NATIONAL CANCER INSTITUTE

NCI Cancer Bulletin

Celebrating Excellence in Cancer Research

July 10, 2007
Volume 4 | Number 21

In this issue:

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

http://www.cancer.gov

NCI Research Grant Payline Higher Than Anticipated

The R01 payline for fiscal year (FY) 2007 will be higher than expected, NCI Director Dr. John Niederhuber has announced.

Speaking to NCI's Board of Scientific Advisors (BSA) on June 28, Dr. Niederhuber explained that the end-of-year payline for R01 grants would be the 15th percentile. At the beginning of the year, the payline estimate was the 12th percentile, the same level at which NCI finished in 2006.

The payline for the R01 program for first-time investigators will be the 21st percentile, Dr. Niederhuber reported, which also is higher than what was anticipated at the beginning of the fiscal year.

The payline represents the cutoff above which an application will be funded, as determined by its scientific review and priority scores. The payline is established based on the number of expected applications and the available funds designated for competing grants, meaning that it can change throughout the year as NCI can more accurately assess the number of incoming applications and available resources.

(continued on page 2)

Director's Update

Guest Director's Update by Drs. James Doroshow and Ernest Hawk

Moving Ahead with Translational Research

Dr. James H. Doroshow (left), Director, Division of Cancer Treatment and Diagnosis; Dr. Ernest T. Hawk (right), Director, Office of Centers, Training and Resources

The recent release of the final report of the Translational Research Working Group (TRWG) and its approval by the National Cancer Advisory Board, marks an important milestone for NCI. After 2 years of work, we're hopeful that TRWG's recommendations, along with activities already taking place as a result of recommendations made 2 years ago by the Clinical Trials Working Group (CTWG), will lead to more rapid progress in translating important research findings into new, effective interventions.

TRWG was led by co-chairs Drs. Ernest Hawk of NCI's Office of Centers, Training and Resources; Lynn Matrisian of Vanderbilt University; and William Nelson of Johns Hopkins University. It's important to stress that the TRWG report—developed by

(continued on page 2)

(Grant Payline continued from page 1)
"In reality, we'll be funding quite above the 15th percentile after exceptions," Dr. Niederhuber said. "I don't think any of us a year ago felt we had a chance of reaching this [level]."

R01 competing grants funded as "exceptions" are those with a priority ranking that put them beyond the final payline, but were judged to be deserving of support after all other grants that met the payline were funded. Those grants are paid from a pool of competing grant funds that are set aside at the beginning of the fiscal year to fund exceptions. For 2007, that pool represented approximately 20 percent of the competing grant budget.

Dr. Niederhuber praised NCI's senior leadership team for their efforts to review programs across the institute's divisions and centers, setting the stage for the higher payline. That process, he continued, involved regular meetings of senior leaders to review programs and make decisions about "what we could slow down, what we could phase out, and really prioritize our best science, our best investigators."

Overall, NCI's current research project grant portfolio, excluding small business grants, includes well over 5,000 awarded grants. NCI received nearly 6,600 competing grant applications in FY 2007, which represents a flattening of the steady increase in grant applications that followed the doubling of NIH's budget.

"I think that should be expected as a new equilibrium gets established," Dr. Niederhuber acknowledged.

BSA Chair Dr. Robert Young, of Fox Chase Cancer Center, was concerned that, because the negative impact of budget constraints on research grants was not as great as had been expected, members of Congress might not understand the extent to which "programs aren't being funded, investigators aren't being funded."

Dr. Niederhuber responded that he and NIH Director Dr. Elias Zerhouni, in their appearances before Congress, have stressed the impact of flat budgets on research funded by NCI and NIH, and that "there is a new level of understanding at present" among legislators.

That's reflected, he continued, in the budget increases for NIH and NCI in House and Senate legislation that goes beyond the administration's budget requests, and the targets for overall grants and grants to new investigators that are included in the language accompanying those bills. ◆

By Carmen Phillips

(Director's Update continued from page 1)

some of the most well-respected translational and clinical research experts within and outside of NCI, with additional input from literally hundreds of scientists and members of the cancer community—focuses on "early translation," that is, the work done to move basic research discoveries into phase I and II clinical trials. The recommendations are a natural complement to several CTWG-related activities, which are focused on "late translation," primarily phase III clinical trials.

At their core, the TRWG recommendations are intended to help define and facilitate the appropriate "handoffs" so that fundamental discoveries—such as those related to potential new imaging-based risk assessment methods, new immunotherapy approaches, or lifestyle interventions, among others—can be efficiently evaluated in early-phase clinical trials. That includes activities such as developing project management plans, establishing access to core services such as imaging libraries and well-annotated biospecimens, and developing intellectual property agreements with industry or other third parties.

The recommendations are not intended to replace or impinge upon discovery research. Quite the contrary, they are intended to create a coordinated and collaborative national enterprise focused on the distinctive needs of research that follow from promising basic discoveries.

In total, TRWG developed 15 recommendations—with suggested plans for implementing them—categorized into three main themes: coordinated management, tailored funding programs, and operational effectiveness.

Under coordinated management, for example, are specific recommendations for establishing an organizational approach to managing the diverse early translational research portfolio that exists throughout NCI's divisions and centers, and a transparent, inclusive prioritization process to identify the most promising early translational research opportunities.

Several tailored funding programs are recommended, including the establishment of special programs to advance specific projects deemed especially promising and to support collaborations between extramural investigators and industry. The former program, called the Special Translational Research Acceleration Project (STRAP), would support an integrated research and development program designed to achieve a specific clinical or product development goal.

(continued on page 6)

Cancer Research Highlights

Genetic Markers of Colorectal Cancer Risk Identified

Three separate genome-wide association studies published online July 8 in *Nature Genetics* have identified a locus on chromosome 8 (8q24) in which several single nucleotide polymorphisms (SNPs)—changes in a single nucleotide of DNA—confer significantly increased risk of colorectal cancer (CRC). This locus has been implicated in previously published research as playing a role in prostate cancer risk.

The first study, led by a Canadian research team, used a four-stage process to identify and validate SNPs associated with CRC risk. The first stage evaluated three different sets of SNPs, containing more than 50,000 single nucleotide changes, in 1,257 people with colorectal cancer and 1,336 controls from Ottawa. The second stage tested 1,143 potential markers of risk identified in stage 1 in two different case-control populations: one from Seattle, Washington, and one from Newfoundland. The third stage tested 76 markers replicated in the previous 3 populations in a case-control population from Scotland with early-onset CRC. The nine markers further validated in this population were then tested in a fourth stage in a second, independent case-control series from Scotland.

Two of the risk associations confirmed in stage 3 were replicated in stage 4, and the investigators compared these loci, 8q24 and 9p24, with results from several European studies, leading to validation of two SNPs in 8q24 that confer significantly increased risk of CRC. This multistep replication process is in keeping with recent guidelines published in *Nature* by the NCI-NHGRI Working Group on Replication in Association Studies.

The second study, from the University of Southern California, directly examined 6 variants previously identified as genetic markers of prostate cancer risk in 1,124 patients with invasive CRC and 4,573 controls, all taken from a multiethnic study population including people of African American, Japanese American, Native Hawaiian, Latino, and European descent.

One variant on 8q24 identified as significantly associated with CRC risk in this group was then tested in 683 additional CRC cases and 938 controls in 2 substudies of patients of Japanese American and European descent. The variant was replicated as a marker of CRC risk in one study but not the other; however, the marker remained significantly associated with CRC risk in a pooled analysis of all three studies.

The third study, from the United Kingdom, successfully genotyped more than 550,000 SNPs in 930 people with familial CRC and 960 controls, designated as panel A in the study. They also identified SNPs at 8q24 as being associated with CRC risk. The investigators then tested the SNP most strongly associated with CRC risk in 3 different case-control panels (panel B comprised 4,361 patients with CRC and 3,752 controls; panel C comprised 1,901 people with CRC and 1,079 controls; and panel D comprised 1,072 people with CRC and 415 controls). Only patients in panel D had a familial history of CRC.

Pooled data from the original set of patients and the three validation panels "provided unequivocal evidence for a relationship between [the SNP] and risk of CRC," stated the authors. Further analysis of the data provided evidence that the SNP may also be associated with an elevated risk of developing adenomas—noncancerous tumors—in the colon or rectum. This observation led the investigators to suggest that the locus on chromosome 8 may be involved in tumor initiation rather than progression.

Genetic Variations Linked to Increased Prostate Cancer and Decreased Diabetes Risks

A genetic study in Icelandic men with prostate cancer and several healthy control groups uncovered two genetic variations associated with moderate increase in the risk for prostate cancer and, in the case of one variation, a simultaneously protective effect against type 2 diabetes (T2D), according to results published online July 1 in *Nature Genetics*.

The study involved a genome-wide association scan to search for gene sequence variants conferring risk of prostate cancer using 1,501 Icelandic men with the disease and 11,290 control subjects. Follow-up studies with three additional case-control groups confirmed an association of two variants on chromosome 17 with prostate cancer. One of the variants is in the TCF2 gene, which the scientists demonstrated also confers protection against T2D.

(continued on page 4)

(Highlights continued from page 3)
The two genetic variations pose only relatively small increased risks in individuals for prostate cancer. However, because the variations are so common, they have an estimated joint population-attributable risk (PAR) of 36 percent for the disease, "which is substantial from a public health viewpoint," the researchers noted.

The scientists were "most intrigued" by the counterbalancing of risks for prostate cancer and T2D with the TCF2 variation. "The discovery of a sequence variant in the TCF2 gene that accounts for at least part of the inverse relationship between these two diseases provides a step toward understanding the complex biochemical checks and balances that result from the pleiotropic [multiple effects] impact of singular genetic variants," they commented. Previous explanations of the well-established inverse relationship between prostate cancer and T2D have centered on the impact of the metabolic and hormonal environment of diabetic men.

Second HPV Vaccine Shows Early Positive Results

Positive interim results for a candidate vaccine to prevent infections by human papillomavirus (HPV) types 16 and 18 were published online in *The Lancet* June 28. The vaccine Cervarix was 90 percent effective in preventing grade 2 or 3 cervical intraepithelial neoplasias ($CIN2^+$) that contained DNA from either virus type.

The results come from a large international trial of 18,644 women aged 15–25 sponsored by the drug's manufacturer, GlaxoSmithKline Biologicals. The trial design called for analysis of early results after 23 cases of $CIN2^+$ were detected. Two of these cases were among the 9,258 women receiving the vaccine, and 21 were among the 9,267 controls who received a hepatitis A vaccine. The mean follow-up time was 14.8 months.

In an editorial, Drs. Jessica A. Kahn of the University of Cincinnati and Robert D. Burk of the Albert Einstein College of Medicine wrote, "These interim data are encouraging." But they noted that the paper does not provide information about the public health impact of vaccination "in real world settings" because the report does not provide estimates of the reduction in overall rates of $CIN2^+$. They stress that vaccination of young adolescents is likely to have the greatest public health benefit, but that continued screening will still be required after vaccination.

A separate phase III trial testing Cervarix, cosponsored by NCI with support from the NIH Office for Research on Women's Health and the Costa Rica Ministry of Health, is now underway in Costa Rica. This trial should provide additional information about the public health impact and efficacy of the vaccine.

International Programs Seek Applications

NCI's Office of International Affairs (OIA) is seeking applications to two projects.

The U.S.-Japan Cooperative Cancer Research Program (USJCCRP) began in 1974 and is coordinated by NCI and the Japan Society for the Promotion of Science. With the assistance of OIA, USJCCRP is establishing an annual workshop in basic, clinical, or epidemiological/behavioral science to support cancer research and clinical care.

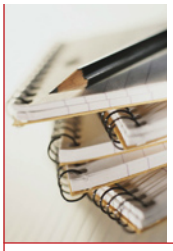
The workshop venue will alternate between Japan and the U.S. For 2007–2008, USJCCRP will provide support for a basic science cancer workshop. Participation will be limited to 20 attendees from each country, allowing for a small number of participants from other countries. Requests for proposals (RFPs) will be conducted by an open call each June, with an application deadline in September, selection in October, and the workshop held between November and March.

The RFP for the 2007–2008 meeting was released on June 29. Individuals with the skills, knowledge, and resources to plan and conduct the proposed workshop are invited to develop an application for support. The first workshop can focus on any area of basic science. However, USJCCRP is particularly interested in receiving proposals in 1) regulation angiogenesis and lymphangiogenesis in cancer cells, 2) nanotechnology applications in cell imaging, diagnosis, and treatment, and 3) genomics and proteomics of cancer cells. More information and an application form can be found at http://www.cancer.gov/oia/US-JAPAN-CCRP.

The Ireland-Northern Ireland-NCI Cancer Consortium recently announced a call for applications in its Joint Research Projects in Cancer 2007.

This project aims to develop strong and sustainable relationships between cancer researchers and institutions in Ireland and the U.S. by supporting a shared postdoctoral researcher working on a research project of mutual interest. The project is awarded on a full-time basis over 3 years and is open to cancer researchers working on the island of Ireland or in the NCI intramural or extramural program.

The closing date for applications is 5 p.m. on August 17. Full details and application guidelines can be found at http://www.allirelandnci.com/fellowships_and_training/joint_research_fellowships.shtml. ◆



Special Report

The Mathematics of Cancer

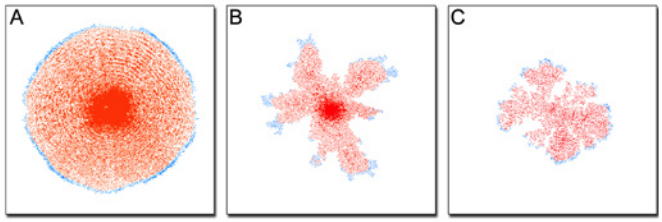
To most people, soil nematodes—microscopic parasites critical to the breakdown of organic matter in soil—would appear to have no relation to cancer research. But Drs. Vito Quaranta and Alexander "Sandy" Anderson might beg to differ. A collaboration between the two to develop complex mathematical models that drive computer simulations of tumor invasion began with adaptation of a model developed by Dr. Anderson designed to predict soil nematode migration.

"Mathematicians have been doing cancer modeling for 50 years," says Dr. Quaranta, director of the Vanderbilt University Integrative Cancer Biology Center. But it's only in the current decade, he adds, that cancer biologists have connected with a new generation of mathematicians like Dr. Anderson, from the University of Dundee in Scotland, to develop mathematical models intended to capture and integrate the complex factors involved in cancer development, progression, and metastasis.

This *in silico* movement in cancer research truly is in its nascent stages. Only a handful of laboratory and clinical cancer researchers are seriously collaborating with biological mathematicians, and *in silico* studies are only now breaching the upper echelons of oncology journals.

But according to Dr. Daniel Gallahan, head of NCI's Integrative Cancer Biology Program, which is supporting the development of *in silico* cancer research, the time and need for it have arrived.

Cancer researchers have done a remarkable job of discovering and characterizing the important biological and molecular parts of the cancer process, Dr. Gallahan stresses, including genes, intracellular signaling pathways, and, more recently, microRNA.



Images courtesy of Alexander R.A. Anderson

Results from an in silico *model of tumor invasion after approximately 3 months of growth. The tumor morphology switches from round in a mild microenvironment (A) to "fingered" in harsh microenvironments (B, C). The blue cells in B and C are the most aggressive cells (red cells are dead from necrosis).*

"But once you start trying to assemble all of those pieces, that's when it becomes daunting," Dr. Gallahan says. "That's when it becomes a real challenge for human understanding and intuitiveness to look at a situation and extrapolate what is actually happening."

Computational modeling, he continues, can help to develop a fuller picture of cancer as a complex biological system, and help better assess what factors within and around a given tumor decide its fate. Evidence to support that belief is mounting. *In silico* studies published over the past few years, for instance, have highlighted the tumor microenvironment's potentially critical influence on tumors.

These studies include an October 2005 study published in *Clinical Cancer Research* by Dr. Vittorio Cristini and a team from the University of California, Irvine, that described computational simulations of brain tumors suggesting that a tumor's aggressiveness, as indicated by its shape, or morphology, was greatly influenced by factors such as the amount of oxygen in its environment. Sufficiently oxygenated microenvironments led to spherically shaped, localized tumors, while oxygen-choked surroundings, including those created by simulated anti-angiogenic treatment, generated tumors that snaked out into nearby tissue.

And in December 2006, Drs. Quaranta and Anderson, building on a paper published in March 2005 in a mathematics journal, published computational simulations in *Cell* predicting that a harsh tumor microenvironment driven by tissue heterogeneity or lack of oxygen availability caused more aggressive cells to dominate the tumor and form finger-like protrusions that invade adjacent tissue.

The implication, Dr. Quaranta notes, is that malignant cells are most likely to develop in certain microenvironments and that altering the microenvironment may make tumor cells less invasive.

Importantly, Dr. Cristini explains, published findings from lab experiments using brain tumor cell lines have offered some validation of his team's *in silico* results. He also has received less formal validation from some neuro-oncology researchers.

(continued on page 6)

(Special Report continued from page 5)

"These neurosurgeons are telling me that that's what they have seen over and over in their patients," he recalls. "The model predicted those [tumor shapes] and it did not use any of their data."

Now at the University of Texas School of Health Information Sciences at Houston, Dr. Cristini has begun collaborating with researchers at the University of Texas M.D. Anderson Cancer Center. Using one of the most powerful supercomputers in the world at the Texas Advanced Computing Center, they will run intensive simulations to do things like predict tumor responses to various microenvironmental conditions, including those caused by therapies, and use the simulation results to develop and test new treatment strategies.

Generally speaking, the mathematical models that drive these computational simulations use the available data—both previously published and new experimental data—to populate the "parameters" of the activities they are trying to simulate. This includes, for example, measurements over time of gene and protein activity within cells or of important cell behaviors, such as adhesion to other cells.

Although some models are devoted to whole tumor simulations, Dr. Gallahan notes, a number of models are focused strictly on intracellular signaling networks that control all cellular processes.

Dr. Thomas Deisboeck's computational modeling work, which also has involved brain tumors, represents a blended approach, with a particular focus on how the intracellular signaling pathway directed by the epidermal growth factor receptor (EGFR) influences tumor development.

Dr. Deisboeck, the principal investigator of the Center for the Development of a Virtual Tumor—housed at Massachusetts General Hospital, but composed of researchers from around the world—believes computational modeling is beginning to make important inroads.

"We're...generating exciting hypotheses that can be experimentally tackled and getting data back from those experiments that help to fine-tune and improve our models," he says.

For example, Dr. Deisboeck's team recently collaborated with researchers from the Arizona-based Translational Genomics Research Institute to conduct experiments in cell lines that followed from their *in silico* simulations. Those simulations assessed EGFR's role in whether brain tumor cells proliferate or migrate (it's believed they tend to do only one or the other at a given time), and the impact those cellular "decisions" have on tumor development. The results (soon to be submitted for publication), he says, "validate our *in silico* predictions quite nicely."

Such experimental validation is critical to expanding the *in silico* field and, eventually, integrating computational models into traditional wet lab experiments, clinical trials, and even clinical care, says Dr. Gallahan.

"It's still far off, but we can envision a time when we can establish a specific model for a specific cancer, plug in an individual's own parameters, and see…how an individual will respond to treatment before we even try it, based on a sophisticated model of the cancer process," he says. "The key will be achieving that level of sophistication." ◆

By Carmen Phillips

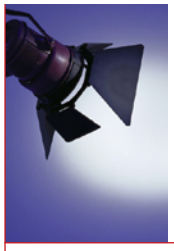
(Director's Update continued from page 2)

Recommendations that fall under operational effectiveness include building a project management system that would involve staff at NCI and investigators' institutions to help oversee projects and develop enhanced approaches for negotiating with industry over issues related to intellectual property and access to investigational agents.

TRWG sees these recommendations as evolutionary, not revolutionary. This is particularly evident in how some of the recommendations dovetail with ongoing CTWG-related activities. One excellent example is the establishment of a subcommittee of the Clinical Trials Advisory Committee that will focus on translational research.

We already have received excellent feedback on the TRWG recommendations. Several foundations, for instance, have indicated they would be interested in helping to support the STRAP program, and industry representatives who met with TRWG during its deliberations were very enthusiastic about supporting and expanding collaborative efforts and working through logistic and legal hurdles to early translational work.

Decisions about how NCI will address the TRWG recommendations must still be made. But we're hopeful that, combined with ongoing activities spurred by the CTWG recommendations, these recommendations will lead to measurable and meaningful progress in getting new, more effective risk assessment strategies and interventions to those at risk and those diagnosed with cancer far more quickly than has been possible in the past. ◆



Spotlight

An Update on Cancer Vaccines—New Paradigms

Many deadly infectious diseases that were capable of killing millions are now tamed because of vaccines, which stimulate the immune system to recognize and attack pathogens before they can cause disease. Soon it may be the same for cancer.

The first major step toward this goal came recently when the FDA approved and Merck began marketing Gardasil for the prevention of human papillomavirus (HPV) infection, a major cause of cervical cancer. HPV vaccines represent one type of cancer vaccine, which may prevent cancer before it occurs, while therapeutic cancer vaccines may help turn a patient's immune system against already-existing cancer cells.

"There is an enormous amount of progress being made in the field of cancer vaccines," says Dr. Jeffrey Schlom, chief of NCI's Laboratory of Tumor Immunology and Biology, in the Center for Cancer Research (CCR).

However, he points out, therapeutic cancer vaccines—those that attack solid tumors, rather than preventing conditions that cause cancer—will most likely be used to treat early-stage disease or metastatic disease where the overall tumor burden is low.

"There are limits to what vaccines can do," Dr. Schlom says. This is because with a large tumor mass, the lymphocytes activated by the vaccine must pit themselves against a large number of cancer cells, where the odds are unfavorable. "A good analogy is hand-to-hand combat," he explains. Research in the last few years has indicated that vaccines may be most effective following surgery to remove the bulk of the cancer and when used in conjunction with other standard treatments.

The strategy may be particularly effective if a vaccine is administered simultaneously with chemotherapy or radiation, which seems to make tumors more vulnerable to detection and attack, as well as with vaccine boosters and cytokines to augment the immune response. Dr. Schlom described this phenomenon in a review article in the July 1 issue of *Clinical Cancer Research*, where he contrasted the dynamic immune processes triggered by vaccines with passive therapies such as drugs or radiation.

"We have preliminary evidence that therapeutic cancer vaccines can provide patient benefit."

Randomized phase II trials testing these vaccine strategies have shown an increase in median survival of 4 to 8 months over controls, with overall survival as long as 3 to 5 years at the time the data were published. Survival could be much longer, as many of these trials continue.

Dr. James Gulley of NCI's CCR is leading five phase I and II clinical vaccine trials at the NIH Clinical Research Center to test immunostimulant additives, antibodies, and viral vectors that produce tumor-associated antigens, as well as the effect of vaccines injected into tumors.

"With vaccines alone we have seen clinical responses in patients with prostate, ovarian, and breast cancer. The addition of an anti-CTLA-4 antibody to a vaccine appears to further improve the clinical benefit in a proportion of patients with metastatic prostate cancer," he notes.

Dr. Philip Arlen of CCR collaborates with Dr. Gulley and is leading two phase II trials at the Clinical Research Center to test the combination of hormones or low-dose, single-agent chemotherapy (which is less toxic than standard multidrug regimens) with vaccines in patients with prostate or breast carcinomas. Preliminary results of these studies show that the vaccine treatments are well tolerated, and some patients have received treatment for more than a year without disease progression.

"We have preliminary evidence that therapeutic cancer vaccines can provide patient benefit," Dr. Arlen says. "Here at NCI, we're able to go further with small, cutting-edge studies that address how we should utilize them—in what populations, for example, and with what combination of treatments." He is currently planning clinical trials to test hormone therapy and allogeneic stem cell transplantation as part of the vaccine treatment strategy.

More than a dozen vaccines are in or nearing phase III trials to refine their use, including dosing, booster schedules, and the site of vaccine administration. But for now, the FDA has not approved any therapeutic cancer vaccines.

"I'd like to think that cancer vaccines

(continued on page 8)

(Spotlight continued from page 7)

will be approved by the FDA within the next 5 years," says Dr. Schlom, "perhaps one or two within the next couple of years. But we can't say for sure because we need a paradigm shift, first, in the way that vaccine trials are designed and how they are evaluated."

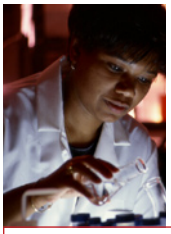
Dr. Schlom points out the case of Provenge, a vaccine for advanced prostate cancer that was reviewed by the FDA this past spring, showing an increase in patient survival but not a reduction in tumor progression, which was the study's primary endpoint. "Most likely, this was because the vaccine was able to keep the disease in check, but not able to reduce the overall tumor load," he says.

Ethically, patients must be offered treatments with demonstrated benefit before they are offered experimental ones. So a patient who enters a therapeutic vaccine trial has likely already gone through surgery, disease metastasis, and then one or more rounds of adjuvant treatment, including chemotherapy, radiation, or hormone treatments. "By this time, many patients have large tumor masses again, which is not the ideal setting for a vaccine trial," says Dr. Schlom.

"We're just getting to the point where we're able to think about doing these studies in combination with or versus standard-of-care therapy," says Dr. Schlom, noting that NCI and FDA held a conference at NIH last February to discuss how vaccines and other immunotherapies can best be brought through development to licensure. "But for advanced disease," he says, "other immunotherapies will likely be more useful."

For more information about cancer vaccines, go to: http://www.cancer.gov/clinicaltrials/learning/cancervaccines. ◆

By Brittany Moya del Pino

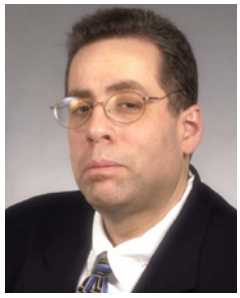


Featured Clinical Trial

Biological Therapy for Advanced Kidney Cancer or Melanoma

Name of the Trial
Phase I Study of Human Anti-TGF-Beta Monoclonal Antibody GC1008 in Patients with Unresectable Locally Advanced or Metastatic Renal Cell Carcinoma or Malignant Melanoma (NCI-06-C-0200). See the protocol summary at http://cancer.gov/clinicaltrials/NCI-06-C-0200.

Principal Investigator
Dr. John C. Morris, NCI Center for Cancer Research



Dr. John C. Morris

Why This Trial Is Important
Many cellular proteins have been identified that play a role in the development and progression of cancer. These proteins initiate or transmit signals that help cancer cells 1) grow and evade the process of programmed cell death (apoptosis), 2) stimulate the growth of new blood vessels (angiogenesis) to ensure tumors have an adequate supply of nutrients, 3) break away from the initial tumor site and spread to other locations in the body (metastasize), or 4) block the body's immune response against tumors.

One of these proteins is called transforming growth factor beta (TGF-β), which is overproduced by many types of cancer cells. Therefore, researchers are interested in developing new drugs or biological agents that can bind to and possibly block the activity of this protein.

This trial will assess the safety and tolerability of a new biological agent called GC1008 in patients with advanced kidney cancer or melanoma. GC1008 is a monoclonal antibody specifically designed to target TGF-β and block its activity.

"TGF-β is known to play a major role in the progression of kidney cancer and melanoma, two types of cancer that are notoriously difficult to treat when advanced," said Dr. Morris. "We hope that treatment with GC1008 suppresses TGF-β in these tumors and leads to a delay in cancer progression or even causes tumors to shrink."

Who Can Join This Trial
Researchers will enroll 36 patients aged 18 or over with inoperable locally advanced or metastatic renal cell carcinoma or melanoma that has not responded to previous treatment. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/NCI-06-C-0200.

Study Sites and Contact Information
Study sites in the United States are recruiting patients for this trial. See the list of study sites at http://cancer.gov/clinicaltrials/NCI-06-C-0200 or call the NCI 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://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

NCI Cancer Bulletin Wins Award

The *NCI Cancer Bulletin* received a Gold 2007 Hermes Creative Award for communications excellence in the E-Newsletter category. The Hermes Creative Awards program is an international competition for communications professionals involved in the concept, writing, and design of traditional and emerging media. The judges are industry professionals who evaluate finalists based on the highest standards of communications excellence. This year, there were more than 3,500 entries from throughout the U.S. and several other countries.

Disparities Summit Scheduled for July 16–18

The 2007 Cancer Health Disparities Summit will take place July 16–18 at the Bethesda North Marriott Conference Center and Hotel in Bethesda, MD. The theme of this year's conference is "Catalyzing Trans-Disciplinary Regional Partnerships to Eliminate Cancer Health Disparities."

The summit will bring together some of the nation's top researchers in the field of cancer health disparities. NIH grantees, health professionals, and community advocates from across the country will gather to discuss their research, successful program strategies, challenges, and accomplishments.

This year's summit is sponsored by NCI's Center to Reduce Cancer Health Disparities, the National Center for Research Resources, and the National Center on Minority Health and Health Disparities. To register or obtain additional information, go to: http://cancermeetings.org/CHDSummit07/.

CCR Publishes New Magazine

NCI's Center for Cancer Research (CCR) recently published the first issue of a new publication, *CCR connections*. The 32-page magazine, to be published twice a year, highlights CCR's basic, translational, and clinical research, as well as its patients, scientists, and alumni to show CCR's unique role in the cancer and HIV research community. Copies of the first issue are available at http://ccr.cancer.gov/news/connections/CCR-Magazine.pdf.

Advocacy Summit Summary Available

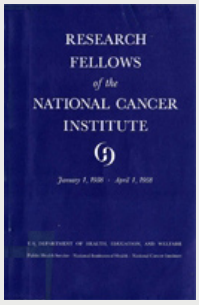
NCI Office of Liaison Activities (OLA) announces the availability of a new brochure, *2006 Listening and Learning Together: Building A Bridge of Trust Summit Summary & Evaluation*.

The first summit meeting between NCI and cancer advocates was hosted by the NCI Director's Consumer Liaison Group in June, 2006. The meeting brought together consumer advocates from 33 states and 111 cancer advocacy organizations to enhance collaborations and partnerships between the advocacy community and NCI. Copies of the summit summary and evaluation can be requested from liaison@od.nci.nih.gov.

BSA Meets in Bethesda

NCI's Board of Scientific Advisors (BSA) met on June 28–29 on the NIH campus in Bethesda, MD. The public portions of the meeting can be viewed at http://videocast.nih.gov/PastEvents.asp. ◆

70 YEARS OF EXCELLENCE IN CANCER RESEARCH



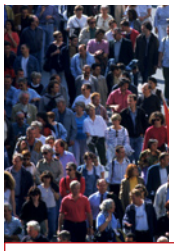
If Memory Serves…

During its first 2 years, NCI established research fellowships to train cancer researchers from many different fields. By 1943, 40 people had completed these research fellowships. ◆

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

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_071007/page9. ◆



Community Update

Major Journals Expand Clinical Trial Public Registration Requirements

The International Committee of Medical Journal Editors (ICMJE)—which includes the editors of many of the world's best-known, prestigious medical research publications—recently announced an expansion of its 2005 policy requiring that clinical trial investigators and sponsors provide detailed information about their studies in a publicly accessible registry before the start of patient enrollment as a prerequisite for publication of the results in an ICMJE member journal.

The expanded policy was announced last month in an editorial in the ICMJE member publication *New England Journal of Medicine*. Effective July 1, 2008, the expanded policy for the first time requires registration of all studies designed to investigate a medical intervention on a health-related outcome, including phase I studies and phase II studies not covered by the earlier policy. Previously, phase I studies and phase II studies that lacked a comparison or control group were exempt from trial registration requirements.

"The ICMJE recognizes the potential benefit of having information about preliminary [phase I] trials in the public domain, because these studies can guide future research or signal safety concerns," noted the editors of the 12 ICMJE member journals, which also include the *Journal of the American Medical Association, The Lancet*, and MEDLINE, which is published by the National Library of Medicine.

When the ICMJE announced its original policy 2 years ago, requiring the registration of some phase II trials and all phase III and phase IV trials, it generated controversy and concern that the requirements would prove cumbersome or stifle competition. Since then, however, "the research community has embraced trial registration," the editors noted. Before the ICMJE policy, ClinicalTrials.gov, the largest trial registry at the time, contained 13,153 trials. In April 2007, the registry contained more than 40,000 trials, with more than 200 new trial registrations occurring weekly.

The ICMJE's trial registration requirements have been widely adopted by non-member medical journals. "We hope that [non-ICMJE journals] will also adopt the modifications discussed in this update," the editors wrote.

The requirements have caused many investigators and trial sponsors to request that the ICMJE recognize their local databases as registries in compliance with the registration policy. In response, the ICMJE has supported efforts by the World Health Organization (WHO), through the WHO International Clinical Trials Registry Platform (ICTRP), "to develop a coordinated process for identifying, gathering, de-duplicating, and searching trials from registries around the world." In addition to the five currently approved registries, the ICMJE will now also accept registration in any of the primary, nonprofit clinical trial registries that participate in the ICTRP.

NCI, through its Physician Data Query (PDQ®) Cancer Clinical Trials Registry, has also become an active participant in the worldwide clinical trials registration movement. PDQ works with ClinicalTrials.gov to ensure that NCI-sponsored trials are registered in that registry in compliance with ICMJE requirements. Furthermore, the PDQ registry is a partner register within the ICTRP Network of Collaborating Clinical Trial Registers; Lakshmi Grama of NCI's Office of Communications and Education, who manages the PDQ registry, has recently been appointed chair of the ICTRP Registers Working Group. ◆

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.

NCI Cancer Bulletin staff can be reached at ncicancerbulletin@mail.nih.gov.