NATIONAL CANCER INSTITUTE

NCI Cancer Bulletin

Eliminating the Suffering and Death Due to Cancer

September 26, 2006
Volume 3 | Number 37

In this issue:

A Publication of the
National Cancer Institute
U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
NIH Publication No. 05-5498

http://www.cancer.gov

Tanning Study Suggests Strategies for Preventing Skin Cancer

Researchers have identified a drug that bypasses a genetic predisposition and induces tanning in mice prone to sunburns and skin cancer. The result is "sunless" tanning that offers mice some protection against skin damage from ultraviolet (UV) light.

The drug, called forskolin, supplies a signal that's weak or missing in the skin cells of fair-skinned mice. Without this signal, the cells make red or blond pigment rather than brown or black.

By rubbing forskolin cream on fair-skinned mice once a day for several weeks, researchers at the Dana-Farber Cancer Institute caused the mice to produce dark pigment that was largely indistinguishable from that of brown or black mice.

The forskolin-induced tans offered protection against UV rays, even among mice predisposed to develop skin cancer, the researchers reported in the September 21 *Nature*.

"Many mice still got tumors, but darkening their skin significantly delayed the tumors and reduced their number," says Dr. David Fisher, who directs Dana-Farber's Melanoma Program and led the study.

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Director's Update

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis

Guest Update by Dr. James Doroshow

Workshop Helps RAID Program Adapt, Evolve

Launched in 1998, NCI's Rapid Access to Intervention Development (RAID) program has become an important resource for investigators engaged in anticancer therapeutics development. In July 2005, a workshop was held to comprehensively review the RAID program, and determine ways to improve its effectiveness and overall operation.

The report from that workshop—which was chaired by Dr. John Mendelsohn of the University of Texas M.D. Anderson Cancer Center, and involved experts in cancer research and drug development from the country's top academic centers and industry—includes important recommendations that should greatly strengthen NCI's drug development capabilities.

As Dr. Niederhuber explained earlier this year in the *NCI Cancer Bulletin*, RAID provides a bridge between

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The work was done completely in mice, Dr. Fisher adds, and more research is needed to understand the tanning "pathway" in humans and to assess potential treatments.

"The importance of this study is to show that you may be able to bypass genetic deficiencies in tanning that exist in people through topical agents," says Dr. Glenn Merlino, chief of Laboratory of Cell Regulation and Carcinogenesis in NCI's Center for Cancer Research (CCR), and a melanoma researcher.

"This study provides proof of principle that this concept could work, and its application to humans will depend on safety and other factors," adds Dr. Merlino.

Dr. Fisher's team began by characterizing the tanning pathway in mice. They reasoned that the pathways are similar in light- and dark-skinned mice except for a single protein, the melanocortin 1 receptor.

When dark-skinned mice are exposed to UV light, the melanocortin 1 receptors produce a strong signal that activates the chemical cAMP. This is essential for producing dark pigment.

But under the same conditions, the melanocortin 1 receptors of fair-skinned mice do not generate a strong signal. To bypass this "block" in the tanning pathway, the researchers gave the mice forskolin, one of several drugs that activates cAMP.

Forskolin effectively introduced a tanning response in mice that had never had one.

The melanocortin 1 receptor functions differently in light-skinned mice compared with other mice because of an alteration in the *melanocortin 1 receptor* (*mc1r*) gene.

Many fair-skinned people, particularly redheads, have inherited this variant gene, and the gene is associated with an increased risk of UV-induced skin cancers.

For people who live in Nordic regions with limited sunlight, a tanning response may block out UV rays that are needed to help process Vitamin D, leading to a deficiency or even death, notes Dr. Fisher.

But in sunny climates, tanning evolved as a response to UV light. "Tanning prepares the body for more UV exposure and protects against damage," says first author Dr. John D'Orazio, who is now at the University of Kentucky.

Forskolin protected mice against a form of squamous cell carcinoma, the most common skin cancer in humans. The researchers will investigate whether it protects against melanoma, an aggressive and often deadly skin cancer that is increasing in incidence worldwide.

"I think this research is a great example of how mouse models can be successfully used to gain novel insights into human disease and its prevention," says Dr. Merlino. ◆

By Edward R. Winstead

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discovery and the introduction of an agent into phase 0 or phase I human clinical trials by offering invaluable support—including bulk drug production, formulation, pharmacokinetics, and toxicity testing, among others—to principal investigators (PIs) working on the development of small-molecule drugs and biologics.

While drug company scientists have such services at their disposal, many academic researchers do not, so RAID offers access to crucial drug development resources to the research community. In addition, RAID fills an important niche because it supports PIs who are working on rare diseases and pediatric malignancies, and attempting to validate new therapeutic targets.

Overall, the recommendations from this new report call for NCI to actively monitor individual project milestones and achievement of timelines, and to intercede with changes or "go/no-go" decisions. This will ensure that RAID resources are being used in the most efficient manner possible.

NCI will immediately begin to implement a recommendation for the establishment of a two-tiered review system to optimize the prioritization and use of RAID resources. This will entail the creation of a standing committee of extramural experts to oversee the overall operation and function of the RAID program—the RAID Oversight Committee—and two subcommittees, one for biologics and one for small molecules, to aid in the review of specific applications, feasibility, and project management plans.

In response to another recommendation, NCI will also establish teams to advance RAID-approved projects. Project managers with expertise in both science and managing therapeutic development teams will work with PIs and NCI staff to formulate and implement comprehensive development plans for the RAID agents, including timelines, milestones, and resource requirements.

Other changes that will be made in response to this report include:

- Mentoring and training for RAID PIs, including training programs on the development and submission of Investigational New Drug (IND) applications to the FDA and an annual workshop

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Cancer Research Highlights

Common Prostate Cancer Treatment May Increase Diabetes Risk

Even for just a few months, the use of androgen deprivation therapy to treat men with prostate cancer that hasn't metastasized may significantly increase the risk of diabetes and cardiac-related effects, including heart attack, according to a study in the September 20 *Journal of Clinical Oncology (JCO)*.

Conducted by Dr. Nancy L. Keating and colleagues of Harvard Medical School and Brigham and Women's Hospital, the observational study followed more than 73,000 men 66 years of age or older who were diagnosed with locoregional prostate cancer between 1992 and 1999. More than one-third of the men in the study received a gonadotropin-releasing hormone (GnRH) agonist, while approximately 7 percent of the men underwent a complete orchiectomy (surgical removal of the testicles).

GnRH agonist use was associated with a 44-percent increased risk of patients developing diabetes, with smaller—yet still statistically significant—increases in the risk of heart attack, coronary heart disease, and sudden cardiac death. Although diabetes risk also was significantly increased with orchiectomy, it did not appear to have the same cardiac effects. Because so few men underwent this procedure, the authors cautioned, the study may have been underpowered to detect such a risk.

The increased diabetes and cardiac risks associated with GnRH agonist use appeared as early as 1 to 4 months after treatment initiation.

"Our findings suggest that, for men who require GnRH agonist therapy, strategies to mitigate modifiable risk factors for diabetes and coronary heart disease may be warranted," they concluded.

Dr. Lori Minasian of NCI's Division of Cancer Prevention (DCP) cautioned that the study may have been unable to account for preexisting comorbidities in the study population. "So it's too soon to say from this study alone that there is a clear increase in risk," she said.

Gemcitabine Plus Carboplatin Benefits Women with Recurrent Ovarian Cancer

A phase III randomized trial has shown a statistically significant improvement in progression-free survival for women with platinum-sensitive recurrent ovarian cancer given gemcitabine with carboplatin compared with carboplatin alone, without any significant differences in quality of life. The results, published early online September 18 in *JCO*, come from an international collaborative trial comprising investigators from Europe, Canada, and the United States.

Investigators randomly assigned 356 women with recurrent ovarian cancer whose tumors had previously responded to first-line therapy with a platinum-based regimen to receive either carboplatin alone or carboplatin plus gemcitabine, and compared progression-free survival, side effects, and overall quality of life.

Though more high-grade hematologic side effects and a greater incidence of alopecia (hair loss) were seen in patients taking carboplatin and gemcitabine, few patients in either arm discontinued treatment. The median progression-free survival was 8.6 months for patients taking carboplatin and gemcitabine, and 5.8 months for patients taking carboplatin alone. The benefit provided by the addition of gemcitabine persisted even after adjusting the data for other factors that could affect progression-free survival. Quality-of-life questionnaires showed no statistically significant differences between the two groups of patients.

"Gemcitabine plus carboplatin represents a new treatment option for patients with platinum-sensitive recurrent ovarian cancer," stated the authors. Such new therapeutic regimens are badly needed, they explained, because cumulative neurotoxicity limits the reuse of taxane and platinum combinations often used as first-line therapy in the disease.

Advanced Cancer Patients Benefit More from Aromatase Inhibitors than Tamoxifen

Aromatase inhibitors (AIs) have proven superior to tamoxifen as a hormonal treatment for early-stage breast cancer in women with estrogen-sensitive tumors. The third generation of these agents—letrozole, anastrozole, and exemestane—is also widely used to treat advanced or metastatic breast cancer, though clinical results about their value in that

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setting have been mixed. Researchers from Greece analyzed published trials and found that third-generation AIs provide a definite, if small, overall survival advantage.

"Our results may represent a departure from the standard management of advanced breast cancer with hormonal therapy that has been used for the last two decades," wrote Dr. John P.A. Ioannidis of the University of Ioannina School of Medicine and colleagues in the September 20 *Journal of the National Cancer Institute (JNCI)*. "The standard of care may need to be reconsidered."

The AIs reduced the risk of death by 13 percent—about 5 months more life in women whose median survival is projected to be 40 months. Though they may produce more hot flashes, the AIs are generally more tolerable than tamoxifen and also improve quality of life.

In an accompanying editorial, Drs. Catherine H. Van Poznak and Daniel F. Hayes of the University of Michigan agree that AIs are the drug of choice for women with endocrine-responsive metastatic breast cancer, without ruling out some use of tamoxifen. They cite surveys of oncology practice patterns which show that only about half of these women will receive AIs as adjuvant therapy, despite a recent recommendation by the American Society of Clinical Oncology (ASCO).

Rising Kidney Cancer Mortality Challenges Treatment Standards

Although rates of surgery for renal cancer have increased with the rising incidence of this malignancy over the last 20 years, a new study published in the September 20 *JNCI* suggests that a corresponding increase in survival has not been realized.

Investigators from the University of Michigan collected data from 34,503 patients with kidney cancer recorded in the Surveillance, Epidemiology, and End Results (SEER) registries from 1983 to 2002, and compared yearly incidence of the disease, incidence of renal surgery, pretreatment tumor size, and demographic data.

Their results showed an increase in the incidence of kidney cancer from 7.1 per 100,000 U.S. population to 10.8 per 100,000—an increase of 52 percent. This was attributed largely to an increase in small (≤4 cm) renal tumors, which are now often found incidentally during newer, more powerful diagnostic procedures for other conditions. "This increase in incidence of the small renal mass has been paralleled by an increase in surgical treatment," explained the authors. However, despite the increased incidence of surgery, kidney-cancer-specific and overall mortality for patients still rose by 155 percent and 323 percent, respectively.

"Despite increased detection and treatment of small masses, mortality rates for kidney cancer have continued to rise. Collectively, these trends raise questions about the effectiveness of the current treatment paradigm for kidney cancer," stated the authors. They suggest that a proportion of small kidney tumors may be a more indolent form of renal cell carcinoma that "may not merit surgical removal."

Age Associated with Type of Breast Cancer Treatment

Women 75 or older with early-stage breast cancer are more likely to receive nonstandard primary tumor therapy in an integrated health care setting, reported a study in the September 18 *JCO*.

Dr. Rebecca Silliman of Boston University Medical Center and colleagues identified 1,859 women 65 years of age or older with stage I and II breast cancer between 1990 and 1994 from 6 geographically diverse integrated health systems of the Cancer Research Network. Using SEER cancer registries, as well as clinical and administrative databases, researchers collected data on demographics, tumor characteristics, breast cancer treatment, and comorbid conditions prior to diagnosis.

Researchers then compared women who received standard primary tumor therapy, defined as axillary lymph node dissection and radiation therapy after breast-conserving surgery (BCS), with women who received nonstandard primary tumor therapy. They also compared women who received a tamoxifen prescription or chemotherapy with women who did not.

Women with higher comorbidity index scores, and women 75 or older, were more likely to receive nonstandard primary tumor therapy. While risk of recurrence was also associated with receipt of nonstandard primary tumor therapy, no link exists for standard primary tumor therapy. Additionally, researchers found that African American women were less likely to be prescribed tamoxifen and Asian women were more likely to undergo BCS than were white women.

The study's authors concluded that "Age is an independent risk factor for nonreceipt of effective therapies, even when comorbidity and risk of recurrence are considered."

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Spotlight

Answers, and More Questions, Emerging on Pediatric Leukemia

It's a vexing question: When an infant or very young child develops leukemia, how did it happen? Fewer than 5 percent of pediatric leukemia cases are hereditary. And if cancer is caused by a series of genetic mutations in key regulatory genes that, as much of the data on adult cancers suggests, may take years to develop, how does this happen so rapidly in these children?

For some types of pediatric leukemia, plausible answers have begun to emerge. But it's clear that researchers are just scratching the surface of a complex disease development process that may be influenced by factors such as the contents of a pregnant woman's diet or a child's ear infection history.

One of the more remarkable findings is that many cases of infant and childhood leukemia—diagnosed at 0 to 18 months and 18 months to 14 years, respectively—appear to be initiated prior to birth.

The most convincing evidence of *in utero* origin, explained Dr. Julie Ross of the University of Minnesota Department of Pediatrics, comes from analyses of archived newborn blood (ANB) samples—the blood samples generated by heel pricks of newborns that are used to screen for disorders like PKU—from infants and children who later developed leukemia.

"Molecular studies of ANB cards have identified mutations that were also found in those children" at the time of diagnosis, Dr. Ross said.

These analyses have turned up what have become the hallmark genetic mutations of pediatric leukemia: specific chromosomal translocations or the presence of too many chromosomes, often referred to as hyperdiploidy.

However, added Dr. Ross, who is leading the largest-ever epidemiologic study of infant leukemia, the available evidence doesn't suggest that all pediatric leukemias are initiated *in utero*.

That is supported by analyses of ANB blood spots from children with leukemia that failed to detect the genetic mutations associated with their particular cancer.

"These could be postnatally initiated cases," said Dr. Mel Greaves of the Institute of Cancer Research in London. "Or it is perfectly possible that many of these cases are indeed initiated *in utero*, but the blood spots are negative because there are either too few preleukemic cells in blood at birth to detect…or the molecular marker used is not the initiating event."

The number of demonstrably proven *in utero*-initiated cases is most likely "underestimated by the available technology," Dr. Greaves argued.

Identifying the Transforming Event

The conclusion that some pediatric leukemias have an *in utero* origin raises a tough question—one that derives from Dr. Alfred Knudson's widely accepted "two-hit" model of cancer development that (at least) two genetic mutations, or hits, are needed to transform a healthy cell into a cancer cell: In a case in which the first hit occurs *in utero*, what causes the second, postnatal hit?

For childhood leukemia, the available evidence suggests that chromosomal translocations or hyperdiploidy on their own likely are not enough to cause cancer. In a cross-sectional study published in 2002, for instance, a specific chromosomal translocation (TEL-AML1) often seen in childhood acute lymphoblastic leukemia was also present in cord blood samples from children who had not developed disease. The study authors concluded that for every child who developed TEL-AML1-positive leukemia, 100 children with this translocation would never develop disease.

There is mounting, yet still inconclusive, evidence to support a theory put forth by Dr. Greaves that the transforming event is an abnormal immune response to a common infection. This would especially hold true for children who have had extremely limited exposure to infectious agents such that, when their immune system is finally confronted by a significant infectious threat, it overreacts, fostering genetic instability among the immune system cells in which leukemias take hold.

Several epidemiologic studies, including ongoing large case-control studies led by Dr. Greaves and Dr. Joe Wiemels of the University of California, San Francisco, have put this theory to the test using day care attendance or levels of social activity among other children as a proxy measure of exposure to infectious agents.

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An accompanying editorial by Dr. Jeanne Mandelblatt of the Lombardi Comprehensive Cancer Center in Washington, D.C., noted that, "What we need is an understanding of the biology of cancer in this population [women 65 or older with breast cancer], tools that can help clinicians identify physiological reserve and ability to withstand the rigors of more aggressive treatment, and more consistent elicitation of women's informed preferences." ◆

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The results have been remarkably consistent: The more time spent in day care or engaging in social activity with other children, the lower the risk of childhood leukemia.

"The evidence is indirect but, overall, I believe, persuasive," Dr. Greaves said. "But we still lack unambiguous proof," he continued, such as "identification of a cellular/biochemical mechanism by which an abnormal immune response might trigger and select preleukemic clones."

The situation may be entirely different for infant leukemia, added Dr. Wiemels.

Most infant leukemias have a specific translocation involving the *MLL* gene, and "some people think that it's sufficient to cause cancer," he explained. "It takes less than a year or so to develop the disease, and that may be because the *MLL* location has a strong oncogenic stimulus. So there may not necessarily be a secondary event, at least at the level of DNA mutation." ◆

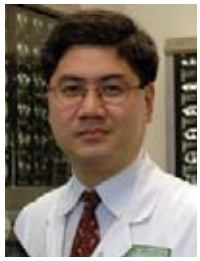
By Carmen Phillips

Featured Clinical Trial

Combining Targeted Therapies for Thoracic Cancers

Name of the Trial
Phase I Study of Romidepsin (Depsipeptide; FK228; FR901228) and Flavopiridol in Patients with Advanced Primary Lung or Esophageal Cancer, Malignant Pleural Mesothelioma, or Lung or Pleural Metastases (NCI-05-C-0010). See the protocol summary at http://cancer.gov/clinicaltrials/NCI-05-C-0010.

Principal Investigators
Drs. Dao Nguyen and David Schrump (Protocol Chair), NCI's CCR



Dr. Dao Nguyen

Why This Trial Is Important
Romidepsin is a new anticancer agent that belongs to a family of drugs called histone deacetylase inhibitors. These drugs can turn on genes in cancer cells that regulate cell growth and induce cell death (apoptosis). Unfortunately, the protein product of one of the genes activated by romidepsin, called p21, also interferes with the drug's ability to induce apoptosis. Researchers think that combining romidepsin with other anticancer drugs may improve its ability to kill cancer cells.

The drug flavopiridol has been shown to have a weak anticancer effect. However, when administered to cancer cells treated with romidepsin, it suppresses the expression of the *p21* gene and increases the anticancer effect of romidepsin. Laboratory studies that combined romidepsin and flavopiridol demonstrated that the combination was up to 10 times better at inducing apoptosis in lung and esophageal tumor cells than either agent alone.

In this trial, patients with advanced thoracic cancers (cancers of the chest) or other cancers that have spread to the chest will be treated with romidepsin and flavopiridol. Researchers will study the safety of this combination, and how these agents affect gene and protein expression in these patients.

"Based on our preclinical studies, we believe that combining these agents will dramatically improve the cancer cell killing power of romidepsin in thoracic cancers and potentially in a broad range of solid tumors," said Dr. Nguyen.

Who Can Join This Trial
Researchers will recruit 48 patients aged 18 or over with advanced lung cancer, esophageal cancer, malignant mesothelioma, or nonthoracic cancer that has metastasized to the lungs or pleura. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/NCI-05-C-0010.

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

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

Notes

NCI Director's Awards Ceremony Scheduled in October

The NCI Director's Awards ceremony will honor NCI staff for their outstanding contributions over the past year on October 25 at 11:00 a.m. in the Natcher Auditorium on the NIH campus. A reception will follow in the Natcher Atrium.

Awardees will be announced in the following categories: NIH merit (group and individual); leading diversity (group and individual); length of service (30 and 40 years); outstanding mentor; mentors of merit; and Commissioned Corps' Public Health Service citation, outstanding service medal, and commendation medal.

The list of award recipients can be found at http://cancer.gov/nciawards2006. The ceremony will be videocast at http://videocast.nih.gov.

Save the Date for AIDS Malignancy Program Conference

The International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies—supported by NCI's Office of AIDS Malignancy Program and the Office of International Affairs, with help from the NCI Office of Women's Health—will be held October 16–17 at the Bethesda North Marriott Conference Center in Bethesda, Md.

The conference will bring together scientists, physicians, health care workers, and community and patient advocates to focus on the viral oncology, immunology, genetics, epidemiology, pathogenesis, early diagnosis, and clinical investigation of malignant diseases associated with AIDS and other acquired immune-deficiency states. The event's objective is to facilitate the exchange of information between laboratory and clinical researchers to accelerate the translation of basic scientific discoveries into clinical applications.

The conference is free, but registration is required by October 9. For more information, go to http://www.palladianpartners.com/aidsmalignancy/index.htm.

FARE 2007 Winners Are Awarded

The Fellows Award for Research Excellence (FARE) Poster and Awards Day was held September 25 in the Lipsett Amphitheater at NIH. Following the ceremony, FARE winners presented their abstracts in a poster section.

The annual NIH-wide FARE competition—sponsored by the NIH Fellows Committee, the Scientific Directors, the NIH Office of Research on Women's Health, and the NIH Office of Intramural Training and Education—provides recognition for outstanding scientific research performed by intramural postdoctoral fellows.

This year's FARE awardees include 91 fellows from NCI's CCR, Division of Cancer Control and Population Sciences, Division of Cancer Epidemiology and Genetics, and DCP. They also receive a certificate and $1,000 in support to attend a scientific conference of their choice, and are asked to serve as judges for the following year's competition.

To apply, each April, fellows submit abstracts of their research, which are then peer reviewed by a jury of scientists whose work received awards in previous years. Visit http://felcom.nih.gov/FARE for more details.

SBIR Program Announces New Contract Funding Opportunities

On August 8, NCI's Small Business Innovation Research (SBIR) program announced 13 new funding opportunities for small businesses in a range of novel technology areas. Funding is available to support research and development of anticancer agents, biomarkers, nanotechnology, proteomics, pharmacodynamics, and other areas. The deadline for receipt of proposals is November 6. Additional information about the new contract funding opportunities and applicant eligibility is available at http://sbir.cancer.gov/funding/contracts/ or by e-mailing ncisbir@mail.nih.gov. ◆

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- When needed, regulatory assistance in the filing of INDs
- If feasible and when necessary, conducting initial clinical trials at the NIH Clinical Center to ensure that agents in which a substantial investment has been made will be tested in first-in-human trials; assistance with conducting trials at a PI's institution may also be available

A number of other changes to the RAID program also will be implemented over the coming year. Our goal is to ensure that we are getting the maximum return on our investment.

As some of the exciting results from early-stage trials involving RAID-supported agents suggest, this program has the potential to make a substantial difference in the lives of many patients. We believe the reviewers' recommendations will make the RAID program stronger and lead to many new effective cancer treatments. ◆

Community Update

NCI Cooperative Groups Celebrate 50th Anniversary on Capitol Hill

Representatives from ASCO and the Coalition of Cancer Cooperative Groups (CCCG) hosted a September 19 congressional briefing to celebrate the 50th anniversary of NCI's Clinical Trials Cooperative Group Program. Research leaders from the two groups used it as an opportunity to highlight the tremendous advances in cancer research achieved by the cooperative groups, and to stress the need to maintain federal funding and support.

Since its founding in the mid-1950s, the Cooperative Group Program has completed more than 4,000 clinical trials and treated more than 500,000 patients. The program currently involves more than 1,700 institutions that contribute patients to group-conducted clinical trials. Cooperative groups place more than 25,000 new patients into cancer treatment clinical trials each year.

"Clinical trials are the vital link between laboratory discoveries and improved patient outcomes," explained Dr. Joseph Bailes, ASCO's CEO and interim executive vice president. "The cooperative groups' research through these clinical trials has brought improved outcomes to millions of people with cancer."

Dr. Bailes and CCCG President Dr. Robert Comis noted examples where research led by the cooperative trial groups has contributed to long-term survival and cures for the majority of pediatric cancers; proven that breast-conserving lumpectomy is often a better surgical option than radical mastectomy; developed paclitaxel as a premier treatment for ovarian and metastatic non-small-cell lung cancers; and defined the role of targeted therapies, such as trastuzimab and bevacizumab, in the major solid tumors.

"A significant portion of the cooperative groups' budgets—about $150 million per year—comes from NCI," Dr. Comis explained. "Unfortunately, declining funding has caused the institute to decrease cooperative group funding over the past 2 years, and we cannot hope to continue to provide the types of treatment advances that help people with cancer unless we reverse the trend of decreasing NCI funding."

When a congressional aide asked about the impact of the doubling of the NIH budget in previous years, Dr. Comis expressed appreciation for Congress' support, but noted that cooperative group funding is currently at the same level as in 2001. NCI funding has never covered the entire cost for each enrollee in a trial, he explained, so a lot of cooperative group efforts are on a volunteer basis, which is becoming harder to sustain, particularly among community-based clinicians and hospitals.

Dr. Norman Wolmark, chair of the National Surgical Adjuvant Breast and Bowel Project Cooperative Group, said, "The Cooperative Groups received a $3 million decrease in 2006 compared to the previous year, and the projected decrease for next fiscal year is in the range of 10 to 15 percent. We really are at a crossroads and a crisis." For example, he added, the initiation of promising follow-up research on chemopreventive agents for breast cancer is in serious question due to the current budget uncertainties. ◆

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 ◆

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. Contact the *NCI Cancer Bulletin* staff at ncicancerbulletin@mail.nih.gov.