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Common Cancers May Involve Fused Genes

New research suggests that gene fusion—the coming together of DNA from different parts of the genome—may be an important event in the development of common cancers.

Fused genes and the chromosomal rearrangements that cause them are a hallmark of leukemia, lymphomas, and other blood cancers, but they were not identified in a solid tumor until 2005. In a landmark study, Dr. Arul Chinnaiyan of the University of Michigan Medical School and his colleagues reported that 70 percent of prostate cancers may harbor fused genes.

Now, a follow-up study on fused genes in prostate cancer by the Michigan group and the first reported study of gene fusion in lung cancer appear in the August 2 *Nature*. The findings suggest that identifying fusion events could lead to diagnostic tools and targeted therapies modeled on the leukemia drug imatinib (Gleevec), which inhibits the protein product of the fused gene *BCR-ABL*.

In the lung study, Japanese researchers detected a fused gene in patients with non-small-cell lung cancer (NSCLC). The fusion event between the *EML4* and *ALK* genes activates

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Director's Update

Trial Breaks New Ground in Collaborative Research

Last month a teenage girl from Indiana became the first patient enrolled in an important early-phase NCI clinical trial at the NIH Clinical Center. Diagnosed with an aggressive form of a rare cancer, hereditary medullary thyroid carcinoma (MTC), this young woman will help determine whether the investigational agent vandetanib may be the first effective nonsurgical treatment in young patients with this cancer.

The trial is significant for another reason. It's the first being conducted at the NIH Clinical Center under the joint leadership of an NIH intramural clinical investigator and an extramural scientist. Dr. Frank Balis, from the Pediatric Oncology Branch in NCI's Center for Cancer Research (CCR), is the principal investigator (PI), while Dr. Samuel Wells, from Washington University in St. Louis and one of the world's foremost MTC experts, is the adjunct PI.

Dr. Wells was involved in the discovery of the proto-oncogene, called RET, associated with the hereditary disorder multiple endocrine neoplasia (MEN). Patients with subtypes of MEN are at high risk of developing

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(Fused Genes continued from page 1)
the ALK tyrosine kinase, which controls other proteins and is likely a factor in the cancer.

Tyrosine kinases are involved in many cancers and have become important drug targets. For instance, the kinase inhibitors erlotinib (Tarceva) and gefitinib (Iressa) have benefited lung cancer patients with mutations in the *EGFR* or *HER2/neu* genes.

The structure of the *EML4-ALK* fusion gene suggests that it might be a potential drug target, researchers from the Jichi Medical University report in *Nature*. They found the *EML4-ALK* fusion in 5 of 75 patients studied.

Given the need for potential drug targets in common cancers, the discovery is "momentous," says Dr. Matthew Myerson of the Dana-Farber Cancer Institute in a commentary.

In the prostate study, Dr. Chinnaiyan and his team identified additional gene fusions in prostate tumors. These gene fusions represent distinct types of chromosome rearrangements, and each type may be associated with distinct subtypes of prostate cancer.

Each subtype may require a therapy tailored to the underlying genetic flaw, as is the case for the subtypes of leukemia, the researchers say.

Some fusion events create hybrid genes that are activated by androgen hormones, which can fuel prostate cancer growth. But others do not. For example, one of the identified fusion genes is inactivated by androgens. Androgens have no effect on the activity of yet another identified fusion gene.

This information may prove useful to physicians in making decisions about whether to use hormone therapy in individual patients.

Dr. Chinnaiyan's team also reports that the fusion genes were sufficient to cause prostate cancer in cells and animal models of prostate cancer.

"This is the first study to show that the products of gene fusions initiate an oncogenic cascade in cells or animal models," says Dr. Chinnaiyan. He is supported by NCI's Early Detection Research Network and the Specialized Program of Research Excellence in prostate cancer.

Together, the findings on lung and prostate cancers suggest that activated fusion genes that result from chromosomal rearrangements "are probably both common and important in solid tumors," notes Dr. Myerson.

Discovering the fusions and using them in clinical practice could provide "a great leap forward" in understanding the causes of common cancers, he adds. ◆

By Edward R. Winstead

(Director's Update continued from page 1)
MTC and other endocrine tumors. Dr. Wells also helped to establish the efficacy of prophylactic thyroidectomy in children with RET mutations associated with these MEN subtypes.

After leading early-phase trials that demonstrated the activity of vandetanib in adults with MTC, Dr. Wells approached NCI about conducting a trial in children. It offered an ideal opportunity to pursue something which NIH Clinical Center Director Dr. John Gallin has strongly advocated: an intramural/extramural scientist-led trial. NCI worked with NIH leaders to make the arrangements allowing Dr. Wells to serve as a PI of a Clinical Center trial.

It's gratifying that we were able to make this first-of-its-kind collaboration happen at the NIH Clinical Center, especially because it is with rare cancers that the Clinical Center's value truly shines.

For example, because NIH can recruit patients from around the country and provide them with financial and travel support, trials performed at the Clinical Center are more likely to enroll enough patients with rare diseases to provide the statistical power needed to produce meaningful results and inform clinical care.

Conducting the trial at the Clinical Center also allows investigators from three other NIH institutes with expertise in endocrinopathies and MEN syndromes to participate. In addition to helping to write the trial protocol, these investigators will provide clinical care to trial participants. And many patients in this trial—as well as members of their families, since this is a hereditary syndrome—will likely participate in additional studies, ensuring that we can achieve the most scientific value from and clinical benefit for each patient during their treatment.

The trial's phase I/II design allows it to both determine the safest drug dose that can be given to pediatric patients, and to evaluate its potential efficacy. The trial also will involve biomarker and pharmacokinetic analyses, as well as analyses of tumor samples in the laboratory of Dr. Paul Meltzer from the CCR Genetics Branch to study whether there are genetic mutations associated with resistance to the agent.

Taken as a whole, this trial highlights a new vision of collaboration and partnership. It maximizes the potential of a single trial to provide as much data as possible so that the results can be quickly translated into patient benefit. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Cancer Research Highlights

Treatment Regimen Effective for Metastatic Testicular Cancer

Researchers from Indiana University and the Walther Cancer Institute have developed an effective treatment for metastatic or relapsed testicular cancer, using high-dose chemotherapy with carboplatin and etoposide, supplemented by peripheral-blood stem-cell rescue. Their retrospective review, published in the July 26 *New England Journal of Medicine* by Dr. Larry Einhorn and colleagues, includes 184 consecutive patients from 1996–2004 who did not respond to first-line treatment. (Most patients with metastatic testicular cancer respond to initial treatment.)

Positive results in disease-free survival were found in both patients with seminomas and in those with nonseminomas. After a median follow-up of 48 months, 116 of the patients remained in complete remission.

The favorable outcomes varied according to some significant prognostic factors, however. More patients who received second-line therapy were disease-free, compared with those who received later therapy (70 vs. 45 percent). Also responding better were patients whose tumors were sensitive to cisplatin (68 vs. 45 percent); those who had a better response to initial chemotherapy (73 vs. 55 percent); and those with a more favorable prognosis (80 vs. 55 percent).

The researchers developed a new algorithm to capture the relevant prognostic factors present before salvage treatment that are associated with long-term survival. Their model includes the International Germ Cell Cancer Collaborative Group stage status and, they explained, effectively stratifies patients into low-, intermediate-, and high-risk groups.

PET Can Predict Hodgkin Lymphoma Relapse

A positron emission tomography (PET) scan performed after two cycles of standard chemotherapy for Hodgkin lymphoma (HL) was able to predict, with 92-percent accuracy, which patients' cancer would progress during treatment or relapse immediately afterward, according to study results published online July 23 in the *Journal of Clinical Oncology*. Doctors can use this prognostic data to determine which high-risk patients might benefit from a switch to more intensive chemotherapy.

Investigators enrolled 260 patients into a prospective, single-arm clinical trial. All patients had advanced HL and were scheduled to receive six cycles of the chemotherapy drugs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Participants received a baseline PET scan and a second scan after the second cycle of chemotherapy.

At least two different experts scored the scans as PET-positive (showing residual cancer activity) or PET-negative, and those scored as positive were reviewed by a third expert. The investigators recorded progression-free survival and overall survival over a median follow-up period of 2 years and determined whether the second PET scan or a patient's International Prognostic Score (IPS) could better predict the risk of disease progression or relapse.

Fifty patients had positive PET scans after 2 cycles of treatment; 43 of these (86 percent) had disease progression during treatment or relapsed after treatment. Of the 210 patients with a negative PET scan after 2 cycles of treatment, only 10 (less than 5 percent) experienced disease progression or relapse. In a multivariate analysis, the IPS did not add any prognostic information.

"In conclusion," stated the authors, "an early interim [PET] scan seems to be the most useful prognostic factor in advanced [HL]. This prognostic tool is a surrogate test for the chemosensitivity of the tumor, and it identifies two different categories of patients for which different therapeutic strategies are appropriate."

Inactivated Gene May Indicate Aggressive Lung Cancer

Inactivation of a gene known to have a role in tumor suppression in some cancers may indicate an aggressive form of lung cancer, researchers from the Dana-Farber Cancer Institute reported online in *Nature* on August 5.

Using mouse models of the three subtypes of non-small-cell lung cancer (NSCLC), the researchers demonstrated that inactivation of the gene *LKB1* in combination with mutations in the gene *KRAS*—which is commonly seen in NSCLC—led to increased differentiation of tumor cells and metastasis compared with mice in which *LKB1* was unaffected. Additional studies in NSCLC cell lines found that *LKB1* was often

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FDA Update

ODAC Recommends Raloxifene Approval for Breast Cancer Prevention

An advisory panel to the Food and Drug Administration (FDA) has recommended that the agency approve the anti-osteoporosis drug raloxifene (Evista) for the prevention of breast cancer in postmenopausal women at high risk of the disease.

The panel, the FDA Oncology Drugs Advisory Committee (ODAC), also recommended approval for raloxifene's use to prevent breast cancer in women with osteoporosis. The committee's vote on this latter recommendation was close, 8–6, while the margin of the vote for the high-risk indication was somewhat larger, 10–4.

The recommendations stem from the results of four clinical trials, including the pivotal NCI-supported STAR trial, which showed that raloxifene was as effective as tamoxifen at reducing breast cancer risk in postmenopausal women but with a generally better safety profile. Tamoxifen is the only drug that has received FDA approval for breast cancer prevention.

Dr. Peter Greenwald, director of NCI's Division of Cancer Prevention, said he was pleased with the recommendation. Should FDA follow ODAC's recommendation, he said, it will provide an important new option for breast cancer prevention that women can discuss with their physicians.

"This is a positive step for women's health and for cancer prevention," he said.

Some breast cancer advocacy groups, however, were disappointed in the recommendation, arguing that the benefits of tamoxifen or raloxifene don't outweigh their risks.

In their presentation to ODAC, FDA's own reviewers concluded it was "especially important" that raloxifene's risk/benefit ratio be carefully considered based on the available trial results.

In the STAR trial, both raloxifene and tamoxifen reduced the risk of invasive breast cancer by approximately 50 percent. Women on raloxifene were less likely to develop blood clots, endometrial cancer, and cataracts compared with women on tamoxifen, although not all were statistically significant reductions. Also, raloxifene did not decrease the risk of noninvasive breast cancer compared with tamoxifen.

The three other clinical trial results reviewed by the committee found that raloxifene was associated with a decreased risk of breast cancer in postmenopausal women, but none of these trials included that measure as a primary endpoint.

Although FDA often follows the advice of its advisory committees, it is not bound to do so. According to one media report, Eli Lilly, which manufactures raloxifene, said it expects a decision from the agency by September. ◆

(Highlights continued from page 3)
inactivated or mutated in all three NSCLC subtypes.

In the NSCLC mouse models, mutated forms of *KRAS* "cooperated" with two other genes commonly inactivated in lung cancer, *p53* and *Ink4a/Arf*, to develop tumors and metastases. However, lead investigator Dr. Kwok-Kin Wong and colleagues explained, "the strongest cooperation was seen with homozygous (both gene copies) inactivation of *Lkb1*." Tumors with mutated *KRAS* and inactivated *LKB1* took less time to develop, progressed into all three NSCLC subtypes, and were more likely to generate metastases.

Gene expression profiling of the mouse model tumor samples and tumor cell lines identified several genes whose expression levels were significantly affected by LKB1, including *NEDD9* and *CD24*, and that influenced tumor initiation, differentiation, and progression. When the researchers used short hairpin RNAs to reduce NEDD9 levels in an NSCLC cell line in which LKB1 was inactivated, tumor cell migration and invasion were decreased by more than half.

"These studies establish LKB1 as a critical barrier to pulmonary tumorigenesis," the authors concluded.

Guidelines Address Neurocognitive Problems in Childhood Cancer Survivors

More than a quarter-million children diagnosed with cancer are alive 5 years after treatment, but 50 to 60 percent of these survivors are at risk for neurocognitive impairment because of toxic treatments to the developing brain. A Children's

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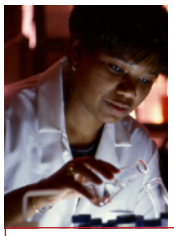
(Highlights continued from page 4)
Oncology Group (COG) task force recently issued long-term, risk-based, exposure-related guidelines to help caregivers identify these effects, and to guide intervention and advocacy for such children.

At highest risk are survivors of brain tumors and acute lymphoblastic leukemia, the most common childhood cancer. Impairments to thinking and reasoning probably stem from treatments that are standard for a number of childhood cancers—cranial radiation therapy, chemotherapy with drugs such as methotrexate and cytarabine, and corticosteroids such as prednisone and dexamethasone.

The problems can be subtle or dramatic, and often emerge as late effects years after treatment. Scientists believe they come primarily from the effect of therapies and surgery on brain functions that are still developing in children—such as attention and concentration, processing speed, visual perceptual skills, executive function, and memory.

The authors urge that these difficulties "be recognized and addressed in a timely and appropriate manner. Primary care practitioners who care for survivors should be aware of those at greatest risk, be able to recognize the school difficulties associated with these outcomes, and have an approach to screening, intervention and advocacy."

These recommendations emerged from the COG Long-Term Follow-Up Guidelines Task Force on Neurocognitive/Behavioral Complications After Childhood Cancer. They are published in the August *Archives of Pediatrics and Adolescent Medicine*. The guidelines can be found also in the COG master document containing all long-term follow-up guidelines. ◆



Featured Clinical Trial

Adjuvant Treatment for Resected Lung Cancer

Name of the Trial
Phase III Randomized Study of Adjuvant Chemotherapy with or without Bevacizumab in Patients with Completely Resected Stage IB-IIIA Non-Small-Cell Lung Cancer (ECOG-E1505). See the protocol summary at http://cancer.gov/clinicaltrials/ECOG-E1505.

Dr. Heather Wakelee

Principal Investigators
Dr. Heather Wakelee, Dr. Alan Sandler, and Dr. Steven Keller, ECOG; Dr. David Gandara and Dr. Eric Vallieres, SWOG; Dr. Stephen Graziano and Dr. Richard Battafarano, CALGB; Dr. Charles Butts, NCIC-Clinical Trials Group; and Dr. Alex Adjei, NCCTG

Why This Trial Is Important
More Americans die each year from lung cancer than from breast, colon, and prostate cancer combined. Although surgery can be curative, many patients will experience a relapse and eventually die from their disease. Consequently, doctors often give chemotherapy after surgery (adjuvant chemotherapy) in an attempt to kill any remaining cancer cells.

The addition of the monoclonal antibody bevacizumab (Avastin) to chemotherapy has helped extend the lives of some patients with inoperable advanced or metastatic non-small-cell lung cancer (NSCLC). Now doctors are interested in determining whether the addition of bevacizumab to adjuvant chemotherapy can help patients with early NSCLC live longer following surgery to remove their tumors.

Bevacizumab blocks the activity of a protein called vascular endothelial growth factor (VEGF), which promotes the growth of blood vessels (angiogenesis) to tumors. Angiogenesis is essential for tumors to get the oxygen and nutrients they need to grow bigger than a few millimeters.

"Bevacizumab in addition to chemotherapy is proven to help people with advanced lung cancer live longer," said Dr. Wakelee. "Because of the way this agent works, we're hopeful that giving it along with chemotherapy to patients with completely resected early-stage lung cancer will help block the development of advanced disease and possibly produce a cure for some of these patients."

Who Can Join This Trial
Researchers seek to enroll 1,500 adult patients with stage IB-IIIA NSCLC that has been completely removed by surgery. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/ECOG-E1505.

Study Sites and Contact Information
Study sites in the United States are recruiting patients for this trial. See the list of study contacts at http://cancer.gov/clinicaltrials/ECOG-E1505 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.

Notes

Ray Named Deputy Director for Management

Lawrence Ray was recently named NCI's new Deputy Director for Management and Executive Officer. In this role, Mr. Ray will serve as the chief operating officer of the Institute and will oversee administrative management of NCI's programs. He will have key responsibilities in execution of the budget and work force management.

Mr. Ray spent 26 years in federal service, principally at NIH. Fourteen of those years were with NCI as chief administrative officer of the Division of Extramural Activities, coordinator of patent licensing and collaborative research and development agreements for the Institute, chief administrative officer of the Division of Cancer Treatment, and deputy associate NCI director, responsible for all aspects of administrative management. From 2003 until just recently, he served as vice president for research operations at Beth Israel Deaconess Medical Center. Before that, he was vice president of clinical program development at Dana-Farber/Partners CancerCare and program administrator for clinical sciences at Dana-Farber/Harvard Cancer Center.

Mr. Ray received his B.A. and M.A. from the University of Kentucky. He also holds a law degree from Catholic University and is a member of the Pennsylvania and District of Columbia bars.

Steeg Named a Deputy Editor of *Clinical Cancer Research*

Dr. Patricia Steeg, of NCI's Center for Cancer Research (CCR), has been named a deputy editor of the journal *Clinical Cancer Research*. Dr. Steeg is head of the Women's Cancers Section in the Laboratory of Molecular Pharmacology and director of CCR's Molecular Therapeutics Program.

Clinical Cancer Research focuses on innovative clinical research and translational research that bridges the laboratory and the clinic. The journal publishes original articles on clinical trials evaluating new treatments for cancer; research on molecular abnormalities that predict incidence, response to therapy, and outcome; and laboratory studies of new drugs and biological agents that will lead to clinical trials in patients.

Dr. Steeg assumes her new editorial position in September 2007. She will join Dr. Ken Anderson from Harvard University, who will be the journal's new editor-in-chief.

All-Ireland NCI Cancer Consortium Web Site Wins Award

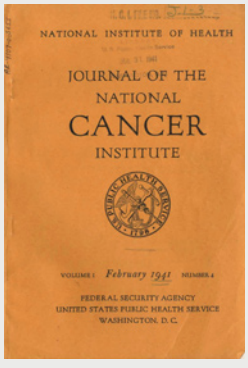
NCI has received an Outstanding Achievement award from Interactive Media Awards for excellence in the design, development, and implementation of the All-Ireland NCI Cancer Consortium Web site. Creation of this Web site was a collaborative effort by NCI's Office of International Affairs and Office of Communications and Education.

The award recognizes that the project met and surpassed standards of excellence that comprise the Web's most professional work. The judges evaluated design, usability, innovation in technical features, standards compliance, and content. To win this award, the site had to meet strict guidelines in each area, a standard achieved by only a fraction of sites in the competition each year. ◆

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_080707/page8. ◆

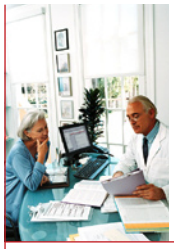
70 YEARS OF EXCELLENCE IN CANCER RESEARCH



If Memory Serves…

The National Advisory Cancer Council sponsored its first conference in 1937 to provide administrators and directors of cancer research institutions input on the development of activities proposed under the National Cancer Institute Act. In 1940, the Council sponsored its first scientific conference to discuss gastric cancer and encourage gastric cancer research. ◆

For more information about the birth of NCI, go to http://www.cancer.gov/aboutnci/ncia.



CCOP Profile

Columbia River Oncology Program

Principal Investigator: Dr. Keith S. Lanier. Manager: Mary Brunetti, R.N.
Columbia River Oncology Program, 9450 SW Barnes Road, Suite 140,
Portland, OR 97225. Phone: 503-216-6260. Web site: http://www.cropor.org

Background

In 1986, a consortium of five hospitals in the Portland, Oregon–Vancouver, Washington region was formed to respond to the second NCI Community Clinical Oncology Program (CCOP) RFA. The resulting Columbia River Oncology Program (CROP) received NCI approval and funding the following year. Dr. Gordon Doty was the first principal investigator. In 1993, Dr. Keith Lanier was elected principal investigator after the death of Dr. Doty.

The mission of CROP is to improve community health by promoting the understanding, prevention, and optimal management of cancer patients through participation in state-of-the-art cancer clinical trials. CROP includes an executive board with representative committee structure and a central office that includes six staff members who manage the large cancer prevention studies, as well as the CCOP administrative and regulatory functions.

Fifteen clinical research nurses and 11 clinical research associates employed by the consortium hospitals recruit patients to cancer control and treatment protocols and collect and submit data to the research bases.

Community Characteristics

Today CROP comprises four large health care systems: Providence Health System, Legacy Health System, Southwest Washington Medical Center, and Northwest Cancer Specialists.

Residents of the Portland metropolitan area are evenly distributed by age, with 20 percent of the population over the age of 55 and 24 percent under age 19. Cancer patient demographics generally follow the profile of the region's population. The Portland-Vancouver area has a low-percentage minority population, with Hispanics the largest group at 7.5 percent, followed by Asian and Pacific Islanders at 5.2 percent, African-Americans at 3.0 percent, and Native American and Alaska native at 1.0 percent.

Front row (left to right): Ruth Jacob, clinical research assistant; Mary Brunetti, manager; Dr. Keith S. Lanier, principal investigator.

Back row (left to right): Scot Lary, cancer prevention and control coordinator; Janice Christoffersen, administrative assistant; Cheri Wick, research nurse and regulatory coordinator.

Recruitment and Outreach Activities

Serving a metropolitan population of 1.9 million, the consortium provides care for residents of Multnomah, Clackamas, Washington, Yamhill, and Columbia counties in Oregon and Clark County in southwest Washington. Since its inception, CROP has enrolled 3,267 patients in clinical trials. Scot Lary, the cancer prevention and control coordinator, attends rounds at satellite facilities' tumor boards and communicates with support group leaders and community agencies about opportunities for clinical trial participation.

Other Key Facts

The Children's Cancer and Blood Disorders Program at Legacy Emanuel Children's Hospital provides the most up-to-date therapies available through the Children's Oncology Group. Three pediatric oncologists and principal investigator Dr. Janice Olson offer many services to help children and families through the diagnosis and treatment of childhood cancer.

CROP has participated in several cancer prevention studies including the Breast Cancer Prevention Trial, the Study of Tamoxifen and Raloxifene, the Prostate Cancer Prevention Trial, and the Selenium and Vitamin E Cancer Prevention Trial.

CROP is also an active member of the Oregon Partnership for Cancer Control, a statewide initiative to bring all the stakeholders in cancer care together to develop a state plan for cancer prevention and control in Oregon. ◆