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Trials Suggest Potential Expanded Use for HER2-Targeted Agents

Results from two phase III clinical trials presented last week at the San Antonio Breast Cancer Symposium (SABCS) suggest that there may be an expanded role for HER2-targeted therapies in breast cancer treatment, according to the trials' leaders.

The smaller of the two trials, dubbed NOAH, tested the combination of trastuzumab (Herceptin) and chemotherapy given prior to surgery, called neoadjuvant therapy, compared with neoadjuvant chemotherapy alone in 327 patients with HER2-positive breast cancer.

Data on "event-free survival" (time between randomization and disease recurrence, disease progression, or death from any cause) and response rate were available. According to the trial's principal investigator, Dr. Luca Gianni from the Istituto Nazionale Tumori Milano in Italy, the 3-year event-free survival rate for patients receiving the combination therapy was significantly better than that of patients receiving chemotherapy alone, 70.1 percent vs. 53.3 percent.

Rates of overall response and pathologic complete response (disappearance of all signs of the tumor) were also superior in the combination therapy arm, Dr. Gianni stressed, and cardiac side effects were limited, with serious cardiac events in less than 2 percent of patients.

"We think that this establishes preoperative trastuzumab with chemotherapy as a standard treatment option in women with locally advanced HER2-positive breast cancer," Dr. Gianni said. The results, he added, "most likely will translate into…an advantage in terms of survival."

Preoperative systemic therapy is commonly used in women with locally

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Cancer Research Highlights

Surgery Alone May Be Best for Early Uterine Cancer

Most uterine cancers are diagnosed at an early stage, while still confined to the body of the uterus. In addition to surgery to remove the uterus and ovaries, some doctors perform lymphadenectomy (lymph node removal), external-beam radiation therapy (EBRT), or both, in the hope of preventing local recurrence.

However, a large randomized trial, published online December 13 in *The Lancet*, showed no improvement in survival associated with lymphadenectomy or EBRT.

Investigators leading the international ASTEC study randomly assigned 1,408 women to receive surgery or surgery plus pelvic lymphadenectomy. Women in both groups at intermedi-

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Director's Update

Cancer Research in a New Light

In the past, the final *NCI Cancer Bulletin* issue of the year has been used to reflect on some of the important research news from the past 12 months. And, indeed, the news this year has been encouraging. Most recently, the annual *Report to the Nation* documented that, for the first time since the report was initially produced a decade ago, both incidence and death rates from cancer are declining.

Although the decline in incidence must be interpreted with caution, the continued downturn in mortality demonstrates that translating the research of cancer prevention, early detection, and treatment into clinical practice pays significant dividends. Our progress toward more individualized prevention and treatment will undoubtedly build on this promise.

In today's global economic climate, however, it's difficult not to ponder how the current financial tumult will affect future gains against cancer. Flat budgets over the past 5 years have already dramatically reduced NCI's purchasing power. We've had to make difficult funding choices, and there are continued concerns about the impact on the pipeline of young cancer investigators.

If some of the economic stimulus proposals that have been discussed in Congress are any indication, including one proposal that would increase the NIH budget by $1 billion, there could be reason for optimism. And although we tend to think of an investment in biomedical research in purely clinical terms, there is evidence that such an investment can provide a boost to the economy.

According to leading economists, in an "underemployed economy"—that is, an economy where skilled workers, such as basic scientists and lab technicians, are not engaged in jobs that maximize their skill sets—there can be a two- to threefold return for every dollar spent by the federal government that puts such people back to work.

At its most rudimentary level, that government investment in research ends up, for instance, as a grant to a researcher. The largest part of that grant ends up as salaries and some funds are used to purchase materials to conduct research. But the investigator and laboratory staff receiving this government grant support use those salary dollars to purchase a new vehicle or a home or goods and services. All of that is money going directly back into the economy again, multiplying well beyond the initial investment.

But this type of government stimulatory effect is even more complex than what can transpire through tax breaks or direct spending on infrastructure projects, such as roads and bridges. While it is difficult to measure the payoff in terms of individual research projects, in the aggregate, a significant investment in biomedical research is the type of government spending most likely to produce long-term gains for society—such as the unexpected innovations that create new markets for economic growth, the increased productivity of the populace whose health is improved and who are thus able to be more productive citizens, and the opportunity through science to decrease health care costs.

When you look just at NCI, let alone the 26 other NIH institutes, you get a sense of the potential of this type of investment. NCI has a budget of approximately $5 billion. It supports approximately 5,700 researchers who are focused on efforts to improve the outcomes of a disease that, according to a recent NCI analysis, will have an economic burden in the United States of $1.8 trillion by 2017.

Many around the country are dealing with the fallout from the current economic difficulties. Both policymakers and homemakers are faced day after day with tough decisions about how to spend their available resources wisely. But even in these difficult times, I see a groundswell of support at all levels, from local communities to the highest sectors of government, to do what it takes to overcome the cancer burden.

It's for that reason that I'm hopeful we'll see the type of investment in cancer research we know can pay dividends for people's health and well being, and that very well could produce the type of financial gains that can help our struggling economy recover.

In closing this, the 200th issue of the *NCI Cancer Bulletin*, the NCI staff and I would like to extend our best wishes for a joyful and safe holiday season. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

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advanced breast cancer (see sidebar), notes Dr. Jo Anne Zujewski, a senior investigator in NCI's Cancer Therapy Evaluation Program who specializes in breast cancer. Trastuzumab in combination with chemotherapy is standard therapy for women with HER2-positive breast cancer, and the NOAH trial is the first large study to demonstrate that a high pathological complete response rate can be obtained in women with HER2-positive locally advanced breast cancer when the combination is used prior to surgery.

But before this regimen, which used anthracycline epirubicin, can be considered for standard use in the clinic, there needs to be more data, said Dr. Zujewski. "Given the relatively small number of patients in the trial, oncologists may still be apprehensive about the potential for cardiac effects from the concurrent use of trastuzumab and anthracycline-based chemotherapy," she said.

Additional data will be available from ACOSOG Z1041, an ongoing, U.S.-based clinical trial of epirubicin-based chemotherapy with concurrent trastuzumab in women with operable HER2-positive breast cancer.

The second trial presented at SABCS, known as EGF30008, compared the combination of the HER2-targeted agent lapatinib (Tykerb) and the aromatase inhibitor letrozole with letrozole alone in women with advanced, metastatic breast cancer.

Although the trial enrolled 1,300 patients, the results presented focused on a subset of 219 patients who were HER2-positive and hormone receptor (HR)-positive, for whom endocrine therapy with letrozole or other aromatase inhibitors is a standard first-line treatment.

Progression-free survival was markedly improved in the lapatinib/letrozole arm, 8.2 months versus 3.0 months, explained the study's lead investigator, Dr. Stephen Johnston from the Institute of Cancer Research in London. Patients in the combination arm also had superior rates of overall response and stable disease.

"These patients would previously be treated with endocrine therapy alone," Dr. Johnston said. "Now the suggestion is that combined therapy may certainly be a better approach."

The trial, he explained, builds on the fact that lapatinib is a dual-targeted tyrosine kinase inhibitor, targeting both HER2 and EGFR, another cell-surface receptor in the same family. Trastuzumab, by comparison, is a monoclonal antibody that targets only HER2. Women with advanced metastatic breast cancer often have, or eventually develop, resistance to endocrine therapy with tamoxifen or aromatase inhibitors, Dr. Johnston explained, and studies indicate that this resistance is associated with the expression of both HER2 and EGFR.

"So there exists this complex cross-talk between these pathways," he said, "and it therefore makes sense to think about targeting both pathways together with drugs available to do that, to try and improve on just using hormonal treatments alone."

Based on these results, Dr. Zujewski noted, breast oncologists may opt to use this combination approach in some patients with HR-positive, HER2-positive metastatic breast cancer. ◆

By Carmen Phillips

NCI sponsored a state-of-the-science conference on preoperative therapy for locally advanced breast cancer in 2007. A series of papers based on the conference, and updated results from two breast cancer neoadjuvant therapy clinical trials, were published in the February 10, 2008 *Journal of Clinical Oncology*. ◆

Two Prevention Trials Show Antioxidants Do Not Cut Cancer Risk

Data are now available from more than 35,000 men aged 50 and older who participated in the NCI-funded Selenium and Vitamin E Cancer Prevention Trial (SELECT), indicating that selenium and vitamin E supplements did not prevent prostate cancer, when taken either alone or together. The data also show small, statistically insignificant increases in prostate cancer cases among men who took only vitamin E and also in adult-onset diabetes cases among men taking only selenium.

Another trial, the Physicians' Health Study II, followed more than 14,600 male physicians aged 50 years and older who took vitamin E, vitamin C, a combination of both, or placebos over a 10-year period. The rates of prostate, colorectal, lung, and other cancers were similar among all study groups.

Results from both trials were published online December 9 in the *Journal of the American Medical Association*. "Physicians should not recommend selenium or vitamin E—or any other antioxidant supplements—to their patients for preventing prostate cancer," wrote Dr. Peter Gann of the University of Illinois at Chicago in an accompanying editorial. ◆

Cancer Research Highlights

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ate or high risk of recurrence were randomly assigned a second time to receive either EBRT or no EBRT.

In the lymphadenectomy arm of the trial, more women who underwent lymph node removal reported moderate or severe treatment-related side effects than women who had standard surgery. Five-year overall survival was 81 percent in the standard surgery group and 80 percent in the lymphadenectomy group.

Five-year recurrence-free survival was 79 percent in the standard surgery group and 73 percent in the lymphadenectomy group. Similar proportions of women in both groups had received postoperative radiation therapy. These results "show no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer. Pelvic lymphadenectomy cannot be recommended as routine procedure for therapeutic purposes outside clinical trials," concluded the authors.

To determine the effectiveness of EBRT, the results from the second randomization in the ASTEC trial were combined with those from a Canadian trial (EN.5) for a total of 905 participants. Similar proportions of women in the EBRT or no EBRT arms received brachytherapy, which was part of the standard treatment at several participating hospitals.

Both acute and late toxicity was greater in the EBRT group. No difference in overall survival was seen between the two groups. The 5-year recurrence-free survival was 84.7 percent in the EBRT group and 85.3 percent in the control group. EBRT did help prevent local recurrences, but only 35 percent of recurrences were isolated local recurrences. The authors concluded that "adjuvant [EBRT] cannot be recommended as part of routine treatment for women with intermediate-risk or high-risk early-stage endometrial cancer with the aim of improving survival."

Studies Assess the Economic Impact of Cancer Deaths

The estimated annual loss of productivity due to cancer deaths is the equivalent of approximately 1 percent of the 2007 U.S. gross domestic product, according to a new study published online December 9 in the *Journal of the National Cancer Institute* (*JNCI*). When the productivity costs associated with caregiving for cancer patients and household activities are factored in, the estimate nearly doubles.

Using a model based on a "human capital approach," which factors in the value of lost years of work due to premature mortality, Dr. Cathy J. Bradley and colleagues from Virginia Commonwealth University, the Massey Cancer Center, and NCI estimated that the total productivity cost in 2000 due to cancer mortality was $115.8 billion. Based on current mortality rates, that figure will jump to $147.6 billion by 2020. Incorporating caregiving expenses and household duties into the model raised the cost estimates of cancer mortality to $232.4 billion in 2000 and to $308 billion in 2020.

The authors also determined that, starting in 2010, reducing cancer mortality by 1 percent for the six cancers most costly in terms of lost productivity due to death—colorectal, breast, pancreatic, leukemia, brain, and lung (which had the highest cost for lost productivity)—would reduce the economic burden by approximately $814 million annually.

A companion study in the same issue of *JNCI*, led by NCI's Dr. Robin Yabroff from the Division of Cancer Control and Population Sciences' Health Services and Economics Branch, used a different method to assess the economic impact of death from cancer: the "willingness-to-pay" approach, which uses a previously published value of people's willingness to pay for one additional year of life, $150,000.

Compared to estimates based on the human capital approach, estimates of the cost associated with cancer mortality from the "willingness-to-pay" model were dramatically higher, $960.7 billion in 2000 and nearly $1.5 trillion by 2020.

In an accompanying editorial, Dr. Scott D. Ramsey from the Fred Hutchinson Cancer Research Center noted limitations to the methodologies used in both studies. Nonetheless, he acknowledged the use of these estimates to aid policymakers in deciding research priorities and assessing current investments, as well as helping insurers with coverage decisions.

Meta-analysis Highlights Progress in Treating Advanced Breast Cancer

Because randomized clinical trials of non-hormonal therapies for meta-

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static breast cancer tend to be small, it has been difficult for researchers to fully understand the survival benefits of different chemotherapy regimens and targeted treatments. To fill this knowledge gap, researchers led by Dr. John Ioannidis of the University of Ioannina in Greece performed a meta-analysis of 128 randomized clinical trials that compared at least two different regimens involving chemotherapy, targeted therapy, or both. Their results appeared December 9 in the *Journal of the National Cancer Institute*.

The researchers found that taxanes (such as paclitaxel and docetaxel)—in combination with novel chemotherapy agents, trastuzumab, or older treatment agents—provided the greatest decrease in mortality risk. Several other drug combinations and newer single agents provided "considerable survival benefits" compared with single-agent treatments using older drugs, stated the authors. Most of these regimens showed similar benefits when given as first-line or later therapy, indicating that several could be given in sequence to prolong survival.

These results show that "many classes of modern breast cancer therapy, including anthracyclines, taxanes, novel nontaxanes, and trastuzumab, either as monotherapy or as combination therapy, would produce tangible gains in absolute survival over older single agents, ranging from 4.2 to 12.5 months for a patient with an anticipated survival of 1 year treated with the reference standard alone," explained Drs. Philippe Bedard and Martine Piccart-Gebhart in an accompanying editorial.

"Several regimens [of newer agents] have shown effectiveness, and for some of them, the treatment effects are practically indistinguishable in magnitude," stated the authors. Therefore, choice of therapy should be tailored to individual patients, taking into account known side effects and the patients' overall health, they concluded.

Rituximab Improves Outcomes for CLL Patients

Two international phase III studies presented last week at the American Society of Hematology meeting in San Francisco show that advanced chronic lymphocytic leukemia (CLL) patients who received the monoclonal antibody rituximab (R) in addition to standard chemotherapy with fludarabine and cyclophosphamide (FC) had outcomes far better than those patients who received FC alone.

The first study included 817 previously untreated advanced CLL patients whose mean age was 61 years. They were randomized to receive six 28-day courses of either FC or FCR. After a median follow up of 25.5 months, the complete response rate in the FCR group was 52 percent, compared with 27 percent in the FC group. Progression-free survival was also higher in the FCR group, with 76.6 percent progression-free after 2 years versus 62.3 percent in the FC arm.

In the second study, 552 patients (mean age 63 years) with relapsed or refractory CLL were randomized to receive six 28-day courses of FC or FCR. Most of these patients had previously been treated with single-agent alkylator therapy, a purine analog therapy, or combination chemotherapy. Those in the FCR group had a median of 30.6 months without disease progression, compared with 20.6 months in the FC group. Complete response in the FCR group was nearly twice that of the FC group, 24 percent versus 13 percent.

While the overall response with rituximab was better in both studies, negative side effects were more common in the patients who received the drug, including diminished leukocytes and neutrophils. The incidence of these side effects was associated with age, sex, renal function, and the patient's relative health.

"While these studies clearly indicate that rituximab improves both response and progression-free survival when combined with FC, they do not address whether the addition of cyclophosphamide to fludarabine should become the standard chemotherapy platform for the treatment of CLL," cautioned Dr. Wyndham Wilson, head of the Lymphoma Therapeutics Section in NCI's Center for Cancer Research. "The increased toxicity associated with cyclophosphamide requires that physicians weigh the risks and benefits of FCR versus RF." ◆

NCI Cancer Bulletin Publication Break

Today's issue is the final one of 2008. On December 30, current subscribers to the *NCI Cancer Bulletin* will receive an e-mail message from Editor-In-Chief James Mathews announcing some exciting changes to the newsletter. These changes will debut when we resume publishing on January 13, 2009.

If you are not yet a subscriber, go to http://www.cancer.gov/NCICancerBulletin and submit your e-mail address on the left side of the page. ◆

Special Report

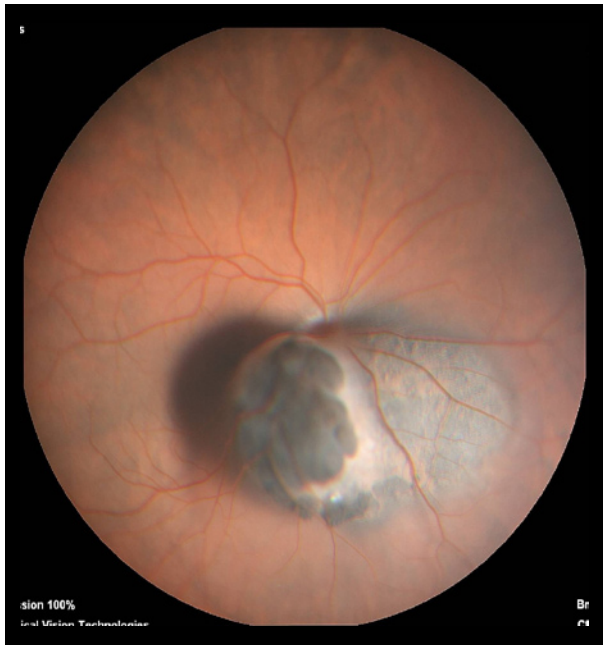
Researchers Uncover Gene for Melanoma of the Eye

If ever a cancer gene were discovered in the right place and at the right time, *GNAQ* may be it. The gene has been known for years but not linked to cancer. Now researchers say that it is mutated in patients with uveal melanoma and may be an important cause of this rare cancer, which arises from cells that give color to the eye.

The gene is in the right place because it belongs to a pathway that is activated in melanomas of the skin and has been the subject of considerable research. Drug companies are already investigating the pathway, known as the MAP kinase pathway, to develop targeted therapies for cancers other than uveal melanoma.

The time is right because of these investigations, and also because uveal melanoma may be a candidate for emerging RNA-based therapies. For example, the cancer frequently spreads through the bloodstream to the liver, and RNA delivery works particularly well in the liver.

Melanomas of the skin and the eye are biologically distinct diseases, though some of the same pathways are overactive in each. *GNAQ* mutations are an alternate trigger for the MAP kinase pathway, according to results published online in *Nature* December 10.



A wide-angle fundus photograph of a uveal melanoma and secondary retinal detachment in an adult before treatment. © Photo courtesy of Dr. David Abramson.

"Mutations in *GNAQ* activate a critical signaling pathway in melanoma, but it somehow enters the pathway from a different branch than melanoma of the skin," said lead investigator Dr. Boris Bastian of the University of California, San Francisco. "This may explain why the gene has not been found to be mutated in cancer until now."

GNAQ mutations were present in half of the uveal melanoma cases surveyed, and the mutations were not found in surrounding tissues. The findings are confirmed by a follow-up study in the December *Investigative Ophthalmology & Visual Science* led by Dr. William Harbour of the Washington University School of Medicine.

"These authors have uncovered a mutation that certainly makes sense as a critically important mutation for uveal melanoma," said Dr. David H. Abramson, chief of ophthalmic oncology at Memorial Sloan-Kettering Cancer Center. "And what's exciting is that the discovery has the potential to go quickly from a lab experiment to a clinical treatment. Drug companies are already looking at this pathway because of other cancers."

About 1,500 cases of uveal melanoma are diagnosed each year in the United States. Although local treatment such as surgery and radiation is somewhat effective in uveal melanoma, half of the patients develop metastases to the liver even if the primary site has been effectively dealt with and controlled.

Given that some patients have metastatic disease at the time of diagnosis, what's desperately needed is a systemic therapy, said Dr. Abramson. The discovery of *GNAQ* represents an important step in that direction, he added.

GNAQ had been analyzed in large-scale cancer genome projects, but it went undetected as a cancer gene because the collections of melanoma samples have not been sufficiently diverse to include this rare subgroup, Dr. Bastian noted.

The project began serendipitously at a pigment cell biology meeting in 2003. Dr. Bastian heard a talk about mice developed in the laboratory of Dr. Gregory Barsh at Stanford University. The mice had a mutation that caused pigment cells to accumu-

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late in the deep layer of the skin and resulted in bluish-black coloring on their ears and tails.

The coloring reminded Dr. Bastian of a skin condition in humans known as blue nevus, and he wondered whether the same mutations were involved. An analysis of DNA from blue nevi revealed *GNAQ* mutations in 80 percent of the samples. The mutation turned up only once in skin melanoma samples, however. But because a type of blue nevus is associated with a risk of uveal melanoma, the researchers looked for *GNAQ* mutations in that disease, and they found them.

"It's fascinating how similar the mice and the humans were in this situation," said Dr. Catherine Van Raamsdonk of the University of British Columbia, who did the analysis. "In each case, the mutations caused pigment cells to accumulate in the deep layer of the skin."

The findings raise an interesting question: Why are *GNAQ* mutations relatively harmless when they occur in the skin but may cause cancer in the eye? "We don't yet know why that is," said Dr. Van Raamsdonk. Benign nevi can arise within the eye, but researchers do not know whether they also carry the mutation because the nevi are not biopsied.

In recent years Dr. Bastian and others have been making the case that melanoma is actually more than one biologically distinct disease, as has been demonstrated for many cancers. The finding of *GNAQ* mutations in uveal melanoma and blue nevi potentially identifies them as biologically related subtypes. Mutations have also been reported in melanomas of the mucosa, palms, soles, and nail beds, suggesting that these are biologically distinct.

A critical task for the future, said Dr. Bastian, is to classify melanomas and develop therapies targeted at the genetic features underlying each form of the disease.

His laboratory is collaborating with Alnylam Pharmaceuticals to develop a therapy for silencing *GNAQ* in the liver. Experiments in cells showed that introducing a small piece of genetic material (siRNA) to silence the gene caused the cancer cells to die. Alnylam has developed siRNAs for delivery to the liver in animal models, and the goal will now be to develop a panel that could selectively silence *GNAQ*.

Dr. Abramson praised the new studies as examples of synergy in science that does not happen often enough. "In both cases, excellent basic scientists were collaborating with excellent clinicians in work that is basic science and that could be quickly applicable to humans," he said. "That's a credit to all of them." ◆

By Edward R. Winstead

Cancer.gov Update

Insurance Coverage Laws for Patients in Clinical Trials

NCI recently updated its list of states that require health plans to cover patient care costs in clinical trials. The online feature, found at http://www.cancer.gov/clinicaltrials/ctlaws-home, is a useful resource for those who work to increase enrollment in cancer clinical trials. In the wake of new legislation, the Ohio entry was updated and a new entry for Washington, DC, was added. In addition, the interactive map was enlarged for easier use.

Some health plans don't cover routine care costs once a person joins a clinical trial, posing a barrier to enrollment. The NCI State Cancer Legislative Database Program tracks laws and voluntary agreements that require health plans to cover such costs. The Cancer.gov feature provides user-friendly links to current laws or agreements and their key provisions, as well as links to related resources. ◆

Profiles in Cancer Research

Dr. David Sidransky

Director, Head and Neck Cancer Research
Johns Hopkins Sidney Kimmel Cancer Center

Chair, NCI's Early Detection Research Network

A longstanding and cruel fact of oncology is that the earliest stages of cancer are both the easiest to treat and the most difficult to detect. Most types of cancer have few symptoms in their early stages, and they have often spread throughout the body by the time of diagnosis.

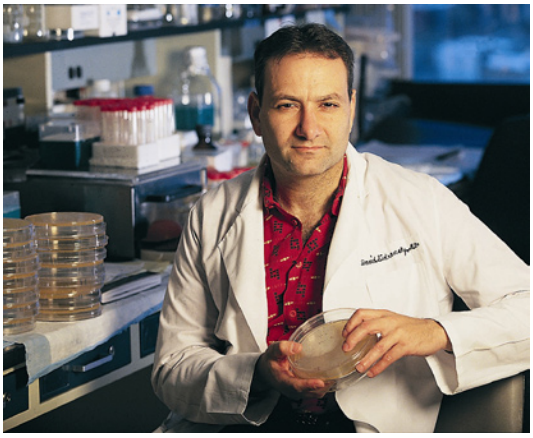

Photo courtesy of Keith Weller

Dr. David Sidransky has focused his career on looking for new and better ways to detect cancer early, before symptoms develop. His family encouraged him to be a doctor, and at Baylor College of Medicine he became fascinated with basic science while working with Dr. C. Thomas Caskey, a medical geneticist. He went on to train with Dr. Bert Vogelstein at Johns Hopkins University, a researcher "who was instrumental in my understanding of what I wanted to do in genetics and translational cancer research," he said.

Dr. Sidransky stayed on at Johns Hopkins to establish his own laboratory. In the early 1990s, in collaboration with Dr. Vogelstein, he published the first two studies (of bladder and colorectal cancer) showing that DNA shed from tumor cells could be measured in body fluids such as urine and stool. "When we found that we could detect these clonal genetic changes in bodily fluids, I think it was kind of a game-changer for everybody in the field," said Dr. Sidransky.

Much of the search for cancer biomarkers then and now has focused on measuring proteins produced by cancer cells. But few if any proteins are produced solely by cancer cells, and the same proteins produced at lower levels by normal tissues can complicate protein-based early cancer detection. In contrast, changes to DNA can be extremely specific for indicating the presence of cancer in the body.

The Sidransky laboratory is exploring the possibility of using DNA methylation, a type of epigenetic change that can contribute to cancer development, as a new type of biomarker for detecting early cancer. In a recent paper they identified cancer-specific DNA methylation in 28 out of 53 genes that they tested. Eight of these genes showed cancer-specific DNA methylation in 300 tumor samples representing 13 different types of cancer.

"We believe that some of these methylation changes exist only in tumors; they're specific for the transformation process, and so they at least theoretically allow for more specific detection of cancers at an early stage," said Dr. Sidransky.

These new biomarkers are being discovered at a time when they could have immediate clinical applications, explained Dr. Sidransky. As recently as a few years ago, detecting some types of cancer early would not have been useful because practical treatments were not available. For example, precancerous changes in the oral cavity (preneoplastic disease) often develops over a large area of the oral cavity at once. Surgery cannot be used in this case, and traditional chemotherapeutic drugs are so toxic that the risk-to-benefit ratio does not balance in favor of early treatment.

However, many newer biological agents such as some monoclonal antibodies and small-molecule inhibitors have a better safety record than traditional chemotherapy, making it feasible to use them for the prevention of disease progression. Dr. Sidransky's group is now testing the monoclonal antibody cetuximab (Erbitux) in a clinical trial for patients with severe preneoplastic disease of the oral cavity.

"We wouldn't have thought of giving a traditional chemotherapeutic agent for even advanced preneoplastic disease," said Dr. Sidransky. "But the toxicities of the antibody are minimal and the survival advantage for patients is high, so we decided to try identifying the lesions that are likely to respond and giving those patients the drug now."

His laboratory is also exploring areas of research that may have both diagnostic and therapeutic applica-

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Spotlight

Tweaking and Testing Cancer Stem Cell Models

After modifying a common experiment used to test the cancer stem cell hypothesis, researchers are reporting that melanoma, a deadly form of skin cancer, may not follow the model predicted by this theory.

The cancer stem cell hypothesis states that some cancers are driven by a small subset of self-renewing cells. One way to explore this idea has been to transplant human cancer cells into mice and observe the results. For a number of cancers, including melanoma, colon, and pancreatic, this experiment has shown that only some cells form tumors.

Citing the importance of this work to the field, Dr. Sean Morrison of the University of Michigan and his colleagues decided to scrutinize the model. Using melanoma as a test case, the team conducted the experiment twice, first with the original study design and then with some modifications.

The changes, such as using mice with weaker immune systems and extending the observation period, led to dramatic differences in the results. With the original design, tumor-initiating cells were rare (about one in a million), but they were much more common in the new model (about one in four), according to findings in the December 4 *Nature*.

The researchers propose that melanoma may not follow the cancer stem cell model but caution against applying the results to other cancers.

"We expect that some cancers really will follow the cancer stem cell model," said Dr. Morrison. "But there probably will be plenty of other cancers like melanoma in which the ability to form tumors is a common attribute of the cancer cells."

His team transplanted cells from 12 patients with melanoma into mice, including cells from both primary and metastatic tumors. The tumor-initiating cells had diverse features, and no single feature was associated with the ability to form tumors.

The cancer stem cell question has potentially broad implications, because new therapies designed to eradicate these deadly cells may be needed for cancers that follow the model.

"This is an important and rigorous study," said Dr. Jeremy Rich, who studies cancer stem cells at Duke University Medical Center and had no role in the research. "It shows that you can, through the manipulation of your mouse model, get a dramatic difference in the frequency of human cancer cells that are able to grow a tumor."

Whether tumors form in the mice depends highly on how the transplantation is done and on the nature of the recipient, added Dr. Stewart Sell of the Ordway Research Institute, who studies adult stem cells and cancer and also was not involved in the study.

Dr. Morrison's laboratory specializes in purifying cells, and for the first time the researchers describe transplanting single human cancer cells into mice. Of the individual transplanted cells, 27 percent formed tumors.

A big unknown is whether the cells that initiate tumors in mice also play a role in human cancers. The researchers note that an even greater—or a much smaller—fraction of

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tions in the future. For example, they have recently focused on identifying changes in mitochondrial DNA that help drive cancer progression.

Dr. Sidransky enjoys mentoring young scientists who study in his laboratory because of the new and fresh perspectives that they often bring to research questions, but also because of what he believes will happen with the results of their hard work.

"I tell young investigators that this is an incredibly exciting time in cancer research. I think that in the next 5 years the entire human genome and epigenome is going to be mapped out in most major cancer types," he explained. "And I think that once we understand those key pathways, then we'll be able to both diagnose and treat cancers in the way that we thought was only remotely possible 25 years ago." ◆

By Sharon Reynolds

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melanoma cells may actually contribute to the disease in patients. They also stress that the results, in their view, do not refute the cancer stem cell hypothesis.

Nonetheless, said coauthor Dr. Timothy Johnson, "the study provides a new tool so we can now go back and repeat previous experiments to prove which cancers are following the cancer stem cell model and which are not."

The findings may apply to a subset of tumors and only under certain conditions, but it is equally possible that the observations are more commonly applicable, wrote Dr. Connie Eaves of the British Columbia Cancer Agency in an accompanying commentary.

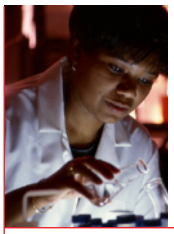
Asked which of the two models might be more relevant for investigating cancer stem cells, Dr. Eaves replied, "We don't know. Both are only surrogates for the real test, which is: What causes tumors to grow and cause relapses in humans?"

Tumors do not grow in a vacuum, she continued, and few grow in the complete absence of host immune components. "So it is not yet clear that going to extraordinary lengths to promote human tumor growth in a mouse will ultimately be the best test of what propagates a tumor in a person," she said.

Despite progress, none of the models can yet predict what might happen in humans. This study, noted Dr. Rich, may "push people to do a better job monitoring how well cancer cells grow in different environments. And that is important."

The next step, said Dr. Morrison, is to optimize the models and start testing cancers. ◆

By Edward R. Winstead



Featured Clinical Trial

Targeted Treatment for Advanced Solid Tumors

Name of the Trial
Phase I Partially Randomized Study of Dasatinib and Bevacizumab in patients with Metastatic or Unresectable Solid Tumors. See the protocol summary at http://www.cancer.gov/clinicaltrials/NCI-09-C-0019.

Principal Investigator
Dr. Elise Kohn, NCI Center for Cancer Research

Dr. Elise Kohn

Why This Trial Is Important
The prognosis for patients with advanced-stage solid tumors is often poor. Not only are their tumors frequently recurrent and no longer responsive to standard treatments, but their cancer also has likely spread (metastasized) to other parts of the body.

Solid tumors depend on new blood vessel formation—a process known as angiogenesis—to obtain oxygen and nutrients for continued growth. A variety of drugs designed to inhibit tumor blood vessel formation, called angiogenesis inhibitors, have been developed for the treatment of many tumor types.

An angiogenesis inhibitor called bevacizumab (Avastin) is approved for the treatment of several solid tumors. In earlier trials, NCI researchers tested the combination of bevacizumab with another targeted drug called sorafenib. In those trials, "We saw a surprising frequency of partial responses, and also prolonged disease stabilization," especially in patients with ovarian cancer, said Dr. Kohn. However, patients experienced a large number of side effects with that drug combination, most likely because both drugs target the same cell signaling pathway involved in blood vessel formation.

The researchers designed the current trial to use the drug dasatinib instead of sorafenib. They believe that the combination of bevacizumab and dasatinib may have fewer side effects, since the two drugs target different cell signaling pathways. "We think we'll get less interactive toxicity, but similar antitumor activity," explained Dr. Kohn.

The researchers plan to enroll 48 patients with ovarian cancer, renal cell cancer, gastrointestinal stromal tumors, melanoma, or other solid tumors that cannot be removed surgically or have metastasized and that have not responded to standard treatment.

For More Information
See the lists of entry criteria and trial contact information at http://www.cancer.gov/clinicaltrials/NCI-09-C-0019 or call the NCI's Clinical Trials Referral Office at 1-888-NCI-1937. The toll-free call is confidential. ◆

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

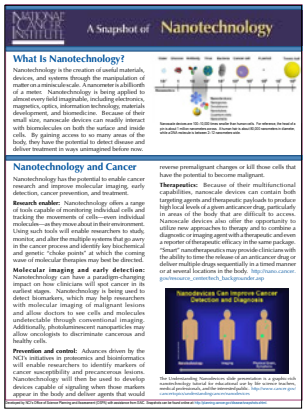
Notes

Winn Named DCCPS Deputy Director

Dr. Deborah Winn was recently appointed the deputy director for the Division of Cancer Control and Population Sciences (DCCPS). Dr. Winn has served as the division's acting associate director for the Epidemiology and Genetics Research Program (EGRP) since 2006. Prior to that, she served as a senior epidemiologist and as chief of the former Clinical and Genetic Epidemiology Research Branch in DCCPS. During her tenure in DCCPS, Dr. Winn has directed and coordinated NCI's extramural program of population-based research in cancer epidemiology. She has played critical roles in NCI's bioinformatics efforts in population sciences and has served as a key NCI spokesperson on epidemiologic topics to Congress and the public. She also represents NCI on several NIH working groups and advisory committees for genetics research. In addition, Dr. Winn has served on national and international committees concerning issues such as women's health and the environment and tobacco-related health risks and regulation.

Prior to joining DCCPS, Dr. Winn was a senior investigator and branch chief for oral epidemiology at the National Institute of Dental and Craniofacial Research. She also served as the deputy director of the Division of Health Interview Statistics at the CDC's National Center for Health Statistics. Dr. Winn holds a Master of Science in Public Health and a Ph.D. in epidemiology from the University of North Carolina School of Public Health.

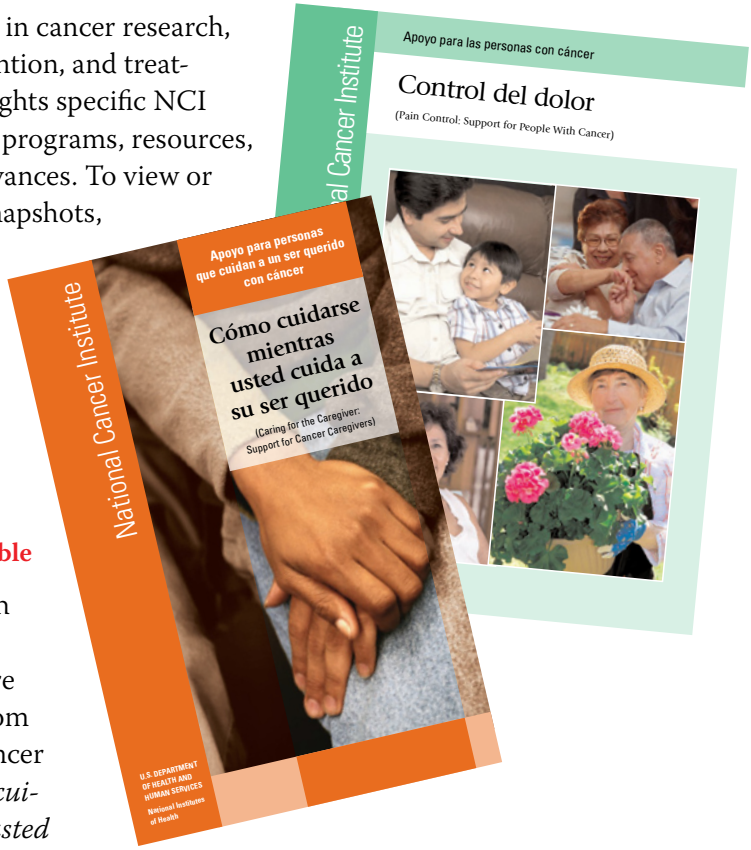
Cancer Snapshots Collection Updated

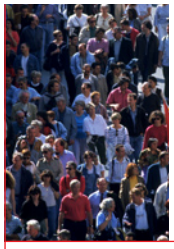


NCI's Office of Science Planning and Assessment recently updated and released a collection of 24 Snapshots, including two new ones on nanotechnology and cancers in adolescents and young adults (AYA). The two-page Snapshots convey key information on disease incidence and mortality, NCI funding trends, relevant research activities, and recent scientific advances. The AYA Snapshot highlights common types of cancer affecting AYAs and includes plans for advancing research on those populations. The Nanotechnology Snapshot provides an overview of the field; its uses in cancer research, detection, prevention, and treatment; and highlights specific NCI nanotechnology programs, resources, and research advances. To view or download the Snapshots, visit http://planning.cancer.gov/disease/snapshots.shtml.

New Spanish Language Education Resources Available

Two new Spanish language education resources are now available from the National Cancer Institute. *Cómo cuidarse mientras usted cuida a su ser querido: Apoyo para personas que cuidan a un ser querido con cáncer* (How to Take Care of Yourself While Taking Care of a Loved One: Support for people who care for a loved one with cancer) is a culturally adapted translation of the NCI booklet, *Caring for the Caregiver: Support for Cancer Caregivers*. The second booklet is *Control del dolor: Apoyo para las personas con cáncer* (Pain Control: Support for People with Cancer), a culturally adapted translation of the English booklet. Both booklets are available from NCI's Cancer Information Service at 1-800-4-CANCER or www.cancer.gov/publications. All of the materials are free; a shipping charge is applied to orders of more than 20 items. ◆





Community Update

Cancer Communications Initiative Expands into the Real World

After showcasing the culmination of their 5-year effort last spring in Atlanta, the NCI-funded Centers of Excellence in Cancer Communication Research (CECCR) initiative grantees are prepared for the next step of the initiative, CECCR II.

"We're taking the knowledge that we've gained and applying it in large-scale studies to existing health care systems in real world settings," said Dr. Matthew Kreuter, principal investigator of the Washington University CECCR in St. Louis.

During CECCR I, his team piloted a clinical tool using a touch screen computer tablet that allowed African American women to navigate a library of stories by their peers "to see whether, through the power of narrative, we can increase the quality of life-related outcomes and social support and adherence to follow-up treatment," he said.

Now they plan to have National Public Radio's Story Corps project come to the NCI-designated Siteman Cancer Center in St. Louis, MO, to record conversations between African American adult cancer survivors and their children. "We hope to use excerpts from those stories to build an educational tool using touch-screen computers for parents who are newly diagnosed that can help them think about how to talk with their kids about what their diagnosis means," he explained.

Another change in CECCR II—and a tremendous boost for the research infrastructure—is the addition of the Kaiser Permanente Colorado (KPC) health care system as a grantee, which will provide access to the Cancer Research Network (CRN) of 14 large health care delivery systems (HMOs) covering nearly 11 million individuals.

"The key perspective and experience that folks in this CRN will bring to CECCR is really an emphasis in organizational studies and organizational communications," explained Dr. James Dearing, principal investigator of the KPC CECCR, noting, "We focus on those instances where people are communicating about cancer within these complex organizations. This is both the bane and promise of managed care." The goal is to lessen "the missed hand-offs, the errors, and the frequent lack of coordination that occur" within large health systems, he said.

The addition of KPC and CRN to the CECCR II network is important for several reasons, said Dr. Bradford Hesse, who oversees the initiative and is chief of the Health Communication and Informatics Research Branch in NCI's Division of Cancer Control and Population Sciences.

"The science in cancer communications has matured across the entire cancer care continuum, and it's ready to start moving into serious effectiveness trials," he explained. "Health communications is going to get a lot of emphasis, especially in the new White House administration, which is focused on how to use electronic medical records and information technologies to improve patient-centered communications." Kaiser currently holds the largest private electronic medical records system in the world, with more than 8.6 million patient records in its collection.

Another real world application during CECCR II is a collaboration between Dr. Kreuter's center and the United Way's "211" national social services referral hotline. "We're taking very poor adults who call 211 needing help paying their electric or utility bills, or because they're being evicted or lost a job," he explained, "and we're proactively screening them for cancer risks. We then refer them to clinical preventive services in the community, where they can get a free mammogram, Pap smear, colonoscopy, smoking cessation counseling, or an HPV vaccine."

"Evidence-based communication approaches are essential for moving what we currently know about the prevention and treatment of cancer into practice," said Dr. Hesse. "This next round of CECCRs should help us take advantage of dramatic changes in biomedical communication to accelerate successes against cancer now." ◆

By Bill Robinson