

NCI Cancer Bulletin

Eliminating the Suffering and Death Due to Cancer

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http://www.cancer.gov

New Combination Prolongs Survival in Previously Treated Patients with Advanced Colorectal Cancer

Previously treated patients with advanced colorectal cancer who received the anti-angiogenesis agent bevacizumab (Avastin) in combination with an oxaliplatin (Eloxatin)-based chemotherapy regimen lived longer than patients who received chemotherapy alone, researchers announced yester-

day. The Data Monitoring Committee (DMC) overseeing the NCI-sponsored clinical trial in which the patients were enrolled, E3200, recommended that the results of a recent interim analysis be made public because the study had met its primary end point of demonstrating improved overall survival.

Colorectal Cancer Incidence, Mortality and Survival Rates				
	Incidence* 1992–2001	Death Rate* 1992–2001	5-Year Survival Rate* 1995–2000	
Male	64.5	26.6	63.7	
Female	46.6	18.5	63.1	

* per 100,000 population Source: Annual Report to the Nation on the Status of Cancer, 1975–2001, *Cancer*, Vol. 101 (1), July 1, 2004 Patients in the trial who received the combination of bevacizumab and a chemotherapy regimen called FOLFOX4 (oxaliplatin,

(continued on page 2)

Progress on HPV Vaccine Offers Great Hope to Developing Countries

Data published earlier this month have created an opinion among many in the public health and research communities that we are on the brink of significantly eliminating the threat of cervical cancer. This would be a public health boon to many developing countries, which bear the brunt of the 230,000 annual deaths from this cancer.

According to the results of a phase II clinical trial published earlier this month in *The Lancet* involving more than 1,100 women, a human papillomavirus (HPV) vaccine was safe and effective at preventing viral infections, as well as the abnormalities in the cells often associated with them. The vac-

cine targets two HPV types, 16 and 18, which together cause about 70 percent of all cervical cancers. Although the women in the *Lancet* study were only followed for 27 months, the study provides evidence that immunization with this type of HPV vaccine can confer a high degree of protection against infection with specific types of HPV and could be a valuable tool in the battle against the primary cause of cervical cancer. Encouragingly, similar results with longer follow-up were reported a few weeks ago at an American Society of Microbiology meeting with an HPV vaccine that targets HPV type 16.

(continued on page 2)

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(Bevacizumab continued from page 1) 5-fluorouracil, and leucovorin) had a median overall survival of 12.5 months compared with 10.7 months for patients treated with FOLFOX4 alone, a 17 percent improvement. Combination therapy patients had a 26 percent reduction in the risk of death compared with those who received chemotherapy alone.

"As this treatment was, at the very least, second line, this is a real and quite remarkable finding," says the study's lead investigator, Dr. Bruce Giantonio, of the University of Pennsylvania's Abramson Cancer Center. "These data—taken along with the advances seen with the introduction of irinotecan, oxaliplatin, bevacizumab, and cetuximab for treatment of colorectal cancer—suggest that the median survival for patients with metastatic disease will be 2 years or more."

The clinical trial, conducted by the Eastern Cooperative Oncology Group, included 829 patients enrolled between October 2001 and April 2003. Trial participants, all of whom previously had received a fluorouracil-based chemotherapy and irinotecan (Camptosar), were randomized to one of three treatment groups: the FOLFOX4 regimen plus bevacizumab, the FOLFOX4 regimen alone, or bevacizumab alone. On the DMC's recommendation, study investigators suspended randomization to the bevacizumab alone arm in March 2003 because early results suggested that patients in that group might have lower overall survival than patients in the other two arms.

Part of a new class of targeted therapies, bevacizumab binds to and inhibits vascular endothelial growth factor, which is thought to help tumors grow by providing a blood supply through the formation of new blood vessels. "The use of targeted therapies

is a fundamental shift in the way we treat cancers," Dr. Giantonio notes, "and here we see evidence that even in more advanced, previously treated disease, such an approach carries benefit."

According to Dr. Meg Mooney, a senior investigator in the NCI Cancer Therapy Evaluation Program, laboratory and clinical research has pointed toward anti-angiogenesis as a logical route for treating colorectal cancer. As a result, she explains, the bevacizumab/FOLFOX approach is now being tested in the adjuvant (post-surgical) setting for colon cancer "to see if we can increase the cure rate." NCI is currently sponsoring a trial led by the National Surgical Adjuvant Breast and Bowel Project, NSABP C-08, that is testing FOLFOX with or without bevacizumab in stage II and III colon cancer. That trial comes on the heels of the MOSAIC trial, published in June in the New England Journal of Medicine, which showed that use of FOLFOX increased 3-year disease-free survival in patients with stage III colon cancer, compared to standard therapy. *

(Director's Update continued from page 1) It was Drs. Mark Schiffman, Allan Hildesheim, and colleagues in the Division of Cancer Epidemiology and Genetics (DCEG) who made the initial discoveries that linked infection with HPV to the development of cervical cancer. And the companies producing these vaccines—GlaxoSmithKline (GSK) and Merck, respectively—did so based on technology developed by NCI scientists, led by Drs. John Schiller and Doug Lowy in NCI's Center for Cancer Research (CCR). Work by Drs. Lowy, Schiller, and CCR colleagues laid the foundation for a "virus-like particle" HPV vaccine and the subsequent development and testing of the vaccine in animal models and early stage human trials that set the stage for the promising results seen in these recent phase II trials.

NCI involvement in HPV vaccine development has not abated. As reported recently in the NCI Cancer Bulletin, DCEG has initiated an 8year, phase III study involving 12,000 to 15,000 women in Costa Rica to test GSK's HPV 16/18 vaccine. Costa Rica is just one of many developing countries that could benefit from an HPV vaccine. Cervical cancer rates there are alarmingly high, especially in coastal areas, where access to basic health care is extremely limited. Most developing countries do not have the infrastructure to operate cancer screening programs, lack the systems to ensure that women with a positive Pap smear get appropriate follow-up care, and must overcome cultural barriers that limit the effectiveness of available screening programs.

In addition to our efforts in HPV vaccine clinical trials, Drs. Schiller, Lowy, and colleagues are continuing their research in this area. Among other things, they have developed the first high-throughput assay that can allow researchers developing HPV vaccines to more efficiently and affordably perform tests to determine if the vaccines can induce an immune response against other oncogenic HPV types. They have made this assay available to other researchers, generating increased interest and potentially accelerating the production of vaccines that protect against multiple HPV types.

As was highlighted in the recent international issue of the *Bulletin*, NCI has a mandate to prevent and ease the suffering and death due to cancer worldwide. We have seen exciting advances in our international collaboration over the past decade and, with NCI leading the way in research to pursue new paths of cancer prevention and treatment, we are committed to translating these advances into a reduced global burden of cancer. *

Dr. Andrew C. von Eschenbach Director, National Cancer Institute



Cancer Research Highlights

Brain Cancer Stem Cells Identified

Canadian researchers have identified brain cancer stem cells that. even at extremely low levels, can propel tumor growth. Reporting in the November 18 Nature, Dr. Peter B. Dirks and colleagues from Toronto's Hospital for Sick Children and University of Toronto found that, in a xenograft mouse model, brain tumor cells from both pediatric and adult brain cancers that expressed the cell surface marker CD133 (CD133+) could initiate the development and growth of tumors. The architecture and cellular makeup of the tumors that developed in the mice closely resembled the human tumors from which the CD133+ cells were derived. the researchers said.

In comparison, when the researchers injected anywhere from 50,000 to 100,000 cells from these same human tumors in the mice that lacked the CD133 surface marker, they reported, "Human cells could be found in small clusters near the original injection site, but these cells did not form a nodule or mass." To confirm that the tumor-forming cells were cancer stem cells—that is, that they had the ability to self-renew—the research team performed serial transplantation, taking CD133+ cells from the tumors that developed in the first set of mice and injecting them into a second set of xenograft mice. These mice also developed tumors that closely resembled the original human tumors from which they came, as well as the tumors in the primary mice.

"The identification of cancer stem

cells is a significant step in the fight against [cancer]," wrote Dr. Michael F. Clarke, of the University of Michigan in Ann Arbor, in a related commentary. "Because self-renewal is essential if tumors are to grow, agents that target such cells may be effective treatments."

Efficiency of Targeted Clinical Trials Evaluated

Targeted clinical trials can be a more efficient way to study the effectiveness of certain cancer drugs, according to a paper by NCI researchers in the October 15 Clinical Cancer Research. "Most tumors at a given site are heterogeneous with regard to their underlying molecular and genomic signatures," said Dr. Richard Simon of the Division of Cancer Treatment and Diagnosis (DCTD). "It is not reasonable to expect such tumors to have equal sensitivities to a drug that inhibits a particular target." As a result, the potential of many drugs may be hidden in standard clinical trials that use broad eligibility criteria.

Dr. Simon and colleagues developed a model to compare the efficiency of targeted versus untargeted trials for a cancer drug that primarily benefits a specific subset of the population. They found that in most cases a targeted trial would require fewer participants to reach the same end point than a generalized trial, even when including enough patients to screen for the desired subpopulation. A targeted trial would be less efficient in cases where the drug would also be fairly effective in the general population.

Dr. Simon also noted that beyond understanding the mechanisms of drug

action, being able to easily screen patients who may respond to these drugs is critical. As understanding in both areas increases, clinical trials tailored to population subsets may become more prominent for finding new therapies.

Smokeless Tobacco Causes Oral and Pancreatic Cancer; Nitrosamines Classified as Human Carcinogens

The International Agency for Research on Cancer (IARC) recently reported that smokeless tobacco, including snuff and chewing tobacco, causes oral and pancreatic cancer in humans. In a separate report, two tobacco-specific N-nitrosamines (TSNA), N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were together classified as human carcinogens. The chemicals occur in all smokeless tobacco products and are formed during the curing and processing of tobacco and during storage of manufactured smokeless tobacco products. Many studies in animals have shown that different routes of exposure to NNN and NNK cause benign and malignant tumors. Results of epidemiological studies of smokeless tobacco users and studies of the mechanisms of action of TSNA plausibly associate NNN and NNK with cancer in humans.

"The working group reaffirmed that smokeless tobacco use causes oral cancer in humans, and concluded that it causes pancreatic cancer as well. These findings reinforce that tobacco use is not safe in any form," said Dr. Deborah Winn of NCI's Division of Cancer Control and Population Sciences. Dr. Winn served on the IARC working group. Conclusions will appear at http://monographs.iarc.fr. A summary of the scientific evidence will be published in the December 2004 Lancet. *



Spotlight

Policies and Events Influencing Colorectal Cancer Screening

An Examination of State Policies and Significant Events that have Influenced Colorectal Cancer Screening

NCI's State Cancer Legislative Database Program presented a poster at the recent meeting of the American Public Health Association on events influencing state policies on colorectal cancer screening. The poster highlighted the influence of NBC Today host Katie Couric on public awareness of screening for colorectal cancer, and is excerpted here. For more information on colorectal cancer screening, see the Special Report "Prostate, Colorectal Screening Affected by Numerous Factors," NCI Cancer Bulletin, July 20, 2004; information is also available at http://www.cancer.gov/cancertopics/ screening/colon-and-rectal. For additional information on the poster, contact the SCLD program office at http://www.scld-nci.net/

contact_us.cfm.

Background and Study Overview

- Despite its prevalence, colorectal cancer has received less attention in general than other types of cancer.
- We explored the timing and nature of efforts to increase awareness of and screening for colorectal cancer to determine whether there were similar increases in legislative attention to screening for colorectal cancer.
- We analyzed data on state laws from NCI's State Cancer Legislative Database (SCLD) Program.

We also obtained Web-based statistical data, news, and literature on risk factors, symptomology, prevalence, mortality, and various public awareness campaigns.

Prevalence of and Mortality from **Colorectal Cancer**

- Colorectal cancers—cancers of the colon and rectum—are the second leading cause of cancer death for both men and women, surpassed only by lung cancer. Colorectal cancer is the third most commonly diagnosed cancer among men and women.
- The American Cancer Society estimates that 56,730 Americans (28,320 men and 28,410 women) likely will die of colorectal cancer and that another 146,940 new cases (73,620 men and 73,320 women) will be diagnosed in 2004.
- Incidence has decreased by 3% per year from 1998 to 2000, which researchers have attributed to increased screening and other preventive measures.
- Colorectal cancers posed the third highest lifetime risk of dying from cancer for both men and women in the United States from 1999-2001. Lung cancer was first for both men and women, prostate cancer was second for men, and breast cancer second for women.

Risk Factors and Symptomology

Linkages posing higher than average risk for developing colorectal cancer:

- Family or personal history of colorectal cancer
- Age (risk increases after age 50)
- Polyps (growths protruding from inner wall of colon or rectum)
- Ulcerative colitis (causes inflammation and sores in the colon)
- Diet high in fat and calories and low in fiber
- · Lack of regular exercise

Symptoms may include the following:*

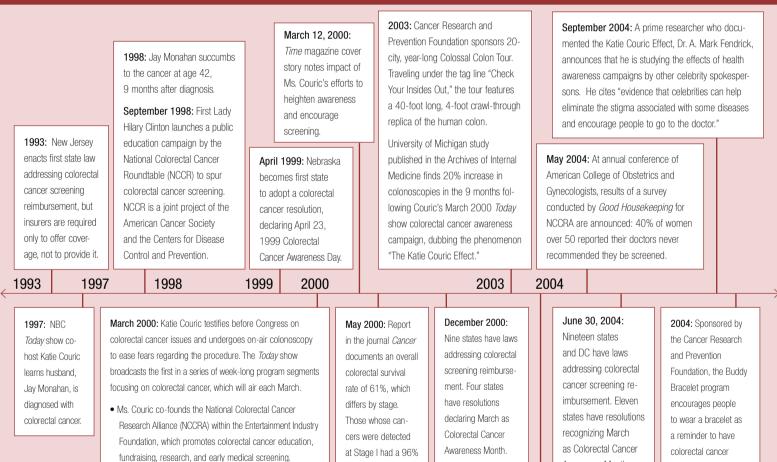
- Pain, aches, or cramps in the stomach
- Blood in stool
- Change in bowel habits
- Unexplained weight loss
- * Many who develop colorectal cancer exhibit no symptoms

Summary

- More states passed laws addressing third-party reimbursement for screening tests as well as awareness resolutions after Ms. Couric's televised awareness campaign and other such activities were undertaken.
- Ms. Couric's personal interest and high profile efforts provide a unique paradigm for examination because of their apparent efficacy, as confirmed both by reported anecdotal evidence from doctors and scientific study.
- Another factor contributing to increased screening is the aging of the Baby Boomers who are far more knowledgeable about and active in seeking out preventive health care than earlier generations.
- For this presentation, we did not quantitatively analyze whether a direct association or correlation exists between the seminal events (e.g., Ms. Couric's efforts) and the state legislative actions. •



Significant Events Affecting Colorectal Cancer Screening Policy at State and Local Levels



survival rate while

were detected at

5% survival rate.

Stage IV had only a

those whose cancers

Regina el Arculli, M.A. • Joanna M. King, J.D. • Jill Freudenwald, M.A. NCI's State Cancer Legislative Database Program, Bethesda, Maryland • www.scld-nci.net

· President Clinton proclaims National Colorectal Cancer

Awareness Month, urging that such cancer screening

over age 50, particularly since the risk of developing

colorectal cancer increases with age.

become a routine part of preventive health care for anyone

screening, then pass

others once they have

the bracelet on to

been screened

Awareness Month.

April 2004: NCCRA and the American Gastroenterological

Association release "2004 Colorectal Cancer Legislation

Report Card," grading the states on the extent of their

colorectal cancer screening coverage requirements.

Funding Opportunities



Featured Clinical Trial

Decision Making in Health: Behavior Maintenance

Application Receipt Dates: Jan. 10, May 10, Sept. 10, 2005; Jan. 10, May 10, Sept. 10, 2006; Jan. 10, May 10, Sept. 10, 2007

This funding opportunity will use the NIH investigator-initiated research project grant (R01) and the NIH exploratory/developmental grant (R21) award mechanisms. For more information see http://cri.nci. nih.gov/4abst.cfm?initiativeparfa id=2441. Inquiries: Dr. Wendy Nelson—nelsonw@mail.nih.gov

Decision Making in Cancer: Single-Event Decisions

Application Receipt Dates: Jan. 10, May 10, Sept. 10, 2005; Jan. 10, May 10, Sept. 10, 2006; Jan. 10, May 10, Sept. 10, 2007

This funding opportunity will use the NIH investigator-initiated research project grant (R01) and the NIH exploratory/developmental grant (R21) award mechanisms. For more information see http://cri.nci. nih.gov/4abst.cfm?initiativeparfa id=2442. Inquiries: Dr. Wendy Nelson—nelsonw@mail.nih.gov

Leadership for HIV/AIDS **Clinical Trials Networks**

RFA-AI-05-001

Letter of Intent Receipt Dates: April 11, 2005 Application Receipt Dates: May 11, 2005

This funding opportunity will use the U01 award mechanism(s). For more information see http://cri. nci.nih.gov/4abst.cfm?initiativeparfa id=2440. Inquiries: NIAID Office of the Director—MMurguia@niaid. nih.gov ♦

Chemotherapy for **Inoperable Liver Metastases** from Ocular Melanoma

Name of the Trial

Phase II Study of Isolated Hepatic Perfusion with Melphalan Followed by Temozolomide in Patients with Unresectable Hepatic Metastases Secondary to Ocular Melanoma (NCI-03-C-0221). See the protocol

summary at http:// cancer.gov/clinicaltrials/NCI-03-C-0221.

Principal Investigator

Dr. H. Richard Alexander, NCI Center for Cancer Research

Why is This Trial **Important?**

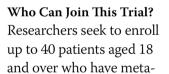
Ocular melanoma is the most common cancer of the eye in adults. If left un-

treated, it can spread (metastasize) to other areas of the body. Most often, ocular melanoma spreads to the liver. No effective treatment currently exists for metastatic ocular melanoma.

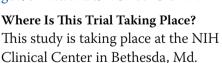
In this study, researchers are testing a procedure called hyperthermic isolated hepatic perfusion, which involves temporarily separating the liver's blood supply from the blood circulating throughout the rest of the body. High concentrations of the drug melphalan are then administered to the liver. Once treatment with melphalan is completed, the liver's blood supply is reconnected to the rest of the circulatory system and patients are treated with the drug temozolomide.

"Isolating the liver allows us to deliver a higher dose of melphalan than could be tolerated systemically," said Dr. James Pingpank, a surgeon involved with the trial. "Isolated perfusions have been used to treat cancer in other organs, but this is the first time isolated hepatic perfusion is being used with a large number of patients. The technology just wasn't there before.

> "In phase I and II testing, this therapy did produce a response in 62 percent of patients, so it does have established efficacy," said Dr. Pingpank. "Now we are trying to prolong the duration of response, which is currently about 1 year."



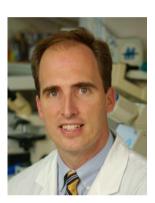
static liver tumors secondary to ocular melanoma that cannot be removed surgically (unresectable). See the list of eligibility criteria at http://cancer. gov/clinicaltrials/NCI-03-C-0221.



Whom to Contact

For more information, call the NCI Clinical Studies Support Center (CSSC) at 1-888-NCI-1937. The CSSC provides information about cancer trials taking place on the NIH campus in Bethesda, Md. The call is

toll free and confidential. * An archive of "Featured Clinical Trial"



Dr. James Pingpank Study Surgeon

columns is available at http://cancer.gov/ clinicaltrials/ft-all-featured-trials.

Notes

2001 Cancer Incidence and Mortality Report Available

The most comprehensive federal report available on state-specific cancer rates for the first time includes information on incidence and death rates, as well as data for Hispanics and a new section on mesothelioma and Kaposi's sarcoma. U.S. Cancer Statistics: 2001 Incidence and Mortality includes quality-assured incidence data from 43 states, 6 metropolitan areas, and the District of Columbia, covering 92 percent of the U.S. population—up from the coverage rate of 84 percent for the report issued last year. The report supplies essential state, population, racial, ethnic, and gender information for tailored cancer prevention and control programs nationwide.

The latest report shows prostate cancer as the leading cancer diagnosed overall in men in the United States and breast cancer as the most common form of cancer diagnosed in U.S. women. The leading cause of cancer death for both men and women is lung cancer.

United States Cancer Statistics: 2001 *Incidence and Mortality* marks the third time NCI and the Centers for Disease Control and Prevention (CDC), in collaboration with the North American Association of Central Cancer Registries, have combined data to produce federal cancer statistics. The annual report provides a basis for individual states and researchers to describe the variability in cancer incidence and death rates across different populations and to focus on certain populations for evidence-based cancer control programs. Future United States Cancer Statistics reports will include data for American Indians/Alaska Natives. The full report is available at http:// www.seer.cancer.gov/statistics.

2004 Outstanding Mentor Award Winners Announced

Investigators from the NCI's Center of Cancer Research (CCR) Dr. Daniel McVicar, Dr. Joost Oppenheim and Dr. Stuart Rudikoff were the winners of the 2004 Outstanding Mentor Award. 2004 Mentors of Merit were Dr. Shine Chang, Dr. Wong-Ho Chow, Dr. Adam Glick, Dr. Nancy Jenkins, Dr. Neal Copeland, Dr. Ilona Linnoila, Dr. Alan Perantoni, Dr. Paul Randazzo, and Dr. Michael Smith of CCR. These investigators were nominated by their trainees and received the highest ranking in a competitive review by an advisory committee of postdoctoral fellows. The awardees were honored at the NCI Awards Ceremony on October 28.

Input Wanted to Improve the Cancer Clinical Trials System

The Clinical Trials Working Group (CTWG), a broadly constituted panel established earlier this year and comprising researchers from academia and industry, advocates, and patients, has developed an interactive Web site to solicit input about the cancer clinical trials system.

"We are looking for insights from anyone interested in the future of cancer clinical trials," said Dr. James Doroshow, chair of CTWG and director of NCI's Division of Cancer Treatment and Diagnosis.

The Web site—http://ncicbforums.nci.nih.gov/ictQuestions/login_form—asks users to log in by first choosing a description that best identifies the group they represent. All responses are confidential. Users are also required to enter the following password—CTWGstakeholder—prior to providing their thoughts. (The password is also given on the log-in page.)

The Web site is open for feedback through Jan. 15, 2005 and addresses the following areas:

- Standardization of clinical trial procedures and infrastructure
- Coordination of clinical trials across Cancer Centers, SPORES, PO1s, and Cooperative Groups
- Enhancing interactions between the clinical research community, NCI, the pharmaceutical industry, FDA, regulatory agencies, and patient advocates
- Developing core facilities to improve scientific support for trials
- Improving clinical trial accrual management
- Refining the protocol prioritization process

TV Appearance Rescheduled

The CBS Sunday Morning feature with Dr. Julia Rowland, director of NCI's Office of Cancer Survivorship, has been rescheduled and will air in the near future. *

CCR Grand Rounds

December 14: Dr. Christopher Logothetis; Chairman and Professor, Department of Genitourinary Medical Oncology; Director, Genitourinary Program Center; University of Texas M.D. Anderson Cancer Center, "Biological Basis for the Development and Application of Therapy for Prostate Cancer" CCR Grand Rounds will not be held on December 7, 21, or 28. They will resume on January 4. CCR Grand Rounds are held 8:30 to 9:30 a.m. at the NIH campus in Bethesda, Md., in the Clinical Center's Lipsett Auditorium. •



Featured Meetings

This is a list of selected scientific meetings sponsored by NCI and other organizations. For locations and times and a more complete list of scientific meetings, including NCI's weekly seminars and presentations open to the public, see the NCI Calendar of Scientific Meetings at http://calendar.cancer.gov.

NCI Advisory Committee Upcoming Meetings

Date Advisory Committee

Nov. 30- National Cancer Advisory Board

Dec. 1

Dec. 14 NCI Director's Consumer Liaison Group

Selected Upcoming Meetings of Interest

Date	Meeting	NCI Speakers
Jan. 6-11	Molecular Targets for Cancer Therapy	Dr. J. Carl Barrett, Director, Center for Cancer Research; Dr. Elise Kohn, Laboratory of Pathology, Center for Cancer Research
Jan. 16-21	New Frontiers in Cancer Detection & Diagnosis	Dr. J. Carl Barrett, Director, Center for Cancer Research; Dr. Peter Greenwald, Director, Division of Cancer Prevention; Dr. Richard Simon, Chief, Biometric Research Branch, Division of Cancer Treatment and Diagnosis; Dr. Sudhir Srivastava, Chief, Cancer Biomarkers Research Group, Division of Cancer Prevention
Jan. 20-22	6th Annual Meeting of the Society for Personality and Social Psychology	Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences

NCI Exhibits

NCI Exhibits are presented at various professional and society meetings. Further information about the NCI Exhibits program can be found at http://exhibits.cancer.gov.

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.

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