NATIONAL CANCER INSTITUTE

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Canadian Breast Cancer Chemo Regimen May Be Superior to Standard Chemo

Results from a Canadian-led clinical trial suggest that a standard chemotherapy combination regimen for breast cancer is not as effective as chemotherapy regimens more commonly used in Canada in preventing recurrence of breast cancer. The preliminary findings were presented by the lead researchers December 17 at the San Antonio Breast Cancer Symposium.

The trial involved 2,104 women under age 60 in Canada and the U.S. who were diagnosed with lymph node-positive or high-risk, node-negative breast cancer, which accounts for almost 50 percent of breast cancer cases in North America. Following surgery, they were randomly assigned to one of three different 6-month, intravenous treatment regimens: AC/T (doxorubicin and cyclophosphamide followed by paclitaxel administered every 3 weeks), one of the standard of care regimens used in the United States; CEF (cyclo-

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Director's Update

Director's Office Reorganizing to Better Support NCI

With budgets declining in 2005, 2006, and now, apparently, in 2007, there has been an absolutely essential NCI-wide effort to downsize. This process has, of course, affected our extramural grantees, but every effort has been made—and continues to be made—toward downsizing the infrastructure that supports the activities of the Institute, as well. For example, efforts are underway to improve work efficiency, to ensure that we are spending every infrastructure support dollar wisely, and to streamline how specific NCI offices work together as a team, so that we can continue to respond to changing needs, both within and outside the Institute. We recognize that the realities of a decreasing annual appropriation, the increasing demands of an expanding extramural research community, and the changes at NIH resulting from the recent passage of the NIH reauthorization bill require immediate action.

The Office of the Director (OD) is the home of almost all of NCI's support structure and, therefore, has been the subject of much of our reviewing and planning over the past 6 months. Using the recommendations of the Executive Committee (EC) based upon a series of staff presentations and detailed personnel and bud-

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(Chemotherapy continued from page 1)
phosphamide, epirubicin and fluorouracil), which was developed and used in Canada; or the experimental regimen dose-dense EC/T (epirubicin and cyclophosphamide followed by paclitaxel).

An interim analysis showed that the 3-year, recurrence-free survival rate was 85 percent for patients on AC/T, compared with 90.1 percent for patients on CEF, and 89.5 percent for those on EC/T. Final trial results are not yet available, but half of the patients included in this interim analysis were followed for at least 30 months.

Initial data analysis shows that AC/T is "significantly inferior" to the CEF and EC/T regimens in preventing a recurrence of the disease, commented research co-leader Dr. Margot Burnell, an oncologist from New Brunswick, Canada.

The study was funded in part by the Canadian Cancer Society and coordinated by the National Cancer Institute of Canada Clinical Trials Group, with additional funding by NCI and several pharmaceutical companies.

Although final results from this clinical trial "may change the way many [breast cancer patients] are treated in the future," Dr. Burnell cautioned that use of AC/T will not likely be totally discontinued. "AC/T administered at the standard 3-week intervals may still be the right choice for some patients depending on factors such as their general state of health and how well they tolerate the side effects of different chemotherapy drugs."

"The results are interesting," said Dr. Jo Anne Zujewski of NCI's Cancer Therapy Evaluation Program. "Although there is interest in the CEF and EC/T regimens used in Canada, there was more toxicity, including serious and long-term toxicity. There were a lot of variables in this trial so that it is hard to identify what factor is accounting for the results." She also noted that the U.S. cooperative group, CALGB, reported in their study that administering AC/T every 2 weeks—called "dose dense"—was superior to the 3-week schedule of AC/T used in the Canadian trial.

The study's researchers say it is too early to determine whether CEF is more effective than the experimental EC/T treatment. It is also premature to say whether overall survival, as opposed to recurrence, is better on any one of the three regimens. ◆

By Bill Robinson

(Director's Update continued from page 1)
get reviews, we have been working through a reorganization of the OD, with the ultimate goal of enhancing how it supports NCI—and doing so at significant cost savings.

With this reorganization, we have made considerable progress toward streamlining the organizational structure and building on the synergies that exist between parts of OD that already work closely together. Although the reorganization is not entirely finalized, there are a number of important changes that the EC has formally approved.

One important change is to broaden the role of the deputy director for management (executive officer) to serve as a chief operating executive for NCI. The executive officer, who will report directly to the NCI director and sit on the EC, will provide leadership on many day-to-day operational matters.

A number of offices will report to the executive officer, including those related to budget, financial, and planning issues, along with the offices of human resources and workforce development.

In addition, the newly created Office of Communications and Education—a merger of the Office of Communications and the Office of Education and Special Initiatives—will report to the executive officer. The decision to bring together these two offices came at the recommendation of a special EC subcommittee that spent the summer reviewing NCI's communication and education programs.

Another key change relates to the Director's Consumer Liaison Group (DCLG) and Consumer Advocates in Research and Related Activities, both of which will be more closely aligned with OD. This is particularly important for DCLG, whose mission will be redefined to include activities related to cancer care delivery, disparities issues, and patient outreach.

Although some centers and offices that previously reported to OD will now report to the executive officer, a number of OD "direct reports" are being retained, including, of course, all of the intramural and extramural divisions, along with the Center for Bioinformatics; the Center for Scientific Strategic Initiatives; the Center to Reduce Cancer Health Disparities; the Office of Centers, Training, and Resources; and NCI-Frederick.

While this restructuring is not complete, we have made great progress. I am confident that, with input from the Institute leadership and staff, we are creating a logical organizational structure that provides the best possible support for the entire Institute.

One final comment: As many *NCI Cancer Bulletin* readers may be aware, all of the agencies under the

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Cancer Research Highlights

Low-Fat Diet May Help Prevent Breast Cancer Recurrence

Interim results from the first large-scale randomized clinical trial testing an intervention to reduce dietary fat intake as part of postsurgical breast cancer management have shown that women who reduce their consumption of fat after treatment for early-stage breast cancer may also reduce their risk of recurrence. This report from the NCI-sponsored Women's Intervention Nutrition Study (WINS) was published in the December 20 *Journal of the National Cancer Institute*.

Between 1994 and 2001, WINS investigators recruited 2,437 women with invasive breast cancer who were between the ages of 48 and 79 at the time of enrollment into the study. At the start of the study, both groups consumed similar amounts of calories from fat. At the end of the first year of observation, the women in the dietary intervention group had reduced their fat intake by an average of 23 grams per day compared with only a 5-gram-per-day drop in the control group.

The difference between the two groups was maintained throughout the trial. By the fifth year of the trial, the women in the intervention group weighed an average of 6 pounds less than the women in the control group. After a median of 5 years of follow-up, breast cancer had recurred in 9.8 percent of the women on the low-fat diet and 12.4 percent of those on the standard diet. This amounted to a 24-percent reduction in the relative risk of recurrence for the women on the low-fat diet.

The authors acknowledge several limitations to their study, including the possibility that weight loss in the intervention group or other dietary factors may have influenced the outcome. However, stated lead author Dr. Rowan Chlebowski of the Los Angeles Biomedical Research Institute in an accompanying press release, "Although further confirmation is needed…these results suggest that an intervention aimed at reducing dietary fat consumption can reduce the risk of breast cancer recurrence."

Bevacizumab with Platin-Based Chemo Improves NSCLC Outcomes

The results of a phase III study performed by the Eastern Cooperative Oncology Group show that when the monoclonal antibody bevacizumab is added to a paclitaxel-carboplatin chemotherapy regimen for patients with non-small-cell lung cancer (NSCLC), their overall survival, progression-free survival, and response rates significantly increase. These benefits, however, are tempered by an increased risk of treatment-related death. Study results were published December 14 in the *New England Journal of Medicine*.

Researchers recruited 878 patients with recurrent or advanced NSCLC, excluding those with squamous-cell tumors, brain metastases, or who were coughing blood or bloody sputum. Nearly half of the participants received paclitaxel and carboplatin every 3 weeks for 6-week cycles, while the remaining group received bevacizumab every 3 weeks in addition to the same chemotherapy, until their disease progressed or the side effects became intolerable.

Regardless of baseline vascular endothelial growth factor levels, the results showed that patients who received bevacizumab had a median overall survival of 12.3 months, compared with 10.3 months for those who did not. Also, 35 percent of patients who received the bevacizumab showed a response to treatment, compared with 15 percent in the group that did not receive it. These results are expected to change clinical management of NSCLC patients.

The authors note that the risks of side effects, including neutropenia, pulmonary hemorrhage, and toxicity, should be weighed against the survival benefit conferred by adding bevacizumab to NSCLC chemotherapy.

Study Suggests Viruses Play Larger Role in Cancer

A new study suggests that common viral infections may play a larger role in cancer than has been previously thought. The nearly 29,000-participant population-based cohort study, conducted in Australia, found a significantly increased risk of 25 different cancers following kidney transplantation, including a more than threefold risk for 18 of those cancer sites.

The study authors argued that the immune system suppression required to carry out a kidney transplant was behind this increased risk, demonstrating a broader role of "common viral infections in the etiology of cancer."

Published in the December 19 *Journal of the American Medical Association*,

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(Highlights continued from page 3)

the study included participants with end-stage kidney disease (ESKD) enrolled in an Australian dialysis and transplant registry between 1982 and 2003. They evaluated cancer incidence during three periods: the 5 years before participants started to receive therapy related to eventually undergoing a kidney transplant, the time from dialysis initiation to a first transplant, and from the date of the first transplant forward.

In addition to the increased risk following transplantation, a significant increase in the incidence of nine cancers also was seen during dialysis, with a greater than twofold increase for seven of them.

Analyzing the three separate time periods, the authors argued, "demonstrates that preexisting personal cancer risk factors, and factors related to primary renal disease, ESKD, or dialysis can be excluded as major contributors to the posttransplantation excess risk."

Zoledronic Acid Decreases Aromatase Inhibitor-Induced Bone Loss

Preliminary results from two randomized clinical trials published online December 11 in the *Journal of Clinical Oncology* indicate that zoledronic acid can prevent treatment-induced bone loss in both premenopausal and postmenopausal women taking aromatase inhibitors after surgery for hormone-receptor-positive breast cancer.

The first study tested whether zoledronic acid could prevent treatment-induced bone loss in premenopausal women undergoing hormonal suppression with an aromatase inhibitor or tamoxifen and the drug goserelin after surgery for early-stage hormone-receptor-positive breast cancer. All patients underwent bone densitometry of the lumbar spine and the upper part of the thigh bone at the start of the study and after 6, 12, and 36 months of treatment.

After 36 months of treatment, patients receiving anastrozole without zoledronic acid lost 17.4 percent of the bone mass in their lumbar spine and 11.3 percent in their thigh bone. Bone-mineral density remained stable in patients who received zoledronic acid in addition to anastrozole. No patients given zoledronic acid in addition to anastrozole developed osteoporosis of the lumbar spine, though osteopenia did increase by 15 percent from levels measured at the beginning of the study.

The second study examined whether zoledronic acid could prevent loss of bone-mineral density in postmenopausal women taking the aromatase inhibitor letrozole after surgery for invasive, hormone-receptor-positive breast cancer. All women in the ongoing trial are scheduled to receive letrozole for 5 years or until their cancer recurs, and were randomly assigned to receive zoledronic acid intravenously every 6 months starting either at the beginning of the study or delayed until bone loss reached a specified level or a nontraumatic bone fracture was observed.

All patients underwent dual-energy x-ray absorptiometry scans to measure bone-mineral density at the beginning of the study, and after 6 and 12 months of treatment. The percent change in bone-mineral density in the lumbar spine and hip was compared between patients who received upfront or delayed zoledronic acid. After 12 months of therapy, there was a mean difference in bone density of 4.4 percent in the lumbar spine and 3.3 percent in the hip between the two groups, with the upfront group retaining more of their bone density.

NCI Researchers Modify Immunotoxin for Cancer Therapy

NCI researchers have developed a genetically modified version of a Pseudomonas-based immunotoxin (PE38) that may improve its effectiveness in humans. PE38-based immunotherapy already is used to treat certain leukemias and lymphomas, and the new agent may open immunotherapy to a broader range of cancers, according to study results published in the December 15 *Journal of Immunology*.

Dr. Ira Pastan of the Laboratory of Molecular Biology at NCI's Center for Cancer Research (CCR) and colleagues have used recombinant DNA techniques to make immunotoxins by combining a 38 kDa piece of Pseudomonas exotoxin A (PE38) with portions of several different mouse antibodies. One of the difficulties encountered by patients who chose PE38 immunotherapy is that their own immune systems can interfere with the treatment. To investigate how PE38 provokes production of neutralizing antibodies in some patients, the researchers used the mouse as a model. Mice immunized with PE38 produced 60 different types of reactive antibodies. The researchers found that these 60 antibodies were directed to only 7 regions on PE38, and these same regions were the sites that triggered an immune response in patients.

Researchers then used the mouse antibodies to identify the specific amino acids in these seven regions that trigger the neutralizing immune response in mice. Based on this information seven mutant immunotoxins were created that did not react with the antibodies, but were able to kill cancer cells in these animals. Studies are

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under way to incorporate these seven mutations into a single immunotoxin molecule that is anticipated to be less reactive with the mouse's immune system during immunotherapy.

Crosstalk Between Tumor and its Microenvironment Marks Cancer Progression

A new study from NCI researchers has found that the expression of CLIC4, a protein that promotes cell death, is reduced in human cancer cells but increased in cells of the normal connective tissue, or stroma, in the tumor microenvironment.

In a study published in the January 1 *Clinical Cancer Research*, Dr. Stuart Yuspa, in NCI's CCR, and colleagues used tissue array analysis to compare CLIC4 protein levels in normal and tumor tissues derived from patients. In about 80 percent of all major cancer types tested, CLIC4 was absent in the nucleus of tumor cells and reduced in tumor tissue, but increased in the stroma surrounding the tissue. Decreases in CLIC4 levels in the tumor and increases in the stroma also correlated with tumor progression and disease severity.

"At the moment, we're not sure what happens in tumor cells to silence production of the CLIC4 protein, since the gene is still intact," said Dr. Yuspa. "Hopefully, once we have more information, targeting CLIC4 in the tumor, the stroma, or both, will provide new opportunities for inhibiting tumor growth."

Using a mouse model, Dr. Yuspa and his colleagues also found that increased levels of CLIC4 protein in stromal cells coincides with conversion of stromal fibroblasts to myofibroblasts. This transition involves increased levels of a second protein called α-smooth muscle actin (αSMA), which has a role in cell structure and movement. In the laboratory, myofibroblasts contribute to tumor progression by secreting enzymes and promoting the development of new blood vessels.

When the team grew fibroblasts and human tumor cells together in the laboratory in such a way that the tumor cells formed a small colony with fibroblasts surrounding them, they found that the fibroblasts in the

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FDA Update

New Rules Proposed to Expand Availability of Experimental Drugs

On December 11, the FDA proposed significant regulatory changes to make experimental drugs more widely and easily available to seriously ill patients who have no other treatment options and to clarify the costs and the circumstances under which a manufacturer can charge for an experimental drug.

Under the proposed rules, expanded access for experimental drugs would be available to individual patients, small patient groups, and larger populations under a treatment plan when there is no satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.

The proposed rules, which are open for comment for 90 days, are described in detail at http://www.fda.gov/cder/regulatory/applications/IND_PR.htm. Additional information is available at http://www.fda.gov/bbs/topics/NEWS/2006/NEW01520.html.

Von Eschenbach Confirmed as FDA Commissioner

On December 7, the U.S. Senate confirmed the appointment of former NCI Director Dr. Andrew C. von Eschenbach as Commissioner of the U.S. Food and Drug Administration. Additional information can be found at http://www.hhs.gov/news/press/2006pres/20061207.html.

Warning Issued on Rituximab

The FDA and Genentech have sent new warning letters to health care professionals about rituximab (Rituxan), a monoclonal antibody used in the treatment of a type of non-Hodgkin lymphoma (NHL). Two patients died after being treated with rituximab for systemic lupus erythematosus (SLE). The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML).

Rituximab is approved for the treatment of CD20-positive, B-cell NHL and for moderately to severely active rheumatoid arthritis when there has been inadequate response to other treatments, but it has also been prescribed off-label for other serious diseases and conditions, such as SLE. The FDA and Genentech, which manufactures rituximab, warned physicians to "maintain a high index of suspicion for the development of PML in patients under treatment with rituximab."

Additional information is available at http://www.fda.gov/medwatch/safety/2006/safety06.htm#Rituxan. ◆

(Director's Update continued from page 2)

Department of Health and Human Services are operating under a "continuing resolution" (CR) until February 15. Until then, NCI is operating at fiscal year 2006 budgetary levels. Reading the news, as all of you do, you already are aware that we are uncertain what will occur regarding the CR in early 2007. We are obviously monitoring this closely and will continue to keep the cancer community apprised of budgetary matters as they happen.

As the New Year dawns, with all its challenges, I remain excited about the future for NCI and the tremendous opportunities that science is bringing forward each and every day: opportunities that very clearly can—and will—be translated into improved diagnosis and treatment for patients with cancer. I am committed to supporting the highest quality research, to finding solutions to our challenges and, most of all, finding innovative ways for maintaining our momentum. I believe that we will not only be able to sustain the progress that is evident by a continued decline in cancer mortality rates, but to accelerate the decline in 2007. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

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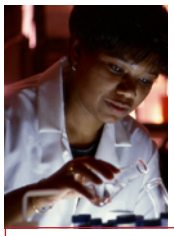
regions immediately adjacent to the tumor cells increased their production of both CLIC4 and αSMA proteins, but fibroblasts distant from the tumor cells did not.

This observation, they explained, indicates that tumor cells somehow stimulate fibroblasts in the microenvironment to increase production of these two proteins and suggests that crosstalk between tumors and healthy tissue is essential for tumor growth. ◆

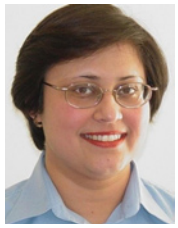


Featured Clinical Trial

Targeting a Common Characteristic of Advanced Tumors

Name of the Trial
Phase I Pilot Study of Topotecan in Patients with Metastatic or Unresectable Solid Tumors Expressing Hypoxia Inducible Factor-1a (HIF-1a) (NCI-05-C-0186). See the protocol summary at http://cancer.gov/clinicaltrials/NCI-05-C-0186.

Principal Investigators
Drs. Shivaani Kummar and Giovanni Melillo, NCI Center for Cancer Research



Dr. Shivaani Kummar

Why This Trial Is Important
Hypoxia is a state of oxygen deficiency that can develop in tumors when they outgrow their blood supply. When this condition develops, tumors must adapt to the new hypoxic environment in order to survive and keep growing. A protein called hypoxia inducible factor-1a (HIF-1a) helps tumor cells (and normal cells) adapt to hypoxic conditions by activating genes needed for cell survival, resistance to apoptosis (programmed cell death), and the growth of new blood vessels (angiogenesis). Cancer cells may also produce HIF-1a as a result of genetic changes not related to hypoxia. Many solid tumors overproduce HIF-1a, and high levels of this protein have been associated with tumor aggressiveness and resistance to treatment.

The FDA-approved chemotherapy drug topotecan is one of only a few agents that have shown the ability to inhibit HIF-1a in laboratory studies. Animal studies conducted by Dr. Melillo and his colleagues suggest that giving topotecan at lower doses over a longer period of time can reduce the level of HIF-1a in tumors and inhibit angiogenesis.

In this trial, doctors are testing the ability of topotecan to inhibit HIF-1a production and prevent tumors from growing and spreading further.

"HIF-1a gives tumors a selective growth advantage," said Dr. Kummar. "We're hoping to exploit a novel characteristic of an FDA-approved drug to take away this selective advantage and cause tumors to stop growing."

Who Can Join This Trial
Researchers seek to enroll 20 patients aged 18 or over with metastatic or unresectable solid tumors expressing HIF-1a for which standard therapy either has not been effective or does not exist. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/NCI-05-C-0186.

Study Site and Contact Information
This study is taking place at the NIH Clinical Center in Bethesda, Md. For more information, call the NCI Clinical Trials Referral Office at 1-888-NCI-1937. The call is toll free and confidential. ◆

An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

Clanton to Head ACS Divisions

Dr. Mark Clanton, NCI deputy director for cancer care delivery systems, resigned from NCI in December to join the American Cancer Society (ACS) as their chief staff medical officer for the High Plains Division and the Hawaii Pacific Corporation.

During his 2½-year tenure at NCI, Dr. Clanton provided leadership to NCI's Center to Reduce Cancer Health Disparities and Office of Science Planning and Assessment, and was involved in major conferences on tobacco control, international research organizations, and complementary and alternative medicine.

"Since he arrived at NCI, Mark has contributed in bringing his expertise to bear on expanding and enhancing NCI's research portfolio to have a greater impact on cancer care delivery," said NCI Director Dr. John E. Niederhuber. "Mark's high level of dedicated service to cancer patients and communities in need was epitomized by his volunteering to lead NCI's efforts to bring relief to displaced cancer patients and others in the wake of Hurricanes Katrina and Rita last year. He and many others from NCI, NIH, and HHS were true heroes by bringing in the resources and personnel to ensure the safety and well-being of medical personnel and patients in the area."

NCI Hosts Science Writers' Seminar on Second Cancers

On January 24, NCI's Media Relations Branch will host a Science Writers' Seminar on new cancers that arise in people whose first cancer occurred in a different site in their body—often called second cancers or multiple primaries. Four NCI scientists will discuss the incidence and prevalence of such cancers, their possible causes, and how they are treated in the clinic. Presenters include Rochelle Curtis, Dr. Crystal Mackall, Dr. Lois Travis, and Dr. Peggy Tucker.

Registration will be at 9:45 a.m. in Rooms F1/2 in the Natcher Conference Center on the NIH campus. Talks will begin at 10:00 a.m. Following an 11:00 a.m. coffee break, additional presentations will run until noon. To register for the seminar, contact the NCI Media Relations Branch at 301-496-6641 or ncipressofficers@mail.nih.gov.

NCI Web Site Expands Drug Information Resources

NCI's Office of Communications (OC) has increased the drug information resources available on the NCI Web site, www.cancer.gov. Since its inception in 2005, the NCI Drug Dictionary (http://www.cancer.gov/drugdictionary) has more than doubled its number of entries from approximately 500 to more than 1,200.

OC has also developed an online collection of consumer-friendly drug information summaries. The collection, which was launched in early October 2006, compiles information from the Food and Drug Administration, the National Library of Medicine, and NCI on drug approvals, proper drug usage, drug interactions, side effects, clinical trial results, and NCI press releases and news stories. In addition, each summary contains a link to current clinical trials in which the drug is being used. The drug information summaries are available online at http://www.cancer.gov/cancertopics/druginfo/alphalist.

NCI FY 2008 Budget Proposal Available Online

NCI's annual plan and budget proposal, *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008*, is now available in HTML format, providing access to information about Institute programs and the future directions of cancer research. The content is accessible through assistive devices as needed. Visitors to the site will also be able to view or print a copy of this publication from a PDF file. Printed copies can be ordered via e-mail at cisocc@pop.nci.nih.gov, phone at 1-800-4-CANCER, fax at 301-339-7968, or online at http://plan.cancer.gov. (Click on "Order this publication.") ◆

Funding Opportunities

For a complete listing of current NCI funding opportunities, please go to the HTML version of today's *NCI Cancer Bulletin* at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_010307/page8. ◆

Featured Meetings and Events

A calendar of scientific meetings and events sponsored by the National Institutes of Health is available at http://calendar.nih.gov. ◆

Community Update

DCEG Celebrates 20th Anniversary of Benzene Research Collaboration with China

In December, investigators from NCI's Division of Cancer Epidemiology and Genetics (DCEG) and the China Center for Disease Control and Prevention (China CDC) celebrated the 20th anniversary of collaboration on studies of occupational exposures to benzene. A ceremony recognizing the key players behind the development of this collaboration was attended by the Chinese and U.S. collaborators.

This binational, multidisciplinary effort was established in 1986 to expand an existing cohort study of occupational benzene exposures led by Drs. Songnian Yin and Guilan Li of the Institute of Occupational Health and Poison Control (IOHPC) at the China CDC. The expanded study included a follow-up of approximately 75,000 benzene-exposed workers and 35,000 unexposed workers from more than 700 factories and 12 cities in China.

"This long-standing collaboration has resulted in a series of high-impact findings that have contributed substantially to our understanding of dose-response relationships and biologic mechanisms of benzene carcinogenicity in humans," said Dr. Martha Linet, chief of DCEG's Radiation Epidemiology Branch. Dr. Linet, along with DCEG investigators Drs. Richard Hayes, Nathaniel Rothman, Mustafa Dosemeci, Qing Lan, Roel Vermeulen, Stephen Chanock, Bu-Tian Ji, Graca Dores, and Sholom Wacholder have worked on this collaboration.

In a 1997 paper in the *Journal of the National Cancer Institute*, lead author Dr. Hayes explained, "We found conclusive evidence that workers exposed to benzene were at significantly higher risk of developing acute non-lymphocytic leukemia (ANLL), myelodysplastic syndromes, and possibly non-Hodgkin lymphoma (NHL)." Risk was found to be increased at doses initially determined to be safe, and the risk of hematologic outcomes differed by temporal exposure patterns; recent exposure in workers was most strongly linked to ANLL and myelodysplastic syndromes.

In parallel research efforts, NCI investigators and their collaborators have made steady progress in elucidating the mechanisms of benzene-induced carcinogenesis and biomarkers of benzene's early effects, as well as identifying genetic markers of susceptibility. In 2004, a paper by Dr. Lan and colleagues in *Science* showed evidence of hematotoxicity in workers exposed to under 1 ppm benzene, the current U.S. occupational standard. Findings from both cohort and molecular epidemiological studies have contributed to lowering the benzene occupational standard in China and greatly affected the risk assessment process for environmental exposures in the U.S.

Dignitaries from IOHPC and the China CDC attended the December ceremony. Dr. Joseph F. Fraumeni, Jr., DCEG director, honored Drs. Yin and Li for their commitment to benzene research in China and for their early case-control study, which served as inspiration for this 20-year partnership.

Other guests at the ceremony included Dr. Chunming Chen, former director of the Chinese Academy of Preventive Medicine; Dr. Anshou Zhou, vice director of IOHPC; Dr. William Blot, the former lead investigator at NCI, now with the International Epidemiology Institute and Vanderbilt University; Dr. Martyn Smith of the University of California, Berkeley; Dr. Robert Rinsky of HHS; and Dr. Babasaheb Sonawane of EPA. ◆

The *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads the national effort to eliminate the suffering and death due to cancer. Through basic, clinical, and population-based biomedical research and training, NCI conducts and supports research that will lead to a future in which we can identify the environmental and genetic causes of cancer, prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://www.cancer.gov.

NCI Cancer Bulletin staff can be reached at ncicancerbulletin@mail.nih.gov.