THE CANCER LETTER

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Special Report:
The NCI 2015 Goal

The 2015 Goal: Science Or Science Fiction?

The NCI goal to "eliminate suffering and death due to cancer" by 2015 is based on the agenda of the National Dialogue on Cancer. Critics say it is unclear how the goal could be achieved, and advocates offer no step-by-step war plan.

This Special Report demonstrates that the NCI plans rely on early science, depart from peer review, and include spinning off NCI programs. Many of the key recommendations for meeting the goal are emerging behind closed doors under the aegis of the Dialogue.

This report includes articles from **The Cancer Letter**, starting in February through August 2003.

NCI Director Sets A Goal: Eliminate Suffering, Death From Cancer By 2015

(The Cancer Letter, Feb. 14, 2003, Vol. 29 No. 7)

NCI Director Andrew von Eschenbach has a goal: "to eliminate the suffering and death from cancer by 2015."

This goal figures as the key element of a strategic plan currently under development at the Institute, von Eschenbach said to the National Cancer Advisory Board Feb. 11.

"I have set out—and it has been embraced, I'm pleased to say—a challenge goal that shapes our mission and shapes our vision," von Eschenbach said to the board. "And the challenge goal that we have accepted as an Institute is to eliminate the suffering and death due to cancer, and to do it by 2015." Von Eschenbach said the goal includes solving health care delivery problems and eliminating health disparities.

By setting an ambitious goal on the threshold of what is likely to be a period of modest budgetary increases, von Eschenbach is taking a controversial step in a field that has a history of unrealistic promises.

An argument can be made that NCI owes its current $4-billion budget—the largest of the NIH institutes—to the "war on cancer," the public relations and legislative effort that led to the National Cancer Act of 1971. However, many observers argue that the rhetoric used to increase funding for cancer research also led to heightened public expectations for quick cures, and resulted in disappointment when the cures didn't materialize. Two previous NCI directors, Samuel Broder and Richard Klausner, set no deadlines for curing cancer, and deliberately avoided the war metaphor.

The Institute's new goal provoked no reaction from the NCAB. The board members did not use the question-and-answer session that followed von Eschenbach's remarks to discuss the goal. Instead, discussion focused on plans for funding investigator-initiated grants under the Bush Administration's proposed 3.5 percent increase for NCI for fiscal year 2004.

"We need to have goals," NCAB Chairman John Niederhuber said when asked by a reporter about the 2015 target. "All of us would like to do it next year, or next week. What you heard this morning was an impressive and ambitious

(Continued to page 2)

NCI Goal Evolved From ACS "Challenge" To Cut Mortality

(Continued from page 1)

agenda."

Several oncologists and cancer activists contacted this week declined to comment on feasibility of the Institute's goal, saying that they needed further information about von Eschenbach's plans.

An American Cancer Society spokesman said the society did not want to comment without viewing a transcript of von Eschenbach's remarks. In 1996, ACS published a book titled "Horizons 2013: Longer, Better Life Without Cancer," that suggested it would be possible to achieve a 45-percent decrease in the age-adjusted death rate for cancer by 2013, the year that ACS turns 100. [*Special Report editor's note*: Subsequently, ACS issued a "challenge" to the federal government, the private sector, and cancer organizations to work for a 2-percent annual decline in cancer mortality, resulting in a 50-percent decline in cancer mortality by 2015 (**The Cancer Letter**, Nov. 22, 1996, Vol. 22 No. 45)].

Von Eschenbach, formerly a surgeon at M.D. Anderson Cancer Center, had been slated to serve as the society's president prior to his NCI appointment. He was one of the founders of the ACS-led National Dialogue on Cancer, which seeks to bring together cancer organizations to develop a common agenda.

3D's: Discovery, Development And Delivery

"I did not say that we would eliminate cancer by 2015," von Eschenbach said in his remarks to the NCAB. "We are committed, and we are pledged to working collaboratively and collectively together to eliminate the suffering and death due to this disease."

To accomplish this, NCI has developed a strategy that von Eschenbach called "the three D's: Discovery, Development and Delivery." The NCI strategic plan has identified goals in each of the three areas, he said.

"Within the portfolio of discovery, our long-range objective is that we will ultimately have defined all of the relevant mechanisms that are responsible for the initiation and progression of cancer, in the cancer cell, in the person, and in populations," von Eschenbach said. "Based on that new knowledge and understanding, we will have developed effective interventions that predict, detect, diagnose, treat, and prevent the disease.

"We will assure that those interventions are delivered as state-of-the-art care to all of those in need, and to do that with special reference to being able to deliver it in the context of clinical trials, so that the very delivery process itself develops and evolves new knowledge in our understanding of the malignant phenomenon," von Eschenbach said. "We will do that in the context also of making sure that all populations are addressed and benefited, and that requires a special effort in the elimination of disparities."

NCI has used its professional judgment budget, known as the Bypass Budget, to lay out year-to-year funding priorities. The new NCI strategic plan will take a longer view, and include short-term, intermediate, and long-term goals, he said. The plan will be used to establish new programs and initiatives.

NCI will invite outside comment on the plan as it is being developed, von Eschenbach said.

"Like Putting a Man on the Moon"

In an interview, von Eschenbach said he believed that it is possible to achieve the 2015 goal.

"It's an ambitious goal, no question," he said to **The Cancer Letter**. "But if you look at the trajectory we are on, there has been an incredible explosion in our understanding of cancer and in the rapidity with which we can process data, and in the technology that is enabling us to do gene expression analysis.

"It almost mimics Moore's Law for chips," he said, referring to the prediction by Intel founder Gordon Moore that the number of transistors on a chip can be doubled every two years.

"Therefore, I believe it's not unrealistic to extrapolate that exponential growth that we can develop enough interventions that we may be able to prevent people from suffering and dying from the disease," von Eschenbach said.

"That is a goal we should establish, and it is like putting a man on the moon in a decade. We can make it a reality. I believe we have to do it. I'm not trying to offer false hope or expectations. But I do think we have to set goals.

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"What I'm laying out there is the commitment. I don't have a crystal ball, but I do believe we can make the commitment."

Beware The "Cycle of Euphoria And Despair"

The comparison with the space program is part of the rhetorical tradition in cancer politics.

Activists who lobbied for the Cancer Act likened the quest for a cure for cancer to the 1960s space program effort to put a man on the moon. In 1970, to build momentum for the Act, Congress passed resolutions calling for a cure for cancer by 1976, the Bicentennial.

In the 1980s, NCI set forth the "Year 2000" goal of a 50-percent reduction in cancer-related mortality. After taking criticism for making too many promises, the Institute stopped referring to that goal well before 2000.

Since 1971, "oncologists and cancer patients have been caught in a cycle of euphoria and despair as the prospect of new treatments has given way to their sober realities," wrote Jerome Groopman, the Recanati Professor of Medicine at Harvard Medical School, in The New Yorker (June 4, 2001).

"Three decades later, the high expectations of the early seventies seem almost willfully naïve," Groopman wrote. "This year alone, more than a million new diagnoses of major cancers will be made and about 550,000 Americans will die of cancer, an average of 1,500 a day…. All the same, the triumphalist rhetoric that animated the war on cancer still shapes public opinion: many people believe that cancer is, in essence, a single foe, that a single cure can destroy it, and that the government is both responsible for and capable of spearheading the campaign. The military metaphors have retained their potency—even thought they have proved to be inappropriate and misleading."

According to Groopman's article, steady progress in scientific discovery, rather than directed research, is the most promising route to eventually improving cancer morbidity and mortality.

Robert Cook-Deegan, a science historian, former executive director of the Institute of Medicine's National Cancer Policy Board, and director of the Center for Genomic Ethics, Law and Policy at Duke University, similarly cautions against setting unrealistic goals.

"I think useful 'grand challenges' come in two flavors," Cook-Deegan said to **The Cancer Letter**. "One is the kind that David Hilbert proposed for math at the turn of last century, which poses interesting and important problems that shed light on fundamental holes in the fabric of knowledge. Another kind of grand challenge is the kind that J.C.R. Licklider and others at Defense Advanced Research Projects Agency posed for technology. Those were scale or scope expansions that seemed just beyond the horizon, but might be possible with enough resources and new ideas. That worked very well in computing. Arguably, it has worked sometimes in biology, like mapping and sequencing the genome in 15 years starting in 1990.

"Solving cancer, however, is a practical and clinical problem, not a purely scientific one. We simply don't know if the solution is science or technology. It seems most likely it is only partly science and technology. Moreover, the problem of cancer seems very hard indeed for science, although we can never know this in advance, and it is surely well beyond current technologies.

"Eliminating suffering from cancer by 2015 seems like it would require eliminating cancer by 2015, either by preventing it all or by having fully effective treatments for all cancers," Cook-Deegan said. "Things are moving fast, but eliminating cancer seems pretty out there, and unless the challenges are really well grounded in the science or technology, I fear that what it invites is regret in 2016, when the historians of biomedical research look at the promise.

"Reading Steve Strickland's book, 'Dread Disease,' or Dick Rettig's book, 'Cancer Crusade,' would augur caution about promising to eliminate cancer in particular," Cook-Deegan said. "Been there, haven't done that.

"The statements of 1971 looked silly when the deadline passed in 1976. I don't think the rhetoric did a lot of harm, but I don't think it did any good, either. The promise was not really sincere. There was at least a little harm in not delivering what was promised. To the degree that credibility matters—and I think it does—this is a dangerous game. Dented credibility is not tangible, but it is real, and it affects political clout," Cook-Deegan said.

"I like the spirit of wanting to eliminate cancer in 12 years, but I would ask lots of questions about the scientific and technical grounding."

Text of von Eschenbach's Remarks

The excerpted text of von Eschenbach's remarks follows:

This morning is my one-year anniversary with the NCAB. It was a year ago at this meeting that I came before you as the new director of the National Cancer Institute. I can't get away with that anymore, so I'm not the new guy anymore. And they asked me, How would you know at the end of the year whether you were successful or not?" I imagined that would mean if I was still standing.

I think you will be pleased to know that not only am I still standing, I'm still smiling. This truly has been an absolutely extraordinary year, and has been extraordinary for me from the perspective of continuously coming to fully understand and appreciate the greatness of this organization and the greatness of the people who are within it….

We are, in fact, at a very difficult period of time with regard to our country and the challenges that it faces. There is much that concerns us and therefore impacts upon us. But it's important in that regard to also keep clearly in focus a couple of very important issues that I would want to share with you.

Three months ago, the President, at the White House, at a special ceremony that was intended to honor cancer survivors, made the emphatic statement that for the first time in human history, we can say with certainty that the war on cancer is winnable, and that this nation won't rest until that victory is complete.

That quote reaffirms the incredible commitment and support that we must have as we face other threats throughout the world to not ever lose sight of the extraordinary threat that we all face from cancer, and our enormous responsibility to make good on the promise, and to fulfill the incredible opportunities that are before us because of this nation's investment in cancer research and what has occurred within this institute, and because of this institute, and we remember that there are those who are destined to suffer and die of this disease that continue to look to us to eliminate that threat.

It's also important to realize that subsequently, at a very important session with Andy Card, the President's chief of staff, who spoke to a group of the senior leadership in the Department of Health and Human Services, he reminded us that presidents get elected because they said they would do certain things.

But once they are elected, they don't necessarily get to do the things they said they would. They get to do the things they have to do. This President is faced with having to be responsive to the challenges of the budget, and recession. He is faced with challenges of protecting this country from terrorism, and he is faced with challenges now with regard to our national policies with regard to Iraq.

But Andy Card's point was, that does not mean that the things that he felt extremely strongly about prior to his election—education and health care—are not still extremely important. But as the focus has shifted, our responsibility has not.

It was a reminder to us within the department of how critically important that we stay focused on the issue of health care, and specifically the issue of eliminating cancer…

I want to tell you about an effort that has been underway for the large portion of the year, my first year, as the director.

It was an effort to bring together the division heads and senior leadership of the NCI to really begin to address long-range strategic planning. The Bypass Budget has been an extraordinary mechanism and has been extremely effective, I believe, in laying out a large portfolio of important initiatives that the Institute was committed to and sought support for. But I thought we could take that process, and broaden it quite significantly, and begin to look at long-range opportunities, and specifically to set in place a long-range mission and objective.

We have been engaged in a number of efforts across the past year with retreats that have been directed and guided by experts, in two areas. One in team building, and we really have put a lot of effort into learning and working effectively, even more than before, in recognizing how important it is for integration across the NCI, as well as the ability to work effectively within the organizational pieces of the division.

But in addition to the team building, the really important effort has gone into long-range strategic planning. Not for the purpose of developing simply a plan, as is usually the case, that then gets stuck on a shelf, but rather to create a process.

The process will enable us to continuously refine and redevelop the strategic plan for the Institute, and to do it in a way that positions us, not only with regard to our own internal operational plan, but also how it interfaces and integrates with the larger agenda that's occurring around us.

One of the things that I think has been quite important from my perspective is to look at where the NCI is today, as compared to where it has been in the past. Even within my own career in oncology, when I began my career in medicine in the late '60s and early '70s, I think it was fair to say that with regard to the world of oncology, the NCI was the universe.

There was very little else out there with the exception of a few cancer centers. But, in fact, what occurred was this incredible resource began to populate and create throughout the entire rest of the country this enormous enterprise that we now have within our grasp as a cancer initiative. Therefore, the NCI is no longer the universe, but it truly still remains the center of the universe….

So that has been the focus of the reason for the process, and I have set out and it has been embraced, I'm pleased to say, a challenge goal that shapes our mission and shapes our vision. And the challenge goal that we have accepted as an Institute is to eliminate the suffering and death due to cancer, and to do it by 2015.

I did not say that we would eliminate cancer by 2015. We are committed and we are pledged to working collaboratively and collectively together to eliminate the suffering and death due to this disease. In order to accomplish that, we have laid out a strategy that embodies the three D's, as we are calling them: Discovery, Development and Delivery.

You've heard me allude to this before, but the strategic planning process has now defined long-range, aggressive, ambitious goals within each of those areas of discovery, development, and delivery, that will ultimately get us to that vision of a world free of the suffering and death due to cancer, by 2015.

Within the portfolio of discovery, our long-range objective is that we will ultimately have defined all of the relevant mechanisms that are responsible for the initiation and progression of cancer, in the cancer cell, in the person, and in populations. Based on that new knowledge and understanding, we will have developed effective interventions that predict, detect, diagnose, treat, and

prevent the disease.

We will assure that those interventions are delivered as state-of-the-art care to all of those in need, and to do that with special reference to being able to deliver it in the context of clinical trials, so that the very delivery process itself develops and evolves new knowledge in our understanding of the malignant phenomenon.

We will do that in the context also of making sure that all populations are addressed and benefited, and that requires a special effort in the elimination of disparities.

We have been engaged in defining specific plans and specific initiatives to complement what is already in place, and to focus what's already in place, that will really enable us in a road-mapping exercise, to put into place short-term, intermediate-term, and then long-term objectives and initiatives that will ultimately fulfill those three criteria in discovery, development, and delivery.

You'll appreciate that if we are going to map that kind of roadmap of planning initiatives, that we also have to superimpose upon that a financial plan that will make certain that we are able to have adequate resources to be able to carry out those initiatives, and that is also a part of our process, to begin to look at mechanisms and ways in which we can plan for appropriate resource acquisition, and resource utilization.

We also have to do this in the context of accountability, and therefore, we will we working to define milestones and outcomes that we can then measure and have metrics to be certain that we are in fact achieving those incremental successes that will ultimately add up to and result in the achieving of our long-range goal.

We also need to do this in the context of the fact that no matter what we do, it will never be done in isolation....

So, the process that we are now embarking upon is to really, for these next months, to focus very intensely upon the NCI's internal intramural program and to crystallize and define it's strategic opportunities so that we add value to the rest of the enterprise.

We will be paying a great deal of attention to the intramural program and the opportunities that present themselves by virtue of the fact that the Clinical Center is going to be opening up in 18 months and we have important opportunities there, and we have also underway an effort to look at the activities and facilities that are up at Frederick and how we might be able to capture strategic opportunities that could be developed there, especially around emerging technologies, and the opportunity to create a biomedical infrastructure of research.

In addition to that, we are also focusing a great deal on how we could integrate the NCI's effort into the larger community. There will be a number of activities underway over these next few months that will be inviting into the planning process, the inputs from the broader community.

We heard reference this morning to Eric Lander joining you as a member of the board. Eric over the past year has been working as a volunteer to help begin to lay out and formulate a process whereby we could begin focus groups to look at longer-range scientific strategic planning.

We are also inviting into our whole process of the Bypass Budget, opportunities for the broader community and organizations to have input early on in the planning process. So those mechanisms for input are underway.

This is also occurring in the context of the fact that there are similar activities that are occurring within the National Institutes of Health, and also within the Department of Health and Human Services. So NCI's planning process is being done in concert with and in conjunction with these other planning processes.

The department has begun its efforts based a great deal on the Secretary's priorities and the President's priorities, but has also worked to define some specific trans-HHS initiatives that would really work as a cross-sectional effort of activity. There have been five that have been specifically identified for immediate attention. The major one, of course, is Medicare reform.

The next one is emergency preparedness. The next one was prevention, and then elimination of health care disparities, and then finally, information technology.

I mention those, because all of them to some degree have impact or implications for NCI, but two in specific will directly involve the Institute in a very important way. The first one being prevention, where the principal focus will not only be on tobacco, but very importantly, on the area of what I describe as energy balance, namely the issue of nutrition and physical exercise, but the overarching concern, of course, is the epidemic of obesity and the implications that has for Type 2 diabetes, heart disease, and cancer.

So the NCI is going to be playing a very integral role in the trans-HHS initiatives to address prevention as it relates to the whole area specifically of energy balance as well as reference to tobacco, as well. That initiative will in a large part be championed by the Surgeon General.

The other area that's very important is disparities and the elimination of health care disparities. In this regard, the department is actually looking to the NCI to provide the infrastructure and the leadership for the launching and support of that initiative.

It will be championed by Claude Allen, the deputy director of the department. We have already been underway with regard to discussions and interactions, particularly with the tremendous support of Cherie Nichols, in building on the great success that's been achieved using the PRG process.

As many of you know, that has been very effective in a variety of ways throughout the NCI, in moving from a strategic plan to an implementation strategy with measurable outcomes and the ability to measure progress. That has been embraced by the department and in fact will be the mechanism that will be used to begin the process of a trans-HHS initiative.

Some of you can appreciate that using cancer as a model and beginning to focus on this particular area, where we have at the table not only the NCI or NIH, but CMS, CDC, the Surgeon General, ARHCQ, HRSA, and the FDA, presents an extraordinary opportunity to really make a tremendous impact…. This will be a very important initiative for us over the next three months.

We are also working with regard to what's occurring at the NIH. Dr. [Elias] Zerhouni has convened a very extensive road-mapping experience and is focusing the NIH effort in a few particular areas at the outset.

One, to foster interdisciplinary science. He is also looking at new pathways for discovery, which brings in the role of important new technologies, nanotechnology, etc. And then the re-engineering of the clinical research enterprise.

Those initiatives have very direct significance to us at the NCI, because they in fact have already emerged as part of our strategic planning effort. We are looking very much in looking at our process of road-mapping around fostering interdisciplinary science and an initiative on integrative cancer biology, or systems biology, if you will.

We are also paying a great deal of attention to the strategic development of cancer initiatives, especially around the whole area of drug development, but that also extends to interventions that reflect behavioral sciences as well.

And then, we also have an effort at early detection, prevention, and prediction, and we're in the process of looking very much at our clinical research infrastructure.

So, the point is, you can see that the strategic planning process is one that is not simply an initiative that's occurring in isolation within the NCI, but rather, it positions us in a very unique way to play a critical leadership role at the NIH and the Department of Health and Human Services as we really begin to look at efforts that could transform the landscape, not only of cancer care, but of health care in general.

You will be hearing much more from us in the next few months as we unfold a lot of the specific initiatives to bring in your input from the broader community into the road-mapping exercises that will really be defining many of the specific initiatives that we will fold into our other processes like the Bypass Budget and our year-to-year planning activities.

The NCI will have to really work exceedingly hard to define its unique role and contributions, but it will also have to work extremely hard to partner and collaborate with the variety of other components.

We have already been fortunate to start a very exciting dialog with the FDA and its new commissioner Mark McClellan in terms of how we can effectively partner and work together to streamline some of the regulatory issues that are impacting upon our ability to move the pipeline of these new biological interventions to actual interventions that are touching patient's lives.

New Grant Program To Fund Partnerships Between Academia, Industry, Non-Profits

(The Cancer Letter, March 14, 2003, Vol. 29 No. 11)

Advisors to NCI last week approved the Institute's plan to create a $20-million grant program that would support up to six partnerships between academia, industry, and non-profit organizations for discovery and development of cancer therapies.

The Academic Public-Private Partnership Program, or AP4, is designed to encourage academic researchers to work with industry and non-profit organizations to conduct basic research that could lead to the development of cancer therapies. Since emerging therapies are likely to target specific subtypes of cancers, the therapeutics market may become fragmented and less attractive to industry, NCI officials said.

"If we can develop these kind of partnerships, then we can reduce the risk to the private sector," said Anna Barker, NCI deputy director for strategic scientific initiatives. "The private sector has got to adopt cancer in a much more major way than they currently embrace cancer, and most of our diseases are going to evolve into orphans, if targeting pays off. Targeting has to pay off for us, actually, to hit our 2015 goals."

NCI Director Andrew von Eschenbach recently announced that the Institute's goal is to "eliminate the suffering and death from cancer by 2015" (**The Cancer Letter**, Feb. 14, 2003).

The NCI Board of Scientific Advisors approved the concept for AP4 at a meeting March 2. Under the proposal, NCI would set aside $1.125 million in fiscal 2004 to fund up to 15 one-year planning grants. The planning grant winners would compete in FY 2005 for the AP4 grants.

AP4 would give academic institutions up to $450,000 a year for five years, if the institution can line up $300,000 a year from industry or non-profit organizations.

Small companies are likely to be more interested in the program than "big pharma," said Edward Sausville, director of the Developmental Therapeutics Program, and program director for AP4. "It may not be terribly attractive to companies of a certain grain size, because, quite frankly, why should they bother? They have their own in-house discovery," he said in presenting the concept to the BSA.

"A Very Big Undertaking"

BSA members who served as primary reviewers expressed enthusiastic support for the concept, but said setting up these partnerships may present a challenge to academic institutions.

"The idea of bringing multidisciplinary groups together to speed drug discovery seems to me something no one could disagree with, and most would agree it's not simple to do," said BSA member Robert Young, president

of Fox Chase Cancer Center. "This grant structure really provides a vehicle to explore the potential of getting academic institutions, for-profits, other governmental funding mechanisms, as well as disease advocacy groups together. There clearly is a lot of interest on the part of states in investing in programs which bring business into their state, and this has the potential of doing exactly that."

Young said the planning grant funding should be larger and last longer than a year. "Particularly getting multiple for-profits to agree on the intellectual property involved with these kinds of mechanisms may be a real challenge," he said.

"I think it's not clear-cut that it can work successfully," Young said. "I view it as an experiment. I think it's an experiment well worth carrying out."

BSA member Susan Horwitz, the Falkenstein Professor of Cancer Research at Albert Einstein College of Medicine, said the planning grant should continue for 18 months. "This is a very big job of setting these centers up," she said. "If you can do it in a year, that would be great, but I really feel this is a very big undertaking."

BSA member Shelton Earp, director of the Lineberger Comprehensive Cancer Center, said planning grants may not be necessary. "I think that putting this together will be somewhat difficult, but getting it together will be the real mark of institutional commitment and your partnership," he said. "You will sharpen the focus quickly about who is involved by not having a planning grant.

"Give it a year's lead-in time," Earp said. "The intellectual property problems are going to be very difficult and probably will not get solved until the last 20 days before the submission."

BSA member Richard Schilsky, associate dean for clinical research, University of Chicago, questioned the necessity of the AP4 program.

"If a center is successful in lining up one or more partners, then why shouldn't they just make a business deal and leave the government out of it?" Schilsky said. "If there are supposed to be multiple partners, and multiple for-profit partners, the probability of reaching a successful conclusion in [intellectual property] negotiations would be extremely unlikely. I'm unclear on what the NCI money is to be used for?"

Sausville said the NCI funds would be flexible, and could be used for research support, core resources, or almost anything the centers might propose. "That's not an insignificant chunk of change," he said. "Companies like the idea of participating in something that has the imprimatur of NIH peer review. Why not do a direct business deal? Sure, if they can, there's no need for us, then do it. Along the lines of the experimental nature, it would be interesting to see whether as a result of this we actually see some things happen."

William Kaelin, professor of medical oncology, Dana-Farber Cancer Institute, noted that his center has a research agreement with Novartis. "The one thing I've been constantly reminded by Novartis and companies like Novartis is that it's not that they have forgotten how to make drugs, or have lost interest in making drugs, it's simply that the only thing they really need from us are the targets, and they are really good at making drugs if we deliver the targets," Kaelin said.

"Getting back to [NCI's] 2015 milestone, a lot of what we need to be thinking about is, How do we deliver the next generation of targets?" Kaelin said. "Because, frankly, by historical standards, they should be on the blackboard now if we're going to have drugs to meet the 2015 deadline."

BSA member Mack Roach, professor in residence, radiation oncology, University of California, San Francisco, said the program didn't appear worth the money, considering that NCI budgets are likely to be tighter in coming years.

"When you have less money available, at a very difficult time, I feel a little uncomfortable being enthusiastic about an intellectual property nightmare in an underserved disease area," Roach said.

"Universities are going to have to think out of the box from the usual ways of dealing with government money and intellectual property," Sausville said.

William Wood, chairman of surgery at Emory University School of Medicine, said NCI should track how the partnerships are formed. "Many of the [concepts] we pass are a bit of an experiment, but I think it would be most unfortunate if this experiment goes unreported," he said. "Somehow, the lessons learned about how the partnerships are formed, which ones are successful, [need to be documented] if this is going to be maximally useful as an investment by the NCI."

NCI's Barker said she is looking at the overlap in some of the Institute's programs. "We have SPOREs, NCDDGs, SBIRs, RAID, centers, and now we have AP4," she said. "This is all directed at development, and we are really struggling with this transition from basic science into development, because academic medical centers are not development centers, generally. They are discovery centers.

"AP4 addresses that," Barker said. "I think it's going to call the question of how much discovery we have that's translatable. I think there's not nearly enough money in this, but that's my opinion. This is potentially something that, if it works as a model, we should put additional funds into it.

"I think this is an interesting model, and we will use it as potentially a synthetic approach to looking at these other models we're using, because there's lots of overlap here and lots of opportunity to bring tech transfer, intellectual property, some of these issues together to facilitate everything we're doing," Barker said. "This will be an interesting discovery process for us. We have a systems development problem here we really have to do something about."

"[AP4] will fit in to a larger array within our portfolio that Anna Barker has the responsibility for looking at overall, and managing," NCI Director von Eschenbach said. "We are looking for the outcome of the experiment, the best practices, and then, how one mechanism may result in the ability to downsize or eliminate or refocus other mechanisms."

The partnership program concept was approved with none opposed and two abstentions, by Wood and Roach.

The planning grant concept was approved with Wood and Earp opposed, and BSA member David Alberts, of Arizona Cancer Center, abstaining.

The edited text of the concept statements follow:

Academic Public-Private Partnership Program. Concept for a new RFA, cooperative agreement, first-year set-aside $4.725 million, six awards for five years, total cost $19.731 million. Program director: Edward Sausville, Division of Cancer Treatment and Diagnosis, tel: (301) 496-8720, email: sausvile@mail.nih.gov.

The cost of discovering and developing a drug to the point of filing a New Drug Application to allow sale to the public is now estimated at more than $800 million, and requires up to 15 years of research, clinical trials, and marketing. At the same time, emerging science has revealed subtypes of human cancers using specific genetic markers that could potentially decrease the population of patients who might be the potential recipients of such rationally designed drugs, diagnostic, and imaging technologies. This raises the possibility of creating "orphan status" markets, traditionally f less interest to large pharmaceutical companies. This concern, that "big pharma" may actually lose interest in an "orphanized" cancer market, might be addressed by defining partnerships that would leverage the risks of cancer intervention discovery and development of the future. NCI desires to catalyze these continuing partnerships, particularly between academia and industry, to realize the promise of the molecular revolution in cancer biology.

In the fall of 2001, the Office of Scientific Planning and Assessment convened a committee of NCI staff charged with outlining an implementation plan which would make the public-private partnership concept a reality. OSPA identified a potential model for NCI activities in the Industrial/University Cooperative Research Center, an initiative originally developed by the National Science Foundation (www.eng.nsf.gov/iucrc/).

NCI proposes that its modification of this approach, to be called the Academic Public-Private Partnership Program (AP4), would constitute a novel mechanism for the NCI. AP4 features are envisioned to include:

—An academic director located in a university setting who conceives of and coordinates the center.

—Academic center-related participants need not be located in the same institution.

—Industry and/or non-profit partners who contribute financially to each center.

—Participation by state or local government is possible and would be encouraged.

—A Steering Committee of the membership of each center which approves ongoing and completed activities and recommends new projects, responding to current dynamic opportunities.

—A membership agreement which specifies how the center is governed, as well as the prospective management of intellectual property issues and publication procedures.

—Facile access to the development contract resources of the Developmental Therapeutics Program for promising lead compounds approved by the center Steering Committee. Criteria for NCI interest would follow the same guidelines as those compounds or biological constructs presented to the Drug Development Group.

The ideal partnership would be anchored at an academic center and include industrial partners, non-profit organizations, and disease-oriented charities, each with an interest in translating novel anticancer therapeutic, prevention, diagnostic, and imaging interventions from the laboratory to the clinic. Each center partner could focus on different functional areas of the intervention discovery and development process. Alternatively, partners could agree to pool their resources to support one aspect of a discovery and development program; the actual roles and goals of each center's corporate members would be articulated by the academic center director in the membership agreement which governs each center's operations. There would be an initial suite of selected research projects, of interest to the partners, to be conducted at the university, and upon which approval of the application would be partially based. Major criteria for review would encourage that the research approach take advantage of the latest technologies, allowing the center to change the way molecules and other intervention technologies are discovered and developed, and focus on diseases that are underserved.

The NCI program director would attend meetings, serve as a non-voting member of the Steering Committee, and facilitate accession of NCI resources, and lend research expertise and advice to the center. The SC would be vested with the authority to make go/no go decisions on current projects and bring new projects to the center. NCI envisions that project management would be dynamic: in the lifetime of a center, funds could be shifted freely from one project area to another at the discretion of the academic center director and with concurrence of the center membership according to processes articulated in the center agreement. The effort would thus differ fundamentally from traditional P01 or other grant arrangements funded by NCI, where defined projects are expected to continue for the life of the grant.

The centers would be catalyzed by a $450,000 per year (direct costs) investment from NCI, with a minimum of $300,000 per year (total) funds coming from center members. For centers with a combined partnership

investment of at least $450,000, the NCI's annual contribution would increase to $600,000 (direct costs). Awards would be for a period of five years, subject to annual review and approval by the NCI program director. For centers where the annual evaluation is deemed unsatisfactory by the NCI program director, a subcommittee of the BSA would be formed to determine if funding should be discontinued. In the event of a recommendation to end funding, an arbitration panel consisting of NCI representation, the center academic director, and an arbitrator acceptable to both parties would make the final decision. Funding in year four would be at 75% of the initial level, and in year five at 50% of the initial level to encourage the centers to acquire additional contributing partners and to prepare to become self-sustaining entities. A second five-year award of $100,000-$200,000 (direct) per year could be made to centers successful in meeting their established goals. After 10 years, the centers which continue to operate would be expected to be fully supported by industrial, non-profit, other federal agency, and/or state and local government partners.

Purpose of RFA: NCI is seeking approval to create partnerships between academia, industry, non-profit institutions, and government to stimulate novel cancer therapeutic, prevention, diagnostic, and imaging intervention-directed research which takes advantage of the latest discovery and development technologies with a focus on orphan diseases, using a multidisciplinary approach. This effort would begin with a one-year planning grant, which will be utilized by the proposed academic director to bring together potential partners and to put together the center application. Applicants to AP4 will emerge from those successful in the competition for the AP4 planning grant, which is the subject of a companion RFA. The actual center proposal would have a clearly articulated roster of committed partners along with a detailed description of how the partners would interact. Additional information in a successful center application would include:

—Definition of the partners who will participate with the academic center as members of the Steering Committee.

—Definition by the membership of the relationships between the investigators that would comprise the multidisciplinary components of the center.

—A membership agreement that would specify the organizational structure of the center, its decision making policies for taking on and termination projects, its administration, core and shared service functions.

—Additionally, the membership agreement which describes prospectively how intellectual property will be shared by center members and define a publication and patenting policy.

The research would occur at the academic centers with the advice and support of industrial and non-profit institute partners and the NCI. NCI anticipates that selected research projects would be of great interest to the pharmaceutical industry as a whole and would be initiated as basic research projects leading to novel interventions for human clinical trials. Applied tasks such as manufacturing issues, pharmacology, toxicology, or formulation research could be taken on by industrial partners, contracted out by charity partners, or by the development contracts of DTP after meeting criteria for NCI interest.

The impetus behind the creation of such a program is to promote public-private partnerships to advance our basic knowledge of the molecular biological events which lead to the cancer phenotype, and to apply that knowledge to the development of novel cancer interventions. The strategy addresses an important problem: how to discover new, more effective treatment, diagnostic, and prevention interventions for cancer and to bring together the necessary expertise over multiple disciplines to shorten the time required to develop and deliver these interventions to cancer patients.

Each center will select research projects of great relevance to the discovery of new agents for cancer therapy, prevention, and diagnosis. The main features of an AP4 center are envisioned to include:

—The center is based at a U.S. academic institution; the academic director is responsible for all coordination and operational aspects of the center.

—Membership includes at least two non-academic partners, ideally with non-overlapping or complementary interests. Local and state governments, non-profit organizations as well as large or small companies would be eligible for membership.

—A Steering Committee comprised of representatives from all center members. This committee will review and approve the continuation or discontinuation of projects, additional resources for projects, and recommend new research projects.

—A minimum of $300,000 in membership fees from participating industrial and non-profit concerns obtained per year would qualify the center for $450,000 in direct costs per year for the first three years from NCI. Centers which obtain at least $450,000 yearly membership fees would qualify for $600,000 in direct costs for the first three years from NCI.

—The center should be multidisciplinary, with representation, for example, from chemistry, biology, immunology, and screening technologies.

—A program administrator must be appointed who will be responsible for assuring that a center evaluation process, which includes standard feedback forms describing the progress of each project, is conducted as part of each SC meeting.

—Selected research projects are anticipated to be of interest to the pharmaceutical industry as a whole and are initiated as basic research which could culminate as interventions. The initial review, to secure funding, should

showcase at least five projects coordinated by the academic director for the initial year of funding, with clear evidence of criteria for go/no go decisions and evidence of the ability to recruit new project areas for the full period of funding.

—AP4 is anticipated to be a dynamic initiative. Not all projects or investigators may be funded for the duration of the agreement. The SC is vested with the capacity to add, delete, or evolve the resources associated with particular projects. The NCI program director will offer perspective on these issues, but will not direct the work.

—Renewal of annual funding will occur according the usual criteria for multiyear commitments.

—Fast access to the development contract resources of the Developmental Therapeutics Program (formulation, bulk synthesis, pharmacology, toxicology) for promising lead compounds approved by the center Steering Committee, provided that the agent selected meets criteria used by NCI evaluate its other drug development opportunities.

—IND-filing assistance through the Cancer Therapy Evaluation Program for an NCI-based clinical trial or a principal investigator-based trial will be afforded on a case-by-case basis. This may involve assistance in putting together INDs when held by the originating center or assumption of the IND if the agent is to be studied more broadly in NCI's existing early clinical trials groups.

—A membership agreement must be signed by all participants which includes membership rights and fees, publication rights, patent rights, and definition of the terms of royalty-free, non-exclusive licenses to members, and must follow "NCI Principles and Guidelines for Sharing of Biomedical Search Resources" to address the sharing of easily-transferable research findings.

Each center would be required to submit an annual report to the NCI DTP program director. These reports would be used as a basis for assessing annual performance and determining continued funding. The reports should include major accomplishments, the operating budget, completed center evaluation, research goals, and the process being used to communicate with center members.

Evaluation metrics should be determined by each center and should be included in the center application. Metrics could include an accounting of the center's success in attaining the goals outlined in the application.

Academic Public-Private Partnership Program Planning Grant. Concept for a new RFA, 15 one-year awards, total $1.125 million. Program director: Edward Sausville.

Only recipients of a planning grant will be eligible to submit an AP4 center application. Elements of a successful planning grant might include:

—A summary of the proposed projects, how the projects would impact the diagnosis, prevention, or treatment of cancer or a specific cancer, and how the areas of research are appropriate to an academic environment.

—A brief description of the capabilities of the university, including faculty and infrastructure.

—The organization of the center, policies, management plans, and operational procedures.

—Costs for the center.

—An outline for a meeting with potential partners designed to determine the research agenda and its viability.

—A description of the managerial experience of the proposed academic director, and the roles of other researchers in performing the proposed studies.

—Letters from potential center members stating that the proposed research agenda of the center in concordant with the organization and that the organization would consider joining if the center were formed.

A letter of intent would precede the application and be reviewed by the NCI program director. A $50,000 (direct) one-year planning grant, which would be competitive and peer-reviewed, would be utilized by the proposed academic center administrator to study the feasibility of developing the pharmaceutical/non-profit/academic interaction necessary to establish and support a center, and to actually prepare the application. The planning grant period should include a meeting that brings together potential members to explore opportunities, define how intellectual property issues would be handled, and establish a research plan. The ideal planning grant would arise from an academic center with a clear track record in cancer biology with an overall theme and/or disease identified, along with a range of potential partners to be sought in actualizing the program, and resources to be brought to the program by the institution—letters of commitment to join a center would be desirable, but not necessary, for the planning grant.

More Aggressive Prevention, Detection Could Save Lives, Cancer Policy Board Says

(The Cancer Letter, March 28, 2003, Vol. 29 No. 13)

More than 60,000 Americans die prematurely each year because of the nation's failure to fully implement proven methods of cancer prevention and early detection, according to a report by the National Cancer Policy Board of the Institute of Medicine.

Behavioral interventions to promote healthy lifestyles and cancer screening could reduce cancer incidence and mortality, but have not been aggressively adopted by individuals and the health care system, the report issued March 10 concluded.

"A 19 percent decline in the rate at which new cancer cases occur and a 29 percent decline in the rate of cancer deaths could potentially be achieved by 2015 if efforts to

help people change their behaviors that put them at risk were stepped up and if behavioral change were sustained," the report said. "This would equate to the prevention of approximately 100,000 cancer cases and 60,000 cancer deaths each year by the year 2015."

The health benefits of behavioral change also would extend to reductions in the rates of cardiovascular disease and diabetes, the report said. The policy board was established by IOM with funding from NCI.

"To save the most lives from cancer, health care providers, health plans, insurers, employers, policy makers, and researchers should be concentrating their resources on helping people to stop smoking, maintain a healthy weight and diet, exercise regularly, keep alcohol consumption at low to moderate levels, and get screening tests for cancer that have proven effectiveness," the report said.

While the health behaviors that increase cancer risk are well-recognized, there is growing evidence that health care providers can intervene effectively to help people change their behavior, the report said. For example, providers have been able to boost smoking cessation rates by adhering to tested guidelines.

The report, "Fulfilling the Potential of Cancer Prevention and Early Detection," reviews the evidence that cancer incidence rates can be reduced, describes effective interventions, and outlines a national strategy to increase the adoption of healthy behaviors, and cancer prevention and early detection interventions.

"The nation needs new strategies to prevent cancer and, when cancer occurs, to catch it at its earliest stages," the report said.

Recommendations of the report:

1. The U.S. Congress and state legislatures should enact and provide funding for enforcement of laws to substantially reduce and ultimately eliminate the adverse public health consequences of tobacco use and exposure.

2. A national strategy should be developed and coordinated by the U.S. Department of Health and Human Services to address the epidemic of obesity, unhealthy diet, and physical inactivity in America, which are all significant risk factors for cancer and other diseases. Effective interventions need to be identified and broadly applied to reduce cancer risk among the general population and among populations at higher risk.

3. Congress should provide sufficient appropriations to the Centers for Disease Control and Prevention to support innovative public and private partnerships to develop, implement, and evaluate comprehensive community-based programs in cancer prevention and early detection. Every state should have and implement a comprehensive cancer control plan.

4. Public and private insurers and providers should consider evidence-based cancer prevention and early detection services to be essential benefits and should provide coverage for them. These services at a minimum should include interventions recommended in the 2000 U.S. Public Health Service's clinical practice guideline on treating tobacco use and dependence, screening for breast cancer among women age 50 and older, screening for cervical cancer among all sexually active women with an intact cervix, and screening for colorectal cancer among adults age 50 and older.

5. Congress should increase support for programs that provide primary care to uninsured and low-income people (Community and Migrant Health Centers and family planning programs of Title X of the Public Health Service Act). These programs increase the use of cancer prevention and early detection services among medically underserved populations.

6. Support for the CDC's National Breast and Cervical Cancer Early Detection Program should be increased so that the program can reach all uninsured women using innovative delivery strategies. Support is also needed for a similar program at the CDC to provide screening for colorectal cancer for uninsured and low-income men and women.

7. HHS should complete a comprehensive review to assess whether evidence-based prevention services are being offered and successfully delivered in federal health programs.

8. Programs are needed for health care providers to improve their education and training, monitor their adherence to evidence-based guidelines, and enhance their practice environments to support their provision of cancer prevention and early detection services.

9. Congress should provide sufficient support to HHS for the U.S. Preventive Services Task Force and the U.S. Task Force on Community Preventive Services to conduct timely assessments of the benefits, harms, and costs associated with screening tests and other preventive interventions. Summaries of recommendations should be made widely available to the public, health care providers, and state and local public health officials and policy makers.

10. Public and private organizations (e.g., the National Cancer Institute, the American Cancer Society) should take steps to improve the public's understanding of cancer prevention and early detection with a focus on promoting healthy lifestyles and informed decision making about health behaviors and cancer screening.

11. Public and private initiatives to reduce disparities in the cancer burden (e.g., initiatives of NCI and ACS) should be supported.

12. Public and private sponsors of research should expand their support of applied behavioral research and how best to disseminate evidence-based prevention interventions.

The policy board's report is available for for purchase or for reading online at no charge at http://search.nap.edu/books/0309082544/html/.

Von Eschenbach Presents His "2015 Goal" As Logical Progression of Cancer Program

(The Cancer Letter, May 16, 2003, Vol. 29 No. 20)

NCI Director Andrew von Eschenbach said science has the tools to "eliminate the suffering and death from cancer" by 2015.

"This is...not a pipe dream," von Eschenbach said in an interview May 12 with ***The Cancer Letter*** *editors Kirsten Boyd Goldberg and Paul Goldberg. "It is a natural extrapolation of the progress that has been made."*

In the interview, von Eschenbach described cancer as a "systems problem" that can be addressed through better coordination of resources. One such effort is the Institute's nascent collaboration with FDA, aimed at streamlining development of cancer therapies, he said.

Von Eschenbach said "proof of principle" has been established for several strategies for preventing and treating cancer. "I don't have to prove to you that chemoprevention is, in fact, a viable strategy," he said. "That has already been done.

"What I have to do is get more of them."

CL: You were scheduled to give a talk at the American Association for Cancer Research meeting last month. The meeting was cancelled. What were you going to talk about?

VON ESCHENBACH: That was really unfortunate, because I was really looking forward to that being a way to flesh out and really provide a lot more detail to the challenge goal of 2015. That is going to still actually occur, because, you know, we rescheduled the meeting.

The unfortunate thing, though, was that I would have loved to have done that at the AACR when it was originally scheduled, and then that would have set the stage very nicely for this presentation that is coming up just in a couple of weeks, which is the joint presentation at [the American Society of Clinical Oncology annual meeting] between [FDA Commissioner] Mark McClellan and myself.

Mark was confirmed at 10 o'clock on a Thursday night by the Senate, and that next morning, Friday morning, at nine o'clock, we had our first meeting. Mark and I have been working, collaborating, and discussing how we could effectively bring the two institutions together. We formed a joint task force that actually had its first meeting a week ago.

We are looking at opportunities where we can work together, because I was really looking at structuring our effort in the context of a portfolio that contained the three D's as they are referred to now—discovery, development, and delivery.

The idea being that we wanted to rapidly and continuously accelerate the engine of discovery, but then based on that knowledge, translate it rapidly into the development of interventions that could then be delivered to patients who are in need, in the context of a clinical research construct that gave us the opportunity, even in the application of these new interventions, the development of new knowledge about the biology of cancer and the disease's process.

So, that really is a circular process in many respects, and part of that ability to really accelerate discovery, development, and delivery calls into play the need for collaboration and cooperation, and so FDA is a critically important partner, because if we can work effectively together in the discovery, in the development, and the approval process, then both of those organizations really, I think, have an opportunity to meet their mission.

One of the things that we want to share is a very strong commitment to put the patient at the center of everything that we do. We have our roles and our responsibilities. The role and responsibility of the Cancer Institute is research. We have to be responsible for developing the knowledge and understanding of cancer. FDA has a responsibility for the safety and the demonstration of efficacy as part of the regulatory process. But in both cases, those missions have a purpose, and the purpose is to improve people's lives.

CL: What specifically would you be doing with FDA?

VON ESCHENBACH: We want to look at two things. We want to look at, first of all, are there programs where we could develop initiatives that would bring the two institutions together to work collaboratively? And, are there processes that are under way in the institutions that could address that, and that would make it more efficient, and more effective. There are a lot of things going on at the grass-roots level, with different people, and for example in NCI's Cancer Therapy Evaluation Program working with people at the FDA.

In the intramural program, we have had [NCI's] Lance Liotta working with [FDA's] Emanuel Petricoin in terms of the proteomics initiative and developing markers for cancer, or signatures for cancer detection.

So, there have been a lot of things that have been going on, but what we are looking at are ways that we can kind of help facilitate those interactions. The task force is looking in the areas where we can begin to try to work collaboratively, for example, in bioinformatics.

CL: How about endpoints?

VON ESCHENBACH: Endpoints is another area in which we are going to be focusing and working together in terms of defining—we are looking at a title or a new label that we consider to be endpoints of clinical benefit, a euphemism for what people refer to as surrogate endpoints.

The point being that there is a lot of work that has to be done in terms of how that gets integrated into the validation process on our end, and how it gets integrated into the approval process on their end. But we both recognize that as we look down the road at the new paradigm, that we are looking at outcomes that are not going to be dependent upon survival, and may not even

be dependent upon the demonstration of objective response to the tumor, but are going to be dependent upon our ability to demonstrate the module to the pathway, or we have affected a marker of gene expression, or a kinase expression, or whatever.

CL: This is being done between FDA and ASCO right now. Is this going to be different, or is it going to be the same process?

VON ESCHENBACH: We are trying to do this in a way that it is all integrated. The ASCO effort, the NCI effort, the FDA effort—these all are going to be coordinated and integrated in a way—the National Dialogue on Cancer effort.

CL: How does the National Dialogue on Cancer fit in?

VON ESCHENBACH: Well, their Research Task Force has been looking at ways of streamlining the development of drugs based on genomics or proteomics, and issues that they have been looking at have to do with surrogate endpoints, and they have also been looking at ways of creating infrastructure, like a national tissue resource repository.

So, again, what you see, and I think what has been the real hallmark of this, is that there are a lot of groups who are working at various parts and pieces, and what really is, I think, our opportunity, is to help provide more integration and coordination among those pieces.

I think that is part of the NCI's leadership role, is to help serve as an integrating force.

CL: Would the FDA be involved in the NCI "State-of-the-Science" meetings and dealings with the European Organization for Research and Treatment of Cancer?

VON ESCHENBACH: Well, I don't have that kind of detail or that specificity for you at this point in time. The task force has had its first meeting, and we had a series of conversations. I have gone down to the FDA and presented to their Executive Committee in terms of what I am hoping to accomplish and achieve. So, we are in the process of looking for the answers to the specific questions you have raised, exactly how this will play out. I think that's a work in progress. The real important thing is that, in addition to there being a lot of effort at what you might call the grass-roots level, now, at the very top, as far as the Commissioner and the Director, you have a cohesive message of the fact that we want to cooperative and collaborate, and we are going to drive that agenda, and out of that should flow opportunities.

CL: What about endpoints for prevention? Is that an issue or is that also something that needs to be looked at?

VON ESCHENBACH: Prevention is another one of the areas that the task force looked at, and the prevention part of it has two pieces. One, prevention from the point of view of needing to look at, for example, things like diet.

CL: I was thinking of chemoprevention.

VON ESCHENBACH: Chemoprevention is the other piece, yes. That is on the agenda. The task force has identified various people who are kind of invested in those particular parts and pieces.

One of the things that I think the ASCO meeting will do is, when we have the joint presentation, immediately following that, I think we will be able to provide you with a lot more specificity in terms of the areas that have been identified, and here are the people who are going to be involved in some of the discussions, and these are the directions that these things are moving in, and I will be able to provide that.

CL: The overall goal is to streamline and speed up drug development and approval?

VON ESCHENBACH: Yes. I think what our vision is, is that if we can kind of partner effectively and synergize the strength and power that we have on the front end of the process, where we are responsible for driving the discovery, and the understanding, and do that in a way that is in concert with what they have to be responsible for, in terms of the approval process, that gives us an opportunity, I think, to streamline and find ways to accelerate, and bring the pharmaceutical and biotechnology, the academic sector, into this in an effective way, so that we are all working from the same page of the book.

We don't want a process that goes on up here, and then when it goes down to the FDA, you find out that, well, you have got roadblocks or barriers that if you had only known up here, you could have steered it in a slightly different direction. We want to make it as fluid a process as possible to go from the very fundamental level of discovery, to the point where we really have an intervention that's being delivered to patients, and that intervention is safe, and that intervention, most importantly, is effective.

The worst thing that we can do, we both agree, is to provide things for people that are ineffective and that don't work. But we have got to find a way to address that, without it being a process that goes on for decades. I mean, that just is not acceptable.

CL: Do you want to talk about 2015?

VON ESCHENBACH: Yes. 2015—let me just back up and say that one of the things that we have not had a chance to talk about after our first interview, was how things have evolved over the first year (**The Cancer Letter**, Vol. 28 No. 13, March 29, 2002). When I came in, I began a process of really beginning to look beyond the Bypass budget, so to speak, or a year-to-year operation, and really began to look at a much longer-range strategic planning process.

What was apparent to me at that time as we discussed in the first interview, was the incredible amount of progress that had been made, and the incredible amount of success that had been achieved by virtue of what had gone on before—before my arrival here, and over the period of time that we have had this tremendous explosion in biomedical research, and since 1971, the tremendous progress that

occurred by virtue of the National Cancer Act.

So, here we were in having this incredible opportunity that I described in the context of a strategic inflection. What we need to do is to look at that progress from the point of view of, number one, focusing on it, or focusing it, rather.

I use the tag line that this was "progress with a purpose," and the purpose, of course, was really for us to be able to alleviate the human suffering and death that is associated with cancer.

I mean, affecting people's lives is the purpose for this progress. So, first and foremost, I really wanted to call that focus into a very clear dimension, and put the patient at the center of everything that we were doing, and then, create a portfolio that drove towards serving that patient, and that portfolio made it clear when you looked at the continuum of discovery, development, and delivery, that everybody had an important part to play in that. That it was as much an important role for the basic scientist, for the population scientist, for the clinical scientist, that everyone had an important part. What we were really doing was not only accelerating the individual pieces, but looking for the integration. The concept that we required that individual excellence, but to win we had to really play as a team. We had to integrate. If one step back and looked at that progress, and looked at the trajectory that we were on, you began to realize that the trajectory is really not linear. It is really exponential. It's truly expanding at an explosive rate. Not only is our intellectual understanding of cancer as a disease process expanding at an exponential rate, it is being supported—that growth is being supported by, one, a significant investment in financial capital, and there has been significant development of intellectual capital. Third, is that that whole thing is being nurtured and supported by an equal expediential growth in enabling technologies. Now, you just step back and realize what is possible today, just because of the tools that we have available to us in informatics, in computational technologies, and you name it, robotics—I mean, pick one.

CL: Some scientists have expressed a lot of skepticism about your saying that you are going to eliminate suffering and death from cancer by 2015.

VON ESCHENBACH: Right. And they should. I welcome the skepticism. I welcome the opportunity to engage in that conversation, in terms of, so why do I think that this is, in fact, achievable? I won't give you the whole lecture, because you have heard it before.

CL: Are there new technologies, or do you see something that others don't?

VON ESCHENBACH: Well, if you take the premises that I just laid out, that we are in the midst of a biomedical revolution, and the strategic inflection, and exponential growth is real, and that we have intellectual capital and financial capital that is greater today than it ever has been, and there is more money being invested in cancer research today than ever before, that there are more people engaged in the process than ever before. So if you take that as a given, and then we step back from it and ask the question, "So where is it leading us? Where can it take us?"

One of the things that came out of that is the conclusion, in my opinion, that I don't know when we will eliminate cancer. I think some day we will eliminate cancer, but I don't have any idea when that's going to be.

But I think that there is a more proximate step, and that is, we may not eliminate cancer, but we can eliminate the burden of the disease by being able to control and modulate the disease. That is the implication of this biomedical revolution, and this paradigm that I talked about; moving from seek and destroy to targeting and control.

If you think about what we have learned about cancer, what we have learned is that cancer is a disease process. It has a pre-initiation, an initiation, and then it has a pattern of progression. Ultimately, it results in people suffering and dying.

CL: But 5-FU is a target and control drug. It's 50 years old. The most recent drug to be approved, Iressa, is helping one [lung cancer] patient out of a hundred, and we don't know how much it is helping them.

VON ESCHENBACH: Think of it this way. Don't think in terms of single individual interventions and whether they are or are not the magic bullet. There is no magic bullet. There is no single intervention that is going to do this. But, first, let's step back in terms of thinking about 2015. The goal is to eliminate the suffering and death due to cancer. I never said we would eliminate cancer. I said we would eliminate the suffering and death due to cancer. The point of that is, is that if you look at what we are dealing with, we are dealing with a disease process. There is some point in time where we begin to become susceptible to the development of cancer. It may be because we smoke. It may be because we are just getting older. It may be for a variety of things.

There is a period of susceptibility and then there is a moment of transformation. Then, at that point, there is a period of time in which that malignant process evolves in a subclinical way to the point where it actually becomes clinical disease that is able to be detected or diagnosed.

At that point, it actually then goes through a series of processes to the point where it becomes a lethal phenotype, almost always involving a metastatic phenotype.

People, with rare exceptions, do not die of primary tumors. It's the metastatic phenotype that is lethal. So you have a cancer burden phenomenon of increasing to the point of death, and you have a time frame over which that occurs. If you look at this then as a process, as a cancer process, you realize that there are multiple distinct steps that have to be involved in this process, steps that involve all the mechanisms that you are well aware of, from proliferation, to evasion, to dissemination, et cetera, et cetera, et cetera.

They are all processes that are associated with this ultimate outcome of suffering and death. We can begin to think, not of a magic bullet. There's not going to be one single intervention that is going to solve this problem. But we can think of multiple interventions that can be applied to essentially pre-empt this process from occurring. If you can pre-empt this progression curve, you can do a couple of things. One, you may even delay the time—what we will have at 2015, is there may be many people by virtue of things that we are doing and have been doing with regard to what we think of as prevention strategies, be they behavioral modification or chemoprevention, or whatever, where you may even shift this curve long before they even develop it.

CL: You are making it into a diabetes, or—

VON ESCHENBACH: Exactly.

CL: —a chronic disease.

VON ESCHENBACH: Chronic disease is the better word. You are doing two things. You are exploiting, one, the opportunity for the fact that there are many of these diseases that, if we detected them early, just the simple fact of being able to move our intervention point to the left. Let's assume, for example, that spiral CT works.

CL: But you are making assumptions.

VON ESCHENBACH: What assumption? Pick an assumption.

CL: Where are the modalities for, say, chemoprevention intervention? If you hit that one, you have hit 2015, but with what? You are assuming a cure.

VON ESCHENBACH: Do I have them today? Do I have all of the—

CL: Or some of them.

VON ESCHENBACH: Sure you have got some of them. I mean, you have got proof of principle with these things. In other words, I don't have to prove to you that chemoprevention is, in fact, a viable strategy. That has already been done.

What I have to do is get more of them. I don't have a full palette of those things, and so we need many, many more. For example, pick a couple. I mean, there are trials underway with prostate cancer and finasteride. You have got vitamin E and selenium. Will those things work? Will there be other things we develop and design?

CL: But you are out on a limb now.

VON ESCHENBACH: The assumption is not that chemoprevention will work. The assumption is, how many effective interventions can we develop and create and apply. So that's one piece. Early detection—I don't have to prove the assumption that early detection works. I just have to increase the palette of options and opportunities. Will proteomics and the work that Petricoin and Liotta are doing with the protein signatures that have looked tremendously exciting in ovarian cancer, and are beginning to be applied to other cancers, will that continue to play out? Will we be able to exploit the opportunities in proteomics for early detection, and be able to shift this curve in certain diseases? Just think of what we could do if we shifted the curve in lung cancer, where the greatest burden of death is right now for us.

CL: How would you shift the curve? That's the question. What are you going to give them, Iressa?

VON ESCHENBACH: No. Don't get trapped in one thing. That is my point. That's why I have got multiple arrows here [referring to a slide showing a cancer progression curve with arrows noting points of potential intervention]. Let's take lung cancer, OK? Look at how many places along this trajectory you have an opportunity to make a difference in lung cancer.

You have got opportunities down here with regard to pre-malignant transformation, OK? That stuff has already been in the bank, for the most part, in terms of smoking cessation, and things of that sort. Look at what you could do with early detection, of being able to exploit "son of spiral CT scanning," OK? I don't think spiral CT scan is the answer to early detection, but it can be, and may very well be, a major step. But we may have other things. Maybe the proteomics. Maybe what Lance Liotta is doing with proteomics will work. Think of what we could do if we could just develop more effective interventions for advanced disease.

CL: It's not as if scientists have not been working on this for some time.

VON ESCHENBACH: That's right.

CL: That's what NCI does.

VON ESCHENBACH: Right. It is not new. It is the realization that we have come to a point where we have the opportunity to now integrate and coordinate all of this opportunity in a way that gets us where we want to go to change the shape of this curve. This is doable. To eliminate the suffering and death due to cancer is not a pipe dream. It is a natural extrapolation of the progress that has been made. What we have got to do is to recognize that goal is within our grasp, and not only continue to rapidly accelerate the development of all of these various opportunities and interventions, especially around our exploiting the phenomena of metastasis and our understanding of the fundamental mechanisms. But, every time we understand one of those mechanisms, to rapidly begin the process of developing and getting available—and that's the FDA story again—approve an intervention, and then be able to strategize the integration of these interventions based on the tumor and the host. And if we apply them in an integrated fashion, some of these diseases we will eliminate, and other diseases we will modulate to a chronic disease. This is doable by 2015.

CL: It's almost like you are discussing this as an engineering problem. Is it?

VON ESCHENBACH: Basically for me, I think it is both. That's why the discovery, development, and delivery piece is important, because as you look at this, there are so many places within this process that we have got to intervene, and we have got to get things aligned.

The clinical trials infrastructure needs to be reengineered.

CL: Why did you feel that you needed to say 2015? Because what you are describing is non-controversial. The controversy comes in when you say 2015, because you are out on a limb. Your two predecessors in this office have specifically said, "I am not making any predictions." Other predecessors of yours have made predictions, with not the best outcomes for themselves.

VON ESCHENBACH: I have established that we have to set a time line and we have to drive to that goal and make the commitment. Every part of this community, I am asking people to commit to doing what is necessary to rapidly accelerate this progress and the integration of the pieces. There is a lot of work that has to be done in so many of these arrows, OK? It's doable, and the NCI is committed to providing the leadership and to try to catalyze and to work collaboratively and cooperatively, and to bring us to the focus of driving to that goal.

CL: Covering FDA, I am trapped thinking of the interventions that are out there that are in the pipeline, and maybe I am missing something.

VON ESCHENBACH: I don't want to overplay the FDA. I mean, the FDA is one opportunity. I think there are multiple places in which we have to collaborate and cooperate. I mean, you know that when you first came to see me that one of the questions you asked me was the Dialogue, and why the Dialogue? There lies another mechanism, and it is another place, and it is another opportunity for us to engage in cooperation, collaboration, and integration, where we can find ways to bring this process to the fore.

I have created a mechanism here—well, not created, but I have emphasized the mechanism here—where all of the major organizations come in for meetings, and there is an opportunity to engage with various staff based on the agenda, and then I have a face-to-face meeting with [them]—AACR, ASCO, and on down the line. Because, we have got to work and find the places where we can interact and synergize, and work towards accelerating this. We have looked the cancer centers, and we had the P-30 and P-50 working group, which has brought its report forward. I am now launching a very active recruitment to bring in another deputy director. We know and recognize that we have an enormous opportunity with regard to the cancer centers, not in terms of just what their individual contributions are, but what our opportunities are with regard to more effective horizontal integration of the cancer centers working with each other, and more vertical integration of the NCI supporting the cancer centers, and the cancer centers becoming much more embedded into the community programs. So, if we can really effectively drive and maximize that kind of integration, and cooperation, and collaboration, that accelerates our ability to get to this endpoint.

CL: You are recruiting a deputy director for clinical research?

VON ESCHENBACH: Well, the deputy director, you know, Anna Barker [NCI deputy director for strategic scientific initiatives] came in, and she brought with her, her background as a Ph.D. basic scientist, and especially in looking at things from the perspective of how could we more effectively accelerate efforts that go from discovery to development. What I am looking for in this other deputy director is a clinician who has great experience in terms of development to delivery, more of a translational effect, if you will, but particularly looking at the delivery component, where we have to bring those pieces together. So that is the kind of effort, and that is the structure.

CL: Would that person also direct the Division of Cancer Treatment and Diagnosis?

VON ESCHENBACH: No, that is a separate recruitment, and that is just about final.

CL: What about other recruitment? You have acting heads of the Office of Communications, the Division of Cancer Control and Population Sciences—

VON ESCHENBACH: Well, again, Bob Croyle [acting DCCPS director] is the designate there, and we are going through the final processes with him on the approval of his position, but Bob Croyle brings a tremendous set of skills to the DCCPS. I mean, his personal investment in behavioral science and his ability to orchestrate the full dimension of that, and he is going to be—and I should let him speak to his plans for the division, but I am really excited about a lot of the things that he is going to be doing. He brings a wonderful mix of leadership to the organization. I really believe very strongly in shared governance, and the role and importance of the Executive Committee and the senior leadership team working effectively as a team has been a part of what we have been working on this past year. We have been through a strategic planning effort, which is really to kind of lay out the broad portfolio, and to really define what our strategic initiatives have to be in terms of getting us to this goal.

So, you will be hearing about specific initiatives that we are going to be undertaking. I mean, part of what's going on is a systems problem, that as you pointed out, it is an engineering problem.

CL: I am not sure it is an engineering problem. I was asking *whether* it is an engineering problem.

VON ESCHENBACH: Well, I think it is.

CL: I mean the biology part of it. Is it an engineering problem?

VON ESCHENBACH: Well, I think it is an engineering problem, if we are saying the same thing and by what we mean by an engineering problem.

CL: Gleevec is an engineering sort of drug, but—

VON ESCHENBACH: Oh, we may not be saying the same thing.

CL: I was wondering whether cancer as you are showing it here—I mean, you are talking interventions, and people working together, and that is sort of an

engineering of a system.

VON ESCHENBACH: Yes.

CL: I am thinking of engineering in biology. Is the underlying biology an engineering problem?

VON ESCHENBACH: Let me answer it in this way and see if we are using the right concepts, and maybe not exactly the right word. Cancer is a systems problem, and the solution to cancer is a systems problem. Cancer in itself is a systems problem, in that it isn't simply the identification of the individual pathways and processes, the identification of the genes, the identification of the circuits, or the signal transduction pathways. It's also the understanding of how those pathways and processes are interrelated. What is the role of robustness and redundancy, in terms of how these systems work? So, one of the things that we are going to be emphasizing programmatically is the whole area of systems biology, because now, it is not only a matter of identifying the various components and pieces in a reductionist way, it is also the need to help figure how they link and integrate. Maybe when you interfere with one particular mechanism, there may be other pathways that also are important if you want to get the desired outcome, because there is redundancy in the system, or robustness in a way that is difficult to do.

So, if that is what you mean by an engineering problem, the answer is yes. It is a problem and it is a challenge for us to do the integrative biology, as well as the identification.

CL: I guess the reason I was asking is that when you come up with a Moon Shot sort of approach, which was a pure engineering problem, you could in principle set a goal. Here, you are setting a goal based on something that is one of the greatest mysteries of the universe.

VON ESCHENBACH: Yes, but where I think there is a critical threshold here is—just like I said, I don't know how long it will ever take us to eliminate cancer completely. I don't know how long it will be before we ever fully understand cancer. We may never. We don't need to know everything about cancer. We need to just know enough. Now, you might ask the question, "So what's enough?" But, the point is, don't set the problem in the context of cancer being so complex and so overwhelming in its biologic profundity, I guess, that it, therefore, is an insolvable problem.

It's not a question of solving the problem of cancer. It is a question of managing the disease process, to preempt it from ultimately taking someone's life and creating the suffering.

People don't die because they get cancer. If that were true, I would be twice dead. People die because they get cancer and we don't preempt it. Either we don't detect it until it is too late, or we don't have the weapons to change or modify its behavior, et cetera, et cetera.

Our goal is to ultimately understand cancer, but our goal right now is to understand it enough, and exploit that knowledge effectively, which is the real part of it, to be able to preempt the disease's ultimate expression of a lethal phenotype.

CL: But it's still really a major goal here.

VON ESCHENBACH: Of course it's a major goal! Of course it is. But in 1971—and so you ask, well, what is this? Another Nixon thing, with the National Cancer [Act]? In 1971, when that goal was established, we didn't have the tools, nor did we even have the fundamental rudimentary knowledge. Just think of what has happened, and think of what has happened even in increments, such as if you just think of what has happened in the past decade.

The point that I am making is, what I have asked the community to do is, to step back and look at the problem from that perspective. Look at the problem from the perspective of the tremendous progress that has been made. Look at it from the perspective of the tremendous investment that we have today in intellectual capital, in resources, in enabling technologies. Look at what we have learned about cancer as a disease process.

The various places along this pathway that we now have real—not imagined, not hoped for—real opportunity to impact and to make a difference. Proof of principle has already been established. We just need to drive the expansion of that principle, whether you are talking about chemoprevention, whether you are talking about mechanistic-based interventions, et cetera.

Just look at all of that, and then recognize that that has positioned us in a way that in 1971 was unimaginable and unfeasible, and being positioned, now in what I expect and look forward to us doing, is to rapidly accelerate and catalyze the effort to pull this all together.

We have got to keep moving with regard to discovery. Of course, we don't know enough about cancer, and we need to know a lot more. Of course, we have got many more things to learn and discover. Of course, all of those things are true.

But, at the same time, having said that, just think about what is within our grasp. So, what the NCI is going to do, is to commit to continuing to drive the research agenda, and at the same time provide the leadership to bring the components and pieces together in a collaborative and integrative way that really get us to the point where we have made a difference in people's lives. That's the vision.

CL: Who do you look to for advice on the science?

VON ESCHENBACH: I am working through a lot of various ways of doing that. This is to be an embracing kind of effort that brings the entire community together. So, with regard to science, we have tremendous resources within the Institute itself, and even today, later this morning, I have a group of the intramural scientists coming in—Steve Rosenberg, and the usual players, and Carl Barrett [director of the Center for Cancer Research], and Dinah Singer [director of the Division of Cancer Biology], and

people like that are fabulous.

Outside the Institute, we have been working a couple of different agendas. Eric Lander [director of the Whitehead Institute's Center for Genome Research] comes on the National Cancer Advisory Board, and shortly, even before I arrived, I went up to Boston and met with Phil Sharp [director of the McGovern Institute for Brain Research, MIT], who at that time was the chairman of the National Cancer Advisory Board, and while I was there, I met with Bob Weinberg [Daniel K. Ludwig and American Cancer Society Professor for Cancer Research, MIT], and Eric Lander, and Tyler Jacks [director, Center for Cancer Research, MIT].

Eric took on some responsibility for helping to drive a lot of discussion of the focus groups that will look at the various scientific challenges that you have been alluding to. We have put together focus groups that Dinah Singer and Carl Barrett have been developing and working, bringing people into the institution to help. I am really looking for a variety of ways of gleaning that real intellectual talent to bear in helping to think about the next step. We have reached out to a number people around emerging technologies, and what we ought to be doing capitalizing on things like nanotechnology, systems biology, the whole area of imaging is extraordinarily exciting, and we have to be sure that we are positioning ourselves in a way to nurture and develop that.

CL: Is the National Dialogue on Cancer serving as kind of an advisory body?

VON ESCHENBACH: No, the Dialogue hasn't really been an advisory body, as much as it has just been just that, an opportunity for dialogue and discussion. The one place that I think we have really had tremendous experience has been with the research team, and Anna Barker has been heading that up, which has made a nice link. But, the research team has really been focusing people on the issue of how can we accelerate the process of the development of these interventions, and I think it has been great to be a part of that discussion, and great in terms of trying to bring all the pieces of the community together.

Because, as I said early on, long before I ever came here, cancer is not just a medical and scientific problem. That is what we are critically focused on here. But it is a societal problem, and it has got all the other components. Just looking at maps the other day—death rates from cervical cancer in Appalachia, which we need to be concerned about, and how can we be thinking strategically about addressing that? Because that's not an issue of, we have to develop a new therapy, and we have to develop a new intervention. We have adequate tools—and we need better tools—but we have adequate tools with regard to cervical cancer, but we have to be sure that we are applying them.

CL: Do you ever see opening up the Dialogue to coverage? What happens now is, you have to be a member to be there. So, it's a problem.

VON ESCHENBACH: We can come back some other day and talk about the Dialogue in a different context. I can't speak for that, because that is not my decision.

CL: Do you see the National Cancer Policy Board as something that is useful to NCI?

VON ESCHENBACH: The National Cancer Policy Board has been useful. I think, like with everything, we have been engaging in conversations, discussions, as to how we can most effectively utilize that opportunity, and with Harvey Fineberg coming in as the head of the Institute of Medicine, he's just really been a great asset.

CL: So it will continue?

VON ESCHENBACH: Well, we are engaged in conversations and discussions, and that is still a work in progress.

CL: I guess the interesting thing about that group is that it is advisory to Congress, and is funded by NCI, but just looking at the reports, they are interesting.

VON ESCHENBACH: Well, I think the point that you are asking, in terms of a work in progress, is that the work in progress for everything that we do is to try to ask the question, "How can we most effectively utilize this mechanism in a way that really adds value?" What Dr. Fineberg and I have been talking about is, how we utilize this process in a way that really gets the maximum impact. That's what I mean by a work in progress. We are discussing and working through how that might come about and how that could best serve.

I am looking at all of these things as tremendous assets, and asking the question, "How could they be even better?" I am looking at the cancer centers and saying, "This is an incredible asset. How can it be even better?" I am looking at clinical trials infrastructure, and the cooperative groups, and everything else, and saying, "This is a phenomenally important part of our agenda. How can it be even better?"

We need to come up with a bioinformatics platform that will enable the clinical trials infrastructure to be even better. We have got a great relationship with FDA. How can it be even better? So, we are always striving to ask the question, "How can this mechanism be even better and more effectively employed?" I don't have the answer for that yet.

CL: Would it be wrong for me to conclude from what you have said that it will probably be around at the next renewal?

VON ESCHENBACH: I don't know about that. I mean, that just has not gotten to that level of discussion. I don't have an answer for you. I don't want you to misconstrue from my lack of an answer that that means it is not. It would be inappropriate to send a signal one way or the other that, yes, it is definitely going to be this or it is going to go away, or whatever. I think the answer to the question is that Dr. Fineberg and I are engaged in conversations and discussions, and I have met with the National Cancer Policy Board. So it is a work in progress.

CL: Is 2015 a goal or a promise? Is a goal the same thing as a promise?

VON ESCHENBACH: Eliminating the suffering and death due to cancer is a goal. It is a goal that is attainable. The promise is that as Director of the NCI, I will be steadfast in the committment to make the goal a reality.

NCI Deputy Barker Hits FDA, Calls For New Incentives For Pharmaceutical Industry

(The Cancer Letter, May 30, 2003, Vol. 29 No. 22)

Facing a crowd at a conference sponsored by the financier Michael Milken, Anna Barker, a deputy director of NCI and one of the architects of the Bush agenda in cancer research, said the criteria used in approval of cancer drugs must be revamped.

"The FDA currently approves cancer drugs only on one basis, with two exceptions, and that is survival," Barker said April 1, at a conference at the Beverly Hilton Hotel. "We have to change that. We are working with [FDA Commissioner] Mark McClellan directly at the NCI now to look at new ways to look at clinical benefit.

"Clinical benefit for cancer and survival are not necessarily the same thing," she continued.

Barker's title—NCI Deputy Director for Strategic Scientific Initiatives—suggests that in matters involving basic research, drug development, and criteria for drug approval, her views are not to be disregarded.

The contention that FDA demands that new cancer drugs demonstrate a survival advantage as a prerequisite for approval has been expressed time and again, usually by officials of pharmaceutical companies and the editorial writers at The Wall Street Journal. As the agency clings to outmoded standards, good drugs are being missed, these critics say.

There is a problem with this argument: it's factually wrong.

It is true that FDA generally requires a survival advantage for the first-line indications, but overall, few cancer agents are approved based on survival. According to a tally published in the April 1 issue of the Journal of Clinical Oncology, 39 of the 57 cancer drug approvals over the past 13 years were based on endpoints other than survival.

Other criteria for approval include tumor shrinkage, response duration, and time to tumor progression. Since April, two more cancer drugs were approved, neither of them on survival. The information is available on the FDA Web site.

It's unlikely that Barker misspoke. She has been making similar points in other venues. Her remarks are available at www.milkeninstitute.org. Barker's boss, NCI Director Andrew von Eschenbach, was in attendance at the conference.

In an interview, Barker reiterated that she regards survival as FDA's "major focus for cancer."

"They do approve drugs based on other endpoints, but survival obviously is the endpoint that leads to most drugs being evaluated on," she said. "We are obviously looking for endpoints that can serve as good clinically meaningful endpoints that might take us beyond survival. Having said that, we have to understand that a lot of people on outside, especially people who are the recipients of drugs, want to know that survival is part of the equation."

After slamming FDA, Barker moved to another target, randomized phase III trials, the gold standard of evidence-based medicine. "We discussed yesterday in a session with Mike Milken, we talked about the randomized, controlled clinical trial as being the poster child for the way we do research in this country in the clinic," Barker said. "But, in fact, that's not probably our best answer going forward. We are going to have to stratify patients, and do very specific kinds of trials."

In addition to being costly, phase III trials take time, and NCI has no time to waste. Recently, von Eschenbach, a urologist, pledged to "eliminate the suffering and death from cancer by 2015." Barker and von Eschenbach have yet to present a detailed plan for meeting this goal (**The Cancer Letter**, Feb. 14, May 16).

"I don't know that we have yet a fix on how to use pharmacogenomics and some of these markers to actually shorten the time that would be required for trials, especially some of the large randomized trials," Barker said in an interview.

In recent months, NCI officials and the American Association for Cancer Research, the professional society that served as a steppingstone for Barker's current job, have been suggesting methods for approval of agents that may prevent cancer.

"Prevention, prevention, prevention—that's where we need to go with cancer," Barker said at Milken's conference. "But there is very little, if any, incentive to do that currently. If you look at the patent life of a new intervention, by the time you actually get to market, in the current paradigm, you would have no patent life. In fact, there are companies out there that have developed interventions for prevention that have run out of patent life before they actually get to the marketplace."

Here, Barker is armed with a recent AACR position paper that proposes designating "intraepithelial neoplasia," an umbrella term for a variety of non-invasive lesions that have been observed prior to the formation of some common cancers, as a surrogate endpoint that predicts the development of cancer. Designating the eradication of these lesions as a medical outcome would accelerate clinical trials of agents for prevention of cancer, AACR said.

Any proposal to give potentially harmful agents to people who have no disease symptoms raises serious scientific, ethical, and legal questions. Harm some people,

and legal consequences may follow. To deal with this problem, one proposal floated by NCI officials suggests developing "thoughtful and fair product liability measures." Risks and benefits of such therapies aren't easy to weigh, especially if you depart from the methodology of rigorously-designed randomized, controlled trials.

"We are working with the FDA [on] how we might deal differently with multiple agents, which we are going to have to do with cancer," Barker said at the Milken conference. "How we might use intermediate endpoints to approve drugs. Very controversial issue right now with the FDA. We obviously have some very good examples of where that's worked quite famously, in cardiovascular disease, and we think we can make this work for selected kinds of cancer."

Asked to elaborate in an interview with **The Cancer Letter**, Barker said NCI is yet to work out the scientific underpinnings of chemoprevention trials. "We know that for chemoprevention, if we want to get those drugs through trials, we are going to have to think through with a lot more of our new science how to provide a foundation for the FDA to think about these things," she said.

Considering the power of the proponents of this agenda, it's not a surprise that skeptics—the mainstream of science—are not jumping up to critique it. Privately, many scientists say they are puzzled by von Eschenbach's 2015 plan. Others cite voluminous literature describing instances where reliance on surrogate endpoints, especially for prevention, caused harm. Many wonder how Barker's vision came to set the course of the National Cancer Program.

Barker's publications are neither numerous nor recent. A Medline search for produces 12 publications under her name. Two list Samuel Waksal, the soon-to-be-sentenced founder of ImClone Systems Inc., as a co-author. According to Medline, over the past 24 years, Barker published one paper in peer-reviewed literature, "Report from The March Research Task Force,"a political document.

In his doctoral dissertation, a copy of which was obtained by **The Cancer Letter**, Waksal acknowledged Barker's help and thanked her for access to a laboratory at Battelle Memorial Institute, where she worked at the time, and listed two publications and six presentations and abstracts which he and Barker coauthored.

"He was a very good investigator early on," Barker said. "He did some interesting and exciting things, and he was always very smart in terms of seeing the next issue in science, so he really pushed technology along. I always thought his science at that early stage was very good and we certainly never found anything wrong with anything he ever did. He did pretty good work."

After leaving Battelle, Barker ran a small company that developed and commercialized "therapeutic and diagnostic products to diagnose, treat and prevent diseases of oxidative stress," and co-founded a start-up company to sell dietary supplements by subscription over the Internet.

Barker's Rise In Oncopolitics

Barker reached the top strategic role in the National Cancer Program by representing the American Association for Cancer Research in its interactions with other organizations.

The story of Barker's rise to power is also the story of oncopolitics over the past dozen years.

For years, cancer patients who served on policy boards or raised money for research saw themselves as team players with the scientific institutions. While AIDS activists protested, cancer patients were either too sick or too old to launch grassroots political movements. Disagreements could be resolved and turf divided behind closed doors.

That orderly world vanished on July 29, 1992, when Fran Visco, president of the National Breast Cancer Coalition, appeared before a subcommittee of the Senate Appropriations Committee.

"When the men in suits all but destroyed the savings and loan system in this country, the nation's economic stability was threatened, and this Congress responded with billions of dollars," thundered Visco, then a Philadelphia attorney. "When this administration decided to wage a war, you found $7.5 billion to fund it. Women have declared war on breast cancer, and you had better find a way to fund that war… We will no longer be passive. We will no longer be polite. We can no longer afford to wait while Congress gets around to significant, decent funding for breast cancer."

Visco's umbrella group of breast cancer organizations demanded $300 million for breast cancer research—a $210 million increase—more money than NCI thought it could spend (**The Cancer Letter**, Aug. 7, 1992).

NBCC established a classic model of advocacy in health politics. First, advocates convened a meeting of scientists who came up with a funding target. Then they fought to get the resources. The strategy worked, creating a multi-million-dollar funding stream for basic researchers, much of it financed by the Department of Defense.

Visco's reference to "war" was unusual for her group. The word is almost never heard at NBCC events. After attaining success, the coalition maintained its focus on breast cancer, and avoided entanglement in the grandiose oncopolitical campaigns that followed.

From "Men In Suits" to Milken

Barker made connections with NBCC, and advised the Defense breast cancer research program. As other groups attempted to emulate the NBCC tactics, she remained the AACR contact for those endeavors.

Three years after Visco's "men in suits" speech, prostate cancer survivor Milken emerged on the oncopolitical scene. After release from prison, Milken

learned that he had metastatic prostate cancer.

After a few years of funding prostate cancer research, Milken set out to energize the entire field of oncology. He began by staging a conference to demand that the war on cancer be modeled on the 1991 Persian Gulf War. "Despite growing fatalities and demoralization of our troops, the war on cancer has been allowed to drift," Milken said at his Washington conference Nov. 14, 1995 (**The Cancer Letter**, Nov. 24, 1995).

Milken wanted the war spending to go up to $20-billion a year, about ten times the NCI budget at the time. His wartime rhetoric appeared especially jarring, because then-NCI Director Richard Klausner and his predecessor Samuel Broder deliberately avoided the military metaphor.

Milken amassed a following of ailing CEOs and scientists seeing possibilities for getting their work funded. His appearance on the cancer scene culminated in a grandiose event—a march on Washington, an undertaking modeled on Earth Day.

The financier wanted major rock stars. He wanted Hollywood. He wanted the Mall. He wanted speeches, T-shirts, posters, and political buttons. Above all, he wanted to create a political constituency, perhaps the biggest political constituency in the U.S.

After announcing the march on Larry King Live, the event's organizers entrusted the preparation of the scientific agenda to Barker and Ellen Sigal, a Washington real estate developer, who entered oncopolitics after her sister died while receiving high-dose chemotherapy and a bone marrow transplant for breast cancer (**The Cancer Letter**, Oct 31, 1997).

Like Milken, Barker talked big. "It is time to make cancer our highest national health care priority and undertake a national initiative that will mark the beginning of the end for cancer," Barker said at a September 1998 hearing suggesting that the cancer appropriations be increased to $10 billion over five years (**The Cancer Letter**, Oct. 2, 1998).

On Sept. 26, 1998, the march brought 250,000 people to the Mall, but the event failed to generate an overarching cancer agenda, and no political constituency clamored to receive the Barker-Sigal report.

After The March

The next political opportunity for Barker was provided by the American Cancer Society, a charity that was threatened by the march and its potential for organizing an independent political constituency (**The Cancer Letter**, Jan. 21, 2000).

On Sept. 29, 1998, three days after the march, Barker and Sigal attended a small, ACS-sponsored meeting at a Northern Virginia hotel. This was the beginning of the National Dialogue on Cancer, an ACS effort to transform itself from political backwater to the principal player in cancer politics. Instead of letting oncopolitics happen in a haphazard, uncontrolled manner, ACS wanted to create an arena for political activity.

The Dialogue leaders described the extraordinarily complex set of diseases as an engineering problem akin to putting man on the Moon and postulated that science had attained "critical mass" of discovery. The time had come to disseminate these discoveries to the public, ACS activists argued.

To propel these efforts, the society recruited former President George Bush, who is widely believed to have been recruited by von Eschenbach, an ACS activist who was later made President-elect of the society. Von Eschenbach was unable to accept the ACS position because the newly-elected President George W. Bush offered him the NCI job, making him the top official of the National Cancer Program.

ACS was unsuccessful in recruiting former President Jimmy Carter as a co-chairman of the Dialogue. For bipartisan flavor, the society brought in Sen. Dianne Feinstein (D-CA).

The second "organizational" meeting of the Dialogue was held Nov. 9-10, 1998, at the Bush Memorial Library in College Station, Tex. At that meeting, Feinstein urged the group to set ambitious goals. According to notes taken by a participant, "Sen. Feinstein cautioned the group not to avoid setting priorities and clear goals simply because we might not meet them."

Someone suggested curing cancer within 10 years, triggering a round of objections. Feinstein did not object. Instead, "she noted that goals are needed so there is something to work for," a participant wrote.

To launch the Dialogue, ACS hired Shandwick International, a public relations consulting firm, to do its Washington work. Shandwick stayed on the job until **The Cancer Letter** revealed that the firm also represented R.J. Reynolds Tobacco Holdings (**The Cancer Letter**, Jan. 28, 2000).

Before it was thrown off the job, Shandwick constructed an intricate system of political organizations pursuing the ACS goal of becoming the master of the cancer agenda. First, there was the Dialogue, an amorphous organization of some important players and some unknowns, who were invited by George and Barbara Bush, and met behind closed doors.

Barker was omnipresent at the Dialogue. She was a "collaborating partner," the Dialogue's name for a participant. She was the chairman of the "public sector research team." She was a member of the "steering committee."

Later, Barker joined a Dialogue spun-off, a committee to draft a white paper laying out the direction for legislation that would replace the National Cancer Act of 1971, the fundamental document of the War on Cancer.

That group, called the National Cancer Legislation Advisory Committee, met in Feinstein's conference room in the Senate. Its name notwithstanding, the group was not a chartered federal "advisory committee." Since it

received no government money, the group was exempt from open-door requirements of the Federal Advisory Committees Act, as well as from corresponding rules in the Senate.

ASC chief executive John Seffrin and former NCI Director Vincent DeVita, an enthusiast of the war metaphor, took charge of the committee. It is a measure of the committee's orientation that the word "war" appeared 20 times and "conquer" 28 times in its 59-page report.

A Hatchery of Ideas?

The committee appears to have been a hatchery for ideas that are now coming forward at NCI:

The committee refused to believe that FDA approves cancer drugs based on a variety of criteria. While first-line treatments for solid tumors must demonstrate a survival advantage to receive full approval, second and third-line treatments are routinely approved based on other criteria, including tumor shrinkage and time to progression (**The Cancer Letter**, Sept. 28, 2001).

Presenting the advisory committee's recommendations, Barker called for creation of geographically distributed "translational cancer centers."

"You are going to have to give these centers enough resources to build the public-private partnerships in areas like drug development or device development," Barker said at a Senate hearing (**The Cancer Letter**, Oct. 19, 2001).

Recently, a similar idea appeared in a concept presented to the NCI Board of Scientific Advisors. NCI proposed to spend $20 million to support partnerships between academia, industry, and non-profit organizations. "If we can develop these kind of partnerships, then we can reduce the risk to the private sector," Barker said (**The Cancer Letter**, March 14).

NCI Director von Eschenbach serves as vice chairman of the Dialogue's 17-member steering committee, and Barker is a committee member and head of the Research Team, which is designing science policy. The industry perspective on the steering committee is represented by Peter Dolan, the embattled CEO of Bristol-Myers Squibb Co.

From the time of the Dialogue's formation, observers wondered whether the group would function as a de-facto advisory committee, and whether it would be appropriate—or legal—for the group that includes federal employees and receives assistance from the government's Executive branch to engage in lobbying Congress (**The Cancer Letter**, Sept. 22, 2000).

"The Dialogue hasn't really been an advisory body, as much as it has just been just that, an opportunity for dialogue and discussion," von Eschenbach said, responding to a reporter's question earlier this month (**The Cancer Letter**, May 16). "The one place that I think we really had tremendous experience has been with the Research Team, and Anna Barker has been heading that up, which has made a nice link.

"But, the Research Team has really been focusing people on the issue of how can we accelerate the process of the development of these interventions, and I think it has been great to be part of that discussion, and great in terms of trying to bring all the pieces of the community together," he said.

The Research Team, which, in the tradition of the Dialogue, meets behind closed doors, is broken up into four working groups: Tissue Access; Surrogate Endpoints; Engaging the Private Sector; and Developing a National Strategy. Each of these groups plans to generate a report.

It remains to be tested whether the Dialogue activities should be covered by FACA. "I think there are serious questions about whether an organization with this composition and function should be complying with FACA," said Eric Glitzenstein, an attorney with Meyer and Glitzenstein, a Washington public interest law firm that specializes in open government issues. "If, indeed, the Dialogue is being used to influence government policy, then openness requirements of FACA should come into play."

From Science Policy To Dietary Supplements

A search of WebMD offers some insights into Barker's view of how cancer can be prevented.

Last September, in an interview, she described the combination of soy and cow's milk as an example of "benign medical foods that you take over a lifetime to reduce the risk of cancer."

A year earlier, Barker told WebMD that she takes vitamins. "I'm interested in the biology of pro-oxidants and antioxidants, so I understand a little more than some people about how this stuff works," she said. "I think people who take vitamins C and E are a bit more protected than people who don't. Vitamin C especially has a very short lifespan, and unless you eat a lot of fruits and vegetables you probably aren't getting enough of it. For vitamin E, you can't really overdose on the stuff, and it's a very good antioxidant. ... I think taking a multivitamin is not a bad idea."

For Barker, antioxidants have been a business pursuit, too.

OXIS International Inc., the small biotechnology company she co-founded and ran until 1998, described itself as "a leader in the discovery, development and commercialization of therapeutic and diagnostic products to diagnose, treat and prevent diseases of oxidative stress. Oxidative stress occurs when the concentration of free radicals and reactive oxygen species, highly reactive molecules produced during oxidative processes, exceed the body's antioxidant defense mechanisms."

After leaving OXIS, Barker founded Bio-Nova, a company that invested in emerging technologies. "We founded it in Oregon, because we felt as though there was a lot of opportunity in Oregon," she said. "There was not the investment capital in Oregon, as compared to Seattle."

At the same time, Barker took a leap from studying antioxidants to trying to sell vitamins and dietary supplements. In 1998, she co-founded a business called Nutri-Logics Inc. to "fulfill an unmet, growing healthcare need for scientifically-based disease risk reduction and prevention products" in cancer, according the company's business plan.

Her partners in the venture were Sigal, who had completed a term on the National Cancer Advisory Board and was at the time a member of the NCI Board of Scientific Adivsors, and Robert Day, director emeritus of the Fred Hutchinson Cancer Institute. Anthony Podesta, a lobbyist who at the time represented Friends of Cancer Research, Sigal's advocacy group, was a Nutri-Logics board member. Podesta was also a Clinton appointee to the Commission on Dietary Supplements, which advised the administration on the implementation of the Dietary Supplement Labels, Health and Education Act of 1994.

The "market opportunity" section of the Nutri-Logics business plan states:

- Scientific advances now provide the capability to predict, estimate, and reduce disease risk through improved diet and lifestyle and nutritional supplementation.
- Disease risk reduction (or "wellness") healthcare models are becoming preferred to treatment-only models by both consumers and health care providers. Increasingly, science-based nutritional products are regarded as critical to a prevention-oriented lifestyle.
- The worldwide nutritional supplement market is rapidly growing due to changing demographics and healthcare approaches. In the U.S., sales of vitamins, minerals and herbal supplements have grown from $6 billion in 1994 to $12 billion in 1999. In Europe, sales were $12 billion in 1998, up 8%.
- Cancer incidence is expected to increase 29% in the next 10 years due to the aging of the "baby boomer" generation and costs for cancer treatment and lost productivity are projected to be over $200 billion per year.
- The Internet provides ideal opportunities for customer interaction, personalized products/and services, and real-time delivery of healthcare information.
- Unprecedented opportunities to assess the efficacy of nutritional supplements through the application of genomics and other new technologies combined with increasing regulatory pressure is moving the field toward more science-based, high quality nutritional supplements (nutraceuticals).

The plan offers the following description of the "Scientific and Research Platform:"

- Nutri-Logics believes that the major future requirement to compete successfully and eventually dominate this industry will be the development of scientifically based, proprietary products.
- Nutri-Logics' has developed a bi-directional, three-tiered approach (The *ORION*™ Process) that utilizes a "levels of evidence" approach to identify critical ingredients for the development of its scientifically based dietary supplement products. The ORION process is the subject of a broad patent application and the products that derive from the process are the focus of individual submissions.
- Nutri-Logics believes that genetic polymorphism (differential gene expression) is very important in the incidence of certain types of cancer, specifically related to metabolic influence of micronutrients. Using contemporary genetic and molecular approaches (e.g. microarray technology) Nutri-Logics will identify genes and clusters of genes in specific cancers to provide a basis for assessing efficacy of its products and to identify at-risk populations.

The company's "Products and Services" were to include:

- Customized, science-based nutritional supplements composed of efficacious combinations of micronutrients, botanical extracts, vitamins, and minerals, offered on a subscription basis. Introductory supplement formulations will focus on cancer risk reduction, with product line extensions for cardiovascular and other preventable diseases.
- A personalized health risk profile provided over the internet to help stimulate product interest, gather personal health information, recommend optimized product formulations, and provide information and references on prevention and various other health education issues.
- Proactive customer communication via newsletters, research alerts, product updates, and other relevant communications.

The plan was marked as "Non-Confidential," and was displayed on the Nutri-Logics Web site. Now, it can be found at the Internet Archive: http://web.archive.org/web/20010305035804/http://www.nutri-logics.com/

Nutri-Logics, incorporated in Oregon in 1998, lists the Washington, DC, address 3299 K Street NW as its official place of business. That is also the address of Sigal Construction Corp. The Oregon registration lists Sigal as president and Day as secretary of Nutri-Logics.

Asked to comment on her involvement in the business, Barker said: "Bob and I, and Ellen ultimately, had a passion for chemoprevention."

The business was consistent with her work in antioxidants. " In my work with OXIS and my interest in reactive oxygen damage, I became convinced that there might be some real substance in looking at the world literature in micronutrients to see if there were first-generation kinds of nutraceuticals," Barker said. "Might you use the world literature for specific kinds of cancer to look at ways that you might formulate mixtures of micronutrients that would be scientifically based?"

The company drew on expert advice, Barker said. "We attracted a stellar scientific advisory board," she said. "We had a great deal of fun looking at various

micronutrient combinations within the realm of specific cancers. I think the general consensus was that, in fact, the chemoprevention in terms of micronutrients scientifically based, by taking the world literature and using the process to start with randomized, controlled trials and working our way down through all the in vitro and in vivo kinds of things that one could find in literature, that you could combine molecular science along with clinical trials to put together pretty exciting kinds of mixtures of micronutrients for specific cancers, looking at the origin of cancer."

Sigal, who served on the National Cancer Legislation Advisory Committee and is currently a member of the Dialogue's Nominating Committee, confirmed that she, Barker, and Day founded the company, which she described as "an ongoing entity."

Barker said the venture failed. "We spent many happy times with our colleagues going through those processes, but as a business model, it was not a good business model, because even if you are formulating highly scientifically viable kinds of mixtures of micronutrients, you are competing in a marketplace where people are able to compete on the basis of nothing," she said. "They have no science behind what they've done. It was not a successful business model. So we elected to put it on the shelf. Bob Day and Ellen are still shepherding it along, but it's been inactive for a year and a half or so."

In recent months, Friends of Cancer Research, Sigal's advocacy organization, has been working on issues involving FDA.

Precancers: "New Front" In War on Cancer

In February 2002, the AACR journal Clinical Cancer Research published a paper titled, "Treatment and Prevention of Intraepithelial Neoplasia: An Important Target for Accelerated New Agent Development."

The paper appears to have directly influenced the von Eschenbach-Barker agenda at NCI.

"Despite increasing research and development efforts, drug approvals for chemopreventive indications have been slow to emerge," said the report. "The critical factor in this regard is defining and then demonstrating clinical benefit. Historically, reduced cancer incidence or mortality has been required to show chemopreventive efficacy. These endpoints make chemoprevention studies too long, large, and costly for most academic research centers and pharmaceutical manufacturers to undertake, thus limiting the number of drug candidates that can be developed. Continuing to rely on cancer incidence and mortality endpoints will lead to significant loss of opportunity to impact cancer."

The paper was written by the AACR Task Force on the Treatment and Prevention of Intraepithelial Neoplasia, formed by Daniel Von Hoff, director of the Arizona Cancer Center, and a former AACR president.

The task force co-chairmen were Joyce O'Shaughnessy, of US Oncology and Baylor-Sammons Cancer Center; Gary Kelloff, of the NCI Division of Cancer Treatment and Diagnosis; Gary Gordon, of Ovation Pharmaceuticals; and Richard Pazdur, head of the FDA Division of Oncology Drug Products. Pazdur attended one of the group's meetings, and his name does not appear on the list of co-authors.

The paper is posted at www.aacr.org/PDF_files/Journals/2002_IEN_article.pdf.

The paper proposed a new endpoint: precancer, or "intraepithelial neoplasia (IEN)," a noninvasive lesion "that predicts for a substantial likelihood of developing invasive cancer" for many epithelial cancers, including those of the colon, head and neck, esophagus, lung, non-melanoma skin, breast, prostate, and bladder.

"Achieving the prevention and regression of IEN confers and constitutes benefit to subjects and, in the opinion of this Task Force, demonstrates effectiveness of a new treatment agent," the paper asserted.

There is a precedent for this approach: the use of lipid-lowering drugs in prevention of cardiovascular disease. "Lowering the cholesterol level has been validated as an endpoint for CHD risk reduction; analogous data might be applied to validating IEN for cancer risk reduction," the paper said.

Another example the task force cited was the FDA approval of Celebrex (celecoxib) for colorectal polyps in patients with familial adenomatous polyposis as an adjunct to standard-of-care.

While FAP is rare and is associated with a high risk for colorectal cancer, it sets a precedent, the paper said. "New drug approvals for treatment of IEN in high-risk populations will provide rationale for incrementally extending studies to lower-risk populations to gain drug approvals that will have broader public health impact," the task force said.

The paper noted one problem with using IEN to demonstrate risk reduction: "relatively small percentages of IEN progress to cancer."

To overcome that limitation, the paper proposed that "in patients with low-risk IEN, which constitute a significant part of the population, it will be important in future drug development efforts to reduce cancer risk to determine that the successfully treated lesions had potential to progress and, thus, that the patient benefited from treatment of IEN."

The potential danger of IEN to the patient could be demonstrated by the extent of genetic and molecular progression in placebo-treated subjects, the paper argued. Gene microarray analyses and genotypic changes measured by gene chips could be used as endpoints for IEN treatment studies.

The task force proposed several clinical trial designs that it said provided "practical and feasible approaches to the rapid development of new agents to treat and prevent precancer."

Announcing the publication of the IEN paper, AACR issued a "position statement" titled, "Precancers: Opening a New Front in the War on Cancer." The statement is posted at http://www.aacr.org/5300f.asp.

According to AACR, "It is now time to take the war on cancer to a new front, featuring the rapid development and deployment of a new arsenal of drugs capable of attacking cancer cells during their formative—precancerous—stage."

The task force had "spelled out a landmark set of recommendations on how to speed the development of drugs that target common precancers," the AACR position statement said. "The task force and the AACR now urge the federal Food and Drug Administration to speed approval of drugs that prevent and treat precancerous lesions when the link between these lesions and cancer is shown to exist. It's hoped that such an effort will encourage researchers in academia, the government and pharmaceutical companies to begin scientific inquiries into 'chemopreventive' agents that would launch preemptive strikes against precancerous cells and tissue."

For those who worry about "the risks of giving medicine to seemingly healthy people—including those with precancers," AACR had a prescription: look at cardiovascular disease and don't worry. "This attitude clearly has changed with the treatment of other life-threatening conditions such as cardiovascular disease," AACR said.

The AACR statement ended with a declaration: "The AACR now believes that reducing precancers lowers cancer risk, and that the FDA should take a similar stance regarding drugs for the approval of this condition. AACR believes the link between some precancers and invasive cancers—particularly in certain high-risk populations—is so clear that drug developers should only be required to prove their proposed medicines are safe and effective in treating or preventing the evolution of precancer to cancer.

"The AACR contends that a revolution in how scientists and the public think about preventing and curing cancer is needed. This revolution has begun in the laboratory and is already well accepted by a public seeking ways—through lifestyle modification as well as medical screening and intervention—to reduce their personal risks of developing cancer" (**The Cancer Letter**, March 1, 2002).

Barker described the IEN report as "a very important study."

"It drew on the expertise of the community to put together what I think is a very cogent argument for looking at and evaluating potential chemopreventive agents," she said. "I think it sets the stage for putting science in perspective in terms of how you might be able to look at chemopreventives. It's a construct for beginning to think about how you might evaluate these agents."

Does a Correlate a Surrogate Make?

The AACR platform does not represent a consensus on the role of "precancers" as a surrogate marker for clinical benefit. Precancers may vary wildly from one disease to another, scientists say.

"You have to look at organ-specific issues, and design trials and interventions based on specific changes in the organ," one cancer prevention expert said to **The Cancer Letter.**

The approval of Celebrex for the narrow indication of FAP doesn't blast the door wide open for the acceptance of polyp formation as a surrogate endpoint for every potential colorectal intervention, colorectal cancer experts say.

Writing in the May 21 Journal of the National Cancer Institute, Bernard Levin, vice president for cancer prevention at University of Texas M.D. Anderson Cancer Center, cautioned against using polyp formation uniformly as a surrogate endpoint for chemoprevention studies.

"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," Levin wrote.

"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," Levin wrote. "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….

"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."

Biostatisticians Thomas Fleming and David DeMets argued in the Annals of Internal Medicine (1996;125:605-613) that "a correlate does not a surrogate make." They provided a case from cardiology—the use of reduction in ventricular ectopic contractions as a surrogate for decreased cardiovascular-related mortality—as "a classic example of the unreliability of surrogate end points."

In that instance, FDA approved three drugs—encainide, flecainide, and moricizine—for use in patients with severely symptomatic arrhythmias, though trials had not been done to determine whether the reduction in arrhythmias would lead to a reduction in death rates.

Unexpected results emerged from the Cardiac Arrhythmia Suppression Trial to evaluate the effect of the drugs on survival of patients who had myocardial infarction: significantly more patients in the treatment arms of the study died, compared to the placebo group.

Fleming and DeMets described several other examples of experiences with surrogates "for which

biological markers were correlates of clinical outcomes but failed to predict the effect of treatment on the clinical outcome."

Surrogate endpoints might provide an acceptable quality of evidence in some studies and for some treatments, but not for others, wrote NCI scientists Arthur Schatzkin and Mitchell Gail in the January 2002 issue of Nature Reviews: Cancer.

"The most that can be said is that surrogates might give the right answers about intervention effects on (or exposure associations with) cancer," they wrote. "The problem is the uncertainty attached to conclusions based on surrogates.

"Except for those few surrogates that are both necessary for and relatively close developmentally to cancer—such as CIN3 and cervical cancer—the existence of plausible alternative pathways makes inferences to cancer from surrogates problematic," Schatzkin and Gail wrote. "Merely being on the causal pathway to cancer does not in itself constitute surrogate validity; it is the totality of causal connections that is crucial.

"There is, unfortunately, a fairly extensive history of plausible surrogate markers that give the wrong answer about the effects of treatments for chronic disease," they wrote. "If anything, the limitations of surrogacy remind us of the complexity of cancer causation and affirm the continued importance of large clinical trials and observational epidemiological studies with explicit cancer end points."

Physicians assumed for 50 years that estrogen plus progestin protects women against cardiac disease. Last year, results from a large randomized trial found that women taking the therapy had a greater incidence of breast cancer, coronary heart disease, stroke, and blood clots. Earlier this week, investigators reported that women who began taking the combination of estrogen and progestin at age 65 or older in a randomized, controlled trial had double the risk of dementia compared to controls.

Beta-carotene was tested as a potential cancer preventive in two large NCI-funded randomized trials in persons at high risk of developing lung cancer. Contrary to expectations, the incidence of lung cancer increased among the former and current smokers who took beta-carotene.

"The magnitude of increased risk in these trials represented approximately six cancers per 1000 participants in the intervention groups, compared with five cancers per 1000 participants in the control groups, a difference too small t be apparent in any observational epidemiologic study," wrote Peter Greenwald, director of the NCI Division of Cancer Prevention, in the Jan. 1, 2003, issue of the Journal of the National Cancer Institute.

If the randomized, controlled trials had not been carried out, "specific dietary guidelines based on epidemiologic evidence might have been considered, an action that would likely have caused harm to public health," Greenwald wrote. "The beta-carotene story thus demonstrates clearly that although epidemiologic evidence can provide a basis for developing hypotheses of benefits of food constituents, these hypotheses must then be tested in randomized, large-scale clinical trials."

AACR, NCI Call For Precancer Treatments

Chemoprevention based on surrogate endpoints is central to the NCI 2015 plan, said James Mulshine, head of the Experimental Intervention Section in the Cell and Cancer Biology Branch of the NCI Center for Cancer Research.

"This is one of [Barker's] primary *raisons d'etre* for coming to the NCI," said Mulshine, who has presented the Institute's plans to patient groups and oncologists. "Industry has got to hear that NCI is going to be committed to this, because if we don't come up with a much more comprehensive ability to do this type of thing, we are going to fail on our 2015 objective."

Mulshine said the plan has von Eschenbach's support as well.

"Andy von Eschenbach and Anna Barker really want to get this done," Mulshine said to **The Cancer Letter**. "There is some tension at some levels with the FDA, but the new Commissioner seems to have a more open mind about this than some of the other people there."

In a recent proposal he presented to an ASCO committee, Mulshine wrote that development of cancer chemoprevention has been "paralyzed by a remarkable paucity of drug development activity."

The long duration of prevention trials and the issue of product liability were identified by a 1995 NCI working group as two "dominant barriers to pharmaceutical investment in cancer preventive drug development," Mulshine wrote.

AACR "has proposed that the field recognize the earliest manifestations of early cancer as a distinct disease entity," Mulshine wrote. IEN would be a surrogate marker for cancer "just as elevated serum cholesterol has been accepted as a surrogate of cardiovascular disease."

The excerpted text of Mulshine's proposal follows:

"In the setting of a compelling public health benefit, there are precedents in establishing a fair product liability mechanism such as with the Orphan Drug Act or with a non litigation-based compensation board as recently suggested by the Institute of Medicine (Fostering Rapid Change in Health Care, www.nap.edu). Either of these mechanisms may serve as important incentives for cancer prevention drug development.

"A recent report outlined an analysis of the consequences of patent life extension relative to their impact on public health and drug cost (Changing Patterns of Pharmaceutical Innovation, www.nihcm.org). Appropriate concerns were raised about rising drug costs in the absence of corresponding improvements in public health. The implication of the study was not that patent

life extension was an inherently flawed approach. Rather the suggestion was that this market tool was left unmodified for an extended period of time without a critical appraisal of its impact. In the setting of creating incentives for the development of prevention drugs, perhaps a more tailored and monitored approach to patent life extension could be of benefit in areas of critical public health need.

"Finally, to assist the FDA in their regulatory responsibility for the specific situation with cancer prevention drugs, a more responsive regulatory mechanism is needed to meet the public health needs of the nation. This proposed regulatory mechanism would involve a two-tiered drug review system. The first conditional approval for cancer prevention drugs would be based upon results of trials designed around surrogate markers such as IEN. For the second and final review, structural post marketing (commonly called Phase IV) surveillance capability would have to be developed. This post marketing surveillance mechanism would be engineered to detect clinically significant drug complications more reliably and earlier. If this mechanism is implemented properly, it would be a resource not only to the integrity of the FDA regulatory review, but to the pharmaceutical industry and the public as well. The feedback about an agent acquired by longer term clinical trials as well as the post marketing mechanism would provide the basis for the FDA's final approval of a cancer prevention drug.

"In order to use this new source of information to protect the American public, the FDA would need new authority to be able to act downstream of initial drug approval to refine its approval language to reflect the post marketing experience to protect the public. This new downstream regulatory authority would allow the FDA be more liberal in acting upon cancer prevention applications in approving early indications for premetastatic cancer (IEN) based on surrogate endpoints. Knowledge about prevention drug utilization out in the community captured by the post marketing mechanism would provided much more comprehensive information about the subsequent costs and benefits to people of this new class of cancer prevention drugs. Considerable enthusiasm exists for this more calibrated approach to prevention drug approval among many stakeholders.

"Proposed actions items to create a more favorable environment to encourage cancer prevention drug development:

- Develop thoughtful and fair product liability measures.
- Develop tailored patent life extension incentives for critical public health needs.
- Develop post marketing infrastructure to reliable capture impact (positive and negative) of new drugs in the population.
- Provide FDA with regulatory authority to refined drug approvals and packaging claims based on clinical information provided by post marketing surveillance.
- Institute a Prevention Drug Advisory Committee comparable to the Oncology Drug Advisory Committee to review the early cancer drug approvals, refine final approvals based on the post marketing data, and perform strategic quadrennial review on prevention drug development.

Jon Steiger, a partner in the Los Angeles office of Quinn, Emanuel, Urquhart, Oliver & Hedges, a premier national business litigation firm, said that the legal aspects of the NCI proposal do not appear to be well planned.

"It is no small undertaking to change product liability laws in the manner they propose, and it appears that they underestimate and oversimplify the magnitude of that task," Steiger said to **The Cancer Letter**. "Trying to reform product liability laws is not something you do to 'incentive' the industry, but instead only with the industry firmly behind you.

"A half-baked and hasty attempt at 'reform' will only scare the industry, as it could make them look foolish and set back otherwise legitimate and potentially successful attempts to create rational legal reforms," Steiger said.

"And yes, products have to be thoroughly tested in clinical trials," Steiger said. "Prematurely launching an ill-conceived legal legislative effort will turn off not only the drug companies, but also the legislators and the public."

The Question of Surrogate Endpoints

ASCO recently sponsored workshops with FDA to discuss endpoints for drug approval.

At the first workshop, conducted last month, academic experts, FDA and NCI officials, and patient advocates reviewed endpoints for advanced lung cancer. The workshop was open to the public, and its report will be presented to ODAC (**The Cancer Letter**, April 25).

AACR was involved in initial planning of the workshop, but ultimately bowed out of the process.

ASCO and FDA planned to hold a series of such workshops for a variety of cancers. However, now NCI seems intent on folding this effort into the Dialogue (**The Cancer Letter**, May 16).

"We are trying to do this in a way that is all integrated," von Eschenbach said in an interview. "The ASCO effort, the NCI effort, the FDA effort—these all are going to be integrated in a way—the National Dialogue on Cancer effort."

Von Eschenbach said Barker's Research Team "has been looking at ways of streamlining development of drugs based on genomics or proteomics."

In recent months, Barker and Mulshine made two attempts to win over the members of ASCO's Cancer Prevention Committee.

Dominated by clinicians, that committee has a keen appreciation of complexities of human subject experiments. While some members of the group admitted to being "shocked" by the NCI proposals, they also understood the practical value of having NCI and AACR return to

discussions, if only to draw on a broader spectrum of ideas.

"It's shocking to see NCI associate its name with anti-science," said one committee member who spoke on condition of not being identified by name. "I have no problem with surrogate markers. My problem is when you don't validate those markers. They are basically saying, 'The hell with validation.'"

Several members of the committee said ill-advised interventions may benefit pharmaceutical companies, but not the public.

"Whom is this for?" asked another member of the ASCO prevention committee.

The NCI proposal seemed to be written to make it easier for the pharmaceutical industry to bring interventions to market, and protect it from product liability suits. "They keep talking about cancer as a horrible thing—desperate diseases are only cured by desperate means," a participant said. "In this case, the target population is healthy people."

At one of the meetings, Mulshine argued that post-marketing surveillance would detect any harm of interventions, possibly by tracking this through the NCI Surveillance, Epidemiology and End Results Program, participants said.

Post-marketing studies are not designed to assess the harm of prevention products such as dietary supplements, experts say. SEER tracks cancer incidence and would be unlikely to detect adverse events from chemoprevention trials.

Another ASCO committee member said he was troubled by the proposal's lack of ethical constructs.

"Remember 'First, do no harm'?" the committee member, a practicing physician, said to **The Cancer Letter**. "If you are going to encourage asymptomatic, or even healthy people to do something they wouldn't normally do, the bar must be higher, not lower. You don't set the bar lower for convenience."

Accelerated Approval Will No Longer Block Competitors, FDA Commissioner Says

(The Cancer Letter, June 6, 2003, Vol. 29 No. 23)

CHICAGO—Cancer drugs approved based on "surrogate endpoints" under the FDA accelerated approval mechanism will no longer block competitors from entering the market, FDA officials said last week.

Under the agency's new interpretation of the accelerated approval regulations, only agents that receive full approval after demonstrating benefit to patients would block competitors from entering the market.

In recent years, some sponsors who received accelerated approvals seemed to be in no rush to complete post-approval studies and convert their agents to full approval. Now, the agency's action is likely to lend urgency to such studies, triggering competition to the finish line of full approval.

"Other drugs would also be able to get accelerated approval status for that indication until one of these therapies demonstrates through phase IV study commitments a clinical benefit in patients," said FDA Commissioner Mark McClellan at the annual meeting of the American Society of Clinical Oncology.

McClellan announced the change during a joint presentation May 31 with NCI Director Andrew von Eschenbach, where heads of the two agencies announced their plans for collaboration in development and approval of cancer agents.

"This is something that we think NCI's recent help in funding more phase IV studies reinforces," McClellan said. "We are going to have stronger incentives than ever for getting phase IV studies completed."

As NCI and FDA pledged to work together, the differences in their positions seemed striking.

FDA is a practical "show-me" agency that seeks to apply scientific standards as uniformly as possible. NCI is an agency with a mission. Guided by a plan by Director von Eschenbach to "eradicate death and suffering from cancer" by 2015, the agency regards FDA as a gatekeeper.

Von Eschenbach said he first came to McClellan's office to discuss ideas for a collaboration the morning after the FDA Commissioner was confirmed by the Senate.

"I kind of barged into his office, and immediately expressed my excitement for the opportunities that we have now available to us, based on the progress that has been made in biomedical research, and how important it was for us to translate that progress into interventions," von Eschenbach said at ASCO.

Speaking with precision, and frequently consulting his notes, McClellan laid out a plan of collaboration built on his agency's reliance on NCI as a science agency.

"We set the world's gold standard for care of patients with cancer and other diseases," McClellan said. "We are going to remain committed to approving only safe and effective drugs."

McClellan said he is concerned about the drop in the number of drug approvals, the rising cost of drug development, and the falling success rate in clinical trials.

"A lot of experts are attributing these trends to the changing nature of medical technology development, with an increasing reliance on biotechnology and emerging sciences like genomics and proteomics that are primarily still in the early stages of development, leading to a lot of research investment, but not new products yet," he said.

"I think we can compress what may otherwise be a very long process of moving these treatments down the pipeline through better support for translational research."

McClellan's plans included:

—Playing a role in NCI's review of the clinical trials process. "We think NCI support for developing methods that can improve our understanding about the relationship

between potential biomarkers that can be observed relatively early in the clinical development process and clinically important endpoints can help our regulatory activities a lot," McClellan said.

FDA and ASCO recently cosponsored a series of workshops to assess the evidence on surrogate endpoints "with the goal of developing clear guidance about efficient pathways to regulatory approval for major solid cancers."

—Leveraging NCI and FDA programs building a "more inclusive bioinformatics platform that can capture and integrate data from clinical research across all of the sectors of the development process," McClellan said.

—Increase FDA representation on NCI advisory boards and NCI representation at FDA boards, and form joint training and joint appointment programs in oncology. "It would enable us to improve the science base and the understanding of the latest scientific knowledge at both agencies," McClellan said.

—Explore the implications of pharmacogenomics. "That work is still really in its infancy, and there is a ton of information out there that we don't have any clear idea of what it means for regulatory decision implication which are based on implications for clinical outcomes in patients," McClellan said. "Our hope is that by pooling our efforts in developing this applied knowledge base, we can eventually permit better-targeted, less costly and more efficient clinical testing in patients."

Von Eschenbach said the two agencies would collaborate to "accelerate the ability to take the fruits of our research and be certain that that's translated into lives that no longer have to suffer and will no longer die because of the disease like cancer." Specifically:

—NCI will involve FDA in an impending review of the clinical trials system.

"Over this next year, NCI will embark upon a very intensive effort to look at our whole clinical trials infrastructure, and to look at ways that we can adapt and modify our clinical trials effort to really be responsive to the tremendous opportunities that are now before us, with the fruits of genomics and proteomics," von Eschenbach said.

"We may need to design new biomathematics and biostatistical models," he said. We may need to look at our ability and will look at our ability to integrate multiple interventions that are based on mechanistic interruptions, recognizing that those interventions singly may appear to be ineffective, but in combination would in fact be quite effective at dealing with progression of disease."

—The regulatory agency will be asked to help in validation of surrogate endpoints.

"Looking at that from the point of view of embarking upon applications of new technologies in molecular profiling, looking at the opportunity of expanding on the surrogate endpoints that FDA currently uses by scientifically evaluating biomarkers for those surrogate endpoints, so that they can appropriately and rationally be incorporated into our process," von Eschenbach said.

—FDA will be involved in the Institute's drive to apply surrogate endpoints to chemoprevention.

"Within cancer prevention [there is] a whole emerging role of chemoprevention, and the work in the science that needs to be done with regard to our ability to integrate chemopreventive strategies into our clinical arena," von Eschenbach said. "Work needs to be done in appropriately validating those interventions and having the science to underpin their approval, and then to be able to monitor them as chronic administration over a period of time."

—FDA would play a role in dietary interventions, von Eschenbach said.

"NCI will be placing a great deal of emphasis on the issue that we describe as 'energy balance,' or the interaction between diet and physical activity," von Eschenbach said.

"With regard to diet, there are extraordinary needs and opportunities in that arena. Diet is an issue that for us—even from HHS—has become a major strategic initiative, because of the epidemic of obesity in this country and for the implications it has with regard to Type II diabetes, and cardiac disease, as well as cancer," he said.

"As we look at diet, and as we look at the need to further develop the science of understanding dietary factors and micronutrients, we also need to be working collaboratively and cooperatively with FDA in terms of how to validate the impact in a way that they can make recommendations with regard to dietary guidelines."

NCI Director Defends Goal To Eliminate Suffering, Death From Cancer By 2015

(The Cancer Letter, June 13, 2003, Vol. 29 No. 24)

As he faced questioning by members of the National Cancer Advisory Board earlier this week, NCI Director Andrew von Eschenbach defended his goal to "eliminate suffering and death from cancer" by 2015.

"We do not believe that it's an unrealistic expectation," von Eschenbach reiterated at the board meeting June 10. "I believe we can look at the American public and the world and set this goal without it being something that is considered unrealistic."

Von Eschenbach first announced his "challenge goal" unexpectedly, in the middle of his remarks at an NCAB meeting last February (**The Cancer Letter**, Feb. 14). Initially, board members greeted the announcement with uncharacteristic silence.

"The last time I presented this, you were, I think, more stunned," von Eschenbach said earlier this week, acknowledging the February surprise. "That's why I wanted to bring it back, so that we did have the opportunity for

discussion…. I welcome critical input. It will help us, not hurt us."

The board responded with a volley of questions: Is there a step-by-step plan? Is the plan realistic? Is NCI abandoning its quest for cancer *cures*? How would you gauge progress?

Von Eschenbach said NCI will not write a prospective plan. Instead, the Institute will rely on an "ongoing strategic planning process," which he said is now in place. "I don't believe in plans that you then put on a shelf," he said. "What we are committed to is a planning process."

However, NCI officials prepared a page-and-a-half-long list of eight "2015 Strategic Planning Priority Areas." A version of the list is posted at http://www.cancer.gov/BenchMarks/archives/2003_04_public/related_article.html.

Every three months, the Institute's leadership meets for a day "as a strategic planning body to look at process," von Eschenbach said.

"Our mantra is: we get ready, we fire, and we steer," he continued. "It's not: ready, aim, fire. It's ready, fire. We are launching. We are moving initiatives ahead that we believe are important strategically to impact on that continuum of cancer process."

The measures of progress are yet to be developed, von Eschenbach acknowledged.

"I would point out that the metrics are not going to occur in a linear fashion," he said. "Just as cancer can be exponential in its growth, the solution to cancer can also be exponential in its realization."

Following are excepts from von Eschenbach's remarks to the board, and the question-answer session:

VON ESCHENBACH: When I spoke to you last, I introduced to you a very important outcome of the NCI's strategic planning process, that outcome being that we had crystallized and had established a very important, long-range strategic goal. That goal was to eliminate the suffering and death from cancer. Looking at that goal, we established a time line in which we would achieve that goal, of 2015.

Subsequent to that, I have had the opportunity to continue to discuss and deliberate in a variety of venues the implications of that goal and the appropriate strategies required for us to achieve that goal. You have received from us a copy of "Benchmarks," in which I attempted to really lay out in much more detail the rationale and underpinning of that goal.

I thought it would be appropriate, in addition to calling your attention to Benchmarks, and inviting you to really look at that in great detail, and take the opportunity to reflect back to me your thoughts and concepts in that regard, I thought it was important to take a few moments this morning as part of my report to you to just touch on a few of the very important pieces contained in that Benchmarks discussion to reiterate some of the rationale behind that goal.

First of all, it's important to once again remind us that the reason why the goal is now feasible is because of the tremendous progress that has been made within our biomedical research enterprise. When one looks at the kind of progress that is being made and what has been achieved since the signing of the National Cancer Act in 1971, I think it's fair to say that one appreciates that this has been a virtual explosion in our awareness and our fund of knowledge of cancer as a disease.

It's also at this point, I think, important to realize that we are at a moment in which, not only has our fund of knowledge been growing at an explosive rate, but as I alluded to earlier, our critical mass of intellectual capital with regard to the number of researchers who are committed to the cancer enterprise, and, in fact, the resources that are available, from the point of view of fiscal resources and infrastructure, has never been greater. We are at a moment in time where the budget of the NCI is the largest it's ever been. The budget of the NIH and other biomedical research enterprises is likewise at a high-water mark. Certainly, one could always look forward that continuing to grow and increase, because the need is so great, but I think it's important for us, for at least the purposes of realization of where we are, and where we ultimately could go, to realize that we are uniquely positioned at this point to capitalize on that incredible opportunity.

We have within our grasp the resources and the tools. We also have, I think, an important need to focus the goal. Remember that I did not say that we would eliminate cancer. I said we will eliminate the suffering and death due to cancer. The reason why it's important to keep that distinction clearly before us, is because what this progress in biomedical research has led us to, is that for the first time, perhaps, we are really beginning to understand cancer as a disease process, and a process in which there are multiple steps that are responsible both for our susceptibility to the disease, the fact that we at some point in time undergo a malignant transformation, and then, the processes and steps that are responsible for progression of that malignant transformation, to the point in which it becomes clinically apparent, and then, ultimately, to the point where it achieves a lethal phenotype by becoming metastatic and resistant to cell death and therapeutic interventions.

As we have begun to understand cancer as a disease process, we now have multiple opportunities to intervene in that disease process in a way that we can preempt the disease initiation and progression, such that we can prevent patients from ever developing the disease. For others, who do develop the disease, we can detect it in time, and we can eliminate disease. For others, we have the opportunity to begin to manage the progression and the evolution of the disease, such that they live with it, rather than die from it.

We have continued to expand and further develop the portfolio of strategic initiatives that we believe are

going to be necessary and central for us to achieve this goal. It will require a collaborative, cooperative, multidisciplinary, integrated effort on behalf of the entire cancer community, for this to be achieved. We have created that effort in the context of a balanced portfolio that continues to look at the elements of discovery, development, and delivery, and will continue to work within the NCI, as well as within the larger context of the cancer community, to continue to drive that agenda.

I hope you will take the opportunity to really look at the issues that have been portrayed in Benchmarks, and I look forward to the opportunity to continue to work with you as we continue to go forward in the planning process and the implementation process to capitalize on the extraordinary opportunity that's within our grasp, and to really begin to revolutionize our ability to deal with cancer as a disease process.

There are a number of initiatives that are underway that I wanted to bring your attention to, with regard to the kinds of things that we are doing with regard to our research process.

You will recall that…the senior leadership of the NCI has been engaged in a series of planning efforts to look at our long-range opportunities. We have begun to focus that on some key strategic initiatives that we will be unfolding over this next year. One of them is in the area of molecular epidemiology. The others are integrated cancer biology; the strategic development of cancer interventions; programs in early detection, prevention, and prediction; integrated clinical trials system; overcoming health disparities; and bioinformatics.

These are going to be key initiatives that we will be embarking upon with regard to specific initiatives that we will look forward to sharing with you as the process continues to unfold. One of the things that I would also make you aware of, is the fact that we are looking at this not only with a contextual effort within the NCI, but also, very importantly, with regard to our opportunities for partnerships and collaborations, for bringing these opportunities about.

One of the very important areas of collaboration and cooperation has been, of course, the emerging effort with the Food and Drug Administration. Those of you who had the opportunity to be at ASCO were present when Mark McClellan and I presented to ASCO, together, our vision for the cooperative effort that we believe is essential for the two institutes or organizations. The genesis behind this FDA-NCI collaborative effort is the fact that there is already a lot going on within NCI and within FDA, if you will, at the grassroots level, in the effort for the two organizations to work together collaboratively. We also recognized from a leadership perspective that if we were going to, in fact, be successful at our individual missions, that finding more formal and more effective ways of bringing the institutions together in a more focused way was a significant opportunity….

What we came to appreciate was that our missions are different, but we are, in fact, bonded together by a common vision. The common vision, is, in fact, to understand the disease, and then to translate that understanding of disease rapidly into the creation of more effective and safe interventions to truly benefit and serve patients. So benefiting and serving patients is, in fact, our common bond, and finding ways for our two missions to be integrated, coordinated, in a synergistic way, is our commitment.

The process has been done already with the creation of a joint task force between the NCI and the FDA. That task force has already had meetings formally and informally, in small ad-hoc groups, and there is an endless amount of momentum beginning to be generated as the task force is looking at two components of opportunity: one being the creation of programs between the two institutes that would, in fact, facilitate and enhance our ability to collaborate on discovery and development of interventions, and those efforts are going to include a variety of initiatives, including a very important focus on bioinformatics infrastructure and platforms, as well as our opportunities with regard to working together through the validation of biomarkers of intermediate endpoints. We are also going to work together to look at an assessment and evaluation of processes to see how they might be more effectively streamlined to rapidly enhance our ability to move through this continuum of capitalizing on the opportunities in genomics and proteomics for the development of effective interventions. Those interventions having to do with devices and opportunities in early detection, capitalizing on proteomics from the point of view of our ability to detect and predict diseases, and also the whole area of chemoprevention.

We have been very blessed, and I am particularly grateful to Dr. Anna Barker, who as deputy director for strategic scientific initiatives, is co-chairing the FDA-NCI task force on our behalf….

We will continue to participate very actively in a variety of other opportunities, including opportunities that are already present to us with regard to the effort through the National Dialogue on Cancer and other organizations….

RALPH FREEDMAN [NCAB member, professor of gynecologic oncology, M.D. Anderson Cancer Center]: Dr. von Eschenbach, these are really ambitious objectives, the 2015 goal. I think it is certainly important to set goals that have time lines in them, but I also think it's important that we have some realism in these objectives. I think this is important not only to maintain the confidence of the many people who care for and are involved in the care of patients, but for the patients themselves. I just wondered if you could expand perhaps for us what would be the major objectives that you would hope to achieve in this period?

VON ESCHENBACH: That's a very important point, and I appreciate it. Let me just start by saying that I think

it's important to keep in mind the framework of reference that I alluded to in which we view cancer as a disease process. When we view it as a process, from the point of view of, even in the phase prior to transformation, we are dealing with issues of susceptibility and carcinogenesis, and then the point where we actually get malignant transformation, and at that point, you have a period of progression of disease to the point where it becomes clinically apparent, and then, the second phase after that, when we go from clinical disease to metastatic phenotype and death. So along that continuum, there are multiple opportunities for us to preempt that process, to the point where we eliminate the burden of cancer and the suffering and death that occurs as an end result of the disease. Our focus is on eliminating the end result by being able to strategically intervene at multiple places throughout that continuum of the cancer process.

We are going to be focusing on the front end as we go through further strategic investments in understanding factors relevant to our susceptibility to cancer, our understanding of host factors, our understanding of the process of carcinogenesis, and opportunities with regard to prevention that can alter or change one's life short of that ultimate malignant transformation. So there's a whole series of strategic opportunities within that phase.

The second phase is once we have cancer to the point where it progresses to clinically apparent disease, again, a very significant series of opportunities for us to strategically look at that phase. Primarily, even from the perspective of our ability to detect that process much earlier than we are able to, because if we can simply move our ability to detect the presence of cancer much sooner in the course of the disease, we already have effective interventions than can eliminate cancer when it is still early and localized. That, in itself, presents us another set of very important strategic opportunities.

Some of the initiatives, even with regard to proteomics and functional imaging regarding early detection, can bear tremendous fruit in making a significant impact on the lethality of cancers, like pancreatic cancer and lung cancer, for example, where just early detection in itself, and application of currently available, effective therapy can have significant impact on elimination of suffering and death.

Finally, we have a whole significant proportion of that spectrum of cancer process where we have the opportunity to intervene even with regard to the process of metastasis, and malignant phenotype, by not only focusing on the cancer, the tumor, the cancer cell, but its interaction with its micro- and macro-environment. So, our beginning emerging focus on micro-environment, for example, our re-emphasis of the importance of tumor host factors, are another set of strategic opportunities within the portfolio.

As far as realistic expectation, what we have available to us is a very broad spectrum of strategic opportunities. At multiple places and multiple combinations of those interventions, we can deliver on the promise by effectively accelerating our progress across that continuum. Although, when we think about this as a linear extrapolation, one begins to raise questions as to whether you can, in fact, achieve this goal within a finite period of time, if one thinks of it as multifactorial, and multifactorial in a way that is integrated, and has an ability to alter or change the curve, to the point where all we need to do is change the slope of the curve, not eliminate the curve, necessarily in all cases. Some we will. Most, hopefully, we will. But for others, even if we don't eliminate cancer, if we just change the slope of the curve, people will live with, and not die from.

In that context, we do not believe that it's an unrealistic expectation, nor do we believe that the timeline, given what is virtually exponential growth in our knowledge and understanding of cancer, and what is a common growth in our intellectual capital, our financial resources, and the virtual explosion in enabling technologies, that now make it possible to more rapidly, even further accelerate this progress, just looking at what's happening in enabling technologies with regard to computational and information technologies. I often use the euphemism, can you imagine what Einstein could have done with a laptop? Look at what the impact of robotics was on the Human Genome Project.

So, when one looks at it from that broad perspective, then I think, I believe we can look at the American public and the world and set this goal without it being something that is considered unrealistic.

FREEDMAN: I think a lot also depends upon the behavior of the population. We know that, for example, we have done a lot in reducing lung cancer through reduction in smoking, but it's a big challenge to get this issue across to the public at large. We know that even if you stop people from smoking at age 30 or 50, it can have an enormous impact on the reduction of cancer. It seems like this has to be part of it, the participation of the public.

VON ESCHENBACH: There's no question that this strategy has to include every element, every component of the problem. Cancer is a systems problem, and the solution to cancer is going to be a systems problem. This is going to require a very important focus with regard to our understanding of biology of cancer, of cancer cells. It's going to require a very important focus on the person, both from the biologic perspective, as well as the behavioral perspective that you are talking about. It's going to require a focus on populations and population science. This is not going to occur in one particular silo or venue. It's going to require a comprehensive strategy that's looking at all of these components. Where I think we have an extraordinary opportunity, is as that the NCI is uniquely positioned to, one, significantly contribute to the actual research endeavor, while at the same time, provide significant leadership to help coordinate and integrate the

larger agenda, that's going to be hard. That's why efforts and initiatives like our partnership with the FDA are an important part of our strategy, because that's ultimately going to be another component to this ultimate solution.

That's why we are working to support a trans-HHS departmental initiative to address the problem of health care disparities and the inordinate burden of cancer, because that's a problem that requires a systems solution, and we need to work effectively with other components of the system—CDC, CMS, etc.—to bring about that piece of it. We are looking at this, not simply from the tunnel vision of our own portfolio, but also looking at it from the point of view of what we need to do across the continuum of discovery, development, and delivery, to bring it about. Behavioral modification and science is a critically important part of that, just as are our efforts in molecules and biology.

SUSAN LOVE [NCAB member, adjunct professor of surgery, University of California, Los Angeles]: It sounds great, and I think it's a really valid goal, but how are you going to measure it? In 2015 are you going to say, "See, we had no deaths from cancer, any cancer this year." Or are you going to say—or how are you going to measure—nobody suffered this year? You know, saying we are going to eliminate suffering and death from cancer, I don't quite understand what's going to allow you to say, "We did it."

VON ESCHENBACH: Ultimately, there are a couple of metrics that I think are going to have to be developed. I would point out that the metrics are not going to occur in a linear fashion. I'm fond of trying to explain this, is that just as cancer can be exponential in its growth, the solution to cancer can also be exponential in its realization, such that, you know the old story of, what you rather have, a million dollars for a month's work, or a penny on day 1 and double it every day until you get to day 30?

When you think of this as exponential, and I believe that we can track things over the past 30 years, and begin to really see, just as occurred with microprocessors and Moore's Law, essentially almost exponential expansion here, we are somewhere around day 20. We are no longer back at week one, where at the end of the week, you've got $3.50 or whatever it is. We are somewhere in day 20. But the greatest progress is still before us, that latter part.

If you want me to speculate, I think between now and 2007, 2010, our measures are going to be still incremental. We are going to see a continuing decline in mortality due to cancer. We will probably continue to see expansion in number of patients who have cancer, but I believe we will continue to see a decline in mortality, and we need to track and measure that.

We will also be seeing the expansion of the portfolio of our ability to manage the disease, such that prolongation of survival will be another measure. I think that that is an important measure….

As far as suffering is concerned, I do think our ability to manage the burden of the disease and the implications of the disease, is again one that is able to be measured. Ultimately, what we will get to is a point where those people dying from cancer, as a direct result of it, does, in fact, come down to baseline of zero.

JOHN NIEDERHUBER [NCAB chairman, professor of surgery, University of Wisconsin]: As with any strategic planning process, it's important that there be flexibility in that process. I wonder if you would share with us what process you have put in place with your executives, your division leadership, to periodically look at the baby steps within the Institute and how to adjust and react to changing environment, to changing accomplishments internally and externally, so that the plan is flexible and reactive.

VON ESCHENBACH: There are a couple of issues in that regard, one of which is, we have committed to an ongoing strategic planning process. We are not writing a strategic plan. I don't believe in plans that you then put on a shelf. What we are committed to is a planning process. We are committed to a schedule, for example, every quarter, we have one full day set aside where we meet as a strategic planning body to look at process.

Our mantra is: we get ready, we fire, and we steer. It's not: ready, aim, fire. It's ready, fire. We are launching. We are moving initiatives ahead that we believe are important strategically to impact on that continuum of cancer process. Strategies having to do with expansion of our early detection opportunities, using the opportunities that proteomics presents to us. Strategies having to do with looking at the metastatic phenotype as the lethal phenotype of cancer that provides great opportunities for us, if we begin to emphasize our understanding of tumor-host micro-environmental interactions, and relationships that exist in the metastatic phenotype and the role that micro-environment plays in that.

My point is, John, that we set out strategies. We look at them from the point of view of their impact on our achievement of the goal. Then, we monitor and steer as we track over time the impact of those strategies, the new opportunities that are becoming available and opportune to us in new areas that we can embark upon, for example, one of those being a very important effort right now to explore the impact of nanotechnology, and that's an initiative that Dr. Barker is heading up.

Our formula is a commitment, a mindset, a process that enables us to manage this portfolio on an ongoing basis to make sure that our investments are wise and appropriate, given what's in fact occurring within the environment, and that we are moving those investments appropriately from completion to opportunity, constantly trying to move an entire agenda towards the goal of seeing a decline in burden of cancer, decline in death rates, prolongation of survival, and diminishing of suffering.

LARRY NORTON [NCAB member, director of medical breast oncology, Memorial Sloan-Kettering Cancer Center]: First of all, I applaud this goal. I think it's an extraordinary achievement just to state it with the boldness that you have. I also want to add that I agree that it's

feasible. Largely, we have to remember the historic precedent, is that when we had truly major impacts on cancer, they sometimes occurred very quickly: gestational choriocarcinoma, pediatric leukemia, Hodgkin's, testicular. We have seen these in our own careers go from certainly fatal to high probability of cure, very rapidly with the introduction of new technologies, largely new drugs. I also applaud this focus on the kinetics of growth, which obviously I've dedicated a lot of my professional life to, because I think that's also a very important focus. Those are just comments. The question concerns this truly historic meeting you had at ASCO, not only the size of the room, which was historic in itself, but also because of the nature of the conversation, how candid it was, how open it was, and major issues you discussed with the FDA. One of the things that occurred to many in the room during that discussion is the relationship between industry, the private sector, and the public sector in this regard. We immediately left that session and then had all of our usual interactions with industry, which is very guarded, very careful. There is enormous screening of potentially useful compounds, many levels of screening before it gets up to phase I trials, based on the likelihood of success at the FDA, the likelihood the endpoints are accepted, in terms of traditional endpoints, and even marketing considerations, in terms of the number of patients who could benefit, the likelihood of producing the product. That seems to be emerging as one of the hurdles we are going to have to deal with. I'm wondering, from the NCI perspective, what your thinking is in that regard?

VON ESCHENBACH: I agree with you that, again, going back to the concept of a systems problem is going to require a systems solution, but that's a very important element of it. The current effort is the NCI and the FDA to work collaboratively first to effectively support each other in our individual missions. That's not occurring in a vacuum, either. I'm aware of a parallel effort that's occurring among the pharmaceutical and will include and reach out to the biotechnology arena, where they are looking at opportunities and models in which they can come together more effectively so that they don't impair their progress by unnecessary conflict. The model that's being looked at as a potential prototype as to how that could occur was the model that was developed when the semiconductor industry was faced with the same problems and the same challenges. They were working in independent silos and pursuing their independent agendas, and their ability to achieve those goals was hampered or undermined, because they couldn't achieve critical mass. Whereas, there was tremendous progress that was being made outside of this country by the Japanese. The semiconductor industry came together around a model called Sematech, which enabled them to create an entity where they could pool resources in a pre-competitive way, that developed infrastructure that they could all benefit from and use to propel their own individual initiatives….

They are looking at that. It may not work. But I'm aware of the fact that they are recognizing the same thing that the cancer community is recognizing, and that is, for us to achieve our goal, we are going to get their much faster working together than not. That's not easy to do, but at least there is a very significant awareness that that's got to be our reference. The genome project is a prime example of that proof of principle…. That proof of principle is being appreciated across the spectrum.

I'm not being Pollyannaish about this and underestimating the complexity or the enormity of the challenge, but I am absolutely convinced that it is within our grasp and is doable.

ELMER HUERTA [NCAB member, director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute]: My comment has to do with a possible confusion that may arise. I got an email some time ago from a cancer survivor whose wife died of cancer. He told me he was really alarmed that the new goal of the NCI was to convert cancer to a disease that you can die with, not due to. He said, "Is it true that NCI doesn't want to pursue a cure for cancer? Are they changing their minds or philosophy?" The American Cancer Society asked the Gallup Organization to ask [people] what do you think is the primary objective of the society? Forty percent of people said they want the American Cancer Society to find a cure for cancer. Forty-three percent said the first priority for the American Cancer Society should be to find a cure for cancer. So, it seems to me that we don't know how to explain this to the public, we don't know how to mobilize our PR, communications, we are going to find a misunderstanding from the public. I think the public has the right to hear from us. They think that we should find the cure, and if that's not the case, if your definition of cure is changing, we should explain that to them.

VON ESCHENBACH: I don't think there's any question that you are right. First of all, I think we have become aware in the cancer community that there is no magic bullet. Having said that, I do think, we are looking at it from the point of view of a disease which can be managed, as well as eliminated. I'm not backing off the fact that we will not eliminate cancer for many, if not most, patients, but I don't believe that's our only goal. I think we can also look at cancer as a disease that can not only eliminate, but a disease that we can manage. Much like we manage diabetes, much like we manage hypertension. We don't propose to patients that there is a cure for diabetes or there is a cure for hypertension. But we do propose to them that if they engage in appropriate management of the disease, it will not present any biologic threat to them. So, I think we have a challenge with the American people to help them understand, and have to understand their role and participation in the cancer problem. They are not passive in this. They have an active part in the equation. We are making the commitment to communications. We are making a commitment through Bob Croyle [director of

the NCI Division of Cancer Control and Population Sciences] and some relationships we are developing, to be conscious of not only what it is we have to do, but recognizing always that the patient is the focus of what we are doing, and the patient is an active component of what we are doing, including helping the patient to understand. That's true of understanding the difference between curing cancer, or eliminating the suffering and death due to the disease….

JAMES ARMITAGE [NCAB member, dean, University of Nebraska College of Medicine]: Anytime you set out to achieve an important, exciting goal like this, there can be bumps in the road. I'm interested in what you think are the biggest threats to achieving the goal you set out. I can imagine them being things like, cancer turns out to be more of a moving target than we understand today, in some way analogous to infectious disease, or a huge scientific problem we never anticipated that we run into, or maybe more likely, the economy or Congress aren't as sympathetic and resources are not available to do what we need to do. What do you think are the biggest threats to your goal?

VON ESCHENBACH: Sometimes I see biggest threats and biggest opportunities as being mirror images of the same thing. Clearly, I think the whole problem of 9/11, and the whole need to begin to acquire a significant focus in our health care agenda to infectious disease and the problem of bioterrorism could be looked upon as a threat to the allocation of resources to solving the problem of cancer. I actually don't see it that way. I think we can turn that into a real opportunity, because as we are working in cooperation with NIAID and Tony Fauci on vaccine development, I think much of what is occurring in our expansion of that area of research can be integrated and coordinated with things that are appropriate for cancer. I think we are seeing a broadening. I alluded to the fact that our budget increases are not occurring at the double-digit level that they were before. I think that we have to partner and find other opportunities in those other places where strategic investments are being made.

The second thing I think is a real potential bump in the road is if we are unable to link to the issue of emerging complementary technologies. Bioinformatics and computational sciences, for example, are one of those areas where we can't create that intellectual capital in our own domain. We need to find ways to import that from other sectors where it's being developed. There are many strategic investments in that area being made in the intelligence community and the military, because of their needs. We have to find ways to not duplicate, but be able to integrate.

Bumps in the road will be if we can't make connections, if we can't access, and work in a way that we can import things that we can't make or can't do or can't create ourselves because we don't have the resources or the expertise within our own biomedical research community.

NIEDERHUBER: Andy, I want to thank you on behalf of the board for this candid and exciting and informative presentation and response to questions. I think all of us, have you have heard, accept the challenge of working with you toward the successful achievement of these initiatives, and of this ambitious, but much needed goal. We are with you, we are behind you, we are committed to helping you.

VON ESCHENBACH: I am very grateful for the interaction. I think this has been a very important opportunity to interact with the board. I do appreciate your questions. The last time I presented this, you were, I think, more stunned. That's why I wanted to bring it back so that we did have the opportunity for discussion. I'm very appreciative of the direction you are providing to me and the NCI, and that the wider community is providing. This is a ready, fire, steer process. Steering has to come from the kind of input and appropriate, critical input that you and the rest of the community are providing. I welcome it. I welcome critical input. It will help us, not hurt us.

Feinstein Introduces Version 2 Of New National Cancer Act

(The Cancer Letter, June 13, 2003, Vol. 29 No. 24)

Sen. Dianne Feinstein is making another attempt to change the fundamental legislation of the National Cancer Program.

The California Democrat has revised and reintroduced a bill that describes the vision of the new cancer program that emerged from the National Dialogue on Cancer, an initiative launched by the American Cancer Society.

An earlier version of the sweeping legislation, which stressed public health measures and proposed that FDA be given the authority to regulate tobacco, attracted 28 cosponsors in the 107th Congress and died in committees.

The second, scaled-down version of the bill, S. 1101, was introduced May 21. Though few observers expect the bill to pass in the 108th Congress, the legislation is significant because it can be presumed to mirror the strategies of the NCI leadership. The bill has 24 cosponsors.

Feinstein is the vice-chairman of the Dialogue. One of the Dialogue founders, Andrew von Eschenbach, now heads NCI. Another top Institute official, Anna Barker, deputy director for strategic scientific initiatives, served as a member of a Dialogue offshoot group that helped Feinstein develop the legislation. Von Eschenbach and Barker serve on the Dialogue steering committee (**The Cancer Letter**, May 30).

"I believe that if we work smart, we could find a cure for cancer in my lifetime," Feinstein said, introducing the bill. "I am the vice-chair of the National Dialogue on Cancer—and in discussions with cancer experts from this

group, it became clear to me that the National Cancer Act of 1971 was out of date. We are now in the genomic era, on the cusp of discoveries and cures that we could only have dreamed about in 1971."

Version 2 of the Feinstein bill differs significantly from Version 1.

—The bill no longer calls for giving FDA the authority to regulate tobacco products.

—While Version 1 called for continuation of steep increases for NCI, Version 2 draws on two non-binding "Sense of the Senate" resolutions, one of which calls for NCI funding at the level of the bypass budget.

Introducing the bill, Feinstein said she pared it down in order to make it viable in the 108th Congress.

"What I have tried to do is take the most important components, in light of the current budget situation, and develop a piece of legislation that could pass the Senate," Feinstein said.

Version 2 includes the following new features:

—Reforming FDA. The bill directs FDA to develop a "strategic plan" for accelerating the process for reviewing cancer therapies.

In recent years, FDA has been breaking its own speed records in approval of cancer drugs, and data indicate that the number of applications in several areas, including cancer, has been dropping.

FDA is emerging as a gatekeeper in many of the measures the NCI Director von Eschenbach intends to carry out in his plan to end "suffering and death from cancer" by 2015 (**The Cancer Letter**, June 6).

In another far-reaching change for FDA, the Feinstein bill would amend the Orphan Drug laws to include therapies for "targets and mechanisms of pathogenesis of diseases."

The Orphan Drug law provides longer market exclusivity and stronger protection from competition for therapies intended for diseases that affect fewer than 200,000 people in the U.S. Currently, the Orphan Drug law is applied on the basis of "disease or condition," not molecular targets.

The bill does not appear to reflect the NCI push to recognize the surrogate marker of "intraepithelial neoplasia" as an endpoint for approval of chemoprevention agents (**The Cancer Letter**, May 30).

—Special Grants for Targeted Drugs. The NCI director would "carry out a research grant program to provide funding to projects that seek to develop cancer treatments that target cancer cells."

The director would "award grants and facilitate the process to award grants to public or nonprofit private entities to conduct research to develop a molecularly-oriented, knowledge-based approach to cancer drug discovery and development," the bill states.

NCI would have to develop a strategic plan for development of targeted therapies. The bill authorizes $20 million a year for this research.

—Patient Navigators. The bill creates a demonstration program run through the Health Resources and Services Administration that would designate "patient navigators" to assist uninsured cancer patients in gaining access to health insurance and treatment, make appointments for follow up and referrals, and translate medical terminology.

—Cancer Survivorship. Under the legislation, the NCI Office on Cancer Survivorship would be headed by an associate director, who would work with other agencies involved in survivorship research.

—State Cancer Registries. The bill would allow the Centers for Disease Control and Prevention to make grants to state cancer registries "to monitor and evaluate quality cancer care, develop information concerning quality cancer care, and monitor cancer survivorship."

The determination of quality of care, one of the most challenging problems in cancer care, would be entrusted to panels convened by the Agency for Healthcare Research and Quality.

These panels would include "cancer experts, providers, patients, representatives of disparity populations, and other relevant experts, including representatives of the Institute, the Health Resources Administration and CDC."

The panels would develop "consensus protocols and practice guidelines for optimal cancer treatments and prevention, including palliation, symptom management, and end-of-life care."

As the preceding bill, the new version describes "translational cancer centers" as the principal pillar of the Feinstein approach to cancer research and cancer care.

The bill describes a "national network of at least 20 existing or new translational cancer research centers to conduct translational, multidisciplinary cancer research." These translational centers would have the authorized budget of $100 million a year.

They would perform the following functions:

—"Perform research for discovery and preclinical evaluation of drugs, biologics, devices, technologies, and strategies with potential to improve the prevention, detection, diagnosis, and treatment of cancer and to improve pain and symptom management and quality of life of cancer patients;

—"Perform clinical research studies on promising cancer treatments or strategies, in appropriate human populations;

—"Evaluate promising cancer diagnostic tests, techniques, or technologies in individuals being evaluated for the presence of cancer;

—"Perform all phases of clinical trials of new drugs, devices, biologics, or other strategies for treating patients with cancer, in collaboration with the existing NCI Cooperative Groups;

—"Develop and implement a plan to ensure the availability of adequate sources of patients for each type

of clinical research study;

—"Create systems and external relationships, which do not duplicate capabilities available in the private sector, to accelerate the findings from translational research to a stage that private companies can assume development and commercialization; and

—"Develop and implement a plan expanding and disseminating the efficacious products of translational research to providers of cancer care, including products approved by FDA."

NCI Chips In $2 Million For AACR Meeting; Advisors, Senior Staff Not Consulted

(The Cancer Letter, June 20, 2003, Vol. 29 No. 25)

NCI has agreed to provide $2 million to help the American Association for Cancer Research pay for its annual meeting next month, **The Cancer Letter** has learned.

Institute officials appear to have circumvented the procedures generally used for reviewing expenditures of this size. Two advisory boards that are consulted in such cases—the National Cancer Advisory Board and the Board of Scientific Advisors—were not informed of the decision, sources said.

Even the NCI Executive Committee, which includes the Institute's top officials, was not involved. The plan for the $2-million expenditure was presented as an "informational item" at the committee's meeting June 12, sources said. Discussion was not invited.

The Executive Committee was not told what mechanism—such as a grant or a contract—would be used to transfer the funds, which programs might be cut as a consequence, and what the government expects to get in return. The committee meetings are closed.

An NCI spokesman confirmed that the Institute will help pay for the AACR meeting, but declined to discuss the matter further. "We are definitely contributing to the meeting, but the exact amount is not known yet," said Caroline McNeil, acting director of the NCI Mass Media Office.

Institute Director Andrew von Eschenbach was traveling in Italy and unavailable for comment, McNeil said.

Margaret Foti, AACR chief executive officer, said NCI officials told her that funds will be disbursed through a contractor, who will pay a portion of the bills related to the AACR meeting. The amount of funding is "still under discussion," she said.

If NCI is acting through a contractor, it's likely that the money is coming from funds set aside for support services, sources said. Government agencies frequently "park" extra funds with contractors.

Often, this is done at the end of the fiscal year, to allow the agencies to avoid having to turn over unused funds to the Treasury. Contractors can hold parked funds for as long as five years, paying the agency's bills, purchasing various services, and even conducting research.

The NCI Director's Reserve is another mechanism that could have been used. The reserve, about 1 percent of the NCI budget, is set aside at the beginning of the fiscal year, to be spent at the director's discretion for internal needs or as supplements to grants.

Last April, AACR suffered a financial loss that could run into millions of dollars. Two days before the society's annual meeting was to have opened in Toronto, its leadership became concerned about the SARS outbreak in that city, and called off the meeting.

At that time, neither the World Health Organization nor the Centers for Disease Control and Prevention had issued travel advisories for Toronto. However, at least one cancer center—Memorial Sloan-Kettering—advised its clinicians either to cancel travel to Toronto, or to avoid contact with patients for 10 days after returning (**The Cancer Letter**, April 4).

AACR expected to make about $1 million on the Toronto meeting. Instead, the society has incurred bills of $5 million to $6 million, Foti said. An insurer has denied the association's claim, and the bills are yet to be paid, she said.

About 16,000 cancer researchers were projected to attend the Toronto meeting. The association rescheduled the annual meeting for July 11-14, in Washington, D.C. About 8,500 have registered to attend.

Foti acknowledged having met with von Eschenbach in April to seek help. "I went to see him to get his advice and counsel, and ask if there would be some opportunity for special support under these circumstances," she said.

However, Foti said she didn't know about the NCI decision until contacted by a reporter.

"The NCI, and especially the director, to whom we are very indebted, saw the benefits of holding the rescheduled meeting and knew that we couldn't hold this meeting without this gesture," Foti said. "We are grateful to the NCI for helping us in these unusual circumstances. The cancellation of this meeting was devastating to the AACR. The ability to reschedule it, and actually have the NCI make a commitment for a significant level of support for this meeting, was a dream."

Foti said she and von Eschenbach "discussed the fact that no other organization presents such high-quality cancer research at its meeting, and that there was an enormous number of presenters who were scheduled to present in Toronto, and even considering at that time the notion that there might be almost 5,000 or so proffered papers that needed to be presented."

AACR operates on a $30 million budget, and has a reserve fund of $12 million, Foti said. The loss of up to $6 million on the Toronto meeting and the $5 million cost of the Washington meeting would have drained the reserve, Foti said.

"If we do not recoup these funds, it's a setback, but not irrevocable," Foti said. "It's not going to affect the viability of the AACR, but could mean we have to be more conservative about launching new programs in response to the information needs of the cancer community."

Foti's remarks earlier this week are consistent with those she made in April, after the cancellation of the meeting. At that time, too, Foti said that she consulted von Eschenbach "and other people at NCI" prior to making the decision to cancel, and that von Eschenbach supported the association's decision to reschedule the meeting (**The Cancer Letter**, April 4).

"I've talked to Dr. von Eschenbach about that, and he agrees that we must work very hard to reschedule this meeting as soon as possible, given the importance of the AACR annual meeting to the cancer program," Foti said in an interview in April.

Asked by a reporter whether that meant NCI would provide funding for the meeting, Foti said, "I don't know yet. I think that we will certainly discuss that."

AACR Emerged As Ally of NCI's 2015 Goal

AACR is a key supporter of von Eschenbach's goal to "eliminate the suffering and death from cancer" by 2015.

Achieving that goal will require new research on interventions to interrupt the "cancer process," von Eschenbach has said (**The Cancer Letter**, June 13).

Last year, AACR proposed that pre-cancers, or "intraepithelial neoplasia," be recognized as surrogate endpoints for the formation of many common cancers.

Designating the eradication of IEN lesions as a medical outcome would accelerate clinical trials of new agents for the prevention of cancer, AACR said in a position statement. Trialists would not have to wait to measure survival, AACR said (**The Cancer Letter**, May 30).

The approach is controversial, because little is known about pre-cancers and the risks they convey. From what is currently known, it appears that only a small percentage of pre-cancers progress to cancer, skeptics say.

The scientific literature contains many examples in cancer, heart disease, diabetes, and other diseases, where interventions to address a surrogate endpoint did not ultimately result in better or longer life. In many cases, interventions resulted in harm.

Therefore, many clinicians argue, the science is insufficient to declare IEN a medical endpoint, and taking this short-cut may result in unnecessary, harmful, and expensive treatment.

Anna Barker, the new NCI deputy director for strategic scientific initiatives and a longtime AACR activist, has championed the recognition of IEN as an endpoint.

"I think the [AACR] IEN report was a landmark report," Barker said to **The Cancer Letter** last month. "It drew on the expertise of the community to put together what I think is a very cogent argument for looking at and evaluating potential chemopreventive agents. I think it sets the stage for putting science in perspective in terms of how you might be able to look at chemopreventives. It's a new paradigm."

An "Informational Item"

The decision to provide money to AACR stunned some NCI officials.

"There was a deal made," one staff member said to **The Cancer Letter**. "You would think that expenditures that high would go to a board. We are tight on funds."

Senior NCI officials first learned about the $2 million transfer from NCI Deputy Director Alan Rabson at the June 12 meeting of the Executive Committee, sources said.

The committee includes the Institute's division directors, and is led by von Eschenbach. The committee's purpose is to formulate scientific and management policy decisions, review concepts for grant and contract programs, and approve exceptions to grant funding plans.

After one committee member raised questions, Rabson replied that the decision to commit money to AACR was being presented as an "informational item," and was not subject to discussion, sources said.

The committee was not told how the funds would be provided to AACR, sources said.

The AACR meeting subsidy would set a record for NCI conference support, sources in the Institute said. NCI funds peer-reviewed conference grants (R13s) in the range of $5,000 to $15,000. For example, NCI is funding a $10,000 conference grant to AACR for its Conference on Mouse Models of Human Cancer, according to an NCI grants database.

The decision to fund the AACR conference did not come up for discussion at the June 10 NCAB meeting, either in public or closed sessions, sources said.

The NCAB, whose members are appointed by the President, is responsible for final external review of all grant applications to NCI, with the exception of those seeking less than $50,000 in direct costs per year.

The NCI Board of Scientific Advisors, another group not consulted, reviews concepts for grant and contract programs and counsels the Institute on scientific program policy.

150 Free Registrations For NCI

Earlier this week, AACR gave NCI staff 150 free passes to the annual meeting.

"The American Association for Cancer Research has granted the NCI additional registration passes to send NCI staff to their annual meeting," Kathleen Schlom, special assistant to von Eschenbach, wrote in an internal email dated June 16.

"These will be distributed to the divisions based on the percentage of registrants enrolled," Schlom wrote. "These free registration passes are not to replace existing

registrations, but to supplement division attendance."

The government normally pays the AACR meeting registration fees for NCI staff. The registration fee ranges from $425 for AACR members to $725 for non-members.

McNeil said 500 NCI staff had registered for the AACR meeting in Toronto.

"We did receive an offer from AACR and we looked into it, and NCI can accept it under our gift authority," McNeil said.

Government ethics regulations include provisions allowing employees to accept free meeting attendance from meeting sponsors if the gift is unsolicited, and if proper procedures are followed, a spokesman for the Office of Government Ethics said. The gift can be accepted either by the employee personally or by the agency under its gift acceptance authorities.

"We thought, since it would be so convenient with the meeting in Washington, D.C., it would be nice to offer complementary registration to those [NCI staff] who had not been able to come to Toronto, to facilitate the participation of more NCI scientists," Foti said. "As you know, our NCI colleagues, their salaries are not very high, and they need help, and so we are trying to help them. We wanted additional people to attend, because of the importance of the science of the meeting."

What $2 Million Can Buy

The Institute's action comes at a time when legislators are examining the outcome of the doubling of the NIH budget between 1999 and 2003 and questioning the value of continuing increases.

The House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions are gathering information about the NIH doubling, possibly preparing oversight hearings.

Though $2 million is a small share of NCI's $4.6 billion budget, it can buy a lot of peer-reviewed research. Alternative uses could include a core grant for an NCI-designated cancer center, eight cancer center planning grants, eight Community Clinical Oncology Program grants, two large Special Population Network grants, or half of the annual budget of a cooperative group biostatistical center.

Other uses could include:

—Accrual of 1,000 patients to cooperative group trials, enough for a definitive phase III study. The budgets of the cooperative groups are being held flat this year.

—Three national tissue repositories operated by the cooperative groups. Though "genomics and proteomics" have become NCI buzz words, the Institute leadership this year declined to provide additional funding for the tissue banks, which are becoming increasingly important for genomic studies.

—Five investigator-initiated R01 grants. By accepting these funds, AACR is, in effect, competing with investigators at a time when the number of grant applications being submitted to NCI is exceeding the Institute's ability to fund them.

"I'm always concerned about funding for cancer research," Foti said. "We spend a lot of our time trying to increase funding for cancer research, and we are always anxious to increase that number. However, I'm assuming that, in fact, this won't interfere with the monies that are going to grants, but I don't have any information on that."

NCI received an increase of $415 million for fiscal 2003. Half of the increase has been committed to research project grants, von Eschenbach said to the NCAB last week. NCI will fund 4,813 research project grants, 325 more grants than last year.

"We are continuing to see a constant expansion in the number of applications that are coming to the NCI," he said.

This year, NCI will fund only the top 20 percent of R01 applications. Last year, R01s were funded to the 22nd percentile.

Funding increases for NCI are unlikely to remain in double-digits, observers say. President Bush proposed an increase of 3.5 percent, or $161 million, for NCI next year.

Addressing NCAB last week, von Eschenbach said researchers should prepare for leaner times.

"You can begin to see that going from 2003 to 2004, we will be looking at a significant reduction in the increase," von Eschenbach said. "We are looking at that quite closely from a strategic point of view to decide appropriate strategies to accommodate that, including the fact that our budget has ongoing out-year commitments that we need to be sensitive to.

"But, we do believe that we have significant opportunity for those resources to be used in effective and creative ways, particularly looking at opportunities to leverage, opportunities for partnerships and collaborations," he said.

Letter to the Editors:

AACR Defends Policy Paper And Work Of Barker, Sigal

(The Cancer Letter, June 27, 2003, Vol. 29 No. 26)

To the Editors:

We read with great concern your May 30 cover article, "NCI Deputy Barker Hits FDA, Calls for New Incentives for Pharmaceutical Industry," in which you criticize the AACR Task Force Report, "Treatment and Prevention of Intraepithelial Neoplasia–An Important Target for Accelerated New Agent Development," published in the February 2002 issue of Clinical Cancer Research, as well as the members of the cancer community who are advocates for the evaluation of surrogate endpoints in cancer prevention. The article you published contains many inaccuracies and lacks objectivity.

Cancer remains a major public health problem. Clearly, we are in great need of new strategies to prevent

and cure cancer. One such strategy was spelled out in the above-cited AACR Task Force Report. This peer-reviewed paper recommended "focusing on established precancers as the target for new agent development because of the close association between dysplasia and invasive cancer and because a convincing reduction in IEN burden provides patient benefit by reducing cancer risk and/or by decreasing the need for invasive interventions."

The use of surrogate endpoints for drug approval is open to legitimate differences of opinion among scientists. This expert Task Force proposed several clinical trial designs that "provide practical and feasible approaches to the rapid development of new agents to treat and prevent precancer." The report was written to open a dialogue among scientists, government officials, members of the pharmaceutical industry, and cancer survivors on what many cancer researchers believe to be a new and highly promising area of investigation.

Your article misrepresented the content of the position paper by stating: "For those who worry about 'the risks of giving medicine to seemingly healthy people—including those with precancers,' AACR has a prescription: look at cardiovascular disease and don't worry."

Although our experts believe the history of drugs approved to treat cholesterol and hypertension, which lower the incidence of heart disease, offers some lessons for how we might begin to prevent lethal cancers, in no statement or report does the AACR or the Task Force recommend a policy of "don't worry," as you paraphrased. Nor is there any suggestion by the AACR that physicians violate their primary commandment, "First, do no harm," when it comes to the development and administration of any new chemopreventive agents. The Task Force Report states: "Clearly, the IEN treatment studies must monitor patient safety and efficacy long enough to ensure that risks associated with the agent do not exceed its benefit. Alternatively, the agent's long-term safety must have been evaluated in other patient populations."

The authors of the AACR Task Force Report are in the mainstream of high-quality science; they are over 50 of the world's leading experts from all sectors and in all fields of cancer prevention, from basic to clinical. They have spent their careers studying the biology of cancer and its progression, and they keenly understand the complexities of molecular targets, along with drug discovery and development. All of the relevant scientific issues you raised in your article have been taken into consideration in their deliberations.

A newly formed AACR Task Force on Cancer Prevention, chaired by Dr. Waun Ki Hong, with more than 25 leading experts in a variety of disciplines, will continue to focus on chemoprevention as an effective way of reducing cancer incidence and mortality. This Task Force will delineate a comprehensive cancer prevention strategy that includes consideration of promising scientific work in the treatment and prevention of intraepithelial neoplasia. The science on this subject is progressing rapidly, and we expect that more articles will be published in the near future to support such new strategies in cancer prevention.

Regarding the NCI Director's "Vision for 2015," ambitious goals are often at first viewed with skepticism. Certainly the elimination of death and suffering due to cancer by the year 2015 is a huge challenge to the cancer community. But which is worse: the disappointment of failure, or the failure to try? The AACR applauds Dr. von Eschenbach's vision and his commitment to accelerating progress against cancer. Exploring new paradigms in chemoprevention based on excellent science is critical to reaching this goal.

Dr. Anna Barker, who recently assumed the post of Deputy Director for Strategic Scientific Initiatives at the NCI, has a unique background encompassing basic science, knowledge of the corporate sector and public-private partnerships, and remarkable achievements in her work with cancer survivors. She also served admirably for over 15 years as the Chairperson of the AACR Science Policy and Legislative Affairs Committee. In this role, she competently and selflessly gave of her personal time and energies to public education, survivor relations, and science policy, and was consistently lauded by the AACR Board of Directors, and also by numerous other cancer organizations, for her passion to conquer cancer. To label her extraordinary work that has greatly benefited cancer research and cancer patients around the world as "oncopolitics" is an injustice.

Dr. Ellen Sigal, who served with distinction on the National Cancer Advisory Board and numerous other important bodies, was also treated unfairly in your article. For decades she has been one of the most dedicated leaders in advocacy for cancer research, and her work has been pivotal to increased funding for cancer research.

The AACR will continue to collaborate with all sectors in the cancer community—academia, NCI, FDA, the pharmaceutical and biotech industries, survivor advocates, and other cancer research and clinical oncology organizations—to make advances in cancer prevention so that we can dramatically reduce cancer incidence and save lives.

Susan Band Horwitz, President
Karen Antman, President-Elect
Waun Ki Hong, Past President
Margaret Foti, Chief Executive Officer

The Cancer Letter responds:

Our story distinguished the AACR position statement on "precancers" from the IEN paper on which it was based. We demonstrated that the AACR recommendation to change the criteria for drug approval reaches beyond the scope of the IEN paper on which it was based.

According to the position statement, in the past,

"many worried about the risks of giving medicine to seemingly healthy people—including those with precancers—to prevent them from getting sick.... However, this attitude clearly has changed with the treatment of other life-threatening conditions such as cardiovascular disease.... The AACR now believes that reducing precancers lowers cancer risk.... AACR believes the link between some precancers and invasive cancers—particularly in certain high-risk populations—is so clear that drug developers should only be required to prove their proposed medicines are safe and effective in treating or preventing the evolution of precancer to cancer."

As the above letter suggests, this is a complicated area of inquiry that requires rigorous study. That was the point of our story.

The story traced in detail Barker's and Sigal's work in cancer policy, using the term "oncopolitics" to refer not only to their work, but generally to activities related to the politics of cancer research, including advocating for funding or policy change. We don't agree that using the term demonstrated unfairness.

Finally, we take this opportunity to point out that science policy, especially when it involves public health and expenditure of public funds, is not above public scrutiny.

We stand by the story.

Cancer Clinical Trials System Needs Comprehensive Review, NCI Director Says

(The Cancer Letter, July 11, 2003, Vol. 29 No. 28)

NCI Director Andrew von Eschenbach said he will appoint a panel to conduct a "comprehensive review" of the Institute-supported clinical trials system.

The panel will be formed in September, after the recruitment of a director for the Division of Cancer Treatment and Diagnosis is finalized, von Eschenbach said to the NCI Board of Scientific Advisors at its June 26 meeting.

The new group would conduct a "comprehensive and systematic review and assessment of our entire clinical trials system and infrastructure," von Eschenbach said. The review "will also integrate and dovetail into the larger NIH agenda to re-engineer our clinical research infrastructure nationwide," he said. "Both the clinical trials process and the clinical trials program is one that will be a major focus of attention in this next year."

The planned review, coupled with other recent actions, has left many chairmen of the 13 NCI-funded clinical trials cooperative groups wondering what von Eschenbach's plans are for future support of their organizations.

In May, NCI officials said there was no money in the Institute's $4.6 billion budget to provide a 3 percent cost-of-living increase promised to the cooperative groups. Overall, the Institute's budget increased this year by 10 percent, or $415 million, during the current year.

The budget for the groups is about $155 million in fiscal 2003, NCI Division of Cancer Treatment and Diagnosis Acting Director Ellen Feigal said to **The Cancer Letter**. Funds may become available later this year from lower-than-expected patient accrual to restore the 3 percent increase, she said.

Meanwhile, von Eschenbach has authorized double-digit increases in four NCI programs. Funding for cancer centers increased 19 percent, from $225 million in fiscal 2002 to $269 million in fiscal 2003. Specialized Programs of Research Excellence saw an increase of 30 percent, from $95 million to $123 million. Funding for NCI training programs increased by 14 percent, and bioinformatics increased by 14 percent.

Leadership of DCTD has been weakened by the lack of a permanent director, which led to an atmosphere in which other programs were able to claim more funds, sources said. Feigal became the acting DCTD director following the departure of Robert Wittes more than a year ago.

Even the tissue banks operated by the cooperative groups will get no new funds, despite strong support for the funding from NCI program staff. Institute officials are working with the National Dialogue on Cancer to develop plans for a "national tissue bank," Anna Barker, NCI deputy director for strategic scientific initiatives, said to the NCI Board of Scientific Advisors at its June 26 meeting.

It's unclear how the cooperative group tissue banks would fit in with the new program

Barker's remarks about the national tissue bank raises questions about the relationship between NCI and the Dialogue. Recently, that relationship became more formal, as the Dialogue became a 501(c)3 organization, and its steering committee became a board of directors. The conversion makes von Eschenbach vice chairman of the board of the Dialogue, and Barker a Dialogue board member.

The meetings of the Dialogue are not open to the public. Though von Eschenbach has maintained that the organization is not advisory to NCI (**The Cancer Letter**, May 16), it may take a court decision to determine whether the Dialogue is being used as a *de facto* advisory committee, lawyers say.

"These are private entities making decisions on public funds, and that's something that ought to be frowned upon, unless it's subjected to public scrutiny and transparency," said Tom Fitton, president of Judicial Watch, a Washington group that challenged the Clinton Administration on adherence to open meeting laws, and is challenging the Bush Administration on the same principles.

The group is suing the Administration over operation of the Energy Task Force, set up by Vice President Dick Cheney. The task force functioned as an advisory committee and should have been subject to open-

meeting regulations, Judicial Watch asserts.

"There is nothing to prevent any government officials from seeking outside advice, but if they are going about it in a systematic way, if they have committees operating and policy being formulated, that outside advice needs to be given some public scrutiny and made transparent," Fitton said to **The Cancer Letter**. "That's because we are a democracy."

"We Are Going To Have Another Meeting"

Several group chairmen publicly expressed surprise at von Eschenbach's plan for a clinical trials system review.

In the past eight years, the groups have gone through two reviews. The reviews—first, by a committee led by James Armitage, professor and chairman of the Department of Internal Medicine at University of Nebraska Medical Center, then, by an implementation panel of outside experts—resulted in several pilot projects designed to speed the implementation of clinical trials, add more rigor to protocol review, and make trials available to more cancer patients.

The work of these committees has been presented to the NCI Board of Scientific Advisors and the National Cancer Advisory Board. Also, the National Cancer Policy Board of the Institute of Medicine, is working on a report that deals with aspects of the clinical trials system, said Roger Herdman, staff director of the Policy Board. The report is scheduled to be completed later this year. Armitage serves on the IOM committee writing the report.

The report, which will be titled, "Shortening the Timeline for New Cancer Treatments," will examine "ways to realize more efficiently and rapidly the new potential for developing targeted cancer therapies depending on recent advances in genomics and other basic science," according to a summary of the board's work. "It focuses on developing drugs for children, cancer vaccines, tissue resources, the FDA, the NCI, clinical trials, intellectual property, and reporting quality-of-life outcomes in trials."

At the BSA meeting, board member Richard Schilsky, chairman of the Cancer and Leukemia Group B, asked von Eschenbach to elaborate on his plans for yet another review of the clinical trials system.

"We have had several large committees that have undertaken to review that program in the last eight years or so, and it may be premature to ask you what the charge to the group will be, but maybe you could give us a general sense of what the goals are," Schilsky asked.

The clinical trials system remains suboptimal, von Eschenbach said.

"I will probably turn the question around and ask you, in spite of the fact that there have been significant number of reviews in the past eight years with regard to clinical trials, is there general agreement that our clinical trials infrastructure is working, functioning as optimally, as efficiently, as effectively as it should?" von Eschenbach said. "I haven't had anyone tell me that that is so overwhelmingly the case that we need not do any more.

"Until we have a clinical trials program and process that I believe is achieving its greatest impact, output, cost efficiency, and is in fact as effective as you want it to be, and as the community demands and expects it to be, I'm afraid, Rich, we are just going to have to have another meeting," von Eschenbach said.

"It's our responsibility to carry out these programs and be certain we are meeting the needs and expectations of the community," von Eschenbach said. "But we want to do this in concert with you, and with the community. Unfortunately, you specifically. Your name is already on the list. There are others who we are very anxious and want to be a part of this process. I fully intend for us to have milestones and outputs."

"What's The Story Here?"

Cooperative group chairmen have argued for years that their groups work efficiently and as intended when given appropriate funding.

In a famous example, the Southwest Oncology Group in 1990 and 1991 responded to then-NCI Director Samuel Broder's demand to increase patient accrual. The group was on track to double its accrual in 1991, but that effort suddenly created financial problems for the group's operations office and statistical center, which were overwhelmed with data.

Despite pleas from the group, NCI declined to provide additional funding, so SWOG Chairman Charles Coltman Jr. raised $270,000 from pharmaceutical companies and delayed the activation of new protocols so that accrual could "come in for a soft landing," to the group's funded level at the time of about 6,000 (**The Cancer Letter**, Oct. 10, 1997, Vol. 23 No. 39).

Last month, NCI's budget priorities came in for scathing commentary at a meeting of the group chairmen.

"There is always a message in a budget," said Robert Comis, chairman of the Eastern Cooperative Oncology Group and president and chairman of the Coalition of National Cancer Cooperative Groups. "Is the senior leadership basically saying that they don't want this system to survive or thrive? Is the senior leadership basically saying that they don't care about the phase III system? If that's the case, they don't understand it…. What's the story here?"

"I can give you a brief story," answered DCTD Director Feigal at the June 13 meeting. "The groups' budget is being held flat not for lack of advocating for an increase in budget from the division. It's a very high priority. What happened this year is that there were a certain number of funds available. Dr. von Eschenbach had competing priorities being presented to him."

The groups shouldn't get the message that NCI is no longer interested in phase III trials, Feigal said. "There is a commitment to running clinical trials and there is also a realization that if we are going to get to the 2015 goal, we

have to get it through conducting clinical trials," she said, referring to von Eschenbach's goal to "eliminate the suffering and death from cancer" by that date.

"So it does seem like a mixed message," Feigal said. "There are going to be some tremendous challenges, but I suppose you can also think of them as opportunities to think of ways to get the important clinical trials done without compromising the system."

In 1998, NCI began what officials said would be a three- to four-year process to close an estimated $70-million funding gap between the amount that peer reviewers say cooperative groups should receive and the amount the Institute actually provides. Then-NCI Director Richard Klausner said that having completed a review of the system, the Institute would make a commitment to "correct the historic under-funding of the clinical trials program" (**The Cancer Letter**, Nov. 13, 1998, Vol. 24 No. 43).

Funding for the groups has increased by $62 million, or 66 percent, from the 1998 level of about $93 million to the current $155 million, Feigal said to **The Cancer Letter**.

During that time, a new group was funded, the American College of Surgeons Oncology Group, and four separate pediatric oncology groups merged to form the Children's Oncology Group.

A new diagnostic imaging group, the American College of Radiology Imaging Network, was started in 1999, but that group's budget is separate from the cooperative group U10 line, Feigal said. The ACRIN base funding was about $2 million in 1999 and $4.2 million in 2003.

Group chairmen say under-funding is still a fact of life for their organizations.

The Children's Oncology Group budget, peer reviewed for about $56 million in fiscal 2003, is expected to receive $29 million from NCI this year, a $27-million shortfall, COG Chairman Gregory Reaman said to **The Cancer Letter**.

"We began as an NCI-sponsored organization, much of what we do is in collaboration with NCI, yet we are expected to find sources of funding outside NCI and the federal government to actually do the work they would like us to do," Reaman said. "I really think there needs to be some special attention to pediatric cancer, and particularly translational research in pediatric cancer, because our plans and efforts to accomplish that through COG have been made nearly impossible with a flat budget."

A group of COG investigators specializing in acute leukemia have submitted an application for a SPORE grant to NCI. "Ninety percent of children with acute leukemia are treated on trials of COG," Reaman said. "COG is uniquely poised to be the cancer center without walls for pediatric acute leukemia."

Most of the groups contribute to research funded through other NCI grants, Comis said. "In ECOG alone, we have 21 R01s that are supported by the tissue bank that basically nurture the national system," he said. The NCI-supported programs are interdependent, and the group system should not be penalized for primarily conducting phase III trials, because the work of the groups contributes to all areas of cancer research, he said.

NCI may be able to restore some or all of the 3 percent increase later this year, Richard Kaplan, chief of the Clinical Investigations Branch in the NCI Cancer Therapy Evaluation Program, said at the meeting of the group chairmen.

The Institute held back a proportion of the budget for patient accrual so that the funds could be distributed as needed throughout the groups, Kaplan said. The groups expect to enroll about 1,000 fewer patients this year than last year, due to the closing of some large studies.

"The other major, major thing we wanted to have funding for was the tissue banks," Kaplan said. "We didn't get money for that this year, despite the fact that Sheila Taube lobbied for it very hard from the Cancer Diagnosis Program, and we lobbied very hard for it from CTEP. That money has not been forthcoming."

"We are going to try again to get some end-of-year funding specifically for the tissue banking effort," CDB Director Taube said to the group chairmen. "We are also trying to think of more creative and innovative ways to provide stable funding for the tissue bank effort that doesn't get plowed into the cooperative group line, and we will come back to you with those ideas as we develop them."

NCI-NDC National Tissue Bank

At the BSA meeting June 26, NCI's Barker said the national tissue bank concept "is a collaborative effort between the NCI and the National Dialogue on Cancer."

The group in charge of developing the concept is co-chaired by Paula Kim, president of the Pancreatic Cancer Action Network, and Jeffrey Trent, director of the Division of Intramural Research in the National Human Genome Research Institute.

A "national" tissue bank is needed, because most tissues currently are not collected or stored in a manner compatible with genomic analysis, Barker said at a June 26 meeting of the NCI Board of Scientific Advisors. Also, existing tissue banks have "ownership barriers" that impede tissue sharing among researchers, she said.

Barker said additional details would be presented to BSA in the fall.

"At a recent meeting of the cooperative group chairs, we were told there would be no additional funds for cooperative group tissue banking activities, despite strong advocacy for those funds from some members of NCI staff," CALGB Chairman Schilsky asked. "I'm curious as to how that reconciles with your view of the importance of tissue acquisition, and if it's not going to be through the cooperative group mechanism, where we obtain the most highly annotated specimens, what do you view as the better mechanism?"

BARKER: It's not clear yet where the resources for

this would come from, but it likely would not be funded solely through the NCI. It would probably be funded, and would have a governance structure that would involve national agencies. I suspect we would be the lead in that.

Legacy systems would continue. This would be a new resource just for this issue of genomics and proteomics that we are trying to underpin. It's a challenge to fund these resources.

SCHILSKY: I'm sure you are aware that the clinical specimens are almost useless by themselves without annotation data, so you need to obtain the specimens in the context of well-annotated clinical data.

BARKER: That is the sole objective of this whole resource, is to collect and annotate specimens, as well as to underpin it with technology. We would see this through a virtual network using a lot of our current resources, but working on a common set of standards.

FREDERICK APPELBAUM, BSA CHAIRMAN: Is the view that this would look more like Napster [the peer-to-peer file sharing software]?

BARKER: I think, probably. It's in process. The business model needs to be worked out.

"Coke vs. Pepsi"

Von Eschenbach doesn't appear to favor the cooperative groups.

Associates say they have come to expect the NCI director to say "Coke vs. Pepsi" when he hears about group trials comparing cancer therapies.

Two weeks ago, von Eschenbach, a urologist and a prostate cancer survivor, passed up the opportunity to address a nationally covered press conference announcing the results of the Prostate Cancer Prevention Trial, led by the Southwest Oncology Group. Only minor shuffling of schedules and a short cab ride would have been required for von Eschenbach to speak at that event (**The Cancer Letter**, June 27).

Von Eschenbach's predecessors have used such press conferences to affirm the capability of clinical trials to improve health care.

"Coke vs. Pepsi is total misrepresentation of the system," said a group chairman, who spoke on condition that his name would not be used.

The trials of high-dose chemotherapy and bone marrow transplantation were of greater significance than a soft drink taste test. Those trials ended a highly toxic, expensive, and ineffective treatment, the group chairman said. The PCPT results were not trivial, either. The trial established the proof of principle that prostate cancer can be prevented, raised questions about the value of screening with the Prostate Specific Antigen test, and established vast banks of pathology samples for future research.

Given von Eschenbach's ties to the Dialogue, it may be useful to consider the Dialogue's vision of NCI.

That vision—described in the bill by the Dialogue vice chairman, Sen. Dianne Feinstein (D-Calif.)—establishes cancer centers as the foundation of the new cancer plan. The centers would be enhanced, geographically distributed, and linked to the pharmaceutical industry and to the public health functions coordinated by Centers for Disease Control and Prevention.

The legislation states that the centers would be involved, together with cooperative groups, in all phases of clinical research. Currently, centers do not conduct phase III trials (**The Cancer Letter**, June 13).

Unlike cancer centers, which are formidable brick-and-mortar structures that appeal to civic pride, the groups are elusive voluntary associations of physicians and scientists involved in clinical research.

Yet, in the coming battles, the groups are likely to demonstrate that their willingness to resist is greatly underestimated, while the Institute is bound to learn—once again—that its power has limits, cooperative group leaders and legal experts said.

A decade ago, the fight over the National Surgical Adjuvant Breast and Bowel Project resulted in Congressional hearings, damage to distinguished careers, public confusion, lawsuits, and—ultimately—a financial settlement from the Institute.

"Tread carefully. That, to me, is the major lesson of NSABP," said Robert Charrow, an attorney with the Washington law firm of Greenberg Traurig, who represented former NSABP Chairman Bernard Fisher in a suit against NCI. "Tread carefully, and think strategically. At the time, NCI did neither."

Chairmen of several groups said they would fight back. "NCI would be making a big mistake," said one group chairman. Another group chairman said he is waiting for NCI to put all the cards on the table. "We need to hear from them what they have in mind, and have a chance to promote our cause and our case," he said.

"I am confident that the cooperative groups are developing a broad-based Washington strategy," said John Engel, an attorney with the law firm of Engel & Novitt, who represented NSABP eight years ago. "By the same token, I would anticipate that the NIH legal advisor's office is seriously evaluating the legal and regulatory ramifications of any effort to undermine, much less eliminate, the groups or their independence."

Group chairmen know that their data are valuable. With genomic analysis, even data and pathology samples obtained decades ago provide insight on a variety of tumors.

"The groups will do everything they can to retain the possession of the pathology specimens, that have been collected as part of cooperative group trials, and that are central to the research mission of the groups," a group chairman said.

If the Institute managed to gain control of the groups' data and tissue banks, it would have to turn around

and build another structure that would perform the same functions as the groups.

"There is no other government-funded system that can do or has done randomized, definitive phase III trials," a group chairman said. "Our national network puts 20,000 to 25,000 patients on study a year, has a 150,000 patients in follow-up, and is recognized everywhere outside NCI as one of the treasures of cancer research in the world."

The Institute has heralded the accomplishments of the groups whenever this serves its needs, maintaining a 134-page document listing the group studies initiated between 1986 and 2001: http://ctep.cancer.gov/forms/accomplish2.doc**.**

The complexity of the groups may be their greatest strategic asset, attorney Engel said. "The databases and tissue banks that have been disparagingly referred to as 'legacy systems' are safe from attacks," he said. "The law and the policies that have governed the cooperative groups for decades are unambiguous. The data and the tissue samples belong to the groups. Indeed, in its guidelines on industry collaboration with the groups, NCI expressly eschews any attempt at control over these fundamental research resources."

NCI will face legal challenges on three levels, Engel said. The cooperative groups, the institutions holding the grants, and individual researchers could file legal actions.

Often, the groups' biostatistical center, administrative offices and tissue banks are located in different institutions, which could mean a multitude of suits.

"If the government—NCI or any third party—tried to get control of the tissues, the only way the tissues would be of any value would be if they were accompanied by the clinical data, which would require that the control be wrested from more than one institution," a group chairman said. "It would be enormously complicated, and cumbersome, and unpleasant."

Also, many researchers at cancer centers are staunch allies of the groups. Many enroll patients in group trials in order to provide state of the art treatment, advancing science and their own academic careers. Will these scientists behave as cancer center constituents, or as leaders of the cooperative groups? Will the patients come to the aid of clinical researchers? Will the national press and Congress get involved?

Ultimately, everyone stands to lose if the groups are damaged, a group chairman said.

"The damage to cancer research would be enormous and irreparable, because the specimens that are collected in cooperative group repositories are the highest quality research specimens that we have available in this country, because they are collected in the context of clinical trials, they are all completely annotated, and accompanied by clinical outcomes," he said.

"If these repositories were destroyed or scattered to the four winds, we would lose an extraordinary resource."

AACR Thanks NCI For Funds, Provides Platform For Von Eschenbach's 2015 Goal

(The Cancer Letter, July 18, 2003, Vol. 29 No. 29)

At the annual meeting of the American Association for Cancer Research earlier this week, the officials of the professional society thanked NCI Director Andrew von Eschenbach for a $2 million subsidy, and provided a sympathetic setting for defense of the Institute's controversial goal to "eliminate the suffering and death due to cancer" by 2015.

In a statement released at the opening of the meeting, held in Washington, D.C., July 11-14, the society commended the goal that many scientists describe as unrealistic.

"When we're offered a challenge to eliminate death and suffering from one of the major diseases of our time—cancer—we applaud the spirit behind the challenge and encourage all to reach out to make it happen," the association said in a three-page statement.

Originally, the AACR meeting was scheduled to be held in Toronto last April, but AACR officials became concerned about the outbreak of SARS in that city, and cancelled. The meeting cancellation insurance claim was denied, and the society is facing $5 million to $6 million in unpaid bills (**The Cancer Letter**, June 20).

Addressing von Eschenbach at the meeting's plenary session, Margaret Foti, AACR chief executive officer, thanked the NCI director for his support.

"Dr. von Eschenbach, without your help at this crucial period, this meeting could not have been held," Foti said. "We are indebted to you not only for your assistance with this meeting, but also for your inspiring leadership and vision as the guiding force of the National Cancer Program. So, we applaud you for your efforts to speed the conquest of this disease."

The NCI funding for the AACR meeting was not discussed by the Institute's top managers, or by its advisory committees, but was presented as an "informational item" at an Executive Committee meeting, sources said.

"The support comes not from me, but from the entire staff of NCI," von Eschenbach said, responding to Foti's words of gratitude at the plenary session. "We are pleased to provide the opportunity to help."

AACR officials asked von Eschenbach to serve as moderator of the meeting's plenary session after Francis Collins, director of the National Human Genome Research Institute, cancelled his appearance, sources said. Collins was to have been the moderator at the Toronto meeting.

The original theme of the plenary session was "Celebrating the 50th Anniversary of the Discovery of DNA." AACR President Susan Horwitz paid homage to James Watson and Francis Crick at the start of the July 11 plenary session, while von Eschenbach wrapped up the

session with his remarks on the 2015 goal, which he first announced last February (**The Cancer Letter**, Feb. 14).

At a press conference with the plenary session speakers, Horwitz called the 2015 goal "an enormous challenge" that will require sustained funding for basic research.

"It is very ambitious to eliminate the suffering from cancer by 2015, but I think it is one that we are ready to face," Horwitz said. "The AACR realizes that to do this, we have to continually have the resources in basic science, in funding, in order to move forward. We look forward to this challenge, very excitedly."

Another plenary session speaker, Thomas Look, of Dana-Farber Cancer Institute, said the addition of Gleevec to the treatment of chronic myelogenous leukemia has made leukemia specialists optimistic.

"We in the leukemia community feel like we are in the lead," Look said at the press conference. "We have hundreds of mutations. We have defined multiple different subtypes of the disease at the molecular level. We're poised to meet the challenge, and to develop new targeted therapies and completely change the outlook for patients with leukemia. I have no doubt that this will occur within the next decade, in other words, by 2015."

Michael Stratton, head of the Cancer Genome Project at the Wellcome Trust Sanger Institute, in Hinxton, UK, said much work still must be done to get to the starting point for interventions. "The issue is, we really don't have hundreds of targets," he said. "We have hundreds of mutations and pathways, and what we need is to dissect these to find the targets."

The rescheduled annual meeting drew 12,126 registrants, the society said. Final tally of actual attendance will be available next week.

"I'm delighted to be here," Horwitz said. "I wasn't sure that we were going to have this meeting."

Horwitz served an unusually long 15-month term before turning over the presidency to Karen Antman, the Wu Professor of Medicine and Pharmacology at Columbia College of Physicians and Surgeons and director of the Herbert Irving Comprehensive Cancer Center.

"We were very doubtful that we could find a place and redo our program," Horwitz, the Falkenstein Professor of Cancer Research at Albert Einstein College of Medicine, said. "The fact that we are here, all of us together, is a tremendous tribute to AACR, but, mainly, I think it is the enthusiasm and excitement and the feeling that so much is going on in this area, that it is very important that we get together, that we exchange ideas, that we network, and collaborate."

The text of the AACR statement on the 2015 goal follows:

Year 2015: Eliminating Death and Suffering From Cancer: A Challenge for Our Generation

Without challenges and goals, our history would be quite empty. Few of the grand accomplishments found in humanity's archives—in art, music, philosophy or science—would exist without the innate desire to better our condition.

And so, when we're offered a challenge to eliminate death and suffering from one of the major diseases of our time—cancer—we applaud the spirit behind the challenge and encourage all to reach out to make it happen.

Is the challenge, as outlined by NCI Director Andrew von Eschenbach, ambitious?

Yes, challenges are meant to inspire and motivate.

Is it doable?

To be succinct, we'll never know unless we try.

Is there concern that we may disappoint if we fall short of the mark?

Sure, but what's worse: the disappointment of failure, or the failure to try?

We, at the American Association for Cancer Research, recognize that much work needs to be accomplished if we are to lend structure to this challenge. Certainly, additional resources must continue to flow into basic research for cancer, the foundation for our future efforts in translational and clinical medicine. But look how far we've come in just the past decade or so, in the areas of diagnostics, prevention and treatment of cancer.

For example, emerging technologies—both imaging and analytical—are increasing the numbers of lesions that can be detected and identified at an early stage. Imaging devices, such as confocal microscopes and the magnifying endoscope for colorectal monitoring, are presenting clearer and earlier pictures of cells and how they change following drug therapy. Likewise, the development of gene chips and protein micro-arrays is helping scientists and clinicians to measure specific cancer-related changes at the molecular, genetic and cellular level during disease progression and in patients undergoing treatment.

What's more, this revolution in diagnostics has set the stage for renewed interest in drugs targeted to prevent cancer in its earliest stages. If we can visualize small molecular changes in cells, we can develop, test and monitor the activity of a new generation of compounds designed to wipe out precancerous cells or even return them to normal.

Studies reported at this year's Annual Meeting and at our Prevention meeting last year are demonstrating how drugs already approved to treat other maladies, even over-the-counter remedies such as common aspirin or ibuprofen, can slow and possibly prevent the progression of precancers to cancer. Our scientists say they are poised to discover and bring to the clinic new drugs that specifically target this

activity.

This year's Annual Meeting marks an auspicious moment in the history of biological science, the 50th anniversary of the discovery of the structure of DNA. We are on the precipice of reaping the rewards of all the basic knowledge we've accumulated during the genetic revolution of the past half-century. This includes a vast range of insights gleaned from the recently completed human genome.

It's incredible how much we've learned since Watson and Crick reported their findings of a structure with "novel features which are of considerable biological interest."

We're just now seeing a glimpse of what's possible as a result, with the development of new drugs targeted to specific tumors, drugs that are reducing death and suffering from previously intractable cancers—without the disabilities and scars commonly associated with our classic armaments of cancer therapies.

These new designer drugs, which treat the tumor with few side effects for the patient, include Gleevec—now being used to attack chronic myelogenous leukemia. Dubbed a "miracle" drug by some, Gleevec is the product of dedicated basic research gathered over the past two decades on the function and the kinase activity of the Bcr-Abl gene.

Then, there's the introduction of Herceptin and Rituxan, monoclonal antibodies directed against cell surface genetic targets in patients with breast cancer and non-Hodgkin's lymphoma. Many other anti-tumor compounds are in the pipeline, including drugs such as Avastin which we've recently heard about that induce angiogenesis, and still others that inhibit telomerase activity, or block specific protein kinase activity or ubiquitination.

All of these advances have been made possible through the combined efforts of cancer researchers and other specialists covering a wide range of biomedical sciences—from the basic researcher trying to understand the fundamental nature of how life works, to the translational scientist who bridges the gap between this basic knowledge and its application, to the clinical investigator who brings the product of this work to the patient.

Certainly, if we are to reach our goals, we must also do a better job of educating the public about what they can do to help. We can truly eradicate death and suffering from cancer now among millions worldwide … if they would only stop smoking cigarettes. We all know that this single act would dramatically lower the incidence and mortality figures for many cancer sites, including larynx, bladder and, of course, the lung.

We also must continue informing the public about the benefits of proper diet and exercise, and how a healthy lifestyle can improve an individual's chances of avoiding cancer. And we, as a people, also need to make medical care accessible to all those in need, particularly the medically underserved. We can never succeed unless everyone has equal opportunity and access to the best medical care we can provide to prevent, diagnose early and treat cancer.

So, that's the challenge. We stand at a unique moment in history where knowledge, technology and resources are coming together to make what seemed impossible a short time ago, now possible. We may never wipe out cancer all together. But we owe it to ourselves, and to future generations, to try to eliminate and control this terrible disease. We at the AACR collectively and in partnership with the NCI and others—will work as best we can to reach this goal.

2015 Goal Not A Dream, But A Vision, Director Says

(The Cancer Letter, July 18, 2003, Vol. 29 No. 29)

Standing at a lectern facing reporters at a July 11 press conference, NCI Director Andrew von Eschenbach held the blue-and-white, 1,496-page, 4.5-pound "Proceedings: American Association for Cancer Research 94th Annual Meeting, Volume 44 2nd Edition" in the air above his shoulder.

"When one looks at just the abstract book of this meeting, and particularly pays attention to the font size, which is something you are very familiar with, what an extraordinary contribution, and what an extraordinary accomplishment this represents," von Eschenbach said.

The text appeared to be set in about an eight-point font, eight lines to the inch. It looked like this.

"The contributions of our scientific and research community have made it possible for us now to imagine things that previously, back in 1971 when the National Cancer Act was signed, were perhaps truly a dream," he said. "But now, in 2003, what we can imagine is no longer, in my opinion, a dream, but a vision to be accomplished."

Von Eschenbach placed the Proceedings on the lectern. "We now have within our grasp the ability to capitalize on our progress and to eliminate the suffering and death due to cancer," he said. "I did not say that we are going to eliminate cancer. I don't know when that day will come."

Then came a question from a reporter: NCI is facing its smallest budget increase in five years, the latest data show that mortality has been flattening out since 1998, and critics say that the 2015 goal, while laudable, is unachievable. What would you say in response to that?

"There's no doubt that we have to continue to have a sufficient resource base to continue to drive this incredible engine of discovery, development, and delivery," von Eschenbach said. "We have more money in the NCI budget than we've ever had before, so we have to view it

as not simply being the glass empty, but there are substantial resources to work with.

"Having said that, we have to look beyond that federal appropriation to other opportunities to leverage and amplify the resources that are being applied to the process," he said. "I do recognize the resource challenge. I do think we have to find creative ways to amplify the resources that are being applied, from the private sector, from the public sector.

"With respect to looking at the problem from the point of view of mortality: I think what I've tried to point out is when you look at the broad breadth of our approach to cancer, you can see multiple places and steps along that pathway of progression in which we have the opportunity for progress, and when that progress is synergized, we will really have the opportunity to really significantly modulate mortality.

"We tend to think that this improvement is going to be a slow, gradual, linear process. I actually think it's going to be much more exponential in nature. It's going to be synergistic in nature. If you just backtrack to how rapidly our knowledge and understanding has occurred in the past 10 years, you can see that it is not simply incremental. It is essentially feeding on itself, almost as if critical mass has been achieved.

"There are barriers, and those barriers are real and they go beyond simply the research enterprise," von Eschenbach said. "We have to address those as well. You will hear about our collaboration with FDA to help streamline some of the issues that create barriers to getting to the patients.

"So the other part of our strategy is not only to amplify the progress, but shorten the timeline."

"I Actually Am An Exclamation Point"

Later that day, in his remarks at the plenary session, von Eschenbach said cancer research has come a long way in 30 years, as evidenced by work the plenary speakers presented.

"For me to stand here this afternoon and discuss with you the critically important role of research, I think I actually am an exclamation point for the incredible presentations that have gone before me," he said.

"We are moving from dreams years ago to what is perhaps vision today, and hopefully, very soon will be reality for tomorrow. That dream and those processes began most emphatically just about 30 some years ago in this city in 1971 when Congress came together and passed the National Cancer Act with the dream, perhaps, at that time, of being able to mobilize the resources in this country, and, in fact, eliminate the problem of cancer.

"Some may say that back in 1971, that was not a dream but perhaps a fantasy. It is true that back then, unlike when we made a commitment to put a man on the moon, it was more than just an engineering problem. It was, in fact, a problem in which we did not understand the fundamental nature of the problem we were hoping to resolve.

"But what that 1971 Cancer Act did do was to begin an incredibly exciting journey of progress, and a journey in which we have seen a tremendous explosion in our ability now to understand cancer, and, it put in place the development of intellectual resources, and it put in place the opportunity for expansion in technology.

"You have been responsible for that evolution and development of knowledge by using those resources, such that today, in 2003, we are in a much different place than in 1971. We are celebrating the 50th anniversary of DNA, and we are on the very cusp of the tremendous progress that has been made in our unraveling of the human genome, and you saw, just in the past few hours, the incredible power that that knowledge is making possible.

"You built the basis and the foundation for this progress going back to the 1970s, and we began a systematic, methodical unraveling of the secrets of cancer."

"The War On Cancer Is Winnable"

Earlier this year, in a White House celebration of cancer survivorship, von Eschenbach said, "the President of the United States made a statement. The statement was that for the first time in human history, we can say with certainty that the war on cancer is winnable. This nation will not quit until our victory is complete.

"We perhaps have moved from that dream to vision, and that has been made possible by the tremendous effort and success of the cancer research enterprise, you who are in this room and colleagues around the world. Now we can begin to look to the next step, of taking our vision that the war on cancer is winnable to now beginning to translate that into the reality.

"The NCI has issued to itself and to the entire cancer community a challenge. A challenge goal, if you will, to build on this knowledge and continue this momentum to eliminate the suffering and death due to cancer, and to bring that about by 2015.

"The strategy that we can embark upon to accomplish that challenge goal of eliminating the suffering and death due to cancer is to use the knowledge and continue the momentum to affect a strategy that will enable us to preempt the disease, to preempt the initiation and progression of cancer as its on its pathway to a lethal phenotype.

"Why this is feasible is because we've begun to understand cancer as a biologic process and there are multiple steps and multiple mechanisms in that process from our very susceptibility to the point where it takes our life, and those steps in that process by virtue of the knowledge we are gaining are now vulnerable. They are vulnerable for us to define interventions to eliminate or control that process.

"Clearly, there will be no magic bullet or single

solution to this challenge, but there can be a magic strategy by not only defining the steps, but by defining their integration.

"The preemption strategy has to include our efforts around prevention, elimination, and modulation. We will accomplish this by promoting a portfolio that includes discovery, development and delivery.

"We do not know enough about cancer, but we know so much more than we did when we began this journey. We must continue to maintain that momentum and drive that engine of discovery to understand the relevant mechanisms at there very fundamental level. But we must also go beyond the discovery of the mechanisms to use that knowledge in the understanding of cancer to develop interventions that will enable better detection, diagnosis, treatment and prevention of the disease and then to use those interventions and deliver them to all who are in need, but deliver them in a process of clinical research that the very delivery of those interventions yields new knowledge and understanding of the fundamental biology of cancer helps to re-inform our discovery process. So we will continue on a circle of discovery, development and delivery."

Intramural Program Reengineering

For fiscal 2004, NCI plans to "reengineer" the intramural program, with the eye toward "ways in which the intramural program will complement what is going on in the extramural community," von Eschenbach said.

Other top priorities include:

—Creating a National Biospecimen Network "to enable us to rapidly accelerate our ability to exploit the opportunities that genomics and proteomics are providing for us."

—Imaging, nanotechnology, and molecular medicine.

—Development of the Cancer Biomedical Informatics Grid, or CaBIG. "This will go out as a pilot project specifically for our cancer centers and SPOREs to create a platform that will enable us to integrate across the entire spectrum," von Eschenbach said.

Dialogue Developing Plans For Biospecimen Network

(The Cancer Letter, July 18, 2003, Vol. 29 No. 29)

The National Dialogue on Cancer said it is working to develop plans for a National Biospecimen Network, which it described as "the first national, standardized tissue resource in the U.S. designed to facilitate genomic and proteomics research."

The NBN will be "openly accessible to cancer researchers" nationwide, according to a July 11 press release by the Dialogue.

The network will collect tissue, blood and serum, pathology data, clinical data and genetic information for use in evaluating new drugs for cancer treatment, according to the Dialogue. "When implemented, the NBN will be the first comprehensive tool allowing researchers to evaluate these samples with new methods for gene and protein analysis," the statement said.

Anna Barker, NCI deputy director for strategic scientific initiatives and a member of the NDC board, first described the network at a recent meeting of the NCI Board of Scientific Advisors (**The Cancer Letter**, July 11).

A "final draft" of the plan is scheduled to be made public in September, the NDC statement said.

The text of the NDC statement is available at www.ndoc.org/pr_july11.html.

In Brief:

NCI Names PR Executive To Lead Institute's "Strategic Dissemination" Of 2015 Goal

(The Cancer Letter, Aug. 1, 2003, Vol. 29 No. 31)

EDWARD MAIBACH was appointed NCI associate director for strategic dissemination by NCI Director Andrew von Eschenbach. Maibach will join NCI on Aug. 11 to "coordinate NCI-wide efforts to create awareness and enhance understanding of the progress we are making toward our goal of eliminating suffering and death due to cancer by 2015," von Eschenbach wrote in a memo to NCI staff. Maibach also will lead a "research initiative to engage the public to fully participate in the biomedical revolution," von Eschenbach wrote. Maibach was worldwide director of social marketing for Porter Novelli, a marketing and communications firm, where he worked on public health issues including cancer and tobacco control, diet and nutrition, physical activity promotion, vaccine education, clinical trials, premature birth prevention and adolescent substance abuse prevention. Maibach also is an adjunct associate professor in the McDonough School of Business at Georgetown University. Prior to joining Porter Novelli, Maibach was an assistant professor of public health communication at the Rollins School of Public Health at Emory University, where he founded the Center for Health and Risk Communication. From 1984 to 1986, he was a member of the staff of the former NCI Division of Cancer Prevention and Control. While at Emory, he served as a member of the Advisory Council for National 5-a-Day for Better Health Campaign and was a 5-a-Day grantee. "Over the past several months, he has been consulting and working closely with me and other members of our Executive Committee on a variety of important issues critical to our agenda," von Eschenbach wrote. Maibach received a Ph.D. in communication research from Stanford University in 1990, an M.P.H. from San Diego State University in 1983, and a B.A. from University of California at San Diego in social psychology in 1980.

A Tissue Bank To Break The Bank? NCI, Dialogue Plan Expensive Resource

(The Cancer Letter, Aug. 8, 2003, Vol. 29 No. 32)

The National Dialogue on Cancer and the National Cancer Institute are developing a plan to take tumor tissue banking outside the Institute and place it under control of a not-for-profit organization.

Documents obtained by **The Cancer Letter** demonstrate that the proposed "National Biospecimen Network" would collect tissue from cancer patients not enrolled in clinical trials and develop an informatics system for life-long follow-up of the donors.

Today, the most significant tissue banks are operated by the NCI-funded clinical trials cooperative groups, which have the capability to correlate any piece of tissue with the treatments and outcomes for each patient over the duration of a trial.

There is no debate that researchers need increasing amounts of tumor tissue for studies of cancer on the molecular level. While basic scientists need tissue for genomic analysis, clinical researchers advocate a two-tiered system, which would provide tissue for hypothesis-generating studies, while preserving the valuable contents of tissue banks maintained by the cooperative groups.

Working behind closed doors, the Dialogue and NCI are preparing to alleviate the shortage of tissue by the most drastic means imaginable: creating an enterprise that would cost between $500 million and $1.25 billion a year to operate and, presumably, billions to construct. Annual operating costs alone would increase current tissue banking expenditures of the National Institutes of Health by a factor of 10 to 20.

"In size, scope, scientific potential, and the number of potential collaborators, … it is most analogous to the efforts to map the human genome; thus it is more like the space station or a particle accelerator than a traditional medical science initiative," states the unfinished, confidential version of the Dialogue's report proposing the biospecimen network.

If the biospecimen network is created in accordance with plans described in the Dialogue report, it would be exempt from open meetings requirements of the Federal Advisory Committees Act, immune to the provisions of the Freedom of Information Act, and free from federal technology transfer regulations. Meanwhile, the existing, government-funded structures for collecting tissue in the context of clinical trials could be undermined, critics say.

The Dialogue, a non-profit group funded through a combination of public and private funds, entrusted preparation of the project to Paula Kim, a patient advocate who heads the Pancreatic Cancer Action Network, and Jeffrey Trent, president and scientific director of Phoenix-based Translational Genomics Research Institute.

The coordination between NCI and the Dialogue was close:

—Documents show that the Dialogue project involved an "NCI Coordinator," Julie Schneider, an AAAS fellow working in the office of the NCI director.

—In conjunction with the Dialogue effort, NCI awarded a sole-source contract to RAND Corp. to evaluate "selected existing U.S. tissue resources to support and guide the development of a design and engineering plan for a new National Tissue Resource model." Sole-source contracts are unusual at NIH. The RAND study, currently underway, is mentioned repeatedly in the Dialogue's draft report, an indication that the two efforts are coordinated.

—The Institute gave no funding increase to the cooperative groups for fiscal 2003. NCI Director Andrew von Eschenbach announced recently that the groups would undergo a comprehensive, top-to-bottom review, even though a similar review was recently completed. Last week, NCI officials said that some new funds would be found for the group-operated tissue banks for next year, but the magnitude of the increase remains unknown.

—Sources said NCI officials recently revealed a plan to switch the cooperative group-run tissue banks from grant funding to funding through contracts. In principle, this administrative change could allow the Institute to remove control of the tissue banks from the scientific leadership of the cooperative groups, transferring the tissues to contractors, observers said.

—The boundary between the Dialogue and NCI is muted in part because Institute Director von Eschenbach is one of the founders of the Dialogue and vice chairman of its board of directors. Anna Barker, NCI deputy director for strategic scientific initiatives, also sits on the Dialogue board.

—Last December, six months before the Dialogue's draft proposal was formulated, Anthony Dennis, a member of the group of ad hoc advisors designing the biospecimen network, filed a letter of intent to apply for $8 million in Ohio state funds to set up the network's Midwestern regional hub.

Dennis, who is married to Barker, proposed to serve as the principal investigator of this public-private enterprise. Though no proposal was filed, the letter of intent mentioned a plan to "collect and redistribute tissue."

"Commercial potential is inherent in the formation of the center itself, in the creation of an advanced logistics system to collect and re-distribute tissue and in the creation of the largest human genetics and proteomics database in existence," the letter of intent said. Dennis served on a subcommittee that designed the "business plan and operations" for the network, documents show.

Ohio to cancer pathology is what Fort Knox is to the U.S. gold reserve. The state's academic institutions maintain pathology samples for Children's Oncology Group, the Gynecologic Oncology Group, Cancer and Leukemia Group B, the AIDS Malignancy Consortium, and the Cooperative Human Tissue Network.

In a statement, Dennis said he ultimately dropped out of the application process because "our existing and long-standing tissue resources and clinical centers were sufficiently advanced that we felt that the desired outcomes would emerge without further organization."

Dennis, a microbiologist and entrepreneur, was recently involved in Nutri-Logics Inc., an Internet-based company that sought to sell dietary supplements for cancer prevention. Barker, too, was involved in that venture (**The Cancer Letter**, May 30).

"Statistical Significance Is Not Our Goal"

The Dialogue started designing NBN last spring, Kim said.

"We brought together a bunch of people, and we talked about what are the rate-limiting steps to getting drug discovery and development in this country," she said to **The Cancer Letter**. "Tissue seems to be on everybody's menu. That's what I keep hearing from people, and I guess if I didn't keep hearing it over and over, I wouldn't think that there is a need."

In addition to obtaining tissue from cancer patients, the system may follow healthy cohorts, perhaps focusing on high-risk groups and precancerous conditions, Kim said.

The Dialogue-designed system would differ fundamentally from clinical trials, Kim said.

"Statistical significance is not our goal," she said. "If you go to a clinical trial, a biostatistician has to figure out what kind of statistical significance this shows or that shows. What we are talking about here in the NBN is developing a resource [for] the researchers, so they could do their research, a resource that will have tissue, and ultimately, it will be a resource that will have tissue and data."

Only a small percentage of cancer patients enroll in clinical trials. "You have special populations, you have underserved populations, you have areas geographically that are underserved," Kim said, characterizing opportunities for tumor collection. "How many states in the country do we have that do not have comprehensive cancer centers? There is so much opportunity out there. There is a huge percentage of available tissue out there that is going totally untapped."

Kim said the system would track the tissue donors in the following manner:

"In a good situation, you would have a patient who consents to donate a specimen, and they donate the specimen, and along with it is the clinical, annotated data that you need to understand what this specimen represents, and then, along with it, would be the capability to [track] this patient longitudinally, as they undergo their treatment, and that information would ideally be recorded back in, and become further critical annotation to the specimen, so that some time from now somebody is looking at that specimen, they would know the history, they understand the specimen history, and what happened to the patient, and ultimately—if that patient dies—you would know what that patient's cause of death was. You have a whole list of information that you understand about that patient."

According to a document titled "NBN Consumer/User Needs Module Summary as of 6/23/03," acquisition would begin with a two-year pilot project involving three "collection sites" that would start with "ten top adult malignancies, based on mortality: lung, colorectal, breast, pancreas, lymphoma, ovary, bladder, kidney, stomach, esophagus and hepatic cancers from both primary and metastatic sites."

The network would collect tumor and matched normal tissue in fresh frozen and formalin-fixed preparation, and provide "quality-controlled RNA and DNA, and a baseline DNA array on all or a subset of samples." Also collected would be serum, blood, plasma, and, possibly, urine.

"Response-to-treatment and outcomes data will be linked to specimens," the NBN report states. "RNA amplification and baseline proteomics would not be performed." Also, "laser capture microdissection would be performed on a very limited basis, if at all."

Collecting tumor and following patients outside clinical trials would be a departure from existing standards of evidence-based medicine, experts say.

"Tumor tissue without relevant clinical data is like Niagara Falls without water," said David Johnson, deputy director of the Vanderbilt-Ingram Cancer Center, director of the Vanderbilt Division of Hematology-Oncology, and president-elect of the American Society of Clinical Oncology.

"Simply collecting large quantities of lung cancers—with no knowledge of the patient's status and therapy—may provide some insights like 'X percent of lung cancer patients have PTEN mutations,' but what does that really mean?" Johnson said.

"If we have the relevant clinical data, we might be able to say, 'X percent of lung cancer patients have a PTEN mutation, and these patients respond better to treatment Y, as opposed to treatment Z.' This is the information that patients want to know—and learning this does not compromise the basic science of the project."

While outcomes can be collected and tumors annotated outside clinical trials, the most promising leads are likely to come from rigorously designed experiments, proponents of clinical trials say.

"Translational research is an iterative process swinging 'back and forth' between the laboratory and the bedside," Johnson said. "Good translational research is dependent on both elements being represented in the early planning of a project—including something seemingly as simple as tissue collection.

"A good laboratory experiment and a good clinical trial both require careful thought and preparation. Collecting tumor tissue within the context of a clinical trial

marries these two processes and enhances both."

The network plans to collect 250,000 tissue samples in five years, documents show. Estimating that it would cost between $2,000 and $5,000 to collect each specimen, the report states that "even using the low estimate, tracking 250,000 samples is expected to cost $0.5 billion a year."

Using this projection, the high estimate would be $1.25 billion per year, not including the costs of analyzing the samples and the costs of starting this gigantic enterprise. According to the report, NIH spends $53 million a year to maintain its existing tissue banks.

The network would contain both public and private sector components, and would make tissues available at varied prices to pharmaceutical companies and academic researchers, documents show.

"The key question is: Which components will be public, which private, and which mixed?" the report states. "Because this is a government system, there is a rationale for government funding. For the private sector to participate, there must be an opportunity for profit. Public and private funding partners and mechanisms need to be identified; fees will almost certainly be part of the mix."

Kim said NCI would be just one "stakeholder" in the network, which doesn't entitle it to control.

"There is a great deal of benefit to bringing all the sectors together," Kim said. "The patient activists have an important role in this. Academics have an important role. Industry has a role. The government has a role… I see NCI as one partner in this project, just as they should be, and just as other sectors that have come to the table."

The working group has consulted a cross-section of cancer constituencies, Kim said.

"We have invited many, many people, to different meetings, to different teleconferences," she said. "We have had cooperative group participation somewhere along the way. I am very comfortable with the fact that we have given all sectors the opportunities to come to the table and participate in this effort."

The Dialogue committee roster includes 35 people, including five staff members of Constella Health Sciences, a consulting firm. "I am comfortable with the fact that we have gone out to a broad group of people," Kim said. "Where else do you see lay advocates right in the thick of it, of having the opportunity to participate in the development and the identification of problems and the development of the solutions, and bringing together of all these various sectors? I think it's remarkable."

The proposal should be evaluated based on its content, not the procedure followed in its compilation, Kim said. "The content is really what matters," she said. "Does this report make sense? If it's good information, it's good information."

According to Dialogue documents, the report was to be completed on Sept. 16, but Kim said the group still has a lot of work to do. Documents show that the Dialogue would establish the non-profit entity for the network and seek public and private funding for the venture in 2004. After that, the organizers of the network would proceed to development of Requests for Proposals.

Since $500 million to $1.25 billion a year is a significant sum, some NCI programs will surely be cut, and chairmen of the Institute's cooperative groups say they fear for the future of their programs. Group chairmen warn that NCI is embarking on construction of a costly, speculative system for generating hypotheses while jeopardizing the existing, functional system for verification of hypotheses.

"I don't think anyone is looking at tearing anything apart, quite frankly," Kim disagrees. "I think what we are trying to do is build a resource that we feel there is a tremendous need for."

Report Urges Study of Existing Resources

The authors of the Dialogue report argue that existing tissue banks are woefully inadequate.

"Although existing resources are plentiful (there are approximately 350 organizations with more than 300 million tissue samples representing almost 160 million cases), materials are in various states of usefulness and readiness, no standards exist across the board, patient consent varies, fresh tissue is not readily available, and annotation of fresh tissue is rare," the report states. "The extent to which parallel systems can or should be maintained and how the value of all resources can be maximized require further study. It was agreed that an enormous amount of money is currently being paid for tissue resources, and it will be difficult to stop the flow of these funds."

The cooperative groups have been collecting tumor tissue for over three decades, and, naturally, tissues obtained in the 1970s would be more challenging to work with than tissues obtained last year. However, even 30-year-old specimens can be analyzed through rapidly-evolving genomic techniques to provide information that is likely to help develop cancer therapeutics.

In recent years, samples have been collected based on standards that are close to uniform, group chairmen say. Obtaining the samples, controlling treatments, tracking the outcomes, and assuring informed consent is part of the day-to-day functions of the cooperative groups.

"If the goal is to develop something like a space station, we must remember that billions have been invested so far in the space station, and we still don't have one that is functional," said Richard Schilsky, chairman of Cancer and Leukemia Group B and chairman of the NCI Cooperative Group Chairs Committee.

Schilsky agrees that researchers need better access to tumor tissues. To solve this problem, he suggests a simple two-tiered system.

"The highest level specimens are those obtained by the groups, because of the clinical annotation that comes with those samples," Schilsky said. "Because the group specimens are so valuable, we also need a second tier of tissue collection that provides tissue and much more limited

clinical data such as patient demographics, diagnosis, and survival. These tissues, currently collected by Cooperative Human Tissue Network, would allow for hypothesis-generating experiments, the results of which would fuel the next generation of definitive trials by the groups."

The group-run tissue banks are not uniformly organized, but they have adopted a set of standards. This was accomplished through the work of the Intergroup Specimen Banking Committee.

"All the groups are now making tissue microarrays from paraffin blocks rather than cutting sections from individual blocks," Schilsky said. "As the technology continues to improve, it will become less important to collect frozen tissues, as most all macromolecules will be recoverable from paraffin."

The cooperative groups need additional resources, Schilsky said. "Many of the groups have limited frozen tissue banks," he said. "For example, in CALGB, we have leukemia specimens and lung cancer specimens. What has held the groups back has been lack of sufficient funding to bring their banks and collection systems to the next level."

Allowing the groups to fulfill their potential would be considerably less expensive than Dialogue's system, said Schilsky, who was asked by **The Cancer Letter** to review the NBN proposal.

"We already have the infrastructure to accomplish the major goals of NCI if we just fund it adequately," he said. "If the NBN diverts funds from the groups, it will do much more harm than good."

Assuring uniformity of standards for preserving tissue is a small part of the enterprise of running a tissue bank, said an executive at a biotechnology company involved in genomics research. The executive spoke on condition of anonymity, after reviewing the Dialogue proposal, which was provided by **The Cancer Letter**.

"Preservation is a straightforward mechanical process," the executive said. "A high-quality repository should be able to obtain and maintain its specimens for $200 per case. The real expense here is the manpower and the informatics commitment needed for rigorous follow-up.

"My biggest question in all of this is the nature of this half-billion-dollar amount. Why are they reinventing the wheel from scratch, instead of improving on existing structures?"

"Legacy Systems"

"The Working Group members agreed that an NBN could not take responsibility for what has been collected by others," the Dialogue report states. "The achievement of standardized results with a rigorous molecular profile requires tissue collection under highly standardized procedures. A majority of the Working Group believed that inclusion of legacy systems in the national model would be difficult… This is not to say that legacy resources are not of value; a catalog of these other valuable resources should be part of the NBN system. They may well be suited for specific needs. However, the NBN focus should be prospective."

The report notes that the NCI-funded RAND study would help determine the fate of existing tissue banks.

"It is suggested that a legacy system committee consist of representatives from all categories: users, tissue resource workers, government, scientists, patient advocates, and consultants," the report states. "Additionally, material from the 2003 RAND study may inform the decisions that will be necessary."

In April, NCI announced the impending award of the contract to RAND. The text of the announcement follows:

"The National Cancer Institute, Office of Science Planning and Assessment plans to enter into a sole source contract with RAND Corp.… The purpose of this project is to provide a written evaluation of selected existing U.S. tissue resources to support and guide the development of a design and engineering plan for a new National Tissue Resource model.

"This effort is a collaborative project and jointly funded by the National Cancer Institute and the National Dialogue on Cancer. The evaluation will consider a collection of government, academic, and private sector tissue repositories to identify `best practices,' and assess whether these resources could be adapted to fulfill the requirements of a new model for a National Tissue Resource.

"In 1999, RAND Corp. published a supplement to a National Bioethics Advisory Commission Report about the ethical and policy issues relation to research on human biological materials. Dr. Elisa Eiseman, an employee of RAND, was the Principal Investigator of the study and this proposed evaluation of selected existing U.S. tissue resources builds upon that effort and relies heavily on the previously-collected data.

"This is not a request for competitive proposals."

RAND employees have been contacting cooperative groups and pathology companies in recent weeks, sources said.

The Ohio Plan

According to the Dialogue report, a non-profit group would run the national system and handle the informatics at a central office. Satellite offices around the U.S. would store the tissue.

Preparations for administering this system appear to have begun long before the Dialogue completed its draft report. The Dialogue report was dated May 28, 2003.

Six months earlier, on Dec. 13, 2002, ad hoc group member Dennis submitted a letter of intent to seek $8 million in Ohio state funds for creation of a "National Oncology Tissue Repository and Genetic/Proteomic Database."

Dennis is president of Omeris Inc., a Columbus-

based non-profit organization funded partly by the Ohio Department of Development. Earlier that month—on Dec. 4, 2002—Von Eschebach announced that Dennis's wife Barker was appointed NCI deputy director for strategic scientific initiatives. For months prior to taking that job, Barker served as a consultant to von Eschenbach (**The Cancer Letter**, Dec. 6, 2002).

The letter of intent described Dennis as the principal investigator of the proposed venture that would include NCI, the Dialogue, and the International Genomics Consortium, an Arizona-based entity founded by Trent, co-chairman of the Dialogue working group. Other applicants listed included The Ohio State University, James Cancer Center, The Ohio Hospital Association, Children's Hospital of Columbus, Battelle, BioEnterprise, Rescentris, Acero, Proctor & Gamble Pharmaceuticals, Roche, and Eli Lilly.

Investigators at Columbus Children's Hospital apparently didn't consent to participate in the Ohio tumor registry project, said Gregory Reaman, chairman of the Children's Oncology Group, who looked into the matter after being contacted by a reporter.

Last fall, investigators at Children's declined Dennis's invitation to collaborate, in part because his proposal required them to provide a staff member for the endeavor, Reaman said. Staff members at the tissue bank are paid under NCI grants, and cannot be shifted to other tasks.

The investigators were assured that the project would be abandoned, and were apparently unaware of the letter of intent, Reaman said. The hospital also stores tumors for the Gynecologic Oncology Group. The letter of intent mentions "re-distributing" tissues.

"Why would we want another initiative to railroad what we think is already a good—albeit underfunded—system?" Reaman said. "We have a system of tissue procurement and banking that is integrally linked to a very robust clinical database, for which in every single pediatric cancer disease category there are active translational research activities."

Though no application was filed, the text of Dennis's letter of intent, a public document, is indicative of the state of knowledge about the biospecimen network six months prior to completion of the Dialogue draft. The text of the document follows:

"The Repository would be the Midwest regional (multi-state) center for acquiring, genetically analyzing, utilizing and distributing normal and tumor tissues from 50,000+ cancer patients to researchers in academic and private organizations in the U.S.

"The purpose of the tissue repository is to significantly accelerate the discovery and development of therapies and prevention strategies for cancer by providing a large, easily accessible repository of uniformly collected, clinically annotated, genetically and proteomically characterized tissues and their associated data.

"The bulk of the cancer data would be provided on a pre-competitive basis (accessible to all potential users in the private, public and academic sectors). The highly characterized data related to other disease states such as heart disease, diabetes, obesity, etc. inherent in such a large human disease database will be used as the basis for proprietary technology development, drug target development, new company formation or licensing to large pharmaceutical firms.

"The center would be one of a small handful of (or the sole) national tissue repositories in the U.S. established cooperatively by federal, state and private funds. The repository would operate an advanced collection, distribution and analysis center and through agreements with state and regional hospitals would place data collection capabilities at all locations advancing the connectivity among regional medical centers.

"The center will leverage significant federal and private funds. The center will represent a new state of the art in bioinformatics with complete genetic profiles of thousands of human patients coupled to annotated clinical data and made available on-line in a useful format for researchers nationwide.

"Advanced logistics for the management of tissue acquisition and re-distribution will be developed. The full database of information will hold statistically valid genetic and proteomic data on most common adult diseases, which can be of great value for both new commercial ventures and for established pharmaceutical companies.

"The potential to nurture genomics, proteomics, bioinformatics and other developing capabilities in Ohio's start-up and established companies is enormous as is the potential for significantly reducing the social and economic impact of cancer. This concept emerged as a high priority element of a national dialog on cancer, which gathered more than 100 of the leading government, academic and industry representatives in Washington, D.C., early in 2002.

"Ohio is extremely well suited to pursue this national center either alone or in conjunction with a developing center in Arizona.

"Commercial potential is inherent in the formation of the center itself, in the creation of an advanced logistics system to collect and re-distribute tissue and in the creation of the largest human genetics and proteomics database in existence.

"The existence of the center will attract the interest of major pharmaceutical and biotechnology companies and will create licensing and company creation opportunities in numerous disease areas for both therapy and prevention. The formation of the center will have the secondary benefit of creating an extensive collaboration among numerous Ohio organizations and creating a state-of-the-art digital data acquisition system among a broad array of regional hospitals."

Dennis declined a request for an interview and

responded to a reporter's questions with a written statement.

"I was pleased to serve as an early volunteer on the working group that identified this concept at an NDC research meeting on removing barriers to genomics/ proteomics based research," Dennis wrote.

"Although this is an exciting and timely idea, it is not a new concept, as other countries, private organizations, and academic institutions are pursuing similar strategies around the globe. As to my role, a couple of individuals were invited to attend the original exploratory sessions to represent states with significant clinical and supportive core resources.

"Ohio has such significant capabilities in these areas and in clinical medicine. In fact, Ohio leads the nation in many clinical science categories and has so for many years. I was able to participate in a very limited way due to demands on my time, but no longer have the time to participate, and recently resigned as a member of the planning group.

"Given Ohio's significant breadth and depth of resources in existing tissue repositories, and the fact that Ohio is the No. 1 state in the nation for per capita clinical trials of all types, we have considered several options for deploying our resources to support the advancement of healthcare and the bioscience industry in our state," Dennis wrote.

"You asked about a non-binding letter of intent that we submitted to the state as part of our planning process for potentially uniting our distributed clinical trails capability—with our nationally recognized tissue repositories as part of those resources. The submission of such 'placeholders' is common practice, and the state receives a number of these in any round of submissions. After completing our planning late last year, we elected not to follow up on this letter of intent with a formal proposal, as our existing and long-standing tissue resources and clinical centers were sufficiently advanced that we felt that the desired outcomes would emerge without further organization.

"However, I believe that if you speak with individuals who have volunteered to work on the concept of a national biospecimen network to support 21st century science, everyone did so unselfishly to create something of real value for the scientific community and for cancer patients," Dennis wrote. "It is an extraordinary group of individuals with in-depth knowledge and capability from all sectors interested in the issue."

Kim said she was unaware of Dennis's letter of intent. "I know that there are several states around the country that have been really terrific at taking a hard look at the tissue issues in their respective states, to see what can be done on the statewide level to facilitate researcher needs in a way of tissue specimens," she said.