NATIONAL CANCER INSTITUTE

NCI Cancer Bulletin

A Trusted Source for Cancer Research News

February 19, 2008
Volume 5 | Number 4

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

Protein May Stop Melanoma Before It Starts

A single protein may enable skin cells to detect genetic damage and stop growing rather than become cancerous, researchers are reporting.

The protein, IGFBP7, regulates an anticancer mechanism in normal cells that allows the cells to enter a state of arrested growth or commit suicide rather than develop into melanomas in the face of genetic damage. Understanding this process could lead to new strategies for treating the disease, the researchers say.

Dr. Michael Green of the University of Massachusetts Medical School and his colleagues reported their findings in the February 8 *Cell*.

The anticancer response of normal cells is thought to be important in preventing cancer, but sometimes it fails. To understand why, Dr. Green's group conducted a genome-wide screen for genes involved in preventing melanoma in cells with cancer-causing mutations in the *BRAF* gene.

The search yielded 17 genes, including some well-known tumor suppressors such as *p53*.

Further experiments indicated that IGFBP7 was both necessary and sufficient to arrest growth. The protein is part of a negative-feedback loop that disrupts the growth-promoting signals of the protein produced by the *BRAF* gene.

The researchers note that the activity of IGFBP7 increases in moles with *BRAF* mutations but not in melanoma cells with the same mutations. This could explain why most moles do not progress to cancer despite the genetic flaws.

"When IGFBP7 is expressed, a mole remains a mole," says Dr. Green. But in melanoma cells, the protein is lost

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Cancer Research Highlights

Experimental Drug for Osteosarcoma Improves Overall Survival

Patients with osteosarcoma who received the experimental drug mifamurtide (L-MTP-PE) along with chemotherapy fared better than patients who received chemotherapy alone, researchers are reporting. Osteosarcoma is a rare but often fatal cancer of the bone. The disease typically affects children and young adults, and no new therapies have been introduced in two decades.

The study—conducted by the Children's Oncology Group—was the largest final-stage randomized trial in this disease and included 662 patients with newly diagnosed nonmetastatic osteosarcoma.

After 6 years of follow-up, overall

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Director's Update

SPOREs Move To Strengthen Program, Vision

Since their creation in 1992, NCI's Specialized Programs of Research Excellence (SPOREs) have been a cornerstone of the Institute's efforts to promote interdisciplinary cancer research focused on a specific organ site. The SPORE program was designed to enable the rapid and efficient movement of basic scientific findings into clinical settings. Now a flourishing program, there are 62 SPOREs, studying 14 organ sites, based almost exclusively at NCI-designated Cancer Centers, where they comprise an important part of the centers' research programs.

My goal since arriving at NCI has been to continue to build and strengthen this vital program, an objective that has been further solidified by the importance placed on the SPOREs in recent reports from the Translational Research Working Group (TRWG) and NCI-designated Cancer Center directors. In keeping with that goal, the SPORE program is about to undergo some changes that NCI leadership believes will enhance its role in promoting interdisciplinary translational research.

The central change is the move of the SPORE program from the Organ Systems Branch in the Office of Centers, Training and Resources to the Division of Cancer Treatment and Diagnosis (DCTD). As I explained last week during meetings of the Clinical Trials Advisory Committee and the National Cancer Advisory Board, this change was prompted, in part, by the departure of Dr. Jorge Gomez, who has ably led the SPORE program for 12 years. Dr. Gomez is moving to NIH's Fogarty International Center, where he will lead NCI's effort to enhance U.S. global research and clinical trial participation in Central and South America. NCI is extremely grateful for Dr. Gomez's distinguished service to the SPORE program and for making it a central component of NCI's translational research portfolio.

This leadership change spurred NCI leadership to more closely consider the SPORE program's future direction, and we concluded that moving the program to DCTD would present an ideal opportunity for it to gain greater prominence and integration within NCI's translational research and laboratory science portfolio. Taking this step also directly responds to the TRWG recommendation to improve coordination and collaboration of translational research across NCI.

DCTD, under the direction of Dr. James Doroshow, is focused on new visions, new ideas, and scientific growth that will be vital to our ability to keep pace with the changes necessary to deliver cutting-edge medical research to patients. Having a program like the SPOREs, which has been such a leader in translational science, included in these endeavors will clearly elevate its role moving forward. NCI's investment in the SPORE program will be significantly enhanced and the SPORE program will assume an even greater position of leadership in NCI's translational portfolio.

Since joining NCI, I have worked directly with principal investigators (PIs) from the SPOREs to carefully make adjustments that continue the growth and improve the structure of the program. As part of that effort, we have created a SPORE PI executive committee, chaired by Dr. John Minna from the University of Texas Southwestern Medical Center. I meet with this committee by conference call almost once a month. From those discussions, it's clear the committee believes that the SPOREs can adapt to the new era of highly targeted and personalized cancer care and become even more relevant to the challenges facing NCI. I couldn't agree more.

Among the many benefits of this change is an opportunity for significant infrastructure cost savings, an important advantage in this time of tight budgets. That said, change is never as easy as we expect or hope. But difficulty is never a reason to avoid change, particularly one so important to the future of NCI. NCI leadership strongly believes this transition can only benefit the SPORE program and, ultimately, patients and their families, who rightfully expect the strongest effort possible to move our most promising scientific advances into clinical testing. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Cancer Research Highlights

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survival was 78 percent in the group receiving mifamurtide plus chemotherapy compared with 70 percent in the group receiving chemotherapy alone. "This is an almost one-third reduction in the risk of death," write Dr. Paul A. Meyers of the Memorial Sloan-Kettering Cancer Center and his colleagues in the February 1 *Journal of Clinical Oncology*.

A second goal of the NCI-sponsored study was to evaluate the addition of ifosfamide to the three chemotherapy drugs used in the study (cisplatin, doxorubicin, and methotrexate). Adding this agent did not enhance event-free survival or overall survival for patients in the trial.

As an experimental agent, mifamurtide is available only through clinical trials. In 2006, its manufacturer, IDM Pharma, sought approval for its use in treating osteosarcoma from the Food and Drug Administration, but the agency requested more information. The company plans to submit new data showing an overall survival benefit in the disease this year.

Low Risk Seen in Monitoring, Not Treating, Some Prostate Cancers

The vast majority of older men diagnosed with localized prostate cancer who initially forego treatment will die of something other than prostate cancer, researchers said last week. The finding supports the view that actively monitoring the cancer's progression until such time as treatment is needed—a strategy called watchful waiting—is a reasonable response to a diagnosis of early-stage disease for some men.

Using data from NCI's Surveillance, Epidemiology, and End Results (SEER) program, Dr. Grace Lu-Yao of The Cancer Institute of New Jersey and her colleagues asked what happened to 9,000 men who chose active surveillance rather than treatment in an era when screening with the prostate-specific antigen test increased.

After 10 years, 3 to 7 percent of those with low- or moderate-grade disease had died of prostate cancer, compared with 23 percent of men with high-grade cancers. The men were diagnosed between 1992 and 2002 and did not have treatment in the first 6 months after diagnosis. Half were over age 75.

Of the approximately 2,600 men who eventually underwent treatment for the disease, about half delayed therapy for more than a decade. Dr. Lu-Yao presented the results at the first Genitourinary Cancers Symposium in San Francisco, which was sponsored by the American Society of Clinical Oncology (ASCO) and other groups.

Prostate cancers detected by screening tend to progress slowly, and many older men die with the disease, not of it. Furthermore, all therapies for prostate cancer entail risks, and some may lead to impotence or incontinence.

This study provides additional support for the use of active surveillance of localized prostate cancer in older men, particularly among those with lower grade tumors, commented Dr. Howard Sandler of the University of Michigan at the meeting.

Partial Nephrectomy to Treat Small Renal Tumors Underused

The use of partial nephrectomy to treat small, newly diagnosed kidney tumors appears to be vastly underused, researchers from the New York University School of Medicine are reporting.

Studies have shown that partial nephrectomy, only removing the part of the kidney in which a small tumor (typically 4 centimeters or less) resides, produces equivalent outcomes to complete removal of the kidney, or radical nephrectomy, and may prevent the development of a serious side effect, chronic kidney disease. Nevertheless, the researchers reported last week at the ASCO Genitourinary Cancers Symposium, it is offered to only one of every five patients with newly diagnosed, small tumors.

To conduct the study, Dr. William Huang, an assistant professor of urologic oncology, and colleagues analyzed data from NCI's Surveillance, Epidemiology, and End Results program on more than 3,000 patients treated for these small renal tumors from 1995 through 2002. The incidence of kidney tumors has been steadily climbing for several decades, largely due to the incidental discovery of these small tumors during imaging procedures for other problems, Dr. Huang explained during a press briefing.

The research team identified preoperative factors that differed between the more than 2,500 patients with small renal tumors who underwent

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radical nephrectomy and the 556 who underwent partial nephrectomy. Patients treated with partial nephrectomy were more likely to be younger, male, and treated toward the end of the period covered by the study, which, Dr. Huang noted, could suggest the beginning of a shift toward more partial nephrectomies in patients with small tumors. Women, older patients, and patients with cerebrovascular disease were less likely to have partial nephrectomy.

"Partial nephrectomy is an option for most patients with newly diagnosed kidney tumors," Dr. Huang concluded, "and actually may be a better option because [patients] with kidney tumors often have other comorbid conditions."

More Genetic Clues for Prostate Cancer Found

A new wave of genome scans for prostate cancer ties additional chromosome regions to the disease while also confirming previously reported associations on chromosomes 8 and 17. The results, from three genome-wide association studies published online this month in *Nature Genetics*, underscore the complexity of prostate cancer genetics.

The first study, from NCI's Cancer Genetic Markers of Susceptibility (CGEMS) initiative, identifies regions of chromosomes 7, 10, and 11 that are associated with moderate increases in the risk of prostate cancer. Dr. Stephen Chanock of NCI's Division of Cancer Epidemiology and Genetics and his colleagues also identify nine other "suggestive" associations and confirm previously reported regions.

Overall, the study "confirms and greatly expands the landscape of genetic factors influencing inherited susceptibility for prostate cancer," the researchers say. Nearly 20 percent of the candidate regions identified in the study are located on chromosomes 5 and 10, which may harbor multiple susceptibility regions for prostate cancer, they note.

The team tested nearly 27,000 single nucleotide polymorphisms (SNPs) in thousands of men with and without the disease. SNPs are variable sites in the genome where a single unit of DNA may change from person to person; the variants may serve as markers of regions containing possible risk factors.

While no susceptibility genes in the regions have been identified yet, the researchers report some candidates. One of the chromosome 10 regions, for instance, contains the gene *MSMB*, which produces a component of semen and is a potential prostate cancer biomarker. The chromosome 7 region is near a gene linked to endometrial cancer, *JAZF1*.

In the second study, Dr. Rosalind Eeles of the Institute of Cancer Research, Sutton, U.K., and her colleagues identify seven regions associated with prostate cancer on chromosomes 3, 6, 7, 10, 11, 19, and X. Some of the regions contain genes which may be linked to the disease, including *MSMB*.

"The results of this study confirm that prostate cancer is genetically complex and help clarify the genetic architecture of prostate cancer," the researchers write.

The third report, from Dr. Julius Gudmundsson and his colleagues at deCODE Genetics in Iceland, identifies associations on chromosomes 2 and X. The variant on chromosome 2 shows a significantly strong association with the more aggressive forms of the disease, they found.

Study Details Risk of NHL in Some Autoimmune Diseases

Researchers found that the risks for developing non-Hodgkin lymphoma (NHL), especially some NHL subtypes, are significantly increased in individuals who reported previously having had certain autoimmune diseases, according to results published online February 8 in *Blood*.

Autoimmune disorders have been recognized as risk factors for NHL in general, but large-scale assessments of the impact on specific NHL subtypes have been lacking. Researchers from the International Lymphoma Epidemiology Consortium (InterLymph), which is spearheaded by NCI, analyzed pooled data of nearly 30,000 study participants from a dozen case-control studies from across Europe, North America, and Australia. The strongest association was found with Sjögren's syndrome, which showed a 6.5-fold increased risk of NHL overall, including elevated risk for diffuse large B-cell and follicular lymphomas, and a 1,000-fold increased risk for parotid gland marginal zone lymphoma among NHL subtypes.

Lesser but still significant risks for NHL were found among patients with systemic lupus erythematosus (SLE), hemolytic anemia, and, for lymphomas of T-cell origin, among patients with celiac disease and psoriasis. However, inflammatory bowel disorders, type-1 diabetes, sarcoidosis, pernicious anemia, and multiple sclerosis were not associated with risk of NHL or its subtypes.

The InterLymph investigators noted the significance of this study. "Our results further suggest new patterns of associations with some NHL subtypes in specified autoimmune disor-

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ders…Besides confirming the known link between all NHL combined and Sjögren's syndrome and SLE, we demonstrated an increased risk of marginal zone and diffuse large B-cell lymphomas in both of these disorders, and an increased risk of specific T-cell NHL subtypes in celiac disease and psoriasis." The researchers also noted that the pattern of associations with NHL subtypes "may harbor clues to lymphomagenesis." ◆

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and the anticancer response fails.

Experiments in mice showed that IGFBP7 has a potent antitumor effect on human tumors derived from *BRAF*-mutated melanoma cells. But the protein may have little or no effect on tumors containing normal *BRAF* genes.

Whether the stunning antitumor effects will be seen in humans remains to be seen. But the findings demonstrate the promise of inducing a state of arrested growth, or senescence, as a therapeutic strategy for cancer, notes an accompanying editorial.

"Undoubtedly, mutations that activate or repress cellular senescence will be crucial in the progression of many other human malignancies," write Drs. Yuchen Chien and Scott W. Lowe of the Cold Spring Harbor Laboratory. ◆

By Edward R. Winstead

Special Report

Thyroid Cancer's Rising Incidence: Reality or Illusion?

The following is the first article in a two-part series on thyroid cancer, the incidence of which has increased dramatically over the past two decades. This first article focuses on what's behind this increased incidence; the second will address its impact on the treatment of thyroid cancer.

Since the early 1970s, the incidence of thyroid cancer has more than doubled. Among women, in fact, it is the cancer with the fastest rising number of new cases.

Nevertheless, it's still a relatively uncommon cancer, with approximately 33,500 new cases annually, and 1,500 deaths, most of which are due to rare, aggressive types.

But not quite 2 years ago, Dartmouth College researchers, relying on data from NCI's Surveillance, Epidemiology, and End Results (SEER) program, concluded that the increased incidence of thyroid cancer was an illusion. The study's authors, Drs. Louise Davies and H. Gilbert Welch, laid the blame for the increase on "greater diagnostic scrutiny"—a byproduct of sensitive imaging technologies and advanced biopsy techniques. It's most likely a case, they argued, of "overdiagnosis."

According to some of the country's leading endocrinologists and endocrine surgeons, who are responsible for diagnosing and treating most thyroid cancers, the study made a convincing case. First, the vast majority of the increase, 87 percent, was attributable to cancers smaller than 2 centimeters, nearly all of which are the most treatable and common type, papillary thyroid cancer. Autopsy studies, in fact, have consistently shown that, at death, a significant portion of people can have small, malignant papillary thyroid nodules, ranging from several percent to 36 percent in one study.

In addition, despite the increased incidence, there was no associated change in mortality rates, which have remained very low. Treatment of truly life-threatening cancers would have to improve to keep mortality stable, they argued, and while treatment trends have changed, there is little evidence to suggest they have influenced mortality one way or the other (the subject of the second article in this series).

Both factors suggest greater detection of "subclinical" disease, Drs. Davies and Welch argued, not some unknown influence spurring the development of more thyroid cancers.

That conclusion, however, leaves one big question: In the absence of any directed efforts toward early detection—such as those for breast or colon cancer, for example—why is anyone looking for these unobtrusive nodules in the first place?

Very often, explains Dr. Keith Heller,

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Spotlight

Probing the Effects of Circadian Rhythms on Cancer

A growing body of evidence from both animal and human studies indicates that circadian rhythms—the biological rhythms that mimic the 24-hour cycle of the turning of the Earth—influence cancer in a variety of ways.

In mice and rats, disruption of circadian rhythms has been shown to increase the rate at which a variety of cancers develop. Epidemiologic studies have found elevated rates of breast cancer in women and prostate cancer in men whose circadian rhythms are disrupted as a result of working rotating day and night shifts.

The efficacy and toxicity of more than 30 anticancer drugs has been shown in animal studies to vary by more than 50 percent depending on the time of day that treatment is delivered. Clinical trials, conducted primarily in patients with colon cancer, have found as much as a twofold improvement in antitumor activity and a fivefold improvement in patient tolerability when infusions of chemotherapeutic agents are timed to circadian rhythms.

At least 12 genes are known to be involved in the regulation of circadian rhythms. Loss or dysregulation of circadian genes has been identified in many types of cancer. Moreover, overexpression of certain circadian genes in cancer cells has been shown to inhibit the cells' growth and increase their rate of apoptosis (programmed cell death).

Until recently, scientists thought circadian rhythms were entirely controlled by a "master clock" in the brain known as the suprachiasmatic nucleus (SCN). Recent research has shown that, in fact, virtually all cells—including tumor cells—possess their own circadian "clocks," a discovery that has opened up new avenues for research.

One intriguing finding is that whereas the SCN is synchronized primarily by the daily light-dark cycle, cellular circadian rhythms are strongly influenced by meal timing. Mice inoculated with osteosarcomas lived longer when fed during the day rather than at night (when they would normally eat, because mice are nocturnal).

Now, with funding from NCI, two research teams whose work has contributed to current understanding of the role of circadian rhythms in cancer are trying to further this line of research by probing the possible links among circadian rhythms, timing of food intake, caloric restriction, nutritional therapy, and cancer prevention.

Nutritional substances

Dr. Jack D. Burton and his colleagues at the Garden State Cancer Center in Belleville, NJ, previously found in a mouse model of breast cancer that the drug celecoxib showed circadian variation in both efficacy and toxicity. At specific times of day, the dose of the drug could be escalated 2.5-fold with no increase in side effects.

Another of Dr. Burton's research interests is the use of nutritional substances to treat and prevent cancer. Because many studies have shown circadian effects for anticancer drugs, he wondered whether nutritional agents might show similar effects.

"Many nutritional substances have been found to have both antitumor and chemopreventive effects in various animal models," he says. "But they hadn't previously been tested in a way that focused on the time of administration."

In pilot studies, the researchers administered selenium and curcumin (an ingredient in the spice turmeric) at various times to mice with implanted, human-derived prostate tumors. They found differences in the degree of inhibition of tumor growth depending on the time of administration and identified potential tumor markers that might explain this effect.

On the basis of this pilot work, Dr. Burton's group obtained NCI funding for a larger study to assess in a rat model of prostate cancer whether the chemopreventive effects of selenium and green tea extract are modulated by circadian-based administration. In this model, the rats develop prostate cancer gradually, mimicking the disease process in humans.

Caloric restriction

Dr. Alec J. Davidson of Morehouse School of Medicine in Atlanta has previously shown that in transgenic rats with chemically induced liver cancer, restricted daytime feeding alters the circadian rhythms in the liver, with the pattern of disruption differing in cancer cells compared with healthy tissue.

"We showed that the clock in liver

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cancer cells differs from that in adjacent healthy cells in the same animal," he explains. "So is there a causal connection? And is the clock altered because the cells are cancerous or did something go wrong with the clock first?"

Previous work by others had suggested that a calorically restricted diet could prevent cancer and lengthen life. "We wondered whether the apparent effect of caloric restriction was really the result of a circadian change. Maybe feeding at the 'wrong' time—that is, during the day for animals that are naturally nocturnal—creates an unnatural state that affects tumors more negatively than the rest of the animal."

With NCI funding, Dr. Davidson and his colleagues are now testing this hypothesis in a mouse model of prostate cancer. "We are using restricted daytime feeding as one of many potential ways to alter the cellular clock, to see whether manipulating circadian timing accelerates or inhibits cancer growth," he says.

"This research is important because the results suggest that, although an emphasis on new drug development is appropriate and certainly necessary, the effect of timing of new and old drugs might be equally important areas of research for potential therapeutic advances," noted Dr. Jeff White, director of NCI's Office of Cancer Complementary and Alternative Medicine. ◆

By Eleanor Mayfield

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an endocrine surgeon at New York University Medical Center, these tiny cancers are discovered "by accident" during imaging procedures being done for other reasons, such as carotid duplex scans looking for peripheral vascular disease in neck arteries or MRI and CAT scans following car accidents or for unexplained neck pain or severe headaches.

It then falls to endocrinologists, many of whom now have ultrasound machines in their offices, to take a closer look at the thyroid.

"That's how I get the majority of my referrals," says Dr. Jennifer Sipos, an endocrinologist at the University of Florida, "nodules that are incidentally found…on an [imaging procedure] taken for another reason."

There also is some unnecessary testing going on, Dr. Heller believes.

"I had a patient the other day who came in because her GP ordered a thyroid ultrasound because she was gaining weight," he recounts.

And thanks to a technique known as ultrasound-guided fine-needle aspiration, these tiny nodules are relatively easy to biopsy.

"When I was a fellow in the early 90s, we couldn't easily biopsy a nodule that was 1 centimeter or less," says Dr. R. Michael Tuttle, an endocrinologist at Memorial Sloan-Kettering Cancer Center. "But, over the last 10 years, techniques have advanced such that we can now easily biopsy nodules that are less than 4 or 5 millimeters."

However, Dr. Tuttle says he's not convinced that the increased incidence of thyroid cancer is solely an artifact of better technology.

"My concern is that if we blame this entirely on early detection, we may be missing some other cause of thyroid cancer," he says. "I don't think any of the data we have rule out some other etiology."

There are some data to support that concern. A more recent, unpublished analysis of SEER data (through 2004) by Dr. Susan Devesa, from NCI's Division of Cancer Epidemiology and Genetics (DCEG), indicates that the increased incidence, while most prominent for smaller tumors, has occurred across all tumor sizes (even 5 centimeters and larger) and stages, suggesting that more intense scrutiny isn't solely responsible for this trend.

Some studies have suggested that factors such as body mass index, diet, and reproductive patterns can influence thyroid cancer risk. One factor now coming under increasing scrutiny, ironically, is diagnostic imaging, namely CT scans.

The number of CT scans performed annually has exploded, from just a few million in the early 1980s to an estimated 62 million in 2006. CT scans require higher radiation doses than other conventional imaging techniques—doses that, according to a recent paper by Drs. David J. Brenner and Eric Hall from Columbia University Medical Center, are in a range that could increase cancer risk.

"Given the relatively short latency period for radiation-induced thyroid cancer…it is quite possible that CT is influencing current thyroid cancer rates in the United States in young people," says Dr. Brenner, of the Center for Radiological Research at Columbia.

Dr. Elaine Ron, an expert on ionizing radiation and thyroid cancer in NCI's DCEG, agrees that CT scans do represent a potential risk. But, she stresses, "We don't have any data that show that at this point."

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A Closer Look

Navigating Access to Investigational Drugs

NCI's mission includes extensive funding and performance of clinical research, better known as clinical trials. The modern clinical trials system takes promising new cancer drugs through three main phases, culminating in approval by the Food and Drug Administration (FDA) for successful agents. Most patients who receive investigational drugs do so through clinical trials.

But not all patients seeking access to investigational drugs are eligible for a clinical trial, due to factors as varied as co-existing illness, time since prior treatment, and extent of disease. Both the FDA and NCI currently manage programs to respond to demands for investigational drugs outside of the clinical trials system.

Expanded Access

Individual patients and their physicians seeking permission to use an investigational drug outside a clinical trial must go through FDA's special exception use process. "In order to pursue access to unapproved drugs outside of a clinical trial, the patient must have been through everything that is currently approved for that disease—not just approved by FDA, but used in practice to treat that disease," explains Patricia Delaney, director of FDA's Cancer Liaison Program.

In addition, to get FDA approval for special exception use, a drug must also be considered safe. "If a patient has a life-threatening disease and has exhausted all of their treatment options, FDA almost always says yes, unless there is a safety issue that the public doesn't know about," says Ms. Delaney. However, a patient cannot simply go directly to FDA and request access, because FDA itself does not control these drugs—they belong to the company developing and testing them. "The first stop [for permission] is the company," she explains. "And that's usually a pretty big threshold, because most companies are not sanguine about providing their unapproved drugs to patients outside of a clinical trial."

Evolving Questions

Risks to patients, drug developers, and the clinical trials system itself underlie the ethical dilemmas surrounding expanded access to investigational drugs. Recently, the Abigail Alliance for Better Access to Developmental Drugs brought a lawsuit all the way to the Supreme Court of the United States, advocating that terminally ill patients had a constitutional right to purchase investigational drugs directly from companies after preliminary—phase I clinical trial—evidence of safety and efficacy.

Although the Court declined to hear the appeal, many questions it raised remain actively debated in the medical community. Would such unfettered access pose undue risk to patients? Does such increased risk matter for patients facing a terminal disease? Would excluding the FDA encourage unethical direct marketing to patients? How would the clinical trials system—which provides the eventual proof that these drugs do or do not work—be affected?

For Dr. Nancy Kass, professor of Bioethics and Public Health at the Berman Institute of Bioethics at Johns Hopkins University, the shifting risk/benefit ratio that patients face when choosing to take drugs with largely unknown side effects and unproven therapeutic efficacy is not the only pressing question. "I think… people who are pretty vocally asking for the drugs are saying that they appreciate there is less known about the risks of the drugs, and they're saying they don't mind."

What interests her is that "we need to navigate a balance between duties to respond to patients in front of us, and duties to learn about what does and doesn't work in cancer treatment, so that the next group of people diagnosed with cancer also has something to help them. If we have something that we know works, the balance gets flipped—we'd give it to you, end of story. But if we have something where we don't know if it works, I would argue…that's exactly the time when that drug should be given in the context of a highly structured, well-organized clinical trial, so we can not only determine if it's helpful for you, but learn about it, to see if it makes any difference for future cancer patients."

Access at NCI

In one of its many roles, NCI functions as a drug developer, creating and testing new anticancer compounds. NCI coordinates its own special exception program with the FDA, as would a pharmaceutical company, through the Treatment Referral Center, located in the Cancer

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Therapy Evaluation Program (CTEP). "We work directly with the company, local oncologist, and FDA to obtain permission to distribute investigational agents to individual patients not eligible for clinical trials," explains Matthew Boron, a CTEP senior clinical research pharmacist.

As with any pharmaceutical company request, the agent must have a safe dose and schedule determined from phase I trials. In addition, "we need to see that there's some evidence of activity in a particular tumor type," says Mr. Boron. If an experimental drug seems promising for an individual patient, CTEP will first try to identify a clinical trial that could enroll the patient. That failing, "we would look to alternate mechanisms," he continues.

One alternative is developing collaboratively with CTEP a Special Exception/Single Patient Protocol. To obtain an investigational agent under this mechanism, the patient must be ineligible for a research protocol and also have exhausted all standard therapies. In addition, the requested agent must have demonstrated activity in their disease with no unacceptable risk to the patient.

NCI has also used two unique programs to provide experimental drugs in the later stages of development to larger groups of patients. These two programs—called Group C/Treatment IND and Treatment Referral Center (TRC) protocols—have provided access to promising new drugs to almost 20,000 patients since their inception. Unlike most protocols sponsored by CTEP, the Group C and TRC protocols are generated from within CTEP in an effort to provide access to promising therapies that would otherwise not be accessible.

The Group C and TRC protocols "are typically instituted to bridge the gap between positive phase II or positive FDA registration data, and drug availability. They're usually designed to get up and running quickly and to close quickly," explains Mr. Boron.

The Group C classification, which is no longer used, went to agents near the end of the approval process that were expected to rapidly change the standard of care. Clinical trials had already shown their reproducible efficacy in one or more tumor types, but wider distribution and marketing awaited FDA approval. Any NCI registered physician could register with NCI to receive Group C agents. Drugs first distributed widely through Group C protocols include paclitaxel for ovarian cancer and levamisole for colorectal cancer. The Group C classification has been replaced by the Treatment Protocol or Treatment IND.

Unlike Group C protocols, TRC protocols are restricted to distribution through NCI-designated Cancer Centers and designated secondary centers. In fact, explains Dr. James Zwiebel, chief of CTEP's Investigational Drug Branch, one of the focuses of the program is to make sure distribution of a new drug "is done in an equitable way, in a way that's sensitive to geographical distribution." They also function more like multicenter single-arm clinical trials with relatively open eligibility criteria and simple objectives. They usually only require limited data collection focusing on safety and efficacy. To be eligible for a TRC, a drug must show highly promising activity or target a tumor type considered to be a high priority by CTEP.

For example, nelarabine (Arranon), now an approved treatment for T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma—both rare cancers—was available for almost 10 years through a TRC while waiting for review, approval, and marketing. "It's a small population of patients… but an effective therapy that they otherwise would not have had access to," says Mr. Boron. ◆

By Sharon Reynolds

For more information

Information about eligibility for particular cancer clinical trials can be found at http://www.cancer.gov/clinicaltrials/search. Information about NCI's Treatment Referral Center is available at http://ctep.cancer.gov/requisition/compassion.html. FDA's Cancer Liaison Program provides information at http://www.fda.gov/oashi/cancer/cancer.html. ◆

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To better assess the risk of all cancers and CT scans, Dr. Ron says, NCI is collaborating with researchers from the United Kingdom on a retrospective "historical cohort study" of close to 200,000 people in the U.K. The study will look at cancer rates in people who did and didn't receive CT scans as children. ◆

By Carmen Phillips

Notes

New DCEG Branch Chiefs Named

NCI's Division of Cancer Epidemiology and Genetics (DCEG) recently appointed four new branch chiefs.

Dr. Nilanjan Chatterjee has been named chief of the Biostatistics Branch. Dr. Chatterjee has a doctorate in statistics from the University of Washington. He specializes in developing efficient design and analytic methods for modern molecular epidemiologic studies.

Dr. Debra Silverman has been selected as chief of the Occupational and Environmental Epidemiology Branch. Dr. Silverman received her doctorate in epidemiology from the Harvard School of Public Health and specializes in the epidemiology of cancers of the bladder and pancreas and the carcinogenicity of diesel exhaust.

Dr. Allan Hildesheim is the new chief of the Infections and Immunoepidemiology Branch, formerly known as the Viral Epidemiology Branch. Dr. Hildesheim has a Ph.D. in epidemiology from the Johns Hopkins School of Hygiene and Public Health and studies DNA virus-related tumors including cervical cancer and nasopharyngeal carcinoma. He is the principal investigator on the NCI-sponsored clinical trial in Costa Rica of the newly developed HPV vaccine.

Dr. Jackie Lavigne has been selected as the new chief of DCEG's Office of Education. She received a Ph.D. in molecular toxicology and an M.P.H. with a concentration in epidemiology and biostatistics from Johns Hopkins Bloomberg School of Public Health. Dr. Lavigne previously was the associate director of the NCI Cancer Prevention Fellowship Program.

First Anita Roberts Young Scientist Scholarships Awarded

The first Anita Roberts Young Scientist Scholarships were awarded to Dr. Anjali Shukla, a postdoctoral fellow in NCI's Center for Cancer Research (CCR), and Dr. Kate Sullivan of the Children's Hospital in Westmead, Australia. Organized by Dr. Roberts's colleagues at NCI and funded by donations from the scientific community, the scholarships were awarded to defray the cost of attending the 2008 Keystone Symposia meeting on Molecular and Cellular Biology in Santa Fe, NM. Funds for the scholarships were collected with the cooperation of the Foundation for the NIH.

Dr. Roberts was an internationally recognized molecular biologist who made pioneering discoveries regarding the protein TGF-β, which is critical in wound and bone fracture healing as well as in cancer suppression and stimulation. She worked at NCI for more than 20 years, heading the Laboratory of Cell Regulation and Carcinogenesis in CCR until her death in May 2006 of gastric cancer.

NCI Sponsors Webinar on Tools to Guide Efforts to Reduce Colorectal Cancer Deaths

NCI's Office of Advocacy Relations will host a webinar on a set of simulation models from NCI's Cancer Intervention and Surveillance Modeling Network (CISNET). The models can be used to support the establishment of policies, guidelines, and evidence-based cancer control planning to decrease colorectal cancer deaths through screening, treatment, and risk factor modification.

This webinar is scheduled for Thursday, February 28, from 3:30–4:30 p.m., EST. No advance registration is required. More information and instructions on how to participate are available at http://cisnet.cancer.gov/webinars/crc_02282008.html.

NCI to Host Science Writers' Seminar on International Breast Cancer Trials

On February 29, NCI is partnering with the Mayo Clinic and the Breast International Group to host a science writers' seminar about how two trends in cancer research—increasing use of targeted therapies and growing global research cooperation—have merged. The seminar will also launch the North American part of the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) study. In the trial, two targeted therapies for treatment of a subtype of breast cancer will be tested with participation of thousands of women across several continents, providing a model for international collaboration that furthers cancer care.

The seminar will take place 9:00–11:45 a.m., in Conference Room 704 at the Millennium Broadway Hotel New York, 145 West 44th Street, New York City.

Journalists can register for the seminar by contacting the NCI Office of Media Relations at 301-496-6641 or ncipressofficers@mail.nih.gov.

Biospecimen Research Symposium Scheduled for March

NCI's Office of Biorepositories and Biospecimen Research and the NIH Office of Rare Diseases have announced that the Biospecimen Research Network symposium, "Advancing Cancer Research through Biospecimen Science," will take place

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March 13–14, in Washington, DC. The symposium is open to the public and expected to be of particular value to research investigators, clinicians, government and industry representatives, hospital administrators, and patient advocates. For more information, to register, or to submit an abstract, go to www.brnsymposium.com.

Registration and Abstracts Accepted for Targeted Therapies Conference

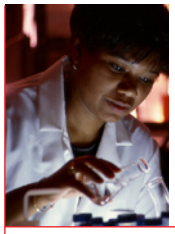
NDDO Research Foundation, NCI, and the European Society for Medical Oncology are still accepting registrations and abstract submissions for TAT 2008, an international conference on targeted anticancer therapies to be held in Bethesda, MD, on March 20–22.

The conference will cover new drugs in pre- and early-phase clinical development and clinical trials of combinations of targeted agents, and will focus on clinical and translational research. An updated program is available on the TAT 2008 Web site: http://www.nddo.org/page_include_tat2008.shtml.

To submit an abstract, send your complete abstract in Microsoft Word format to the conference secretariat, Dr. Marinus W. Lobbezoo, at lobbezoo@mccm.nl. ◆

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_021908/page8. ◆



Featured Clinical Trial

Preventing Chemotherapy-Induced Neuropathy

Name of the Trial

Phase III Randomized Study of Alpha-Lipoic Acid in Preventing Platinum-Induced Peripheral Neuropathy in Cancer Patients Receiving a Cisplatin- or Oxaliplatin-Containing Chemotherapy Regimen (MDA-CCC-0327). See the protocol summary at http://cancer.gov/clinicaltrials/MDA-CCC-0327.

Principal Investigator

Dr. Ying Guo, University of Texas M.D. Anderson Cancer Center

Dr. Ying Guo

Why This Trial Is Important

Peripheral neuropathy is a condition characterized by sensations of pain, tingling, burning, numbness, or weakness that usually begin in the hands or the feet. It can be caused by certain illnesses, for example, diabetes. It can also be a side effect of treatment with platinum-based chemotherapy drugs.

The peripheral neuropathy associated with platinum-based chemotherapy can be either acute or chronic. Acute peripheral neuropathy may begin during or shortly after administration of a platinum-containing drug and usually goes away on its own after several days. Chronic peripheral neuropathy may arise weeks or months after chemotherapy treatment and may be difficult to treat; in some patients, it may be irreversible.

In this trial, researchers are testing the ability of alpha-lipoic acid to prevent peripheral neuropathy caused by the platinum-containing drugs cisplatin and oxaliplatin. Alpha-lipoic acid is an antioxidant produced naturally by the body; it can also be found in some foods and as a nutritional supplement. In patients with diabetes, it has been shown to relieve symptoms of neuropathy.

"Peripheral neuropathy is a potentially disabling condition that affects many cancer patients treated with platinum-based chemotherapy," said Dr. Guo. "We hope that alpha-lipoic acid will help prevent this condition in patients undergoing chemotherapy with cisplatin or oxaliplatin."

Patients in this trial will be randomly assigned to receive oral alpha-lipoic acid or a placebo three times a day for at least 24 weeks.

For More Information

See the lists of entry criteria and trial contact information at http://cancer.gov/clinicaltrials/MDA-CCC-0327 or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) for more information. The toll-free call is confidential. ◆

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

Guest Commentary by Lance Armstrong

Pushing Progress, Maintaining Momentum

As I conclude my second term as a member of the President's Cancer Panel, I would like to thank the President and my colleagues for an enlightening and substantive 6 years, as well as reflect on the progress and future endeavors of the Panel.

I was privileged to have the opportunity to serve alongside Dr. LaSalle Leffall and Dr. Margaret Kripke, who have become my mentors and friends, and it was an honor to serve this country with them. Since my appointment in 2002, the Panel has explored many topics and made recommendations focused on improving the National Cancer Program. I am proud to have been a member of the Panel and of our achievements; however, there is still much to be done to guarantee that all Americans affected by cancer benefit from research and receive adequate treatment and follow-up care.

The Panel's 2003–2004 series, *Living Beyond Cancer: Finding a New Balance*, focused on the needs of cancer survivors. Definitions and perceptions of cancer survivorship, age-specific challenges throughout the life span, gaps in cancer survivorship research, and policy issues were emphasized in the report. In the 2004–2005 report, *Translating Research Into Cancer Care: Delivering on the Promise*, the Panel made recommendations on how to best translate research advances into effective cancer prevention and care for all segments of the population. Overcoming barriers to translating research and the importance of evaluating progress in accelerating research translation were emphasized.

Assessing Progress, Advancing Change, the 2005–2006 report, examined the progress of implementing key recommendations from the two previous reports. Through discussion with key stakeholders, uneven progress and limitations to advancing the National Cancer Program were exposed, allowing the Panel a better grasp of the work yet to be done. The most recent report, *Promoting Healthy Lifestyles: Policy, Program, and Personal Recommendations for Reducing Cancer Risk*, explored ways to reduce cancer incidence and mortality through the promotion of healthy lifestyles. The Panel examined how lifestyle affects cancer risk, and how the government, communities, and individuals can take part in improving overall public health.

The current series, *Strategies for Maximizing the Nation's Investment in Cancer*, addresses the inefficiencies within the current cancer enterprise. Alternative models that approach cancer research and care from a business or economic perspective as a method to facilitate and streamline research, drug development, and delivery of care processes were examined.

During my time on the Panel, I contributed to the creation of many recommendations to the President. But I feel that as much as I contributed, I have learned even more in the process. Through my service on the Panel, I have seen the toll cancer takes on American lives and now recognize it for the epidemic it truly is. I have witnessed the many challenges we face as a nation in overcoming this disease and acknowledge that many of these challenges are entirely of our own making. To beat this disease, we must eliminate bureaucratic roadblocks, address the lack of funding, and sustain dedication at the highest levels of our government—only then can we make true inroads to save American lives.

In the face of a national epidemic, we need action from our country's leaders. There is too much at stake to preserve the status quo and if we don't act, generations of Americans will pay the price for our failure. My hope is that the Panel's recommendations will continue to be regarded as urgent actions necessary to reduce the burden of cancer. I am honored to have had the opportunity be a part of such an influential federal advisory committee and look forward to hearing about the Panel's continued success. ◆

Lance Armstrong
Member, President's Cancer Panel
Founder, Lance Armstrong Foundation