THE CANCER LETTER

Vol. 32 No. 14
April 14, 2006

Remarks On HPV Vaccines, SPORE Funds Create Controversy For NCI's Niederhuber

By Paul Goldberg

Vaccines for human papillomavirus would be more useful in less developed nations where screening isn't as advanced as it is in the U.S., NCI's Chief Operating Officer John Niederhuber told House appropriators last week.

"While we, in this country, have great screening, this adds to the screening for our country," Niderhuber said at the April 6 hearing of the House appropriations committee's subcommittee on Labor, HHS and Education. "But if you think about the world population, that's where the impact of this could be just absolutely huge."

In an internal NCI "debriefing" memorandum written the following day, Niederhuber wrote that members of Congress "acknowledged the great impact of this advance to the lives of women from the middle-and low-income countries of the world, where current methods of screening are too expensive."

Social conservatives are expected to oppose FDA approval of HPV

(Continued to page 2)

AACR Annual Meeting:

Celebrex Studies Show Polyp Reduction, Point To Challenges In Biomarker Validation

By Paul Goldberg

Two studies presented at the annual meeting of the American Association for Cancer Research demonstrated that Celebrex (celecoxib) is associated with a reduction of benign polyps, but increases the risk of cardiac events.

The studies—one sponsored by NCI and the other by Pfizer Inc., the maker of the drug—were presented April 3 at an AACR plenary session titled "Breakthroughs in Clinical Research." Neither study was designed to address the relationship between benign polyps and colon cancer.

If a reduction in polyps is indeed a "breakthrough," its clinical relevance remains to be defined. The question of validity of the decrease in occurrence of benign polyps as a surrogate for colorectal cancer would have to be addressed in studies that would likely take decades and many thousands of patients to complete, experts say.

The studies received considerable press coverage, but reporters—and the writers of headlines—generated a message that went far beyond the data: Celebrex brought about a reduction in colorectal cancer at a cost of cardio-thoracic events, according to several stories.

(Continued to page 7)

Niederhuber Says He Hopes To Increase SPORE Funding

(Continued from page 1)

vaccines in the same way they opposed the emergency contraceptive Plan B. Both would encourage promiscuity, they claim. FDA's failure to act on the application for over-the-counter sale of the contraceptive prompted Senate Democrats to put a hold on NCI Director Andrew von Eschenbach's nomination to head the agency.

"It sounds like the birth of a convenient excuse not to look at what HPV vaccines could do in this country," said Kirsten Moore, president of Reproductive Health Technologies Project, said of Niederhuber's testimony. "I wonder whether this is handwriting on the wall for burying HPV vaccines here."

Rep. Rosa DeLauro (D-Conn.) said she wasn't making a distinction between the vaccine in the U.S. and elsewhere in the world when she posed the HPV question to Niderhuber. "My question had nothing to do with geography, but about cervical cancer causing a tremendous loss of life," she said to The Cancer Letter.

At the same hearing, Niderhuber surprised cancer groups by pledging that NCI's Specialized Programs of Research Excellence would be spared budget cuts—and may even receive funding increases—even as the institute struggles to adjust to growing commitments and a shrinking budget.

"I am not shifting any money out of the program," Niederhuber said at the hearing. "I'm going to do my best to put more money into the program."

It is unclear how Niederhuber was able to make this promise, considering that NCI has begun a year-long review of its translational research programs, observers said.

"This is odd for two reasons," said a member of the Translational Research Working Group who spoke on condition that his name would not be used. "First, Andy [von Eschenbach] has consistently said that at this time of budgetary constraints, all programs have to be on the table for consideration and potential revision. Secondly, TRWG is clearly just beginning a process to examine the best infrastructure for this country to support translational research. Whether or not the SPOREs will continue, and how many, and what their configuration and charge will be, needs to be able to be discussed. Any pledge to the Congress that the SPOREs will remain untouched undercuts a lot of the charge to the TRWG."

Niederhuber hasn't been named acting director at the institute, and von Eschenbach hasn't formally stepped down from his job. Meanwhile, Bush administration officials have asked at least four individuals whether they would be interested in the NCI director's job, sources said.

In public appearances, Niederhuber has stressed continuity of leadership at the institute, pledging adherence to von Eschenbach's often-criticized goal to "eliminate suffering and death due to cancer by 2015."

In testimony submitted to House appropriators, Niederhuber said the institute's goal hasn't changed. "Four years ago, we put the NCI on a trajectory towards the Challenge Goal of eliminating suffering and death due to cancer as early as the year 2015."

The phrase "as early as" 2015 is consistent with the administration's efforts to soften von Eschenbach's goal. While NCI's website and its official publications are still awash in the 2015 goal, even von Eschenbach stops short of mentioning the date when he speaks in his capacity as head of FDA.

After setting the goal, "we have vigorously and aggressively managed NCI's portfolio of investments in cancer research across that entire continuum of the process of cancer, whether we've been focusing on understanding genetic mutations that were responsible for susceptibility to cancer or focusing on issues that have to do with survivorship and living with, rather than dying from, cancer," Niederhuber said in his submitted testimony.

Now, the institute is making adjustments to its

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
Letters to the Editor may be sent to the above address.

Subscriptions/Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
General Information/FAQ: www.cancerletter.com

Subscription $355 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.
Founded Dec. 21, 1973, by Jerry D. Boyd.

lower budget. "We are committed to face the challenge of making difficult choices between those programs that we will continue to grow and nurture and those that have already advanced our knowledge," he said.

In the internal memo, Niederhuber was more explicit.

"I noted how we have vigorously and aggressively managed NCI's portfolio of investments in cancer research," he wrote. "In the face of current fiscal challenges, we are committed to making difficult choices between those programs that we will continue to grow and nurture, and those that have already advanced our knowledge and will be phased out."

It's widely accepted that NCI needs to make cuts as von Eschenbach-era programs, taps from NIH, and shrinking appropriations are pushing the paylines for investigator-initiated grants into the single digits.

Now, observers say, the financial crisis may have enabled the people who led the von Eschenbach revolution at NCI to start reshaping the institute without seeking advice from extramural scientists.

Last month, NCI's outside advisors urged the institute to include the boards in such decisions. "The leadership of the National Cancer Advisory Board, the Board of Scientific Advisors and the Board of Scientific Counselors has expressed their willingness to assist the NCI leadership in any such review," Robert Young, chairman of the BSA and president of Fox Chase Cancer Center, said at a March 13 meeting of the advisory boards (The Cancer Letter, March 31).

Niederhuber Pledges To Maintain SPOREs

DeLauro, a 20-year survivor of ovarian cancer, asked Niederhuber whether funding for SPOREs would be maintained, and what would happen with the funds from the recently eliminated ovarian cancer SPORE at the University of Alabama and Duke University.

DELAURO: "SPORE… has been a program that has moved basic research discoveries into a clinic setting where it begins to directly benefit patients. My understanding is that they have changed the culture of cancer research throughout the United States. And since 1998, NIH has been able to expand the initiative, three types of cancers to 14, from 10 programs to almost 60. While we have not found specific cures, the approach has brought us to the cusp of new breakthroughs.

"During this time of limited resources, do you plan to shift funding away from the research that translates these discoveries and treatments in favor of what you were talking about before, is the research of nanotechnology, and where there's something that's less known and some of the research is not proven?

"But what is your plan in terms of whether or not there will be a shift? If so, why? How much funding are you planning to shift? And when can we begin to see the benefits of some of these new programs?

"Then I want to ask specifically about ovarian cancer, so let me start with that."

NIEDERHUBER: "The SPORE, as many of you know, is the Specialized Programs of Research Excellence.

"It began in 1992, as the Congresswoman stated, with nine grants funded and four disease sites. It's expanded to 60 SPORE grants across the country, 14 different organ sites.

"It is, having been on the outside until a few months ago, working at a major cancer institute and major university, one of the ways that I worked very hard on, to bring my basic laboratory investigators together with my clinicians and my clinicians scientists to focus on in our particular institution, we had a program focusing on breasts. We had a program focusing on lung and one on GI cancer.

"So I've worked, over my career, very hard to bring these disciplines together to create teams, if you will, and to be able to exchange the knowledge in the laboratory of cell models of animal models with the disease that we're treating in the clinic."

DELAURO: "Dr. Niederhuber, I don't mean to interrupt you, because I have a high regard, and we've had the opportunity before. But in terms of being able to accommodate my other colleagues and the chairman's request—what I'm trying to get out is what are your plans for dealing with SPORE and..."

NIEDERHUBER: "I was just about to come to that…"

DELAURO: "OK, thank you."

NIEDERHUBER: "These four groups met with the advocates as well on the 8th of March in Dallas. They met with me this past Tuesday afternoon. *[Niederhuber appears to be referring to a meeting with advocacy groups that took place in Houston March 8. The meeting was called to create an informal coalition to lobby for maintaining the SPOREs.]* There were about a dozen of the leaders of the SPORE programs across the country and another dozen or so of their advocates. We met here in Washington as part of the meeting that was going on in town.

"We had a great hour and a half session. We talked about the program. We talked about the pressures of the budget. We talked about the future of the SPORE program.

I reassured them of my commitment to the SPORE program. My commitment to maintain the number of disease sites that we were investigating—that is, organ site—the resources that we were putting into the SPORE program.

"We agreed to keep this focused on the quality of science and of peer review of that science, that that was the driving force that would take us forward.

"They recognized, to me, that the program had been in place for a good number of years. And they felt very strongly that, with the rapid changes in science, that they should be looking also at this program and whether they needed and we needed at NCI to make..."

DELAURO: "Are you going to shift the money out of the program?"

NIEDERHUBER: "I am not shifting any money out of the program. I'm going to do my best to put more money into the program."

DELAURO: "As you all know, my being a survivor of ovarian cancer, I was concerned about the decision to not continue the funding for the Alabama-Duke SPORE. As I continue to understand it, we're close, not there yet, to a marker for ovarian cancer. And we saw the loss of over 16,000 women in 2005. And ovarian cancer ranks fourth in cancer deaths amongst women.

"I know it's a little self-serving, but 20 years in March for me as a survivor. And we have all kinds of new things today that we didn't have 20 years ago. So this is an extremely important issue for me.

"And we did have a chance to meet Dr. Niederhuber. And I understand that the terminated funding was approximately $2.3 million, all of the money to be used to start up another ovarian SPORE. And will you put that money back into the other four existing programs?"

NIEDERHUBER: "The money stays in the SPORE program. It will depend on applications to the SPORE program. Hopefully, new applications will come in.

As you know, from our previous discussion, we worked very, very hard with the particular SPORE in question. We provided bridge funding for several years at really full direct cost.

"And I think it was more a problem of a loss of some of the faculty that they had at their institution. And what we did is to work with them really intensely to transfer some of the projects of excellence that were part of that SPORE and to fund those through other mechanisms, the program project mechanism and R01 mechanism, so that the things that were excellent as part of that SPORE remained excellent and remained funded today.

"I should point out, because I know of your interest and my interest particularly in finding markers for early disease, that was one of the things that they had strength in at Alabama, and that's one of the things that remains funded.

"So we're continuing to put an emphasis on ovarian cancer as well as several others, but the money stays in the SPORE pool."

DELAURO: "Thank you. I'm interested in that the money will continue to be used in terms of ovarian cancer and the research."

Reflecting on the hearing in the next day's memo, Niederhuber wrote: "I reaffirmed the NCI's ongoing commitment to the SPORE program, and conveyed my experience as a clinician-scientist in the extramural program and my desire to make the changes necessary to further strengthen the translational research effort."

Helping "Middle- and Low-Income Countries"

DeLauro asked Zerhouni and Niderhuber to comment on the HPV vaccines that are going through the approval process at FDA. Merck filed an application for a vaccine last year, and GlaxoSmithKline is expected to file another application in the near future.

"Cervical cancer afflicts near 10,000 women each year, 4,000 are dying in the United States, worldwide 510,000 women diagnosed with cervical cancer, and about 288,000 deaths," DeLauro said at the appropriations hearing. "I noticed, under the NCI's newer and expanded initiatives in last year's committee record, you mentioned a new vaccine to target the infectious agent of human papillomavirus, the cause of virtually all cases of cervical cancer, that a promising prevention vaccine that can suppress the carcinogenic process, either at its inception or in pre-invasive stages.

"You go on to state, and I quote, 'If made available to health care communities around the world, a successful cervical cancer vaccine could save hundreds of thousands of lives every year.'

"This is a very, very exciting prospect… We lost 3,000 people at the World Trade Center on September 11. We did the right thing in my view of going to war with Afghanistan, off trying to turn that around… Every single year, we lose 4,000 women. We need to have that kind of response, in my view, that addresses that issue. So can you tell us, or Dr. Niederhuber, can you tell us the views on the vaccine from a scientific perspective? And what is the status, at the moment, of having that vaccine? And how quickly we can undertake it?"

ZERHOUNI: "Well, let me try to preamble this by saying this is what I tried to describe to you about the

vision of NIH in the future.

"When I say, we're going to transform medicine to what I call the three Ps, predictive, personalized and preemptive. This is one, only one, of the examples of success in what I call preemption. Because if you use that, you would eliminate the possibility of the disease at great cost savings and reduction of the disease burden.

"And that's just a prototype of what may happen. So we clearly see this as a prototype example of this new medicine we're talking about. Perhaps Dr. Niederhuber might comment more specifically."

NIEDERHUBER: "Well, the results of the trial with HPV vaccine were truly stunning, as you know. And while we, in this country, have great screening, this adds to the screening for our country. But if you think about the world population, that's where the impact of this could be just absolutely huge."

DELAURO: "[This] being reviewed by FDA, Dr. [Anthony] Fauci [Director of the National Institute of Allergy and Infectious Diseases]…"

FAUCI: "There are two vaccines, one from Merck and one from GlaxoSmithKline… Based on the data as it appears, the data is, as Dr. Niederhuber mentioned, extraordinary. So again, you don't want to ever anticipate what the FDA's going to do, but the data looked really strong."

In his memo, Niederhuber wrote:

"During the hearing, subcommittee members were receptive to my recounting NCI's leadership in developing a vaccine for HPV that promises to greatly reduce, if not eliminate, cervical cancer worldwide in the years to come," he wrote. "They recognized this advance as a partnership with the private sector and acknowledged the great impact of this advance to the lives of women from the middle-and low-income countries of the world, where current methods of screening are too expensive."

At the hearing, no member of Congress indicated concurrence with the view that the HPV vaccine should be focused on countries other than the U.S.

"My question had nothing to do with geography, but about cervical cancer causing a tremendous loss of life," DeLauro said to The Cancer Letter. "I wanted to know what scientific information these experts had on the potential of this vaccine to reduce cervical cancer.

"Dr. Zerhouni and Dr. Niederhuber's response about the promise of this vaccine in eliminating cervical cancer in the U.S. and worldwide is a dramatic development."

Niederhuber's "D-Brief"

The text of Niederhuber's internal memo follows:

From: Dr. John Niederhuber (NIH/NCI)

Subject: D-Brief: Congress Holds Hearing on NIH and NCI Budgets

Yesterday, the House Appropriations Subcommittee on Labor, HHS, and Education Departments held a hearing on NIH's budget for FY 2007.

I was privileged to participate as part of a small delegation led by NIH Director Dr. Elias Zerhouni. Dr. Zerhouni was masterful in presenting the accomplishments of NIH and the opportunities for even greater advances because of this country's investment. It was clear by the questions I was asked that there is support in Congress for NCI's efforts to accelerate progress toward eliminating the suffering and death due to cancer, as well as concerns about the impact that budget cuts and reallocations may have on achieving that goal.

In my written testimony (http://www.cancer.gov/aboutnci/FY07-budget-request) I noted how we have vigorously and aggressively managed NCI's portfolio of investments in cancer research. In the face of current fiscal challenges, we are committed to making difficult choices between those programs that we will continue to grow and nurture, and those that have already advanced our knowledge and will be phased out. I provided examples of how the Nation's past commitment to cancer research has proven its worth.

During the hearing, subcommittee members were receptive to my recounting NCI's leadership in developing a vaccine for HPV that promises to greatly reduce, if not eliminate, cervical cancer worldwide in the years to come. They recognized this advance as a partnership with the private sector and acknowledged the great impact of this advance to the lives of women from the middle-and low-income countries of the world, where current methods of screening are too expensive. I reaffirmed the NCI's ongoing commitment to the SPORE program, and conveyed my experience as a clinician-scientist in the extramural program and my desire to make the changes necessary to further strengthen the translational research effort.

I look forward to continuing the dialogue with members of Congress as we work to meet our tough and necessary challenges. I promise to keep you fully informed as the budget process continues throughout the year.

—John

Patient Advocacy:

NCCS, ASCO Ask FDA To Set Rules For Expanded Access

By Paul Goldberg

The National Coalition for Cancer Survivorship and the American Society of Clinical Oncology filed a citizen petition asking FDA to put together standards for sponsors to make some cancer treatments available outside clinical trials and prior to approval.

Though many sponsors offer expanded access programs, such programs aren't uniformly structured. The NCCS and ASCO petition asked the agency to issue a guidance to industry for such programs.

The petition reflects the conclusions of a roundtable meeting the two groups held in January to discuss approaches to expanded access. Altogether, NCCS has held three such meetings with the industry, regulators, and patient advocates.

The NCCS-ASCO citizen petition was submitted at a time when FDA is reportedly finishing new rules for expanded access. Though the rules aren't publicly available, preliminary discussions indicate that FDA is about to relax its existing regulations to allow companies to charge for such drugs.

At the same time, another patient group, Abigail Alliance for Better Access to Developmental Drugs, is proposing that cancer therapies become commercially available as early as after conclusion of phase I testing. The group's proposal, called Tier I, has resulted in a citizen petition, a lawsuit, and a Senate bill that also seeks to restrict placebo-controlled trials of cancer therapies (The Cancer Letter, Dec. 2, 2005).

The NCCS-ASCO petition proposes an approach that is closer to reflecting the consensus of mainstream oncologists, the industry, and advocacy groups. According to proponents, the two groups wanted to lay out the criteria for a guidance that would allow patients to get unapproved therapies, yet minimize the risk to accrual to clinical trials and protect patients from unreasonable risk.

"In order to ensure that the needs of cancer patients are met and that accrual to ongoing trials is not impaired, standards are needed for the development and implementation of expanded access programs," Ellen Stovall, president and CEO of NCCS, said in a statement.

Under the current state of affairs, the industry is unclear about the requirements related to expanded access, said ASCO President Sandra Horning.

"Expanded access programs are always voluntary on the part of the sponsors, but responsible sponsors will consider them essential elements of the drug development process," Horning said in a statement. "ASCO is committed to educating providers and patients on available and forthcoming expanded access programs and facilitating patient participation in these programs."

FDA to Allow Charges For Experimental Drugs

The NCCS-ASCO petition states that sponsors should refrain from charging for drugs made available through expanded access programs.

"The treatment IND regulation permits charging for unapproved drugs on a `cost recovery' basis," the petition states. "The custom among sponsors has been to provide drug free of charge, and this would appear to be the preferable practice by far. FDA should urge sponsors to forgo cost recovery and provide drugs without charge to patients in expanded access programs."

However, the petition states that sponsors should be urged to "compensate physicians for the time and other resources involved in administering unapproved drugs outside the clinical trial context and for collecting and reporting clinical outcome data."

FDA's rules, at least in their current form, appear to make it easier for pharmaceutical companies to charge for unapproved therapies.

In a recent speech, FDA Deputy Commissioner for Medical and Scientific Affairs Scott Gottlieb said the agency's rules would define costs that could be recovered by the sponsors.

"We are working on finalizing two new rules that we believe are an important step that will help enable more promising new medicines to be made available to cancer patients through our existing expanded access programs," Gottlieb said in a speech March 7.

"The first rule would better describe the types of investigational uses for which a sponsor may be able to charge for a drug offered as part of an expanded access program and the types of costs that can be recovered. The proposed rule is intended to permit charging for a broader range of investigational uses than is explicitly permitted in current regulations. The goal is to help encourage more sponsors to make drugs available under investigational uses, especially in cases where costs may be an obstacle to doing so.

"The second new proposed rule would allow FDA to amend its regulations on investigational new drug applications to describe the ways in which patients may obtain investigational drugs for treatment use. Under the proposal, treatment use of investigational drugs

would be available to individual patients, including in emergencies; intermediate size patient populations; and larger populations under a treatment protocol or IND. The proposed rule is aimed at improving access to investigational drugs for patients with serious or life-threatening diseases or people suffering from conditions that lack other therapeutic options, where they may benefit from investigational therapies."

The text of Gottlieb's remarks is posted at www.fda.gov/oc/speeches/2006/cancerprogress0307.html.

ASCO, NCCS: Access Should Be Evidence-Based

The petition states that a decision to provide expanded access can be made earlier than phase III or at the completion of clinical trials—"or in unusual circumstances, even prior to phase II."

Expanded access should be regarded as part of the clinical development plan, the petition states. "Accordingly, an expanded access program would normally not be considered appropriate for an indication not being evaluated in clinical trials by the sponsor," the document states. "An exception to this general rule might be in rare instances where there is strong pre-clinical or clinical evidence that the drug is efficacious in a population with virtually no therapeutic option."

According to the petition, the following considerations should determine the decision:

—Nature and strength of the evidence: If the endpoint being measured is response rates, for example, it is important to consider the quality of the responses. Is there a high rate of complete response or substantial tumor regression? Are responses markedly durable, at least in some patients? Are the responses accompanied by relief of cancer-related symptoms in the majority of patients? If so, FDA should feel more comfortable allowing an expanded access program to proceed. In general, the more compelling the data, the more favorably FDA should regard a request for approval of an expanded access program.

—Unmet patient need: To the extent that patients with cancer or other life-threatening disease have no treatment alternative using an approved agent or commonly accepted standard therapy, expanded access should be an option more readily pursued.

—Likelihood and imminence of marketing approval: As approval seems more certain and more immediate, expanded access programs offer greater hope to patient in need and less risk of disappointing outcomes. In such settings, FDA should facilitate expanded access programs that are sought by sponsors.

—Drug availability: The feasibility of expanded access programs is greatly dependent upon the capacity of the sponsor to supply drugs to patients outside the clinical trial setting. Experience has demonstrated that sponsors are better able to deliver significant quantity of drug outside of trials if the agent in question is a small molecule with a relatively straightforward manufacturing process and cost, in contrast to more complex biological products, where supply may pose greater challenges and uncertainty.

The text of the citizen petition is posted at www.canceradvocacy.org/advocacy/pdf/NCCS-ASCO%20Citizen%20Petition%20-%203-27-06.pdf.

AACR Annual Meeting:
Press Coverage Of Celebrex Reached Beyond Trial Data

(Continued from page 1)

"Drug Cuts Risks of Colon Cancer in Two Studies," The Wall Street Journal reported April 4. Celebrex "sharply reduced the risk of colon cancer in patients prone to disease, according to two large studies," the story said.

The New York Times ran a greatly abridged Associated Press story that opened with the following bit of misleading information: "A major arthritis drug, Celebrex, has been found to help lower the risk of colon cancer, but the benefits may be outweighed by an increase in the risk of heart problems, researchers say." Reuters, too, reported that Celebrex "may prevent colon cancer in high-risk patients...."

"That's certainly not the conclusions that I drew from the trials," said Raymond DuBois, director of Vanderbilt-Ingram Cancer Center, a member of the scientific advisory board of the Pfizer trial and discussant at the AACR presentation. "I look at this as really not more than just a proof of concept that you can intervene with a medication and reduce risk of polyp recurrence. We can't take it any further than that at this point."

The misunderstanding illustrates the public's vulnerability to overstatements of findings based on biomarkers and the reporters' apparent tendency to overstate such findings. This is particularly important now that FDA and NCI are advancing a scientific agenda that relies on biomarkers as a gateway to "personalized medicine."

Scientists said they were puzzled by the coverage reaching beyond the data. At the AACR press conference, the investigators presented their results accurately, DuBois said. "The investigators were very truthful and honest, and they didn't reach further. But for some

reason, at least in the headlines, the press picked up on reduction in colon cancer risk, which was not proven by the trials."

The use of the word "breakthrough" may have been unfortunate, DuBois said. "Breakthrough means that now people would be advised to take this drug, and its use would reduce cancer-associated mortality, and that's not my conclusion from these trials," he said. "This just represents an initial step, and we really need to develop a strategic plan for the next steps required to even consider an approval for this drug in high-risk patients."

Studies Lay Groundwork for Further Research

The NCI-sponsored trial enrolled 2,035 patients and compared two doses of celecoxib against placebo.

In the trial—called Adenoma Prevention with Celecoxib Study—patients took either 200 mg or 400 mg twice a day. Colonoscopy was conducted in 89 percent of participants after one year and 76 percent received a follow-up colonoscopy at three years.

The incidence of polyps was 61 percent in patients taking placebo. In patients who took celecoxib, reduction in adenoma detection was 33 percent in the lower-dose arm and 45 percent in the higher-dose arm. The finding was statistically significant ($p<0.0001$).

The relative risk of advanced neoplasms with adenomas more than one centimeter in diameter or with tubulovillous or villous features, severe dysplasia or invasive cancer were also drastically reduced in patients using celecoxib, with 57 to 66 percent fewer tumors in these patients ($p<0.0001$).

"Even when a patient developed disease while taking celecoxib, the disease that was identified was smaller in size and fewer in number," said Monica Bertagnolli, a surgeon at Brigham and Women's Hospital and the study's principal investigator, who presented the findings at AACR

The study found at 33 months a two-to-three-fold increase in serious adverse cardiovascular events. According to an adjudicated analysis, serious cardiovascular events occurred among 1 percent of patients on placebo, 2.5 percent on low dose celecoxib users, and 3.4 percent on the high dose arm.

After the investigators examined past medical histories, they found that 3 percent of patients with a history of cardiovascular disease experienced a serious cardiovascular event.

On the celecoxib arms, 8.8 percent of patients with history of cardiovascular disease experienced new serious adverse events. Among patients with no history of cardiovascular events, incidence of such events was at 0.7 percent for placebo and 2 percent for celecoxib.

"Celecoxib is an effective agent for colorectal adenoma chemoprevention, but it cannot be recommended for prevention of sporadic colorectal adenomas until issues regarding cardiovascular toxicity are addressed," Bertagnolli said. "We believe that this can be done through patient selection for high adenoma risk and low cardiovascular risk."

In the company-sponsored trial, Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP), the decrease in the number of adenomas by the third year of daily use of celecoxib was 36 percent.

Patients who used aspirin along with the daily 400 mg dose of celecoxib experienced a 39 percent reduction, and patients who didn't use aspirin had a 35 percent drop.

However, patients taking celecoxib had a higher risk of cardiovascular events than those taking placebo (7.5 percent versus 4.6 percent).

Confirmed cardiovascular adverse events were at 7.2 events per 1,000 patient years for patients receiving placebo vs. 9.4 events per 1,000 patient years for those receiving celecoxib. Patients with a history of cardiovascular events were more likely to experience them again on celecoxib (16.8 events/1,000 pt years for placebo vs. 27.8 events/1,000 patient years for celecoxib).

"We are all concerned about cardiovascular events, in particular in light of the recent reports on Vioxx and the APC trial," said Nadir Arber, co-principal investigator of the PreSAP trial and head of the Gastrointestinal Oncology Unit, Tel Aviv Sourasky Medical Center.

Hence, all cardiovascular adverse events were adjudicated by the cardiovascular safety committee. The hazard ratio in the intended population was 1.3.

Patients with no history of heart disease were less likely to experience such adverse events on celecoxib (6.1 vs. 6.6 events/1,000 patient years).

Curiously, more colorectal cancers were diagnosed on the treatment arm than on control arm. One patient getting placebo developed the disease, compared to 6 patients who received celecoxib. (The study was randomized 3:2 in favor of celecoxib.)

"We were concerned about six cases of colorectal cancer in the treatment arm and one case in the placebo arm," Arber said. "We did check these seven cases very carefully, keeping in mind the long, multi-step process of colorectal cancer carcinogenesis, spanning over five, 10, or 20 years. Five of these colon cancers were diagnosed at year one. Three of them were carcinoma in situ and

two were stage one, implying that these cases were incomplete resections of malignant polyps."

The trial enrolled 1,561 patients and evaluated the 400 mg single daily dose of the drug vs. placebo in patients who had undergone polypectomy. Patients were evaluated at the end of the first year and at the end of the third year.

"Celecoxib has a greater effect on advanced adenomas," Arber said. "This is a proof of concept of using a selective COX-2 inhibitor in colorectal adenoma prevention. It's the beginning of the new era. In the future, risk-benefit assessment will depend on enhanced patient characterizations and molecular profiling of adenoma, so we will be able to choose subgroup of population that will respond better to the drug."

At the time APC was stopped, PreSAP data indicated a hazard ratio of 1.2 for patients taking celecoxib compared with placebo for death from cardiovascular events and nonfatal heart attack or stroke.

Findings Suggest New Strategies

These findings are dramatic, scientists say.

Surprises begin on the placebo arm, with the polyp recurrence of 60 percent. "This is the first time it's been studied prospectively in this long and this large a group," DuBois said. "It was always estimated to be around 30 to 40 percent."

The drug's activity was more dramatic than anticipated, too.

"I expected that there would be around a 30 percent reduction in polyp recurrence," DuBois said. "I was surprised by two things: that it was more effective in the patients with larger polyps, and that the maximum effect was seen within a year. I don't know if I would call it a breakthrough, but it was a surprise to me."

The toxicity findings for Celebrex were unforeseen, too. However, the data presented at AACR point to a strategy for limiting cardiovascular adverse events.

"It looks like people who got the side effects could be pretty easily identified in advance. They had two or three risk factors for cardiovascular disease," DuBois said. "Those people should probably not take this class of drugs. If you exclude those upfront, you may be able to exclude some of these side effects."

With a high-risk population, a dramatically active drug and rapid occurrence of events, it would be possible to conduct informative follow-up studies that could take a year or less to complete.

"If you were to design a future trial, you could do it in a much shorter time span, a year or less, and probably select patients who have those large and multiple polyps and not worry about people with small polyps who probably aren't at any significant risk for colon cancer anyway," DuBois said. "If you were to think about doing a more definitive trial, you could do a shorter time frame, which would be much less expensive and may be more informative if you just take on the higher risk patients to start with."

This is where the problem becomes more complicated.

"The biggest question I have now is, 'Which polyps are we reducing by the treatment?'" DuBois said. "Are we reducing ones that are going to progress on to cancer, or are we reducing the ones that wouldn't progress on, and we must design some way to answer that question. Not all polyps are alike.

"If there was another trial, I think we would have to interrogate those polyps at a molecular level and see if we can get a signature for progression, a signature of a polyp that won't progress and then try to see which ones go away in the patients that are on the treatment. That's not beyond our realm. We have the technology. We are probably at a point where that trial could probably be done. The cancer prevention community needs to agree on what is the molecular signature for polyp progression whether we can design a trial where the molecular profile of recurrent polyps can be interrogated."

The leap from demonstrating that an agent is shown to be effective in eliminating benign adenomas to demonstrating an effect on colorectal cancer may seem trivial to writers of headlines. To scientists, it represents a profound challenge.

"It takes 20 or 30 years for these adenomas to progress on to a cancer," DuBois said. "That would require lots of patients. And who would pay for such a long-term study?"

The standards of proof would need to be defined, too. "What needs to happen now is the thought leaders in this field of cancer prevention need to come together and try to figure out what these results really mean and what really mean would be the next steps toward getting something that would have a real clinical benefit," DuBois said. "What are the hurdles that have to be gotten over before we can get to that point?"

It's unclear what drugs should be used. "If we are going to figure out what's good for the public, it would be important to design a trial that included aspirin as a comparator, because it's very cheap, we know what the side effects are, and it has been shown to reduce polyps and cardiovascular problems in elderly populations."

Three years ago, Bernard Levin, a cancer

prevention expert at M.D. Anderson Cancer Center and co-principal investigator in the PreSAP study, described the methodological difficulties in an editorial in JCNCI:

"In long-term studies of chemoprevention that are based on the surrogate endpoint of adenomatous polyps rather than on the incidence of colorectal cancer, we must be vigilant to the potential for harm when using an indirect marker, however biologically relevant, in an asymptomatic population.

"This is especially important where an effective method for post-polypectomy management exists in the form of periodic colonoscopic surveillance, albeit expensive and invasive. Stopping trials on the basis of surrogate endpoints such as adenoma incidence rather than on cancer incidence may miss hypothetical harms that may occur later than the surrogate endpoint…

"[Using surrogate outcomes of benefit but clinical outcomes of harm rather than surrogate outcomes of harm can introduce a systematic bias in our assessment of chemopreventive agents. Moreover, when the FDA grants accelerated approval (Subpart H) for the use of a compound on the basis of surrogate endpoint data, formal post-marketing surveillance to evaluate clinical benefit is required.

"Placebo-controlled, randomized trials to suppress adenoma recurrence and thus possibly to diminish colorectal cancer incidence and mortality need to be carefully monitored and to be of sufficient duration to ensure that clinically significant adverse effects can be reliably detected.

"In addition to identifying molecular targets for chemoprevention with greater precision, advances in genomics and proteomics may well enhance our ability to define more accurately entry criteria into prevention trials and to identify biologic heterogeneity for subsequent correlations with outcome."

The editorial is posted at http://jncicancerspectrum.oxfordjournals.org/cgi/content/full/jnci;95/10/697?fulltext=Bernard+Levin&searchid=QID_NOT_SET.

It's unclear whether studies designed to validate the colorectal cancer endpoint would be ethical, cancer prevention experts say.

"Such trial findings create an ethical quagmire, making it impossible to do the clinical trials that truly determine that this class of drugs prevent colon cancer and colon cancer death," said Otis Brawley, associate director for cancer control at Winship Cancer Institute, professor of hematology, oncology and epidemiology at Emory University, and editor of the American Society of Clinical Oncology cancer prevention curriculum, which will be published later this year. "If we believe, but do not know, that reduction of polyp formation in a relative short period time reduces risk of colon cancer, how can we ethically enroll humans onto clinical studies to determine that the drug actually does reduce risk of colon cancer?

"These [celecoxib] trials create a number of questions," Brawley said. "At the same time, surveillance and screening for blood in stool and endoscopic or virtual colonoscopic procedures may save more lives and even be less morbid."

FDA News:

BoozAllen Wins Contract To Study "Phase 4" Process

FDA has awarded a $1.1 million contract for evaluation of the postmarketing study commitment process for collecting medical information.

The contract was awarded to Booz Allen Hamilton, a consulting firm that also holds a management contract for NCI's Cancer Bioinformatics Grid.

According to FDA, over the next year, Booz Allen Hamilton will examine the agency's internal processes regarding these "phase 4" commitments and recommend approaches to improving management of these studies, which are conducted following FDA approval.

"Even the largest and best designed pre-market studies cannot reasonably answer all of the important questions that may arise about medicines," Steven Galson, director of the agency's Center for Drug Evaluation and Research, said in a statement. "Continuing to evaluate drugs after they are approved is an important part of ensuring their safety and learning new things about their benefits."

Funding Opportunities:

PA-06-306: The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery. R21 grants. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-306.html. Inquiries: Vickie Shavers, 301-594-1725; shaversv@mail.nih.gov.

PA-06-305: **Decision Making in Cancer: Single-Event Decisions.** R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-305.html. Inquiries: Wendy Nelson, 301-435-4590; nelsonw@mail.nih.gov.

PA-06-304: Studies of the Economics of Cancer Prevention, Screening, and Care. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-304.html. Inquiries: Martin Brown, 301-496-5716; mb53o@nih.gov.

PA-06-303: Pilot Studies in Pancreatic Cancer. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/

PA-06-303.html. Inquiries: Mukesh Verma, 301-594-7344; vermam@mail.nih.gov.

PA-06-299: Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-299.html. Inquiries: James Tricoli, 301-496-1591; tricolij@mail.nih.gov.

PA-06-298: Understanding Mechanisms of Health Risk Behavior Change in Children and Adolescents. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-298.html. Inquiries: Louise Mâsse, 301-435-3961; massel@mail.nih.gov.

PA-06-297: Protein Biomarkers of Infection-Associated Cancers. R2. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-297.html. Inquiries: Karl Krueger, 301-435-1594; kruegerk@mail.nih.gov.

PA-06-296: Correlative Studies with Specimens from Multi-Site Trials. R21.Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-296.html. Inquiries: Heng Xie, 301-480-4663; xiehe@mail.nih.gov.

PA-06-295: Etiology, Prevention, and Treatment of Hepatocellular Carcinoma. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-295.html. Inquiries: John Cole, 301-496-1718; jc121b@nih.gov.

PA-06-292: Research on the Economics of Diet, Activity, and Energy Balance. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-292.html. Inquiries: Martin Brown, 301-496-5716; mb53o@nih.gov.

PA-06-289: Immunoregulation of Gastrointestinal Carcinogenesis. R01. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-289.html. Inquiries: Kevin Howcroft, 301-496-7815; Howcrofk@mail.nih.gov.

PA-06-290: Immunoregulation of Gastrointestinal Carcinogenesis. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-290.html.

PA-06-283: Diet-Induced Changes in Inflammation as Determinants of Colon Cancer. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-283.html. Inquiries: Young Kim, 301-496-0126; yk47s@nih.gov.

PA-06-282: Stem Cells and Cancer. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-282.html. Inquiries: R. Allan Mufson, 301-496-7815; am214t@nih.gov.

PA-06-280: Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care Delivery. R01. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-280.html. Inquiries: Louise Wideroff, 301-435-6823; Wideroff@nih.gov.

PA-06-281: Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care Delivery. R21. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-281.html

PA-06-306: The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery. R21. Full text: http://grants1.nih.gov/grants/guide/pa-files/PA-06-306.html. Inquiries: Vickie Shavers, 301-594-1725; shaversv@mail.nih.gov.

Distribution Policy for The Cancer Letter

Thank you for your purchase of this issue of The Cancer Letter! Because issue and subscription sales are our major source of revenue, we wouldn't be able to provide you with the information contained in this newsletter without your support. If you have any questions or comments about the articles, please contact the editors (see page 2 of your issue for contact information).

We welcome your use of the newsletter and encourage you to send articles once in a while to colleagues. But please don't engage in routine distribution of The Cancer Letter to the same people week after week, unless your organization has purchased a site license or group subscription. If you aren't sure, ask the person who is paying for this subscription. If you are sending the newsletter to an unauthorized list, please stop; your actions are against Federal law. If you received this newsletter under an unauthorized arrangement, know that you are in receipt of stolen goods. Please do the right thing and purchase your own subscription.

If you would like to report illegal distribution within your company or institution, please collect specific evidence from emails or photocopies and contact us. Your identity will be protected. Our goal would be to seek a fair arrangement with your organization to prevent future illegal distribution.

Please review the following guidelines on distribution of the material in The Cancer Letter to remain in compliance with the U.S. Copyright Act:

What you can do:

- Route a print subscription of the newsletter (original only) or one printout of the PDF version around the office.
- Copy, on an occasional basis, a single article and send it to a colleague.
- Consider purchasing multiple subscriptions. We offer group rates on email subscriptions for two to 20 people.
- For institution-wide distribution or for groups larger than 20, consider purchasing a site license. Contact your librarian or information specialist who can work with us to establish a site license agreement.

What you can't do without prior permission from us:

- Routinely copy and distribute the entire newsletter or even a few pages.
- Republish or repackage the contents of the newsletter in any form.

If you have any questions regarding distribution, please contact us. We welcome the opportunity to speak with you regarding your information needs.

The Cancer Letter
PO Box 9905
Washington DC 20016
Tel: 202-362-1809
www.cancerletter.com