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Fused Genes Found in Some Prostate Tumors

Researchers have identified several genes that are consistently merged, or fused, in some prostate tumors and could potentially be used to detect the disease. The discovery is the first example of gene rearrangements recurring in a solid tumor, although such changes are a hallmark of some blood cancers.

The findings, reported in the October 28 *Science*, suggest that prostate cancer is not a special case and that other common cancers such as lung, breast, and colon may involve recurrent gene rearrangements. The study was completed in less than 4 months, and the initial results surprised even the researchers themselves.

"We were surprised because these types of gene rearrangements have been associated with leukemia and lymphoma but not with solid tumors," says Dr. Arul Chinnaiyan of the University of Michigan Medical School, who led the study. "To find this change in a majority of prostate cancers suggests that it is important in the disease."

The researchers estimate that between 60 and 80 percent of prostate cancers have the rearrangement. They are developing techniques to detect the change in urine and blood.

When the rearrangement occurs, one of two cancer genes, *(continued on page 2)*

Director's Update

Guest Update by Dr. Paulette S. Gray

Electronic Grants Submission: Are You and Your Institution Ready?

The National Institutes of Health (NIH), including the National Cancer Institute (NCI), provide extensive financial support for researchers in the United States and throughout the world to understand, prevent, and cure diseases and chronic disorders. Acquiring NIH support begins with the submission of a grant application. Until now, this process has been entirely paper based, requiring extensive organization, printing, scanning, and data-entry hours—both on the investigator's end and at NIH.

Dr. Paulette S. Gray, Director, Division of Extramural Activities

Beginning this winter, the application process will transition from a paper-based operation to an electronic grants submission system. This ambitious changeover will occur in stages, beginning with the December 1, 2005, submission deadline for small business applicants. We expect the entire transition to be completed by May 2007.

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(Prostate Tumors continued from page 1)
ETV1 or *ERG*, fuses with part of another gene, *TMPRSS2*. As a result of this fusion, the fused genes, which control other genes, become regulated by the hormone androgen and are at risk of stimulating too much genetic activity in the tumor cell.

"This is fantastic work," comments Dr. William Isaacs, professor of urology and oncology at Johns Hopkins University School of Medicine. "The results need to be independently replicated, but I have every reason to think this will happen rapidly."

The rearrangement may have gone undetected until now because solid tumors involve an overwhelming number of nonspecific, random aberrations.

To address this problem, two graduate students in Dr. Chinnaiyan's laboratory, Scott Tomlins and Daniel Rhodes, developed an algorithm that sifts through data on gene activity to find genes that are highly active in subsets of tumors.

Using the algorithm, called Cancer Outlier Profile Analysis, the team determined that *ETV1* and *ERG* were highly active in some prostate tumors.

Further study revealed that one but not both of these genes frequently fuses with *TMPRSS2* in prostate tumors. "This was a clue that the rearrangement played an important role in the development of prostate cancer," says Mr. Tomlins, noting that single fusion events typically cause some types of blood cancer.

Drugs could potentially be developed to inhibit the mutant genes, although this could take years. The drug imatinib (Gleevec), for instance, targets the gene fusion that causes chronic myelogenous leukemia.

"There are profound implications for diagnosis and treatment if it can be shown that this rearrangement occurs at the earliest stages of prostate cancer," says Dr. Sudhir Srivastava, chief of NCI's Cancer Biomarkers Research Program and director of the Early Detection Research Network, one of the NCI programs supporting the study.

The study does not demonstrate cause and effect, but "we know from other diseases that gene rearrangements are one of the major mechanisms in cancer," says Dr. Jacob Kagan, program director of NCI's Cancer Biomarkers Research Group. "We would now expect that there would be recurrent gene rearrangements in other common cancers as well." ◆

By Edward R. Winstead

(Director's Update continued from page 1)

Electronic submission should provide a more efficient system and allow NIH to shorten the cycle from application receipt to award. Early feasibility studies using Academic Research Enhancement Awards saved enough time to allow an extra month between the request for applications and the submission deadline. The new system will save countless hours of human effort and millions of pieces of paper per year—an important contribution to environmental conservation. Applicants also will have faster access to summary statements and peer review outcomes.

For members of the cancer community who will apply for NIH funding using the new system, it is time to start preparing. Many familiar aspects of the grants process will be changing. Perhaps foremost, after the transition we will no longer use the PHS 398 forms. Instead, investigators will need to use the SF 424 Research and Related application. There will also be several new steps to the application process. Importantly, before any of their investigators can submit an electronic application, each institution must register with www.Grants.gov, the government's access point to electronically find and apply for competitive grant opportunities from all federal grant-making agencies.

In addition, both the investigator and the investigator's institution will need to complete a one-time registration with the NIH Electronic Research Administration (eRA) Commons. Unlike before, only the institution's Authorized Organization Representative (AOR) for Grants.gov will be able to perform the actual application submission, and the application must be verified online by the AOR/Signing Official and the principal investigator before submission is considered complete. This will require advance planning and collaboration between investigators and their institutions.

So what are the main things investigators and institutions can do to prepare?

- Register early with Grants.gov and the eRA Commons. Investigators and institutions must do this and should not wait until the last minute. Even if the appropriate forms are complete, a late registration could cause a missed deadline.
- Become familiar with the new process. An extensive amount of helpful material on this subject can be found at http://era.nih.gov/ElectronicReceipt/, which includes the transition timeline and a comprehensive FAQ on electronic submission as well as the NIH Transition Plan.

NCI's extramural staff are ready and willing to help make this transition as seamless a process as possible. We look forward to working with you during these exciting times. ◆

Spotlight

Initiative Tackles Link Between Energy Balance, Obesity, Cancer Risk

During a trip to the grocery store, a Hispanic mother and her teenage son reach for a sleeve of corn tortillas. But, a personal shopper instructs them to choose the low-carb, whole-wheat tortillas. As they move through the store, the personal shopper offers other suggestions, usually to purchase items high in fiber and low in sugar. A few days later, the shopper provides a cooking demonstration for the mother, her son, and other Hispanic parents and their overweight teenagers. One item on the menu: a whole-wheat tortilla quesadilla stuffed with steamed veggies and jack cheese, topped with avocado and tomatoes.

This wouldn't normally be the kind of activity associated with a randomized clinical trial. But under the auspices of NCI's new Transdisciplinary Research on Energetics in Cancer (TREC) initiative, it's part of a trial to help prevent overweight Hispanic and African American teens from progressing to obesity. Led by Dr. Michael Goran and colleagues at the University of Southern California—one of four institutions awarded grants under the 5-year, $54 million initiative—the trial will test whether such nutritional counseling, with or without regular strength training, can decrease body mass index.

"We've already shown in previous work that for a very overweight population, strength training is actually a form of exercise [they] can do and succeed at pretty quickly, so it gets them hooked on the process," Dr. Goran explains.

Strength training also has been shown to have significant metabolic benefits in adults, he adds, such as improving insulin resistance and the expression of related growth factors. Both have been tapped as potential links between obesity and cancer. "We think strength training can improve metabolic health in ways that will influence risk of disease," Dr. Goran says.

The trial is indicative of the broader investigation of the link between energy balance—the combined effects of factors such as diet, physical activity, and genetics over a lifetime—and cancer risk that NCI is pursuing with the TREC initiative.

"We're looking at issues beyond just diet or exercise alone and addressing the link between energetics and cancer risk from cells to society," says Dr. Linda Nebeling, of the Behavioral Research Program in NCI's Division of Cancer Control and Population Sciences (DCCPS).

Research at the four TREC centers, she says, will test interventions, but also holistically assess how body weight, diet, exercise, environment, and other factors affect physiologic systems and intracellular pathways to see whether and how they influence carcinogenesis.

TREC also is part of an important NCI goal, stresses DCCPS director Dr. Robert Croyle.

"NCI is determined to avoid an increase in cancer deaths in the 21st century due to obesity such as the one caused by tobacco in the 20th century," he says.

The available data support that concern. Overweight and obesity are estimated to contribute to about 90,000 cancer deaths a year. Excess pounds are thought to significantly increase the risk of at least nine cancer types, including endometrial, kidney, and colon cancer. Obese men, for example, have twice the risk of developing colorectal cancer as men of normal weight. Obesity is also considered a principal culprit behind the increase in some once-rare cancers, including esophageal adenocarcinoma, which is increasing in incidence in the United States faster than any other cancer.

Obese postmenopausal women have a 50 percent higher risk of breast cancer than their nonobese counterparts, says Dr. Anne McTiernan, the principal investigator for the TREC projects being conducted through Fred Hutchison Cancer Research Center, which also serves as the coordination center for the initiative. One project will assess, in a rat model of breast cancer, how factors such as food restriction and physical activity influence the carcinogenic process. A similar project will be conducted in more than 500 postmenopausal women participating in a clinical trial funded partly through TREC.

Nearly all of the projects at the other two TREC centers—Case Western Reserve University and the University of Minnesota—will attempt to discover the biologic and physiologic mechanisms by which obesity increases cancer risk.

"There are several reasons why it is

(Spotlight continued on page 7)

Cancer Research Highlights

Immune Responses to Chemotherapy Could Lead to New Treatments

Researchers at NCI's Center for Cancer Research (CCR) have discovered a mechanism by which cancer patients' immune systems respond to chemotherapy. The new finding changes the current understanding of how the immune system responds to chemotherapy and could lead to opportunities for new treatments based on enhancing the body's immune response to the disease. The study findings appear in the November 2005 issue of *Nature Medicine*.

The researchers examined immune recovery in 26 young cancer patients with pediatric sarcomas who received cyclophosphamide-based chemotherapy, which depleted lymphocytes—creating a condition known as lymphopenia. The patients were then infused with their own lymphocytes, which had been frozen and stored before chemotherapy began. Researchers examined the effect of this treatment on the patients' immune recovery with or without recombinant interleukin-2 (IL-2), an agent that has been considered capable of restoring an immune system weakened by chemotherapy.

The researchers reported that the patients who received IL-2 showed a marked increase in suppressor T cells after chemotherapy. "This is a surprising result, since IL-2 has been considered an immune activator, not a suppressor," comments Dr. Crystal L. Mackall, head of CCR's Pediatric Oncology Branch Immunology Section and study co-author.

They also discovered that the suppressor T cells that appeared following chemotherapy and IL-2 were derived from existing T cells. "If a patient with lymphocyte depletion was also depleted of suppressor cells, the immune system would be predicted to be highly reactive—and responsive to antitumor vaccines—and therefore may be better able to fight cancer," Dr. Mackall explains. CCR is planning a new clinical trial to test this approach.

Mutations in microRNA Genes Found in Leukemia Patients

About 10 percent of patients with chronic lymphocytic leukemia (CLL) have mutations in genes for microRNAs, and some of these mutations may be involved in initiating the disease, according to a study in the October 27 *New England Journal of Medicine (NEJM)*.

microRNA genes produce small molecules that control the levels of some proteins in cells by degrading or repressing the messenger RNA of these proteins. More than 200 human microRNA genes have been identified, and recent studies have indicated that the genes may play a role in some cancers.

In the new study, Dr. Carlo Croce of the Ohio State University Comprehensive Cancer Center and his colleagues identified 13 microRNA genes that represent a unique genetic "signature" and could potentially be used to distinguish between the two types of CLL. This distinction is critical because it determines the course of therapy.

The researchers then screened the 13 microRNA genes for mutations using DNA from 75 patients with CLL. They identified mutations in 5 of 42 sequenced microRNAs in 11 patients but found no such mutations in 160 individuals without cancer.

One of the mutations affects two microRNAs, *miR15* and *miR16*; without these microRNAs, cells can become cancerous by producing too much of the protein Bcl-2. In the September 27 *Proceedings of the National Academy of Sciences*, Dr. Croce's team reported that introducing the missing microRNAs into these tumor cells in the laboratory killed the cells, suggesting a possible strategy for treating the disease.

"The experiments were pretty stunning because we could kill the cancer cells just by using *miR15* and *miR16*," says Dr. Croce. "microRNAs are so small that they can get into cells, and we might not be too far from developing microRNA-based therapies."

"The importance of microRNAs in cancer now seems clear," notes Dr. Chang-Zheng Chen of Stanford University School of Medicine, who wrote a commentary accompanying the article in *NEJM*. "The results of this study demonstrate that it may be necessary to systematically screen for mutations in all microRNA genes for other cancers."

Urine Test for Bladder Cancer Proves Accurate

A new urine test for bladder cancer successfully identifies 90 percent of cases, Italian authors report in a study

(Highlights continued on page 5)

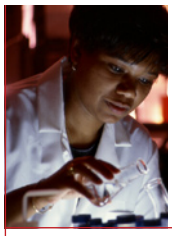
(Highlights continued from page 4)
published in the October 26 *Journal of the American Medical Association*. The test identifies high levels of the enzyme telomerase, a hallmark of most cancers.

The authors say that the invasiveness and limited sensitivity of current detection techniques, such as cystoscopy, beg the development of a better test. "The test...requires a small amount of urine, is noninvasive, inexpensive, and easy to perform.... Furthermore, it is objective, reproducible, and specific, and is not reliant on the expertise of the cytopathologist," they write. The test also identifies low-grade tumors generally missed by traditional techniques.

The study evaluated the telomerase assay in 134 men with bladder cancer diagnosed with traditional techniques and in 84 healthy men. The technicians performing the telomerase assay did not know the status of each volunteer. The researchers included only men because bladder cancer is three times more prevalent in men than in women. A previous pilot study prompted this larger follow-up.

While detecting 90 percent of cases, the test also correctly identified 88 percent of healthy volunteers. The false-positive rate was 12 percent. The test performed slightly better in men younger than 75 years of age than in older men.

While encouraged by their results, the researchers caution that the test should not be used for routine screening. Instead, they advocate testing for people at high risk—namely smokers and those who report blood in their urine. ◆



Featured Clinical Trial

Combination Therapy for Advanced Melanoma

Name of the Trial
Phase III Randomized Study of Carboplatin and Paclitaxel with versus without Sorafenib in Patients with Unresectable Stage III or Stage IV Melanoma (ECOG-E2603). See the protocol summary at http://cancer.gov/clinicaltrials/ECOG-E2603.

Principal Investigators
Dr. Keith Flaherty and Dr. Lynn Mara Schuchter, Eastern Cooperative Oncology Group

Dr. Keith Flaherty

Why Is This Trial Important?
Approximately 60,000 people in the United States will be diagnosed with melanoma in 2005. While early-stage melanoma is typically curable with surgery, melanoma that has spread (metastasized) is difficult to treat and often proves fatal.

In this clinical trial, researchers are testing chemotherapy with the drugs carboplatin and paclitaxel in combination with a new drug called sorafenib (BAY 43-9006). Sorafenib works by blocking the activity of proteins important for cell proliferation and for generating new blood vessels to tumors (angiogenesis). Many melanoma tumors carry a mutation in a gene called B-RAF, which in turn produces a protein called Raf kinase. This protein facilitates cellular processes that lead to tumor cell proliferation and survival. Sorafenib blocks the Raf kinase protein and interrupts these processes. It also inhibits a protein called vascular endothelial growth factor receptor (VEGFR), which helps tumors grow the blood vessels needed for nourishment. Researchers hope that sorafenib will weaken melanoma tumors and enhance the cell-killing effects of chemotherapy.

"No therapy has yet produced a clear survival benefit for patients with advanced melanoma," said Dr. Flaherty. "Because of the dual nature of sorafenib's activity and the results we have seen with this combination in an earlier study, we believe this therapy is the most promising so far for prolonging survival of these patients."

Who Can Join This Trial?
Researchers seek to enroll 800 patients aged 18 and over with stage III or stage IV melanoma that cannot be removed surgically. See the list of eligibility criteria at http://www.cancer.gov/clinicaltrials/ECOG-E2603.

Where Is This Trial Taking Place?
Multiple study sites in the United States are recruiting patients for this trial. See the list of study sites at http://www.cancer.gov/clinicaltrials/ECOG-E2603.

Contact Information
See the list of study contacts at http://www.cancer.gov/clinicaltrials/ECOG-E2603 or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The call is toll free and completely confidential. ◆

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

Funding Opportunities

Integration of Heterogeneous Data Sources (STTR [R41/R42])

PA-06-010

Application Receipt Dates: *New, competing continuation, revised, supplemental applications:* Dec. 1, 2005; Apr. 1, Aug. 1, and Dec. 1, 2006; Apr. 1, Aug. 1, and Dec. 1, 2007. *AIDS and AIDS-Related Applications (New, competing continuation, revised, and supplemental):* Jan. 2, May 1, and Sept. 1, 2006; Jan. 2, May 1, and Sept. 1, 2007.

This is a renewal of PA-05-003. This funding opportunity will use the R41 and R42 award mechanisms. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3273. Inquiries: Dr. Margaret Grabb—mgrabb@mail.nih.gov

Integration of Heterogeneous Data Sources (SBIR [R43/R44])

PA-06-011

Application Receipt Date: *New, competing continuation, revised, supplemental applications:* Dec. 1, 2005; Apr. 1, Aug. 1, and Dec. 1, 2006; Apr. 1, Aug. 1, and Dec. 1, 2007. *AIDS and AIDS-Related Applications (New, competing continuation, revised, and supplemental):* Jan. 2, May 1, and Sept. 1, 2006; Jan. 2, May 1, and Sept. 1, 2007.

This is a renewal of PA-05-003. This funding opportunity will use the R43 and R44 award mechanisms. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3274. Inquiries: Dr. Jennifer Couch—couchj@mail.nih.gov

Manufacturing Processes of Medical, Dental, and Biological Technologies (STTR [R41/R42])

PA-06-012

Application Receipt Dates: *New, competing continuation, revised, supplemental applications:* Dec. 1, 2005; Apr. 1, Aug. 1, and Dec. 1, 2006; Apr. 1, Aug. 1, and Dec. 1, 2007; Apr. 1, and Aug. 1, 2008. *AIDS and AIDS-Related Applications (New, competing continuation, revised, and supplemental):* Jan. 2, May 1, and Sept. 1, 2006; Jan. 2, May 1, and Sept. 1, 2007; Jan. 2, May 1, and Sept. 1, 2008.

This is a renewal of PA-04-161. This funding opportunity will use the R41 and R42 award mechanisms. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3275. Inquiries: Dr. Greg Downing—downingg@mail.nih.gov

Manufacturing Processes of Medical, Dental, and Biological Technologies (SBIR [R43/R44])

PA-06-013

Application Receipt Dates: *New, competing continuation, revised, supplemental applications:* Dec. 1, 2005; Apr. 1, Aug. 1, and Dec. 1, 2006; Apr. 1, Aug. 1, and Dec. 1, 2007; Apr. 1 and Aug. 1, 2008. *AIDS and AIDS-Related Applications (New, competing continuation, revised, and supplemental):* Jan. 2, May 1, and Sept. 1, 2006; Jan. 2, May 1, and Sept. 1, 2007; Jan. 2, May 1, and Sept. 1, 2008.

This is a renewal of PA-04-161. This funding opportunity will use the R43 and R44 award mechanisms. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3276. Inquiries: Dr. Greg Downing—downingg@mail.nih.gov

NIH Support for Conferences and Scientific Meetings (R13/U13)

PA-06-041

Application Receipt Dates: *New, competing continuation, revised, and supplemental applications:* Dec. 15, 2005; Apr. 15, Aug. 15, and Dec. 15, 2006; Apr. 15, Aug. 15, and Dec. 15, 2007; Apr. 15 and Aug. 15, 2008. *AIDS and AIDS-Related Applications (New, competing continuation, revised, and supplemental):* Jan. 2, May 1, and Sept. 1, 2006; Jan. 2, May 1, and Sept. 1, 2007; Jan. 2, May 1, and Sept. 1, 2008.

This is a renewal of PAR-03-176. This funding opportunity will use the R13 and U13 award mechanisms. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3271. Inquiries: David Contois—ncirefof@dea.nci.nih.gov

Dissemination and Implementation Research in Health

PAR-06-039

Letter of Intent Receipt Dates: Dec. 26, 2005; Aug. 22, 2006; Apr. 24, 2007; Dec. 26, 2007; Aug. 25, 2008; Apr. 22, 2009.

Application Receipt Dates: *New, competing continuation, revised, supplemental applications:* Jan. 24 and Sept. 22, 2006; May 24, 2007; Jan. 24 and Sept. 24, 2008; May 22, 2009. *AIDS and AIDS-Related Applications (New, competing continuation, revised, and supplemental):* May 1, 2006; Jan. 2 and Sept. 1, 2007; May 1, 2008; Jan. 2 and Sept. 1, 2009.

This is a renewal of PA-02-131. This funding opportunity will use the R01 award mechanism. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3280. Inquiries: Dr. Jon F. Kerner—kernerj@mail.nih.gov ◆

Notes

President's Cancer Panel Meets to Discuss Recommendations

The President's Cancer Panel held two meetings in Washington, D.C., on October 24 and 25 to follow up on selected recommendations from its 2004–2005 annual report, *Translating Research Into Cancer Care: Delivering on the Promise,* which identified and discussed existing barriers to translating research into clinical practice. Last week's meetings focused on team science and the culture of research, workforce infrastructure, dissemination, and community participation. To catalyze action in these areas, the Panel assembled key stakeholders and decision makers to assess progress, identify critical next steps, and encourage collaboration. The results of these meetings will be published in the 2005–2006 annual report of the President's Cancer Panel, expected to be released in June 2006. For additional information about the Panel, go to http://pcp.cancer.gov or call 301-451-9399.

NCI Staff Honored

On October 26, NCI staff were honored for their outstanding contributions to the institute and to cancer research at the 2005 NCI Director's Awards Ceremony. NCI Director Dr. Andrew C. von Eschenbach presided over the ceremony to thank the staff for their exceptional work.

Among those recognized at the ceremony were the recipients of the NCI Director's Gold Star Award: Dr. Lee J. Helman for his management of the Clinical Research Program and willingness to assume the duties of Acting Director, Scientific Research; Sharon Miller for her innovative work in the Research Contracts Branch; and Dr. Edward Trimble for his efforts on international partnerships to reduce the burden of gynecologic cancer around the world.

In his remarks, Dr. von Eschenbach emphasized that, because of the dedication and hard work of the staff, NCI is making progress toward its goal of eliminating the suffering and death due to cancer.

A full list of this year's recipients is available at http://www.cancer.gov/directors-awards.

ABC News Features Lung Cancer and Smoking in November

During November, ABC-TV's *World News Tonight* will launch "Quit to Live: Fighting Lung Cancer," a series of reports on smoking cessation and lung cancer prevention. The reports, airing three to five times each week, will highlight smoking cessation, public policy on smoking and tobacco, and recent medical advances on lung cancer treatment and prevention.

The network is partnering with NCI, the Centers for Disease Control and Prevention, and the North American Quitline Consortium to provide resources to help people quit smoking. ABC will direct viewers to the national toll-free quitline phone number (800-QUIT NOW, 800-784-8669), which automatically connects callers to their state-based quitlines, and to the smokefree.gov Web site for additional resources on smoking cessation and lung cancer. The network Web site, ABCNEWS.com, will also devote a portion of the site to the series. ◆

CCR Grand Rounds

November 8: Dr. Jeffrey M. Trent, President and Scientific Director, Translational Genomics Research Institute; "Towards Systems Medicine: Applications in Bio-Defense"

November 15: Dr. Mark Levine, Chief, Molecular and Clinical Nutrition Section, Digestive Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases; "Ascorbic Acid in Humans: Tight Control and Unexpected Consequences for Cancer Therapy"

CCR Grand Rounds are held 8:30 to 9:30 a.m. at the NIH campus in Bethesda, Md., in the Clinical Center's Lipsett Amphitheater. ◆

(Spotlight continued from page 3)

important to learn the mechanisms," Dr. McTiernan says. New insights into the mechanisms could influence recommended prevention measures, such as whether exercise alone is sufficient to reduce risk or if being lean is also required.

And learning more about the mechanisms may allow researchers to test new preventive interventions or treatments. "For example," Dr. McTiernan continues, "if we learn that insulin resistance and hyperinsulinemia explain the association between obesity, being sedentary, and cancer risk, then perhaps we could treat patients with metformin, which reduces insulin resistance, either as a chemopreventive agent or as an adjuvant treatment for cancer patients."

By Carmen Phillips

Community Update

Number of Clinical Trial Registrations Increases

In an encouraging sign for both oncologists and patients, the number of open clinical trials listed in U.S. and international clinical trial registries is on the rise. This trend reflects several factors, including an effort by the editors of the world's leading medical journals to broaden the registries' offerings.

Giving physicians and patients a more complete picture of the trials that are currently open to patient enrollment potentially increases the available treatment options they can consider. Because some registries also include information about closed trials, increasing the completeness of those registries makes them more valuable to researchers who may be planning future trials or want to know more about trials that have been conducted in the past.

The availability of a publicly accessible, comprehensive clinical trial registry is a relatively recent event. NCI's Physician Data Query (PDQ®) clinical trial registry, which was started in 1977, is perhaps the world's oldest continuously operating registry, but PDQ focuses only on cancer trials and registration in PDQ is largely voluntary.

Trial registration became more comprehensive and compulsory with the passage of the 1997 FDA Modernization Act (FDAMA). FDAMA requires the registration of all phase II or higher trials conducted under an FDA Investigational New Drug application in which the efficacy of a treatment for a serious or life-threatening condition is being tested. FDAMA also led to the creation of ClinicalTrials.gov (http://clinicaltrials.gov) as the central clinical trial registry for the United States. ClinicalTrials.gov is managed by the U.S. National Library of Medicine at NIH.

Analyses conducted by FDA in 2002 and 2004 revealed that compliance with FDAMA's trial registration requirements was less than complete. For example, during the 3-month period from May through July 2004, FDA found that NIH had registered 95 percent of the required trials it funds in ClinicalTrials.gov. In contrast, only 66 percent of the required trials sponsored by the pharmaceutical industry had been registered.

In 2004, the International Committee of Medical Journal Editors issued a directive: Beginning on July 1, 2005, any trial that is not registered in ClinicalTrials.gov or another acceptable registry before the start of patient enrollment will not be considered for publication in a peer-reviewed journal. Ongoing trials were to be registered no later than September 13, 2005. The result has been just what the editors hoped for: a significant increase in the number of registered trials.

"The number of cancer trials submitted for registration in PDQ and ClinicalTrials.gov has literally exploded, climbing approximately tenfold between April and September of this year," said Dr. Richard Manrow, associate director of NCI's Office of Cancer Content Management, which maintains PDQ.

In an effort to keep the cancer trials listed in PDQ and ClinicalTrials.gov as synchronous as possible, the two registries regularly share trial information. ClinicalTrials.gov also prefers one source of submission for the clinical trials sponsored by each NIH institute or center. For NCI, PDQ is that source. Trials in PDQ are also listed on NCI's Web site, www.cancer.gov. ◆

Featured Meetings and Events

A calendar of scientific meetings and events sponsored by the National Institutes of Health is available at http://calendar.nih.gov/cgi-bin/calendar. ◆

The *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads the national effort to eliminate the suffering and death due to cancer. Through basic, clinical, and population-based biomedical research and training, NCI conducts and supports research that will lead to a future in which we can identify the environmental and genetic causes of cancer, prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://www.cancer.gov.

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