIP2A expression has been found to be higher in smokers compared to nonsmokers. Studies also have shown an increased expression of CIP2A in lung cancer cells and suggest that the overexpression of CIP2A may play an important role in lung cancer proliferation. Studies have shown that LTZ010 (a compound extracted from a traditional Chinese medicinal herb) is a CIP2A inhibitor and is capable of potent anti-lung cancer activity.

Dr. Qingyi Wei, The University of Texas M.D. Anderson Cancer Center, discussed using DNA repair to predict treatment response and survival in patients with lung cancer. Dr. Wei noted that tobacco carcinogens can bind to DNA and contribute to the development of DNA adducts, which block the DNA transcription process and must be repaired. Several DNA repair pathways are associated with damage caused by tobacco carcinogens

and are critical to preventing mutations. Dr. Wei and colleagues examined the role of DNA repair capacity in NSCLC patients who received chemotherapy and radiotherapy and found that: (1) suboptimal DNA repair capacity is associated with greater survival in NSCLC patients treated with chemotherapy, and (2) variation in genes involved in the repair of radiation-induced DNA damage was associated with risk of developing pneumonitis in patients treated by radiotherapy. DNA repair capacity appears to be a “double-edged sword” in that higher levels of DNA repair capacity are protective in cancer-free individuals; once cancer develops, however, higher levels of DNA repair capacity interfere with treatment and are associated with poorer survival. Larger, prospective studies are needed to substantiate these findings.

In addition, Dr. Wei discussed personalized therapy for NSCLC and presented research by Dr. Zhongxing Liao, also of The University of Texas M.D. Anderson Cancer Center. In reviewing epidemiologic data on lung cancer in the United States, Dr. Wei noted that about 87 percent of cases are NSCLC, and 13 percent are small-cell lung cancer (SCLC). Dr. Wei highlighted the potential role of personalized medicine. Issues to consider when determining personalized treatment approaches for advanced NSCLC patients include the risk of local recurrence and need for radiation dose escalation, radiosensitization, risk of distant metastases and need for effective systemic therapy, risk of toxicity and need for advanced radiation technology to reduce dose, volume of the organ at risk, and expected need to revise the treatment approach based on changes in

risks during the course of treatment. Genetic biomarkers that predict risk of toxicity and distant metastases are needed to inform personalized radiation treatment approaches. Dr. Wei presented Dr. Liao's research on the association of TGF β 1 SNPs with radiation toxicity (i.e., radiation pneumonitis) and/or disease outcomes independent of radiation dose and lung/tumor volume in NSCLC patients. Results indicated that TGF β 1 is a biomarker for toxicity risk and distant metastases that may inform treatment decisions. Larger, randomized clinical trials are needed to validate these findings.

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SPECIAL TOPIC:

The Huai River Project

Dr. Michael Greenstone, Massachusetts Institute of Technology, discussed the unintended health consequences of the Huai River Policy, which provided free coal home heating systems to residents north of the Huai River from 1950-1980. He presented work that utilized an econometric model to compare environmental and health outcomes of residents living north and south of the Huai River. Dr. Greenstone noted that the policy appears to have caused dramatic differences in total suspended particulates (TSP) in the north and south and that exposure to TSP was associated with elevated mortality rates due to increased risk of lung-related illnesses in the north. Dr. Xin Sun, China CDC, discussed the Huai River Integrated Program on Cancer Control and Prevention. This program consists of an epidemiologic study and an integrated surveillance system. Dr. Sun noted that the

epidemiologic study, which included three communities north and south of the Huai River, suggested that cancer mortality rates were significantly higher in northern communities than in southern communities and that a spatial cluster analysis of gastrointestinal and liver cancer cases indicates that the Huai River Policy is the likely cause of cancer clusters in areas north of the river where coal home heating systems were provided. The integrated surveillance system includes environmental monitoring, survey data, and birth and death surveillance. A workshop participant suggested integrating Dr. Greenstone's work with the efforts of the Integrated Program so that individual-level data can also be considered. Another participant suggested that it would be interesting to see how levels of TSPs decline over time since the Huai River Policy has ended.

Funding Opportunities

Dr. Joshua Rosenthal, FIC, provided an overview of the NIH and the Fogarty International Center. Dr. Britt Reid, NCI, described the NIH grant application process. Dr. Tongzhang Zheng, Yale University School of Public Health, and Dr. Qingyi Wei, The University of Texas M.D. Anderson Cancer Center, provided advice on grantsmanship. Ms. Huai Chen, NSFC, described the Foundation's funding programs. Dr. Cao, CAS, described CAS' joint international cooperation funding opportunities. Dr. Renguo Feng and Dr. Yi Shen, both of CAS, led a panel discussion.

The presentations provided participants with information about existing funding mechanisms in the United States and China that could support research collaborations in cancer and environmental health. NIH provides multiple mechanisms for funding international research collaborations. Advice was offered on submitting a successful application for cross-country research collaborations. The process for obtaining U.S. funding is more complex than in China, and preliminary data usually are required. Some NIH funding mechanisms can be used to support pilot projects to collect preliminary data.

Most research funding from U.S. organizations, including NIH, goes to a U.S. institution, with international organizations as subcontractors. Less than 2 percent of research funding from U.S. agencies goes directly to foreign institutions/investigators. Requests for Applications (RFAs) will indicate if foreign institutions are eligible to apply for funds.

The CAS and NSFC primarily offer funding for studies in China. CAS, however, has a

large budget for international collaborative activities. Much of this budget supports international meetings and visits and young scholars programs. Funding is available for joint research activities, and CAS provides some support for two cooperative projects with NIH's Fogarty International Center. The new NSFC Department of Health Sciences may provide more resources and funding for population research on environmental exposures in the future. Research funding agencies in China currently do not have a formal mechanism for funding mutual, cross-country research.

Collaborations typically are formed by investigators from the two countries applying separately for funding via their home institutions. Joint research efforts, applications, and solicitations are needed, particularly for long-term, strategic research initiatives. Dr. Novotny suggested that there is a need for separate, formal, "blended" government mechanisms to support authentic bilateral cancer research collaborations with a potential for global impact. The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) and the Biotechnology Engagement Program (BTEP) with Russia are models for these kinds of mechanisms. Such mechanisms should allow for equal levels of support and management from China and the United States. Dr. Rosenthal mentioned that these types of funding mechanisms would require high-level approval (e.g., U.S. Department of State). Challenges to developing these cross-country research arrangements include differing government requirements and timelines. An arrangement is manageable if it is well planned and provides the necessary resources.

Closing Remarks

Dr. Linda Birnbaum, Director, NIEHS, emphasized that a growing body of research suggests that many chronic adult diseases (asthma, diabetes, obesity, heart disease) may be traced back to exposures that occurred during development and in utero or neonatal exposures to environmental, dietary, and behavioral factors. Individuals and populations also may have genetically driven vulnerabilities to exposures, which are not taken into consideration when reporting odds or risk ratios. Knowledge gaps in the study of cancer and the environment include critical exposure times, lifestyle factors linked to disease, measurement of exposure and body

burden, methods for more precisely linking environmental factors to biological effects, early biomarkers of disease, disease mechanisms, therapeutic targets and biomarkers of therapeutic efficacy, and biomarkers of disease progression. Research also is needed in the field of epigenetics, which studies changes in the expression of gene activity on transcriptional, translational, and post-translational levels that occur independent of the underlying DNA sequence. Factors to consider when investigating what makes an environmental chemical hazardous include persistence, bioaccumulation, toxicity, dose, and timing.

Research Collaboration Areas of Interest

In addition to the opportunities for research collaboration mentioned throughout this document, participants discussed other collaboration opportunities and expressed interest in the following:

- Birth cohort studies to better understand the origins of childhood and adult onset of disease.
- “Upstream” and “downstream” studies of the environment and health, particularly with regard to smoking/tobacco.
- Childhood cancer.
- Causes of cancer and ways to eliminate environmental triggers for the disease.
- Risk factors that explain the high rate of lung cancer among nonsmoking Chinese women. These risk factors might include cooking practices and hormones.
- Indoor air pollution and its contribution to ambient air pollution. Engineers could be involved in intervention studies in this area to help design safer cooking stoves and methods.
- Measurement of the contribution of specific risk factors for lung cancer, including SHS.
- Social and behavioral science to better understand tobacco exposure, behavior change, and compliance with related policies. Studies should focus on ways to translate evidence on effective tobacco control interventions into practice.
- Polluted drinking water and its relation to the high rates of liver and stomach cancer in China.
- Meeting of U.S. and China investigators to discuss data-sharing protocols particularly with respect to environmental exposure assessment.



NIH Publication No. 12-7913
May 2012