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CT Scanning Advocates Propose Pooling Data From Randomized Trials, I-ELCAP

By Paul Goldberg

Proponents of CT screening for lung cancer recently launched a campaign to combine data from randomized trials of the procedure with the data from a single-arm demonstration project.

A proposal by the American Cancer Society, Cancer Research UK, and the International Agency for Research on Cancer calls 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 Project.

Also, the document proposes delaying publication of results from the three randomized trials and publishing them together with the pooled analysis.

Such pooling would amount to "sabotaging the NLST," wrote Donald Berry, chairman of the department of biostatistics at M.D. Anderson Cancer

(Continued to page 2)

In the Cancer Centers:

NCI's Hawk To Lead Prevention Division At M.D. Anderson, Succeeding Bernard Levin

ERNEST HAWK, director of the NCI Office of Centers, Training and Resources since 2004, plans to leave the institute at the end of the month to join M.D. Anderson Cancer Center.

Hawk was named vice president and division head for Cancer Prevention and Population Sciences, succeeding **Bernard Levin**, who last year announced his plans to retire.

Hawk was chief of the NCI Gastrointestinal and Other Cancers Research Group in the Division of Cancer Prevention from 1999 to 2004. He earned his bachelor's and medical degrees at Wayne State University and a master of public health degree at Johns Hopkins University. He completed an internal medicine internship and residency at Emory University, a medical oncology clinical fellowship at the University of California, San Francisco, and a cancer prevention fellowship at NCI.

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CANCER THERAPY AND RESEARCH CENTER Board of Directors announced plans to merge the center with the University of Texas Health Science Center at San Antonio. The UT System, the Health Science Center, and the CTRC board signed an agreement on the merger Nov. 14, subject to approval by the UT System Board of Regents. The agreement calls

(Continued to page 8)

Critics Say Plan Would Earn Failing Grade In Epi 101

(Continued from page 1)

Center, one of the three biostatisticians asked by The Cancer Letter to review the proposal. "I-ELCAP is a denaturant; mixing it in would make NLST uninterpretable—and unpalatable." Berry's commentary appears on page 5.

Berry and other biostatisticians say that the science at the heart of this controversy is anything but esoteric. Students in Epidemiology 101 learn that combining randomized trials with single-arm trials literally requires researchers to imagine a control group, which undermines the reason for conducting randomized trials in the first place.

The proposal is endorsed by John Seffrin, CEO of the American Cancer Society, Harpal Kumar, CEO of Cancer Research UK, and Peter Boyle, a biostatistician who serves as director of the International Agency for Research on Cancer. ACS is a financial contributor to NLST. The society developed promotional materials for the trial and has helped with recruitment of participants.

Proposals to pool the data from randomized trials of CT scanning have been discussed systematically since 2001. The plan endorsed by Seffrin, Kumar, and Boyle goes a step further, proposing to include I-ELCAP in the meta-analysis and to refrain from publishing the results of the randomized trials separately.

The document, addressed to the leadership of the trials, is posted at www.cancerletter.com.

"The idea that you can combine non-RCT and RCT data by doing some statistical manipulation, is naïve," said David Ransohoff, an expert in cancer prevention and control at the University of North Carolina Lineberger Comprehensive Cancer Center. "It's close to astonishing that a proposal like this is being sent out over the letterhead of three policy-making organizations. If an MPH or PhD student submitted a proposal like this, it would be judged severely, and you'd wonder whether they were paying attention in class."

On Oct. 17, the idea was presented to NCI Director John Niederhuber at a private meeting with the Lung Cancer Alliance, a pro-screening group. I-ELCAP Principal Investigator Claudia Henschke, professor of radiology at Weill Cornell Medical Center, took part in the meeting.

"We fully recognize that what we are proposing is extraordinary and a departure from the normal, independent path taken by separate studies," Seffrin, Kumar, and Boyle wrote in a cover letter to the proposal to pool the data. "We believe this is an historic opportunity, and hope you will agree to participate in the first step of the venture."

The proposal, dated Nov. 1, lays out a four-step process that begins with examination of trial results for consistency through publication of pooled results.

"We realize that our proposal may be viewed as having the potential to diminish individual academic credit, which we acknowledge also is an important form of currency in the return on investment for the time committed to these studies," the proposal states. "We therefore propose to negotiate in advance the simultaneous publication of the combined and individual studies in a single issue of a front-line journal. We would suggest that an editorial representative of The Lancet be invited to the first meeting to negotiate this in advance. If members of the group would prefer a different journal, please let us know."

The proposal was signed by Robert Smith, director of cancer screening at ACS, Stephen Duffy, professor of cancer screening at Wolfson Institute of Preventive Medicine in London, and Harry deKoning, an associate professor at the Department of Public Health at Erasmus University in Rotterdam.

The authors suggest the following approach to including the data from I-ELCAP, a 32,000-patient single-arm trial into the analysis:

"Absolute rates will be calculated for groups offered spiral CT screening and for control or comparison groups where applicable. Both overall figures and rates

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specific to age, sex and risk groups will be calculated.

"Relative rates will take the form of O/E where O represents observed deaths (or cases) in the group offered spiral CT screening and E represents the expected numbers in the absence of screening. For the randomized trials, E is derived from the control group. For the demonstration projects, E can be obtained from internal modeling of the likely tumor and death rates if the screening had not taken place or by comparison with external groups, with suitable adjustment for demographic and risk data. If several methods are available, all should be used and the range of results examined."

Responding to the proposal, the data and safety monitoring board of NLST will hold a special telephone conference next week, sources said.

"Flat-out Dead Wrong"

The proposal to use modeling to incorporate the I-ELCAP data is unlikely to get much support from mainstream biostatisticians and clinical trialists.

"I am not a statistician, but I wasn't born yesterday, either," said Robert Young, chairman of the NLST oversight committee, chancellor of Fox Chase Cancer Center, and chairman of the NCI Board of Scientific Advisors. "On page 7, they say that for the demonstration projects, E can be obtained from internal modeling of the likely tumor and death rates if the screening had not taken place.

"That's flat-out dead-wrong. That's exactly the problem with a single-arm trial: it assumes that a population screened is the same as the general population, and we just keep getting burned over and over and over whenever we do that. That's classical hormone-replacement trial stuff. I think the numbers from the I-ELCAP trial are big enough that it would seriously skew the data in a way that might be troublesome."

Ransohoff agrees. "If that were really possible to do, we could answer many questions just with mathematical modeling and skip doing studies altogether," he said. "It is precisely because we cannot do that—because we have been burned so many times by observational data and assumptions, where we thought we knew the answer—that we value RCTs so highly. Examples include estrogens to prevent coronary artery disease, medical therapy of ventricular arrhythmias to prevent sudden death, and chest x-ray screening for lung cancer to reduce mortality. What we need now is not to combine RCT and observational data; it's to let the RCTs actually happen and provide an answer."

Meta-analysis has been used in evaluation of lung cancer screening in the past. For example, an exploratory analysis published in the March 7 issue of JAMA pooled the results of three single-arm studies of CT screening, finding evidence of harm to patients.

"It's very flattering to see a reference to the use of a synthetic E as a way of evaluating CT screening," said Peter Bach, a pulmonologist and a member of the Health Outcomes Research Group in the Department of Epidemiology and Biostatistics at Memorial Sloan-Kettering Cancer Center and the lead author of that study. "This is exactly what we did in our meta-analysis of three single-arm studies of CT screening that was recently in JAMA, and we calculated the same statistics that they propose.

"By comparing what happened (O) to what was expected (E) in these studies, we found evidence that CT detects more than three times as many lung cancers as would appear sporadically, drives up surgical rates tenfold, and doesn't appear to reduce advanced lung cancer rates or mortality rates," said Bach after reviewing the proposal.

"The keys to our analysis were, first, that we were analyzing cohorts of people who were screened," Bach said. "Along those lines, we had near complete (i.e. 99%) follow-up on all subjects to a standardized time point. Therefore we could determine O accurately, including the 'observed' deaths due to lung cancer. Second, we were able to determine E using prediction models that had been externally validated, and could be anchored to the person-time of observation for each subject, multiplied by their predicted risk."

Unlike the single-arm studies pooled by Bach, I-ELCAP doesn't lend itself to a calculation of either E or O, he said.

"What the authors of the memo do not seem to know is that I-ELCAP is not a cohort study like the ones we analyzed and reported on in JAMA," Bach said. "It is a case series that includes follow-up only on subjects that were diagnosed with lung cancer through screening. This is clear from reading the I-ELCAP protocol on their website, which states that investigators are to only follow subjects who they diagnose through screening with stage 1 lung cancer, and the same proviso is apparent in their publications. For instance, in their recent NEJM publication, they reported screening about 30,000 people, but only reported outcomes on about 500 of them—those they diagnosed with lung cancer. Hence, that study was a case series of people diagnosed with lung cancer, not a cohort study of people screened for lung cancer.

"This distinction is not trivial," Bach said. "Unlike a cohort study, in which O can be determined through follow-up of all screened subjects, and E can be calculated across all of the enrollees, neither can be determined from a case series. So, there is no way forward for the idea in the memo, to calculate either E or O from I-ELCAP data.

"The proposal begs another question: why one might desire to combine data from the I-ELCAP case series with data from randomized trials, as the idea sort of up-ends well accepted hierarchies of evidence," Bach said. "Case series rank near the bottom in the evidence hierarchy, randomized trials are at the top. In the middle are cohort studies that use historical controls."

Ransohoff said he is concerned about the prospect of the data-pooling process harming ongoing randomized trials.

"Combining data from observational studies and RCTs like this is not only extraordinarily unconventional, but it's dangerous if it causes you to 'stop' the RCT prematurely, so that you never get the real answer," Ransohoff said. "After studies have been completed, results are often 'weighed' to reach some considered overall assessment.

"And in meta-analysis limited to one study type like to RCTs, results may be combined in a quantitative way, but that is done after each RCT has been completed and reported so that each can be examined closely for similarity, difference, and appropriateness for combining. One might even make a case to combine data from ongoing RCTs."

Ransohoff said the proposal to invite a Lancet editor to the meetings is troubling, too.

"This presupposes publication and short-circuits the formal peer-review process," he said. "While peer review is not perfect, it provides important checks and balances in the generation of knowledge."

Political Screening

The drive to pool the data and forestall publication of randomized trials represents a change of course for the I-ELCAP camp.

After the results of the I-ELCAP project were published in the Oct. 26, 2006, issue of the New England Journal of Medicine, supporters of screening declared that CT scans of high-risk populations should become part of mainstream medical practice.

At the same time, screening advocates redoubled their attacks on NLST, describing the trial as unethical and scientifically irrelevant. "They are so wedded to a failed trial that they can't grasp that the technology they are looking at is outdated," Laurie Fenton Ambrose, president and CEO of the Washington-based Lung Cancer Alliance, said of NLST last October.

"The fact that the results will literally underestimate the benefit of screening ought to be of concern to them," Fenton said to The Cancer Letter at that time. "What's going to happen after $220 million, with another four year before we learn the results, we are going to learn that screening doesn't help. Why? Because they've used technology that is outdated. It will underestimate the value of screening, and they know that" (The Cancer Letter, Nov. 3, 2006).

Henschke, too, has said repeatedly that she views NLST as unethical because that trial randomizes patients to a less sensitive screening tool, chest x-ray (The Cancer Letter, Jan. 12).

Henschke appears to have been working closely with LCA, where she serves on the Medical and Scientific Advisory Board. LCA's actions recently included alleging conflict of interest on the part of NLST investigators and convincing the Democratic leadership of the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce to launch an investigation of the trial (The Cancer Letter, Oct. 26).

However, in an apparent shift, Henschke's group and LCA are now insisting on pooling the randomized trial they had been describing as irrelevant and unethical with the I-ELCAP data they deem reliable. The proposal is particularly advantageous to I-ELCAP since the group's findings have been published, and thus wouldn't be affected by any publication moratorium.

On Oct. 17, when a large contingent of LCA leadership presented the idea in a protracted private meeting with NCI Director Niederhuber, no specific agreement was reached, sources said. Also, the Congressional investigation sparked by proponents of CT screening places NCI in an awkward position and may limit its willingness—and, possibly, its ability—to cooperate with the advocates.

In the past, the ACS position has been more moderate than that of LCA.

Last October, when LCA called for immediate change in clinical practice based on Henschke's data, ACS official Smith wrote that data from randomized trials was worth waiting for. However, Smith's statement at the time also included what appears to be an endorsement of I-ELCAP's protocols:

"The bottom line for people at risk for lung cancer who hear this news: Talk with your doctor about your risk of lung cancer screening. After a discussion about

what is and is not known about the value of testing for early lung cancer detection, if you and your doctor decide in favor of testing, then be sure to chose an institution that has experience in lung scanning and that supports a multidisciplinary program dedicated to evaluation of high risk individuals."

The date on the proposal to pool the data—Nov. 1—is significant. It coincides with arrival of Smith's new boss, Otis Brawley, the new ACS chief medical officer. Brawley, an advocate of evidence-based medicine and rigor in clinical trials, declined to discuss the proposal.

CT Scan "Still A Research Issue"

NLST's Young said that he would have no objection to continuing discussion of pooling NLST data with the data from other randomized trials after those trials are published.

Clinical trialists have been working through a group called the EU-US Spiral CT Collaboration to establish minimal data sets for cross-analysis of studies after they are reported.

I-ELCAP leadership, including Henschke, has taken part in these discussions. The most recent workshop, called The Liverpool Statement 2005, published in the June 2006 issue of the Journal of Thoracic Oncology, notes that I-ELCAP produces "a great deal of information on large numbers of screened subjects" and demonstrates "the importance of the definition of the regimen that defines a positive result and the recommended work-up." Smith and Duffy are among coauthors of the statement.

Young said that the most recent discussions of pooling the data from randomized trials concluded that, at least at this time, a meta-analysis wouldn't produce the answer any sooner than individual studies.

"If they want to sit down and talk about whether or not they could, in fact, harmonize the three randomized trials in some sort of a persuasive way, and the time to conclusion would be significantly improved without compromising the integrity of the trials, that's certainly worth talking about," Young said. "My hunch is, it's going to come out the same way it came out when we discussed it a year and a half ago, but there is no reason not to talk about it."

While the idea of pooling data from randomized trials warrants discussion, inclusion of data from single-arm trials in a meta-analysis doesn't, Young said.

"We need to find out whether it's a requirement of this sit-down-and-let's-talk, because I am not so sure that it's going to turn out to be useful if that's the case," Young said. "I just don't see how inclusion of single-arm accumulative demonstration project data into the middle of three randomized trials can do anything but muddy the conclusion."

The three randomized trials are:

—NLST, a 50,000-patient study, which compares CT with standard X-ray.

—NELSON, a 20,000-patient Dutch, Belgian and Danish study that compares CT with usual care.

—ITALUNG, a 3,000-patient Italian study that compares CT with usual care.

ITALUNG Principal Investigator Eugenio Paci credits the single-arm demonstration projects with raising questions that are now being answered in randomized trials.

"The ELCAP and I-ELCAP studies are extremely important and reopened the long story about early diagnosis, but they lack a control group, and the collection of screened subjects and observation of survival rates is not enough," he said to The Cancer Letter. "So I agree that we need randomized trials aimed to mortality evaluation, well done, well monitored, and possibly publishing interim results. This is what we will do as ITALUNG project, a small trial, and are interested in the cooperative international efforts in pooling data with the aim of producing results as soon as possible."

Paci said the debate over CT screening in the U.S. has become excessively political. "I feel the discussion is much too aggressive," he said. "From this side of the ocean, we do not feel such strong emotions about lung cancer screening, and in Europe, the use of CT scan is still a research issue."

Guest Commentary:

Pooling Apples, Oranges, Lemons And Limes Makes A Statistical Fruit Salad

By Donald Berry

The proposal from ACS/CRUK/IARC and Messrs. Smith, Duffy, and de Koning regarding "data sharing" across the various spiral CT lung cancer screening studies is indeed "extraordinary" and "historic." But sometimes there are solid scientific reasons for what history has established as "ordinary."

The goal is to increase statistical power regarding mortality and allow for earlier publication of the results. Increasing power is a standard goal of meta-analyses. One extraordinary aspect of the ACS/CRUK/IARC proposal is to combine the results before publishing the results of the individual studies.

The conventional approach to meta-analysis is to include studies that address the same scientific question. The NELSON and ITALUNG trials address the same question, CT vs. usual care. The NLST addresses CT vs. chest X-ray. The I-ELCAP doesn't address a scientific question, as I'll explain below. Combining the four of them is not just apples and oranges, it is apples and oranges and lemons and limes.

Another aspect of the conventional approach is to avoid pooling non-randomized studies with randomized trials. When randomized trials are available, it is unusual to include anything else. It is true that it is difficult to *not* compare the results of single-armed studies with the corresponding arm of a randomized trial, and I do this myself. But that's after the studies are over and published. The main lesson from such comparisons is that they demonstrate the folly of conducting single-armed trials.

Synthesizing the results of studies is an important way to address scientific questions. And hierarchical modeling as part of the proposal is generally a good way to proceed because it recognizes the possibility of heterogeneity of results across studies. Unfortunately, when the number of studies is small—as in the case at hand—the ability to assess heterogeneity is extremely limited. The sample size for this level of the hierarchical analysis is 4. One is left with having to assume homogeneity and with having to combine the results as though the mortality of CT is the same in all 4 studies.

That means the results of the CT arms of the studies will be combined (averaged), with the bigger studies having greater weight. Restricting to the two largest studies, if I-ELCAP has less mortality than the CT arm of NLST then the estimated mortality of CT will be less than that in CT-NLST. But the X-ray arm of NLST will not be swayed by I-ELCAP because it had no X-ray arm.

So the CT vs. X-ray comparison will be biased in favor of CT, and this bias is potentially huge. On the other hand if mortality in I-ELCAP is greater than in CT-NLST then the bias will favor X-ray in comparison with CT. The only unbiased comparison of CT and X-ray is within NLST itself, which of course is the reason for its design.

To preserve the integrity of randomized trials they must be published separately and evaluated separately, for their conclusions and for their warts. Any other approach alters their fundamental operating characteristics. What is the false-positive rate of the proposed pooling? It is impossible to say. There was no prospective design. The proposers include I-ELCAP. But the results of I-ELCAP are known. Had its results been different, the proposers might not have included it in their proposal. Indeed, they might not be making their proposal at all. This bias is potentially huge, but there's no way on Earth to assess its magnitude.

The results of the various studies can be pooled by meta-analysts after the separate publications, as is standard. These analysts will make assumptions about how they did the pooling, including their choice of studies, and they will publish their assumptions. Readers can decide whether they agree with the assumptions. And if they do not agree then the results of the individual studies will be available and can be used to make suitable modifications.

Including I-ELCAP in the study mix is curious. Like all non-randomized studies, I-ELCAP is worthless for understanding the benefits of screening on mortality. Randomization in clinical research is regarded to be the gold standard. And appropriately so. Still, it is *possible* to draw conclusions about treatment effect in clinical settings without randomizing.

But the story is very different in screening. Given our level of understanding of the biology of lung cancer, conclusions about screening effects on mortality are impossible outside of randomized trials. We know very well that cancers found via screening have much better prognoses than symptomatic cancers. The main explanations are lead-time and length biases. There may be a beneficial effect of screening as well, but it cannot be separated from these biases. Moreover, even for the same characteristics of disease (stage, EGFR expression, etc.) and patient (age, exposure to carcinogens, etc.), cancers found by screening still have much better prognoses. The main explanation is length bias.

The proposers would be sabotaging the NLST. I-ELCAP is a denaturant; mixing it in would make NLST uninterpretable—and unpalatable.

Berry is chairman of the department of biostatistics at M.D. Anderson Cancer Center.

Professional Societies:

ASCO To Open "Proceedings" To Everyone Prior To Meeting

By Kirsten Boyd Goldberg

In a change of policy, the American Society of Clinical Oncology plans to publicly release the research abstracts for its annual meeting at the same time as members see them.

The new policy will take effect for the society's 2008 annual meeting scheduled for May 30-June 3 in

Chicago. About two weeks prior to the meeting, ASCO will send abstract books to members. At the same time, the abstracts will be posted on the society's Web site.

Previously, the society sent abstract books to its 30,000 members and several hundred media, but tried to prevent discussion prior to the meeting. However, "leaks" still occurred, resulting in movement in stock prices for biotech companies before the public had full access to the data—and subjecting ASCO to criticism for its selective disclosure.

"Every year, ASCO reviews its annual meeting policies to ensure they remain current, relevant, and continue to meet the evolving needs of our members, patients, and others," Allen Lichter, ASCO executive vice president and CEO, said to the Cancer Letter. "For 2008, we have decided to make the vast majority of abstracts available online in advance of the meeting—everything but the plenary and late-breaking abstracts. This advance availability online will not only make the abstracts easily accessible and searchable for our members, but for anyone with an interest in the research."

The new policy "is a good thing and it's about time," said Adam Feuerstein, a senior writer for TheStreet.com who first reported "the ASCO effect" on the stock market in 2000.

"ASCO has definitely heard the message coming from Wall Street and some of their own members about these concerns," Feuerstein said. "To their credit, they finally did something about it. I think the new policy is very sensible.

"I think in May you will see more volatility in the trading of biotech stocks, because everyone will have access to this information," Feuerstein said. "That's not necessarily a bad thing. It's a democratic process and everyone will have the same information. The problem we had in the past was that relatively few people could trade based on the information."

ASCO sent letters to members on Oct. 23 describing the new policy. The society plans to publish two annual meeting books. "Proceedings I" will contain the Oral, Clinical Science Symposia, Poster Discussion, General Poster abstracts. These will be publicly accessible online about two weeks in advance of the meeting. "Proceedings II" will contain the full Late Breaking and final Plenary abstracts, and will be distributed at the meeting on Saturday, May 31. These abstracts will be available online during the weekend of the meeting.

For the media, ASCO will have two embargoes on the abstracts, corresponding to the two Proceedings postings online, spokesman Laura Livingston said.

ESA Controversy:

Amgen Takes Down Web Site That Solicited Testimonials

By Paul Goldberg

Two hours after The Cancer Letter reported that a website owned and operated by Amgen Inc. was displaying patients' testimonials that contained claims about off-label uses of erythropoiesis-stimulating agents, the company took down the website.

The Nov. 9 issue of The Cancer Letter was sent to subscribers around 12:20 p.m., and the website, www.protectcancerpatients.org, was replaced with an "under construction" page sometime between 2 and 2:40 p.m.

The site, designed to encourage patients to petition Congress to overturn the National Coverage Decision on ESAs, collected testimonials and encouraged patients to contact Congress.

An Amgen spokesman said the decision to deactivate the website wasn't connected with the story. "In light of the new ESA labeling and in conjunction with Amgen's NCD reconsideration request, Amgen is making modifications to the protectcancerpatients.org website, which enabled patients and others affected by the NCD to engage in political speech directed towards policymakers," said Kelley Davenport, a company spokesman. "The site should be up shortly.

"Amgen continues to believe that the NCD unnecessarily restricts the ability of physicians to use ESAs for many of the Medicare beneficiaries who may potentially benefit from them," Davenport said. "Amgen has now joined the many members of the oncology community who have formally requested a reconsideration of the NCD. Amgen also continues to encourage patients and their caregivers to learn more about the Medicare policy, and voice their concerns directly to government policymakers."

Testimonials posted on the website claimed that ESAs improved the symptoms of anemia and the quality of life. Two of patients noted that they were being treated for hematologic malignancies. The agents are approved only for reducing the risk of blood transfusions in solid tumors for patients receiving chemotherapy. The website didn't display a copy of the drug's label and didn't discuss the side effects.

A call center connected to the website was operated by Direct Impact, a unit of Burston-Marsteller.

Johnson & Johnson, the sponsor of a competing ESA, recently launched a similar website, www.voiceforcancerpatients.com, which didn't solicit testimonial. The site remains active.

In the Cancer Centers:

CTRC Board Approves Merger With UT Health Science Center

(Continued from page 1)

for melding the clinical, research, and administrative structures of the institutions. Health Science Center faculty members treat patients at CTRC facilities, and the two institutions are partners in the San Antonio Cancer Institute, an NCI-designated cancer center. . . .

OHIO STATE University cancer researchers received two NCI grants totaling $17 million. **Michael Caligiuri**, director of the Ohio State University Comprehensive Cancer Center, received $10 million over five years for research in leukemia and other cancers. The grant is a renewal of a study that began in 2002 and encompasses four related projects. **A. Douglas Kinghorn**, the Jack L. Beal Professor, chairman of the College of Pharmacy, and member of the Comprehensive Cancer Center Experimental Therapeutics Program, received $7 million over five years. His research into chemotherapy agents derived from tropical rainforest plants and primitive cyanobacteria and fungi also involves researchers at the University of Illinois at Chicago, Research Triangle Institute, and Bristol-Myers Squibb.

Funding Opportunities:

PAR-08-023: Predictive Multiscale Models of the Physiome in Health and Disease. R01. Letters of Intent Receipt Date: Dec. 14, April 14, 2008, Aug. 15, Dec. 15, April 14, 2009, Aug. 17, Dec. 14, April 14, 2010, Aug. 16. Application Submission/Receipt Date: Jan. 14, May 14, Sept. 15, Jan. 14, 2009, May 14, Sept. 15, Jan. 14, 2010, May 14, Sept. 15, 2010. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-023.html. Inquiries: Jennifer Couch, 301-435-5226; couchj@mail.nih.gov.

PA-08-012: Ethical, Legal, and Social Implications Regular Research Program. R01. Application Receipt Date: Feb. 5, Feb. 16, June 5, June 16, Oct. 5, Oct. 16. Same sequence of dates through 2010. http://www.grants.nih.gov/grants/guide/pa-files/PA-08-012.html. Inquiries: Carol Kasten, kastenca@mail.nih.gov.

PA-08-013: Ethical, Legal, and Social Implications Regular Research Program. R03. http://www.grants.nih.gov/grants/guide/pa-files/PA-08-013.html.

RFP N02-CM-81000-48: Drug Development Support For The Cancer Therapy Evaluation Program. Response Due Date: Dec. 19. Full text: http://www.fbodaily.com/archive/2007/11-November/04-Nov-2007/FBO-01445580.htm. Inquiries: John Manouelian, 301-435-3813, jm486p@nih.gov. or Richard Hartmann, 301-496-8620, rh75f@nih.gov.

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