THE CANCER LETTER

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ACS Chief Medical Officer Brawley Urges Audit Of I-ELCAP Lung Screening Data

By Paul Goldberg

The top physician of the American Cancer Society said an audit of a lung cancer screening study by the International Early Lung Cancer Action Program would be required if its results are to be taken seriously.

"I am very concerned about the I-ELCAP data and the I-ELCAP findings, and I can't justify using I-ELCAP at this time," ACS Medical Director Otis Brawley said at a meeting he called to consider pooling data from lung cancer prevention studies. "I think we can only use the I-ELCAP data if there is an external audit to verify that data, and there is an independent reanalysis of that data."

For nearly two years since the New England Journal of Medicine

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Panel Recommends Against Pooling Results Of NLST, European Studies, And I-ELCAP

By Paul Goldberg

On his first day as the American Cancer Society's chief medical officer, Otis Brawley inherited an initiative he couldn't support.

ACS, Cancer Research UK, and the International Agency for Research on Cancer were calling for pooling data from three randomized trials—the NCI-funded National Lung Screening Trial and two European trials—with the single-arm International Early Lung Cancer Action Program.

The proposal included a description of a modeling method for incorporating the data from the single-arm IELCAP. Moreover, instead of first publishing the data separately, investigators were asked to pool data from unfinished trials and publish the meta-analysis instead.

Critics said the proposal broke fundamental rules set forth in first-year epidemiology textbooks, and one critic, biostatistician Donald Berry of M.D. Anderson Cancer Center, likened it to pooling "apples, oranges, lemons and limes" (The Cancer Letter, Nov. 16, 2007).

Brawley decided to reconsider the proposal publicly, vetting it at a two-day open meeting of experts in epidemiology, biostatistics, lung cancer screening, and auditing of clinical trials. The 15-member panel, which met in Washington Sept. 22-23, heard testimony from investigators conducting five clinical trials as well as arguments for and against early analysis.

The panel determined that there was no advantage to early combined analysis of the NLST with the European trials.

"You could argue that the uncertainty of mixing in diverse other studies

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Concern Raised About Bias In I-ELCAP Data On Deaths

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published an I-ELCAP paper claiming dramatic advantages of computed tomography screening for lung cancer, critics pointed to the trial's non-standard design, and collection and reporting of data. Also, The Cancer Letter raised questions about the I-ELCAP leaders' failure to disclose patents and royalties as well as acceptance of funding from a tobacco company (The Cancer Letter, Jan. 18, March 14, March 28).

Though the word "audit" has been uttered sporadically by skeptics in recent months, ACS may have the leverage to make it happen. "I should note that we had funded I-ELCAP, and four times over four years there had been a certification that I-ELCAP is not using tobacco money, and that our money is not being commingled with tobacco money," said Brawley at the meeting, which was held in Washington Sept. 22-23.

I-ELCAP received over $100,000 in ACS funds.

Documents signed by I-ELCAP principal investigator Claudia Henschke, a radiologist at Weill Cornell Medical College, appear to allow ACS to gain access to the data. "ACS reserves the right to receive a copy of all data sets developed by Grantee related to the grant," the society's standard agreement states. "Grantee also agrees to provide consultation in interpretation of the data sets that ACS requests."

Brawley said the society considered asking Henschke's institution to return the money. "There has been a discussion that we should proceed getting our money back from the financial institution for I-ELCAP, which is Cornell," he said. "I have made the decision not to pursue that."

Brawley isn't alone in calling for an audit. "The results of this key lung cancer prevention trial, heralded as evidence for the value of CT screening for lung cancer, have become increasingly ambiguous, a situation that can only be dispelled by auditing the trial," Bruce Chabner, clinical director of the Massachusetts General Hospital MGH Cancer Center, wrote in the September issue of The Oncologist, a journal he edits.

Chabner's call for an audit was triggered by new information that turned up in an exchange of letters between Henschke and Peter Bach, a pulmonologist and health systems researcher at Memorial Sloan-Kettering Cancer Center. Bach challenged the I-ELCAP claims about the deaths of patients who had declined treatment after being told that they had stage I disease.

The I-ELCAP paper published in the Oct. 26, 2006, issue of NEJM claimed that eight patients who were told that they had stage I disease but declined further care had died. This cohort is important to Henschke's argument for screening, because it would help establish that patients diagnosed through CT have clinically relevant disease. Though the original NEJM paper didn't specify the cause of death, in a subsequent exchange of letters, Henschke noted that the eight patients had died of lung cancer.

Later, in the January 2008 issue of The Oncologist, Henschke claimed that the number of such deaths had gone from eight to 13, and supplied the follow-up times for these untreated subjects.

However, in recent months, the I-ELCAP claim that patients who declined care faced certain death started to erode. In a letter published in the July 30 issue of NEJM, Henschke acknowledged that five of the eight untreated subjects in her original paper had been misclassified and had advanced disease at the time of diagnosis.

Though Henschke's admission to NEJM struck at the heart of her original paper, it was published as a letter to the editor. Also, nothing was said about the author's reasons for correcting the record.

"We find it interesting that this 'correction' was published as a letter to NEJM, rather than a formal correction or retraction," Chabner wrote in his editorial in The Oncologist. "Given the importance of this recent revelation, either would have seemed more appropriate."

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Challenged to respond to Bach's letter, Henschke acknowledged that misclassification of untreated subjects was more widespread than she noted in the NEJM letter less than two months earlier. "I have addressed [Bach's] particular concern regarding classification of the untreated stage I cases of lung cancer recently and acknowledge the same reclassification issue with the five additional cases of this kind reported in The Oncologist," Henschke wrote to The Oncologist.

Henschke's response doesn't address the deeper concerns raised by Bach.

Bach argues that the additional five patients would have had to be placed on the study and die over 15 months between the publication dates of the NEJM paper (October 2006) and the publication date of The Oncologist paper (January 2008).

"This means that all five of the additional subjects had to both enter the study and die from lung cancer during the time that passed between the papers," Bach wrote to The Oncologist. "For this to occur, the time interval between the two publications had to be as long as the minimum follow-up time needed for all five subjects to both enter the study and die. But not that much time actually passed."

According to Henschke's data, the survival time for one of the subjects was 20 months, five months longer than the interval between the two publications. Also, Bach noted that there appear to be no signs of censoring in the untreated group. In a study with a rolling entry, censoring is used to black out patients whenever follow-up data are incomplete at the time of analysis.

Bach writes that the probability that none of the 13 patients were censored was low. "It is 1.6 percent (the product of the individual 13 probabilities of not being censored," he wrote. "Not impossible, but highly improbable.

"Put together, I worry that the data… may be biased in a manner that reduces the survival estimate for untreated subjects," he wrote. "If, for example, I-ELCAP investigators were only capturing information on untreated subjects after they died, this would explain why all the subjects in the graph died, and none were censored.

"But the problem with this approach is that study inclusion is associated with study outcome, and in this case the bias would ensure that the death rate is always 100 percent (because no new subjects are added until they die.)."

Henschke was invited to the ACS meeting, but declined to attend. "All PIs of all known randomized studies and the I-ELCAP were included and were at the same time invited to come to this meeting or to send a representative to discuss their trial, but [Henschke] notified us that she was not available and no surrogate would be available to come," Brawley said at the meeting.

Though Henschke's supporters from the Lung Cancer Alliance, a Washington-based patient group, were present at the two-day meeting, they didn't speak at the public comment session.

No Advantage Seen In Pooling Data From NLST And EU Trials

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would offset any statistical advantage that you would get, and increase the likelihood of confusion about a small effect," Tim Byers, professor of epidemiology at the Colorado School of Public Health and deputy director of the University of Colorado Comprehensive Cancer Center, said at the meeting. "It's our view that the scientific advantage of merging data from all six trials now—in the next year and a half—is not compelling. So we are recommending that this not be done." Byers and Brawley co-chaired the meeting.

Claudia Henschke, the I-ELCAP principal investigator, initially appeared to support the idea of combining the trials. Last October, she was part of a large group of screening advocates who presented the pooling proposal at a private meeting with NCI Director John Niederhuber.

Later, Henschke said to several colleagues that she didn't support the proposal and instead would prefer to compare her data with an arm of the ongoing Prostate, Lung, Colon and Ovary trial, sources said.

Henschke declined to attend Brawley's meeting, saying that she didn't authorize discussion of I-ELCAP data, Brawley said at the meeting. The NLST data safety monitoring board similarly urged NCI to stay away from any discussions of pooling the trial data from the $200 million trial. The board wrote a letter to the trial's principal investigators urging them to refrain from sending anyone "involved in NLST's conduct or direct management."

The NLST scientific leadership and NCI apparently didn't follow the board's advice and sent the trial's principal investigator Christine Berg as well as Barnett Kramer, associate director for disease prevention at NIH and a member of the NLST executive committee.

The meeting went badly for I-ELCAP. The panel

dismissed the idea of using the group's data in pooled analysis, and Brawley called for an audit of the group's data. Also, the ACS chief medical officer dismissed Henschke's informally floated proposal to borrow lung data from the PLCO trial to be analyzed with the I-ELCAP results.

"Mixing I-ELCAP with the control arm of PLCO is a bastardization of science," Brawley said. "It's anti-science, and it should not be done."

Though the panel saw no advantage in combining the studies before publication, it said that efforts should be made to make the ongoing European studies more compatible with each other and NLST to allow pooling in the future.

Some aspects of the European trials caused visible consternation in the audience, particularly when an Italian investigator proceeded to show a slide with the results of an ongoing trial, in effect releasing data that is usually protected by data safety monitoring boards and to which investigators are usually not privy until the DSMB determines that a trial can be stopped.

The European trials have vastly different designs and are testing a variety of interventions.

At least two of the trials, both in Italy, weren't designed to produce an answer on their own, and were intended to be pooled at a later date, and one trial, in the U.K., is in the process of being launched and would likely be accruing patients at the time NLST would announce its results.

Also, sources said that at least one of the trials, NELSON, a 20,000-patient study conducted in Holland, Belgium, and Denmark, has run into financial trouble. This information wasn't presented to the panel.

At the meeting, John Field, of the University of Liverpool Cancer Research Centre, presented a proposal, called the European Collaborative Position Statement, for harmonization of the trials. Field proposed that researchers follow three steps:

—Find ways to make protocols more comparable.

—Evaluate performance parameters employed in the trials.

—Determine feasibility of pooling the data to determine lung cancer mortality.

Materials from the conference are posted at http://www.cancerletter.com/publications/special-reports/Lung_Participants_2008.doc.

No Advantage Combing NLST With Other Trials

A transcript of the panel's joint statement, presented by Byers, appears below:

We all agree that early detection of lung cancer could lead to reduction in the risk of mortality from this terrible disease. We hope and pray for this as the outcome that these trials might lead to.

As we are hopeful for that outcome, our judgment and our answers to these questions about merging and pooling of data across trials and across different kinds of studies really is driven by our hope that we will not only get the right answer to these important questions, but that we can also get the right answer at the earliest possible time.

Let me comment first on the question of combination of information from observational studies with randomized controlled trials. Observational studies have potential for asking and answering some questions. In this particular instance, we see no advantage for the combination of observational data with the trials that are currently underway.

The only theoretical advantage would be to increase the numbers of subjects in the trials if they were to be combined; for example expanding the numbers of people on the intervention arm of the randomized controlled studies. But in this instance, we think the violation of principles of randomization would lead to confusion and perhaps to the wrong answers as to the relationship between screening and mortality.

Having said this, we think that observational data, in observational studies that are well done, can answer questions about process, about repeated screening, but not combined with randomized trial data.

Our recommendation is that this combination not be done.

With regard to combination of data with the ongoing trials, the NLST here in the U.S., and the six trials in Europe, clearly, the combination of data from different trials testing the same basic hypothesis is not a novel idea. It can be done, and it should be done, in some setting and sometimes. Meta-analysis is not a new idea. It's very useful to get a more robust answer to narrow questions.

In this particular instance, where there is one large trial and five smaller trials—the sum of the subjects in the five European trials is about half of the number of subjects in the U.S. trial—the question is what would be gained by doing an earlier combined analysis of the European studies with the U.S. study.

If, in fact, all of the studies had precisely the same protocol—same eligibility, same factor of risk, same technical criteria for how screening was done, same operational criteria for [work-up]—if all that were the same, then it would be an easy call.

But the particular question here, though, is with the NLST being powered for less than a 20 percent mortality benefit, what's the added value of increasing the sample size by 50 percent by introducing heterogeneous other trials to it? The only possible advantage to doing the combined analysis over the next 18 months instead of later would be to increase the statistical power of NLST to be more statistically certain of a benefit that is substantially smaller than 20 percent.

You could argue that the uncertainty of mixing in diverse other studies would offset any statistical advantage that you would get, and increase the likelihood of confusion about a small effect.

It's our view that the scientific advantage of merging data from all six trials now—in the next year and a half—is not compelling. So we are recommending that this not be done.

There is value, however, in planning just exactly [what] the E.U. spiral CT screening statement has outlined. In fact, we are very supportive of the suggestion of our European colleagues that we proceed with steps I and II of this three-step plans.

Step one would be protocol comparison. Step II would be evaluation of performance parameters of the trial. And step III would be a combined look at the mortality arm. We think that there is value now in the harmonization across the six trials of protocol comparability and evaluation of performance parameters. Why? One reason it's a good idea to do this is that eventually these trials are going to be done, and wouldn't it be nice, when they are done, to avoid the chaos that happens from the non-comparability of the approaches and the analysis and the language when the conclusions are drawn.

It may well work out that when the NLST conclusions can be drawn in the 2010-2011 time frame, then the cross-Atlantic dialogue could lead to the publication of the five European trials together. Another outcome of that collaborative discussion could be that if the NLST publication is delayed beyond the 2010-2011 timeframe (the only reason for the delay would presumably be because a smaller effect is seen, much smaller than 20 or 15 percent, and the group needs to be followed longer to see how the effect might mature), then that would be an even better reason for ongoing dialogue between the U.S. and European trials. That is, to revisit later the very question we have been talking over the past two days, whether or not there is any value or justification for combining the data.

One of the important questions in all of these trials is at what point in time, how many years after you begin screening, will a separation be seen in mortality? Clearly, that's uncertain at this time.

If the plan for the NLST publication is 2010 or 2011, then [this is] a relatively early effect. If it's going to be later, that's where we think the ongoing dialogue between trials may be helpful in combining the data. But at this point in time, we don't recommend it.

Our recommendations are these: that the European Collaborative Position Statement be endorsed in spirit, that steps I and II begin to be followed between the trials, that preparations be laid so a pooled meta-analysis be done in concert or side-by-side with NLST. But that discussion needs to be revisited if the NLST results should be delayed beyond the 2010-2011 timeframe.

One more comment: in the background, going on there is one more large trial, Prostate, Lung, Colon and Ovary, the PLCO trial, here in the U.S., with very long follow-up now, comparing chest x-ray vs. usual care, which is no imaging routinely. [The PLCO trial is comparing the control groups used in the U.S. vs. European trials.]

Essentially, all the trials are started at about the same point in history. If we had a lot of trials that were longer out vs. shorter out, then it would actually add value to consider them together. The consideration now is, why increase statistical power for an answer that is still relatively short-term, three or four years out, when there is already adequate statistical power in one study? The only possible advantage there would be that we could be more certain about more effects, but that certainly is threatened by the confusion of the different designs for the different trials.

If in fact there is an effect that is longer-term that we only begin to see an effect five, six, seven years out, after beginning screening, that could justify the combination of trial data later, beyond the 2010-2011 time period.

I think that decision needs to be revisited, and I think it can best be revisited if the trialists have an ongoing collaboration and discussion about commonness of their protocols.

The DSMB Position

The NLST Data Safety Monitoring Board's letter was written by Edward Sausville, professor of medicine at the University of Maryland School of Medicine, and addressed to the trial's principal investigators Christine Berg, of NCI, and Denise Aberle, of UCLA David Geffen School of Medicine.

The text of the letter follows:

Dear Drs. Berg and Aberle:

On Sept. 8, 2008, I received from both of you a communication which summarized a telephone conversation involving Dr. Berg, myself as Chair of the National Lung Screening Trial Data Safety Monitoring Board, and Dr. Robert Young, Chair of the NLST's Oversight Committee, to consider how best to a respond to a request on the part of the American Cancer Society for NLST to participate in a meeting on Sept. 22, 2008, to discuss the potential early mixing of outcomes data from the NLST with data from two smaller randomized trials from Europe and the observational study from the International Early Lung Cancer Action Project.

An outline of the process to be utilized, originating from the American Cancer Society, the Cancer Research UK, and the United Nations International Agency for Research on Cancer, was available to the DSMB. The desired outcome of this process would be an early answer to the important public health question as to whether spiral CT scanning of the lungs conveys an advantage in decreasing mortality from lung cancer and overall mortality in the screened population.

As a result of that conversation, I convened a teleconference of the DSMB on Sept. 16, 2008, at 5 PM EDT. The call was attended by eight voting members including myself, Gene Colice, Scott Emerson, Russell Harris, Jeffrey Klein, David Sturges, Bruce Turnbull, and Thomas Watson, as well as two non-voting members Brenda Edwards and Edward Korn.

During the course of the conversation, the DSMB voting members participating in the conference call unanimously took the following positions, articulated in your correspondence outlining the telephone conversation with Dr. Young, and which I quote here:

—The NLST is adequately powered with its current sample size and compliance rates to provide a definitive answer within the next few years as to whether or not spiral CT screening will lower lung cancer mortality compared with chest x-ray screening.

—The premature pooling of NLST data while we are still in the outcomes phase of data collection could have serious, negative repercussions on the welfare and ongoing participation of NLST participants. Moreover, premature conclusions could prevent the NLST from addressing its primary endpoint.

—There are currently no established techniques for pooling data from randomized trials and observational studies. Any such methodology would necessarily require a number of assumptions that could result in even greater ambiguity and potential misrepresentation of screening risk and benefit.

—Among the studies whose data would be pooled is the I-ELCAP. The results of this trial were published in the New England Journal of Medicine in 2006. Since that time, there have been three retractions. Two resulted from conflicts of interest not disclosed at the time of publication. The third was a disclosure that the data were not properly presented by the investigators. These disclaimers throw into question the validity of any conclusions from the I-ELCAP. We see no valid basis for pooling NLST data with a trial in which the data and conclusions are questionable.

In addition, members of the DSMB unanimously endorsed a fifth concern:

—While the NLST has as a primary endpoint the lowering of cancer mortality as stated above, secondary aims tied to the study include the effect of screening interventions on quality of life, cost effectiveness of screening, additional use of medical services as a result of screening and the complications related to such use, among other goals. While the statistical techniques around pooling to reach the primary endpoint are not established as described above, the orderly attainment of conclusions with respect to secondary aims are not even addressed in the proposal and could be equally threatened by premature analysis and dissemination of conclusions related to mortality.

With these determinations in hand, the DSMB further reached the unanimous conclusion of its voting members that it would be scientifically inappropriate for a member of the NLST active investigator staff, including the principal, associate, or affiliate investigators, or in addition any personnel associated with the study who has or will have access to the blinded data, to attend the meeting on Sept. 22, 2008, as a dialog between such personnel and proponents of differing ways of analyzing the data obtained heretofore on the NLST would not serve a useful purpose at this time.

Members of the DSMB were open to the possibility that if contact occurs between NLST and the Sept. 22, 2008, meeting, it would be best achieved through a National Cancer Institute official who is not involved in NLST's conduct or direct management, but who is knowledgeable about the processes continuing at NCI to assure that this most important study is proceeding on track.

This NCI delegate could bring up to date publicly available information about the NLST to the meeting for consideration by participants. This individual could in turn convey concerns from the meeting to NCI that might facilitate retrospective meta-analyses after the NLST has reached its originally planned endpoints.

NLST Follow-up Extended

In a related development, the NCI Executive Committee gave NLST $22 million, which would pay for an additional year of patient follow-up and two more years of data analysis.

The committee's action Sept. 23 covers the NCI-run portion of the trial, and the money would come out of the Division of Cancer Prevention, sources said.

The trial is a collaboration between DCP and the American College of Radiology Imaging Network. Additional funds are likely to be required to pay for that portion of the study.

With the extension, the trial's follow-up will run through the end of 2009.

NIH News:

Zerhouni To Leave NIH In Oct.; 6 Years Brought Many Changes

By Kirsten Boyd Goldberg

NIH Director Elias Zerhouni, whose six-year tenure was marked by major organizational changes, announced he plans to step down at the end of October.

In a statement Sept. 24, Zerhouni said he will take time off to write before seeking other employment.

Zerhouni, a radiologist formerly of Johns Hopkins University, was appointed NIH director in May 2002 by President George Bush.

He pushed for a large and initially controversial trans-institute initiative called the NIH Roadmap for Medical Research, launched in 2003, designed to fund research in broad areas that could have a major impact on science. While advocates for NCI initially were skeptical of the Roadmap, because it took money away from the institute, many NCI grantees have successfully competed for Roadmap funds.

Zerhouni also began new programs to encourage high-risk innovative research, including the Director's Pioneer Awards and New Innovator Awards. He also drew public attention to problems that new investigators have in winning and keeping grant support, and began efforts to improve funding for them.

Zerhouni also pressed for, and received from Congress, greater authority and funding for the NIH director's office, through the NIH Reform Act of 2006. Earlier this month, Zerhouni formed the NIH Scientific Management Review Board as an outgrowth of the Reform Act. The board consists of NIH officials and outside experts to examine NIH's organizational structure and make recommendations for greater flexibility and responsiveness. Also, last June, Zerhouni announced changes to improve the NIH peer review system, after a year-long study.

Early in Zerhouni's tenure, the institutes were still enjoying the final two years of Congressional doubling of the NIH budget. However, post-9/11 brought essentially flat budgets as well as concerns about security. The previously open NIH campus changed dramatically, with the installation of a perimeter fence and security checkpoints. During this time, NIH completed construction of a new Clinical Center building.

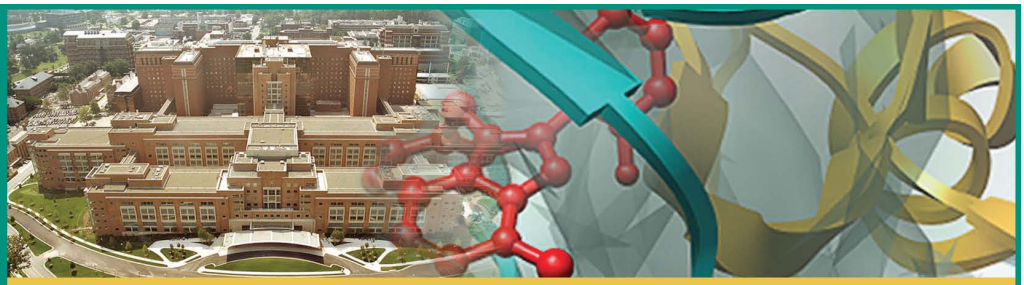
For several years during Zerhouni's tenure, the institutes were subject to Congressional investigations of scientists who supplemented their government income with private consulting deals. In 2005, Zerhouni decided to prohibit NIH scientists from consulting for industry. Recently, a number of medical schools have limited consulting relationships between faculty and industry, and a few pharmaceutical firms are beginning to publicly disclose these relationships as well.

Zerhouni was outspoken in stating that limitations on federal funding for stem-cell research put in place by President Bush are hindering scientific research.

"I have had the privilege of leading one of the greatest institutions in the world for six and a half years," Zerhouni said in a press release. "NIH's strength comes from the extraordinary commitment and excellence of its people in serving a noble mission. It also comes from the nation's scientific community, whose discoveries alleviate the suffering of patients throughout the world. Over the past six years, we experienced a revolution in the biomedical sciences and I feel fortunate to have been part of it. I will miss the NIH and all my colleagues, not only for their friendship and support through 'thick and thin,' but also for their essential role in the progress we made in advancing innovative research, fostering scientific collaboration, supporting young scientists, and enhancing basic, translational, and clinical research, despite great challenges."

"Elias has been a powerful voice for the medical research community as head of the NIH," said HHS Secretary Michael Leavitt. "His tenure has been marked by the spirit of collaboration, good management and transformation. The Roadmap for Medical Research that he developed and implemented will benefit the health of this nation for many years to come. His many achievements include promotion of genetic research, support for advances of biodefense research, and helping raise awareness of women's heart disease. I want to thank Elias for his leadership and wish him the best of luck as he begins this new chapter."

National Cancer Institute



A New NCI Initiative:

The Chemical Biology Consortium
Request for Proposals (RFP)

The National Cancer Institute (NCI) envisions a new drug discovery and development platform whose mission is to advance first in class targeted molecular therapeutic agents to the clinic. As the primary agency for conducting the nation's cancer research efforts, the NCI sponsors many programs including its newly formed NCI Chemical Biology Consortium (CBC).

CBC related activities will span the entire spectrum from target identification and validation through proof of concept ***Phase 0/I/II*** clinical trials. These programs are characterized by scientific excellence and capability to integrate a diversity of research approaches to focus on the problem of cancer through basic research, population sciences research, and translational and clinical research.

NCI, through its Operations and Technical Support Prime Contractor, SAIC-Frederick, Inc., is announcing a Request for Proposals (RFP) for three types of centers (target generation, screening, and chemical lead generation) with complementary capabilities and a high degree of flexibility to address a wide range of biological targets and phenotypes in the CBC. Offerors may submit a proposal for a Comprehensive Chemical/Biology Screening Center, a Biology Screening Center, or a Chemistry Center.

For a complete copy of the RFP, please visit

http://www.fbo.gov

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