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FDA To Once Again Review ESA Label To Reflect Results Of Negative Studies

By Paul Goldberg

Less than a month after placing new cautionary language into the label for erythropoiesis-stimulating agents, FDA is once again updating the document to reflect the results of two negative studies that have emerged over the past week.

Also, on Dec. 6, Amgen Inc., the sponsor of the ESA Aranesp (darbepoetin alfa), said FDA plans to convene its Oncologic Drugs Advisory Committee in the first quarter of 2008 to discuss the safety of these drugs.

This would be the third ODAC meeting in four years convened to discuss on the subject of ESA safety.

Concern about the use of ESAs in oncology deepened in recent days as Amgen and Johnson & Johnson, the sponsor of Procrit (epoetin alfa), announced data pointing to decreases in overall survival and progression-free survival.

On Nov. 30, Amgen announced preliminary results of a German study of

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In the Cancer Centers:

Lurie Comprehensive Cancer Center Wins Five-Year Core Grant Renewal

ROBERT H. LURIE Comprehensive Cancer Center of Northwestern University was awarded a $25.6 million five-year renewal of its Cancer Center Support Grant by NCI to fund infrastructure and facilities that promote research collaboration and innovation. The grant, among the largest awards received by the university, allows the Lurie Cancer Center to maintain its status as the only NCI-designated comprehensive cancer center in Illinois, said **Steven Rosen**, center director. . . . **COLD SPRING HARBOR** Laboratory raised $3.1 million and honored individuals for excellence in biological and biomedical science research at its 2007 Double Helix Medals Dinner. The event honored **David Koch** for corporate leadership, and **Richard Axel** and **Michael Wigler** for scientific research, said **Bruce Stillman**, CSHL president. Koch is executive vice president of Koch Industries. Nobel laureate Axel is university professor and investigator at the Howard Hughes Medical Institute, College of Physicians and Surgeons of Columbia University. He is known for his work in molecular biology, genetics, and neurobiology. Wigler, an American Cancer Society Research Professor at CSHL, is known for his research in genetics, cancer, and cognitive disorders. . . . **GARY KRUH** was appointed director and interim chief, Section of Hematology-Oncology,

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Concern About ESAs Deepens As Negative Results Emerge

(Continued from page 1)

Aranesp in the neo-adjuvant treatment of breast cancer. Then, on Dec. 4, J&J announced a similar result in an update to a study in advanced cervical cancer patients undergoing chemoradiotherapy. The study, conducted by the Gynecologic Oncology Group, was halted in 2003 in response to concerns about potential increases in thromboembolic events.

Both trials aimed to increase hemoglobin beyond 12 g/dL, and neither reached statistical significance with regard to clinical endpoints. The ESA labels issued last month list six studies that point to increased risk of toxicity and tumor promotion (The Cancer Letter, Nov. 9).

The Aranesp breast cancer study, called PREPARE (preoperative epirubicin-paclitaxel-Aranesp), is the more alarming of the two, because it focused on the neo-adjuvant setting, where the treatment goal is to cure the disease. According to breast cancer experts, the study's results are directly applicable to dose-dense chemotherapy, which produces grade III anemia in about 11 percent of patients.

In the 733-patient study, investigators reported 50 deaths among the 356 patients who received Aranesp before surgery and 37 deaths among the 377 patients who received placebo. Tumor progression occurred in 88 of the 356 Aranesp patients and 70 of the 377 patients on placebo.

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The women in PREPARE received Aranesp for 24 weeks in conjunction with chemotherapy prior to surgery.

Since all the patients have been treated, there was no reason to stop the study and no concerns about subjecting new patients to risks. However, Amgen, one of the commercial sponsors of the study, is under obligation to release the results, as SEC requires companies to public release information material to their financial performance, and FDA requires submission of information on potential toxicity and the loss of efficacy.

A formal statistical analysis of survival in PREPARE is expected in early 2009. The principal investigator of the study said Amgen requested that he release the data. "Amgen has the duty to release those data," said Michael Untch, head of Breast Cancer Center Academic Hospital of the University Charite Berlin. "It's your crazy American laws. My usual publication policy is to see the data, to talk to the statistician, to present in an international symposium, and get out a full paper as soon as possible."

Amgen spokesman Ashleigh Koss confirmed that the company was under obligation to release the results. "The PREPARE study is one of five randomized, prospective clinical studies that are part of Amgen's ongoing pharmacovigilance program undertaken in agreement with the FDA following the May 2004 ODAC," she said. "The press release is part of our ongoing commitment to provide updates on the PV program. The interim results were provided to regulatory agencies, including the FDA. The PREPARE study will be part of our ongoing discussions with the FDA around ESAs."

Untch said that the finding hasn't caused him to change his practice. "I wouldn't call it even a trend, because we have seen so many trends in medicine, and you do additional analysis, and then you see that a couple of lines are coming together," he said. "It's very early analysis."

Also, the study sought to achieve hemoglobin levels of 12.5 to 13 gd/L, higher than the 10-12 g/dL level recommended in the guidelines of the American Society of Clinical Oncology. At the end of the trial, patients on the Aranesp arm had the hemoglobin of 13.6 g/dL, and patients receiving placebo had the hemoglobin of 12.6 g/dL.

"According to this data, I would say that to correct anemia, ESAs are perfect drugs," Untch said. "To influence the response to chemotherapy, this is the first study to prove that there is no influence. When we

started, we had a hypothesis that hopefully we might positively influence the response to chemotherapy with the EPO, and that is not true."

Rising Concern About ESAs In Breast Cancer

However, other oncologists say that, in conjunction with previously published trials in breast and other cancers, the Untch finding provides yet another cause for concern, especially in breast cancer.

A finding in the neo-adjuvant setting, if confirmed, would be particularly alarming, since patients received ESAs while tumor was still present—and thus potentially available for stimulation—in their bodies.

"In the neo-adjuvant setting, you have an existing tumor with a potential for stimulation, if, in fact, ESAs stimulate tumor cells," said Howard Ozer, Eason Chair of Medicine at the Oklahoma University Health Science Center and an expert in ESAs as well as breast cancer. "It's not like the adjuvant setting."

A neo-adjuvant trial would be more likely to detect tumor promotion than an adjuvant trial, agreed Joanne Mortimer, vice chair, medical oncology, professor at the Division of Medical Oncology & Experimental Therapeutics at City of Hope Comprehensive Cancer Center and a member of ODAC. "Certainly, many more women receiving neo-adjuvant therapy will develop disease recurrence than in the adjuvant setting, where in most cases, there are no residual cells left," Mortimer said.

"The data tell me, 'Be very careful with ESAs in neo-adjuvant treatment of breast cancer,'" said Michael Henke, professor of medicine, radiation oncology, Freiburg University Clinic, Germany, whose paper on the use of ESAs in head-and-neck cancer started worldwide reconsideration of the agents. "If you have a chance of the cure and you give ESAs, you will hamper this chance. The story is done. Each person who receives this stuff is in danger."

Many head-and-neck cancer experts, particularly academics, point to Henke's 2003 paper in The Lancet as the cause of their reluctance to use ESAs in the adjuvant and neo-adjuvant setting.

"I remember seeing that data, and I just said, wait a minute, the first thing we should be able to tell our patients is, 'We are doing our best, and we are not doing things that we know may well harm you,'" said Fadlo Khuri, Blomeyer Chair in Translational Cancer Research and Deputy Director, Clinical and Translational Research at Winship Cancer Institute at Emory University School of Medicine, who earlier this year wrote a commentary on ESAs in the New England Journal of Medicine.

"The totality of the data suggests that there is little benefit, and in fact, there is harm, to treating patients in the adjuvant and neo-adjuvant setting with ESAs," he said. "I don't necessarily need to see the disease, because in the adjuvant setting we've made the commitment that there is enough possibility of disease that we are treating to eradicate. There is enough evidence that patients treated with curative intent should not be treated for asymptomatic anemia."

Treating Patients, Not Blood Counts

Some breast cancer specialists started to get jittery about ESAs in 2003, following publication of a report that the data safety monitoring board had closed a trial of Procrit in metastatic breast cancer, because of poorer overall survival in the experimental arm.

Concern deepened in 2005, after the Journal of Clinical Oncology published the results of that study, called Breast Cancer Erythropoietin Survival Trial (BEST).

This year's barrage of bad news and the change of ESA label by FDA have made breast cancer specialists even more reluctant to use these agents, particularly in the adjuvant setting.

In conjunction with what's already known, the direction of the PREPARE finding is troubling even in the absence of statistical significance. "This is a real finding," said Mortimer. "It continues to be very worrisome."

"It certainly gives one pause," agrees George Sledge, the Ballve Lantero Professor of Oncology at the University of Indiana. "Michael Untch's statements notwithstanding, in a curative setting, this has legs—short term benefit balanced by long term risk, and it's particularly an issue for regimens like dose-dense chemotherapy that produce anemia regularly."

Sledge has been concerned about the BEST trials and preclinical findings suggesting that ESAs have a pro-angiogenic effect, and even more concerned about clinical data pointing to toxicity and tumor promotion.

"It's the trends that are worrisome," he said. "It's the fact that even though in individual studies we may not be seeing a whole lot, collectively the sense one gets is that this may not be good for you from a cancer standpoint."

While in the past, Sledge considered ESAs a reasonable treatment option for patients who develop grade III anemia as a result of receiving dose-dense chemotherapy, this year he has become even more reluctant to prescribe ESAs in the adjuvant setting.

According to clinical trials data, about 11 percent of patients receiving dose-dense chemotherapy develop anemia. However, not all these patients require ESAs or blood transfusions, Sledge and other breast cancer experts said.

"If I'm in a setting where I expect the red blood cell count to bounce back quickly without a major intervention (e.g., at the end of adjuvant therapy) and the patient is asymptomatic, I'll probably just watch and wait," he said. "There are always exceptions—older patients with cardiac histories don't do well with low red blood cell concentrations."

After patients hear the data, few opt for ESAs, he said. "There are very few patients who would trade off a blood transfusion for a chance for a cure," Sledge said. "I suspect that the Untch data would lead to significantly less use. It's one of several arrows pointing in the same direction."

Sledge said the PREPARE results will further changed the way in which he discusses the treatment options with adjuvant patients.

"In the future, I would tell the patients that both ESAs and blood transfusion are available, but I would be more likely to recommend the blood transfusion," he said. "There are patients who absolutely, positively do not want blood transfusions. Many of them are concerned about the risk of infection. This is a significant enough counter-risk that it might push a fair number of patients in the direction of blood transfusion."

ODAC member Mortimer said that in her practice, very few women who receive adjuvant chemotherapy become symptomatic of anemia. "Fortunately, it's not that big a problem," she said. "In the adjuvant setting, you are usually done with treatment and then they recover their count. It's rare that somebody is under 10 g/dL."

Waiting for symptoms of anemia is a reasonable strategy, because ESAs haven't been demonstrated to be effective as a treatment of the symptoms of anemia, Mortimer said. "Since in this setting there is no definite correlation between fatigue and hemoglobin levels in that range, there is no clear evidence that there is a difference between being 10, 10.5 and 11 g/dL and being fatigued, it's hard to want to treat people unless they are symptomatic of anemia," she said.

Daniel Hayes, clinical director of the Breast Oncology Program at University of Michigan Comprehensive Cancer Center, said the interim results contained in Amgen's press release will not influence his practice. However, Hayes said that his reluctance to use ESAs in the adjuvant setting leaves little room for change. By waiting for the patient to exhibit symptoms of anemia, Hayes is able to eliminate much of ESA use.

"If I have a relatively young and healthy woman, and her hemoglobin is 9 g/dL, and she is very mildly symptomatic, I just don't do anything, because it will drift back up once we finish the chemotherapy, and they usually don't get to that level until several courses of chemotherapy," he said. "For the most part, these are relatively healthy people who can tolerate mild anemia, and the chemotherapy is short-lived," Hayes said. "But if I have a 75-year-old woman who is profoundly fatigued and her hemoglobin is 9, then I try to get it back up above 10 g/dL one way or the other, either by transfusing or ESAs."

When patients become sufficiently anemic to require treatment, about half of them get blood transfusions, he said.

After the BEST trial, Hayes changed the way he writes and monitors standing orders for adjuvant chemotherapy. "If my patient gets an ESA in the adjuvant setting, it's because I said so," he said. "That's my personal practice."

Both Sledge and Hayes said they continue to give ESAs to patients with metastatic disease.

"The reasons are—one—you are usually giving much longer-term chemotherapy, and–two—they are more likely to experience fatigue," Hayes said. "In the metastatic setting, if you are really anemic, these drugs are quite effective, and my patients prefer getting these drugs to getting transfusion, if nothing else, just for the convenience. For a patient who has a limited lifespan, spending all day getting typed and cross-matched, and then it takes six to eight hours to get two units in. That's a whole day of their life that's down the drain. Whereas they get an ESA in ten minutes, and they are out."

In the metastatic setting, too, Hayes and Sledge wait for patients to become symptomatic. "What I don't do is keep an asymptomatic patient above some certain number just to keep it up," Hayes said. "And that's what I believe the company would like people to do, at least that's the marketing I've seen."

Mortimer said she has been reluctant to use ESAs in the metastatic setting, too. "Usually I transfuse them once, and if they continue to be anemic, then I would consider using ESAs according to new guidelines," she said.

If ESAs indeed have the biological effect of promoting tumor, metastatic disease, where the tumor burden is usually high, would be "the worst place to expect a problem," Ozer said. "Plus, usually in the

metastatic setting you have additional problems of potential clotting, thromboembolic events, perhaps more advanced disease leading to cardiac issues. I would rank metastatic disease as the most vulnerable to secondary effects, if there are indeed secondary effects. Neo-adjuvant would be second, and adjuvant least."

PREPARE is an open-label, randomized, multicenter phase III study of Aranesp in 733 neo-adjuvant breast cancer patients receiving dose-dense, dose-intense preoperative chemotherapy compared to a standard preoperative chemotherapy regimen. The study enrolled Her-2-negative patients. Her-2-positive patients were enrolled in a trial called TECHNO (Taxol-Epirubicin-Cyclophosphamide-Neo-adjuvant.)

PREPARE, begun in 2002, was developed, conducted and analyzed by the German Gynecological Oncology Study Group and the German Breast Group. It evaluated the effects of preoperative chemotherapy using a sequential dose-dense and dose-intensified regimen of epirubicin, paclitaxel, and CMF, compared to preoperative sequential administration of epirubicin and cyclophosphamide followed by paclitaxel in patients with breast cancer, with respect to event-free and overall survival, with or without Aranesp to prevent anemia and to potentially augment the therapeutic effects of the chemotherapy regimens.

This study assessed both an experimental use of the drug to prevent anemia and an off-label regimen.

The pre-specified interim results relate to the study period when chemotherapy and Aranesp were administered, and specifically address the tumor response to chemotherapy at the time of surgery. In this analysis, there was no significant difference between the Aranesp and control groups.

Untch said he expected to have the interim data a year ago, but analysis was delayed by a dispute with another sponsor.

In the PREPARE study, patients were randomized to two different chemotherapy regimens and were then randomized to receive either no treatment or Aranesp (at a dose of 4.5 ug/kg every two weeks) to prevent anemia by maintaining hemoglobin concentrations between 12.5g/dL and 13 g/dL, with dose withholding at levels greater than or equal to 13 g/dL. Patients in both groups entered the study with a mean hemoglobin level of 13.6 g/dL.

In the study, Aranesp-treated patients maintained mean hemoglobin levels of 13.6 g/dL by the end of chemotherapy whereas subjects in the control group decreased to 12.6g/dL.

The second study, GOG-191, was initiated in 2001 to evaluate 109 advanced cervical cancer patients undergoing chemoradiotherapy and terminated in 2003 amid concern about thromboembolic events in patients who received Procrit.

The study was designed to evaluate the efficacy of maintaining hemoglobin levels above 12 grams per deciliter of blood (g/dL) with Epoetin alfa in subjects with. The updated analysis, expected to be published in the journal Gynecologic Oncology, found a statistically non-significant trend toward decreased progression-free and overall survival in the patients treated with Epoetin alfa.

According to an abstract posted online, the study closed prematurely, with less than 25% of the planned accrual, due to potential concerns for thromboembolic event) with R-HUEPO. Median follow-up was 37 months (range 9.8–50.4 months). PFS and OS at 3 years were 66% and 74% for CT/RT and 58% and 60% for CT/RT + R-HUEPO, respectively. TE occurred in 4/52 receiving CT/RT and 11/57 with CT/RT + R-HUEPO, not all considered treatment related.

The abstract is posted at http://dx.doi.org/10.1016/j.ygyno.2007.10.011

According to J&J, "the updated analysis provides further evidence supporting the recent ESA class label change to utilize the lowest dose needed to avoid transfusions and not to exceed an upper hemoglobin safety limit of 12 g/dL.

"The safety and effectiveness of Epoetin alfa in its approved uses has been established in well-controlled studies and substantiated clinically over the past 20 years in more than four million patients worldwide for approved indications," the company said.

Amgen recently announced the addition of six new proposed clinical trials to address the safety of ESAs in specific tumor types when used to treat anemia in cancer patients on chemotherapy. The plan is awaiting a nod from FDA. Also, the company said it intends to evaluate the effect of hemoglobin targets on the risk/benefit profile of ESAs.

ODAC Rejects Avastin For Recurrent Breast Cancer

The FDA Oncologic Drugs Advisory Committee Dec. 5 voted 5-4 against approval of Avastin (bevacizumab), in combination with paclitaxel chemotherapy, for the treatment of patients who have not received chemotherapy for locally recurrent or metastatic HER2-negative breast cancer.

Story in next week's issue of The Cancer Letter.

FDA News:

Waxman To Investigate FDA Plans For Reprint Distribution

FDA plans to allow pharmaceutical and medical device companies to send physicians studies on off-label uses of medications, contrary to a longstanding rule prohibiting companies from marketing their products for such uses.

Under the proposal, companies could send physicians unabridged reprints of studies on off-label uses of medications published in peer-reviewed journals, provided that they are not "significantly influenced" by the companies or individuals with financial ties to them. Companies wouldn't be allowed to send promotional materials with the studies.

The proposal drew criticism from Rep. Henry Waxman (D-Calif.), chairman of the House Committee on Oversight and Government Reform. In a letter to FDA Commissioner Andrew von Eschenbach, Waxman said that the proposal "would open the door to abusive marketing practices that will jeopardize safety, undermine public health and lead to an increase in unapproved uses of powerful drugs" and would make companies less likely to apply for FDA approval for expanded uses of drugs.

Waxman asked von Eschenbach to suspend the proposal and cooperate with a committee investigation. Waxman's letter and the draft guidance is available at http://oversight.house.gov/story.asp?ID=1641.

Science Board Calls For Increased FDA Budget

FDA's regulatory systems are at risk due to insufficient resources and higher demands on the agency, a subcommittee of the agency's Science Board said a report released Dec. 3.

The imbalance between stagnant resources and increasing demands "is imposing a significant risk to the integrity of the food, drug, cosmetic and device regulatory system, and hence the safety of the public," the report said.

"Over the last decade, complex scientific advances, globalization and challenging new safety issues have combined to multiply the responsibilities of the FDA. As this new report makes clear: our expectations cannot exceed the resources we give FDA to accomplish its mission. In this regard, more is definitely better," said Mark McClellan, former FDA commissioner and chairman of the new Reagan-Udall Foundation designed to enhance FDA's readiness for future scientific challenges.

The result of a year-long review by a panel of experts, the 300-page report concludes that the state of FDA's scientific and regulatory programs could not be separated from the lack of resources available to support the agency's scientific base, hire and train a broadly-capable scientific workforce, and build a sophisticated and modern information technology infrastructure.

"FDA can't improve its science, prepare for the future, or protect American consumers without significant additional resources," said Donald Kennedy, former FDA commissioner and editor-in-chief of Science. "Congress is negotiating FDA's FY 2008 (current year) budget right now and can start to fix this critical problem."

The report is available at http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_00_index.html.

In the Cancer Centers:

Snyderman Receives Award For Targeted Therapies

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Department of Medicine, University of Illinois at Chicago Cancer Center. Kruh had been senior member of the Department of Medical Oncology and acting chairman of the Department of Pharmacology at Fox Chase Cancer Center. He joined Fox Chase in 1991 after completing a fellowship in the NCI Laboratory of Cellular and Molecular Biology. Kruh, known for plasma membrane drug transporters research, serves as chairman of the NIH Drug Discovery and Molecular Pharmacology Study Section. . . . **RALPH SNYDERMAN**, Chancellor Emeritus, Duke University, and founder and chairman of Proventys Inc., received the 2007 Leadership in Personalized Medicine Award from the Personalized Medicine Coalition for advancing predictive and targeted therapies on a national scale. The annual award recognizes the contributions of a visionary individual whose actions in science, business, or policy have advanced the frontier of personalized medicine. Under Snyderman's leadership as senior vice president of medical research and development at Genentech, the monoclonal antibody Herceptin was put into preclinical development. As chancellor of health affairs at Duke from 1989 to 2004, Snyderman implement Duke Prospective Health, a comprehensive healthcare approach based on predictive health planning. . . . **DOUGLAS FRAKER**, vice chairman for clinical affairs and chief, Division of Endocrine and Oncologic

Surgery in the Department of Surgery at the University of Pennsylvania School of Medicine, was named deputy director, clinical services and programs, at the Abramson Cancer Center of the University of Pennsylvania. In the newly created position, Fraker serves as the senior advisor to the center director and is the health system senior leader for clinical services. "Fraker will provide leadership on strengthening integrated clinical program initiatives to include tumor registry and quality assurance initiatives on cancer," said **Craig Thompson**, director of the Abramson Cancer Center. Prior to joining the cancer center, Fraker was a senior investigator and head of endocrine surgery at NIH. His research includes regional perfusion for melanoma and soft tissue sarcomas of the extremities and metastatic tumors of the liver. . . . **JEFFERSON MEDICAL COLLEGE** named two faculty members to leadership positions at Kimmel Cancer Center. **Erik Knudsen**, professor of cancer biology, was appointed deputy director of research. He succeeds **Renato Baserga**, professor of cancer biology. **Neal Flomenberg**, interim chairman and professor of medical oncology, was named deputy director of clinical science. He succeeds **Walter Curran Jr**.

NIH News:

NCI's Johnson To Direct Communications, Education

LENORA JOHNSON was named director of the NCI Office of Communications and Education, NCI Director John Niederhuber said. Earlier this year, the Office of Communications and the Office of Education and Special Initiatives (OESI) were merged to form the OCE. Johnson has served as acting OCE director and previously was the OESI director. She joined NCI in 2002. "Working closely with senior NCI leadership, Lenora and her staff have done an incredible job of shepherding this new office through a significant reorganization—an action that should have profound benefits for NCI and our key stakeholders," Niederhuber said. . . . **DAVID ABRAMS**, director of the NIH Office of Behavioral and Social Sciences Research, will receive the 2008 Joseph W. Cullen Memorial Award from the American Society for Preventive Oncology. The award recognizes distinguished achievement in national tobacco control efforts. Abrams, a clinical psychologist specializing in health psychology, behavioral and preventive medicine, was selected by the ASPO Tobacco Special Interest Group for his contributions to tobacco control research. Abrams will receive the award March 17 at a ceremony in Bethesda where he will deliver the 2008 Joseph W. Cullen Memorial Award Lecture. . . . **NATIONAL LIBRARY** of Medicine, in collaboration with Stanford University Archives, is making available the papers of biochemist **Arthur Kornberg** on its Library Profiles in Science Web site: http://profiles.nlm.nih.gov. Kornberg, who died Oct. 26, received the 1959 Nobel Prize for his synthesis of DNA. He began his career in the 1940s working in the Nutrition Laboratory at NIH where he studied vitamin deficiency disease. His son Roger won the 2006 Nobel Prize in Chemistry.

Funding Opportunities:

PA-08-030: Exfoliated Cells, Bioactive Food Components, and Cancer. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-030.html. Inquiries: Cindy Davis, 301-594-9692; davisci@mail.nih.gov.

PA-08-031: Exfoliated Cells, Bioactive Food Components, and Cancer. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-031.html

PA-08-032: Molecular Approaches to Diet and Pancreatic Cancer Prevention. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-032.html. Inquiries: Sharon Ross, 301-594-7547; rosssha@mail.nih.gov.

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, and Richard Hartmann, 301-496-8620, jm486p@nih.gov, rh75f@nih.gov.

RFP S08-060: Monoclonal Antibody Generation. Response due date: Dec. 17. Full text: http://www.fbodaily.com/archive/2007/11-November/21-Nov-2007/FBO-01454678.htm. Inquiries: Melissa Borucki, 301/228-4041, mborucki@ncifcrf.gov.

RFA-RM-08-003: Pilot-Scale Libraries for High-Throughput Screening. P14. Letters of Intent Receipt Date: Dec. 12. Application Receipt Date: Jan. 15. Full text: http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-003.html. Inquiries: John Schwab, 301-594-5560; schwabj@nigms.nih.gov.

RFA-RM-08-012: Human Microbiome Demonstration Projects. UH2/UH3. Letters of Intent Receipt Date: April 22. Application Receipt Date: May 22. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-012.html. Inquiries: Jane Peterson, 301-496-7531; hmprfainformation@mail.nih.gov.

RFP S08-062: Radiopharmaceutical Development and Production. Response Due date: Dec. 20. Full text: http://www.fbodaily.com/archive/2007/12-December/01-Dec-2007/FBO-01459926.htm. Inquiries: Shannon Jackson, 301-228-4022; sjackson@mail.ncifcrf.gov.

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