THE CANCER LETTER

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FDA Orders More Changes In ESA Label, Agents Not Indicated In Curative Setting

By Kirsten Boyd Goldberg and Paul Goldberg

FDA on July 30 ordered Amgen Inc. to change the wording of its label for Aranesp in a way that is likely to further restrict the use of the drug in treating cancer.

In ordering the drug sponsor to make the label changes, the agency invoked for the first time an authority provided in 2007. Previously, FDA could only negotiate label changes with sponsors.

The agency also took the unusual step of publicly posting its Complete Response letter to Amgen online: http://www.fda.gov/cder/drug/infopage/RHE/default.htm.

The new label adds the following statement to the boxed warning:

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In NEJM Letter, Henschke Acknowledges Error In 2006 I-ELCAP Paper; Critics Call For Audit

By Paul Goldberg

In a letter to the editor of the New England Journal of Medicine, the controversial researcher Claudia Henschke acknowledged that one of the central findings in her single-arm trial was incorrect.

The letter—which is technically not a correction—alters the original claim that the eight people who died after declining follow-up treatment after an abnormal CT result had died of lung cancer.

Now, Henschke claims that three—not eight—people had died after foregoing further care.

"I just don't know what the hell happened with this study," said Bruce Chabner, clinical director of the Massachusetts General Hospital MGH Cancer Center and editor of The Oncologist, one of the journals that published corrections to Henschke's studies. "The water has become increasingly murky, and God knows what's at the bottom of this. Unless the study is audited, it's not believable."

Henschke has been widely published in the medical literature, and so far top general medical journals, including NEJM, the Journal of the American Medical Association, and The Lancet, have published corrections to her work. However, these corrections stemmed from undeclared conflicts of interest and acceptance of funds from a tobacco company.

Now, the letter to the editor touches on the substance of Henschke's claim that adherence to a screening protocol developed by her research group,

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The Cancer Letter On Publication Break

The Cancer Letter will not be published over the next three weeks while the staff takes a publication break. The next issue will be published on Sept. 5.

New Label More Consistent With CMS Coverage Of ESAs

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"Aranesp is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure."

Also, the label will state that treatment with Aranesp should not begin until a patient's hemoglobin drops to 10 grams per deciliter (g/dl) of blood. Other statements in the label will be removed that implied that the treatment could be given until hemoglobin rose to 12 g/dl.

"This was the first time we invoked the statute to order a sponsor to make label changes," Richard Pazdur, director of the FDA Office of Oncology Drug Products, said in an interview.

FDA and Amgen had been in discussions over the label since the meeting last March of the Oncologic Drugs Advisory Committee. The company didn't agree with FDA on two statements.

"The major change is that ESAs are not indicated in patients receiving chemotherapy when the anticipated outcome is cure," Pazdur said. "We heard comments that some people may need greater clarity on this concept. Most medical oncologists have a clear understanding of when they are treating for cure versus palliation. If there is a question or uncertainty in people's minds, then they should treat conservatively and not use the drug.

"The other issue is, the therapy should not be initiated at hemoglobin greater than or equal to 10," Pazdur said. "This points out a fact that most medical oncologists will transfuse patients below a hemoglobin of 8 unless very specific circumstances intervene. This is clearly in keeping with the CMS coverage decisions.

"Also, we have removed all references to 12 grams of hemoglobin from the label," Pazdur said. "There was a degree of confusion whether or not a hemoglobin between 10 and 12 was safe. The reality is that we simply do not have confirming data. We believe the lowest dose should be used to avoid transfusion. This generally is in the range of 9 to 10 grams of hemoglobin."

FDA officials communicated with CMS since March, but made no attempt to coordinate the changes, Pazdur said. "We have always stated that our label was consistent with the CMS National Coverage Decision," he said. "These changes provide greater clarity."

While ODAC voted to recommend against use of ESAs in breast cancer and head and neck cancer, FDA chose not to put specific wording about those cancers on the label. "We had considerable discussions within the agency about that," Pazdur said. "This was not a unanimous vote at ODAC. These were tumors that were studied and do indicate potential adverse tumor outcomes. However, we felt that we would give the false impression that these were the only tumors associated with adverse outcomes. This simply is unknown."

Pazdur said the label wording "neither prohibits nor prevents a health care provider from prescribing the drug for patients with curative intent, or with different dosing regimens that are not in the label.

"This would fall under the rubric of practice of medicine or off-label use," Pazdur said. "When we say the drug is not indicated, that is not the same thing as a contra-indication. A contra-indication is where risk clearly outweighs benefit. When we are saying a drug is not indicated, we are stating a favorable risk-benefit relationship has not been demonstrated."

FDA posted the Complete Response letter to Amgen online as "an attempt to bring transparency to the review of this labeling," Pazdur said. "This was [the result of] discussion within the FDA, not only the Office of Oncology Drug Products, but also the Office of New Drugs and the Office of Chief Counsel. I can't speak for agency policy that this release sets any precedent about any other applications."

Amgen must file the label changes with the agency by Aug. 14.

Failure to respond to the order would subject the company to monetary fines and other enforcement actions available to the agency, including seizure of the product.

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FDA's "Change Order" To Amgen

The FDA "Complete Response and Safety Labeling Change Order," signed by Pazdur, was sent to Lisa Shamon-Taylor, senior manager for regulatory affairs at Amgen. Following is an excerpt of the text of the letter:

This letter is in regard to the above referenced supplement to your biologics license application, dated May 22, 2008, received May 23, 2008, submitted under section 351 of the Public Health Service Act for darbepoetin alfa (Aranesp).

On April 22, 2008, we sent a letter invoking our authority under section 505(o)(4) of the Federal Food, Drug and Cosmetic Act (FDCA) to require safety related label changes to the labeling of darbepoetin alfa (Aranesp) to address the risk of increased mortality and/or poorer tumor outcomes when erythropoeisis stimulating agents (ESAs) are given to patients receiving treatment for head and neck cancer, breast cancer, non-small cell lung cancer, or cervical cancer and in anemic cancer patients receiving no active anti-cancer therapy. The decision to require safety labeling changes was based on all available relevant information, including the recommendation of the Oncologic Drugs Advisory Committee that considered new safety information developed after Aranesp was approved.

You were directed to submit a prior-approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On May 22, 2008, you submitted the prior-approval supplement containing your proposed safety related labeling changes. We promptly reviewed the prior approval supplement that included numerous versions of your labeling (e.g., 3 versions of the "patient instructions for use" and 106 different types of carton and vial labels) associated with the various formulations and presentations for Aranesp and discussed the proposed changes with you on June 19, 2008.

[Several lines of text are blacked out.]

In a letter dated June 27, 2008, we informed you that we had granted you an extension of the original 30-day discussion period. We determined that an extension was warranted to allow us to reach agreement with you on the content of the labeling. We indicated that all labeling discussions must be completed and your final proposal for Aranesp labeling must be received by FDA by noon EDST on July 15, 2008, as an amendment to this supplement. We received your submission in response to this letter on July 15, 2008. Please refer to the correspondence of these dates for additional information.

We have completed the review of your supplement. Our review finds that we have reached agreement on your proposed changes to the Medication Guide, Patient Instructions for Use, and Package Insert except with regard to two issues described in more detail below. We cannot grant final approval because your proposed labeling changes do not adequately address the new safety information regarding the risk of increased mortality and/or poorer tumor outcomes when ESAs are given to patients receiving treatment for certain types of cancer.

Under the authority of section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in Attachment A. A supplement containing all of the changes to the labeling of the above-named product that are identified in Attachment A must be received by FDA by August 14, 2008. This attachment includes all changes previously proposed in your supplement STN BL 103951/5189 on which we have reached agreement and the changes identified below.

1. In the Boxed Warnings and Indications and Usage sections, replace the statement, "When the anticipated outcome of myelosuppressive chemotherapy is cure, Aranesp® is only indicated for treatment of anemia when red blood cell transfusion is not a treatment option" with "Aranesp® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure."

2. Remove the following qualifying phrases (in italics) from the Dosage and Administration: Cancer Patients Receiving Chemotherapy subsection:

Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL, *except where the patient is unable to tolerate this degree of anemia due to co-morbid conditions.*

Withhold Dose if: Hemoglobin exceeds a level needed to avoid transfusion *or exceeds 12 g/dL*.

We have determined that the foregoing changes are necessary for the following reasons:

Your proposed wording in item 1 above is misleading because it suggests that you have been granted an indication for treatment of anemia in patients receiving myelosuppressive chemotherapy for cancers in which cure is anticipated. Clinical studies supporting the approval of Aranesp were conducted in patients with metastatic disease without the potential for cure. You have not submitted data establishing a favorable risk:

benefit ratio in patients receiving myelosuppressive chemotherapy for cancers in which cure is anticipated. The proposed language is also unclear in that the clinical setting where "red blood cell transfusion is not a treatment option" is not a commonly understood and accepted concept used in the practice of transfusion medicine. In discussions with an external consultant expert to the FDA, neither FDA nor the expert could identify a clinical setting in which RBC transfusions is not a treatment option. Aranesp is not indicated for the acute treatment of anemia and two to six weeks are needed to achieve the pharmacologic effect of Aranesp. This period of time would be sufficient to identify and administer RBC transfusions if needed. Further, the language ordered by FDA does not prevent or prohibit healthcare providers from prescribing Aranesp in the setting where the anticipated outcome is cure under the practice of medicine.

With regard to item 2 above, your proposed inclusion of the qualifying language to the instructions in the Dosage and Administration section is unacceptable because it undermines other components of the dosing directions which instruct healthcare providers to maintain the lowest hemoglobin necessary to avoid RBC transfusions. You have not identified co-morbid conditions in which maintenance of hemoglobin levels of 10.0-12.0 g/dL results in improved survival or decreased serious morbidity. Data from randomized clinical trials indicate that maintaining higher hemoglobin levels in certain patients does not improve survival and may be harmful. For example, randomized, controlled trials of adult and pediatric patients in intensive care units have not shown a benefit to maintaining higher hemoglobin levels (e.g., 10.0 -12.0 g/dL) as compared to lower levels (e.g., 7.0 – 9.0 g/dL). Adults randomized to the lower transfusion trigger (7.0 vs. 10.0 g/dL) group experienced numerically lower 30-day mortality (Hebert, PC; Wells, G; Blaichman, MA; et al. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. N Engl J Med 1999; 340: 409-417). In the randomized trial conducted in patients with active cardiovascular disease and chronic renal failure, a dosing strategy seeking to maintain higher hemoglobin levels resulted in inferior survival compared with a more conservative approach (Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998; 339:584-590). You have not provided evidence from studies in patients with specified co-morbid conditions, who are also receiving myelosuppressive therapy, that demonstrate that the benefits outweigh the risks for an alternate treatment strategy in which Aranesp is initiated at a hemoglobin level of 10 g/dL or higher and maintained at a higher hemoglobin level above that needed to avoid transfusions. The absence of these qualifying statements does not prohibit or prevent a healthcare provider from prescribing an alternate dosing regimen under the practice of medicine.

I-ELCAP Controversy:

I-ELCAP Misclassified Five Of Eight Deaths In Study

(Continued from page 1)

the International Early Lung Cancer Action Program, could make lung cancer mostly a curable disease.

In a development that may expose the I-ELCAP data to further scrutiny, the American Cancer Society said it would hold a workshop to examine the prospect of pooling all lung cancer screening studies. The proposal to combine the data from randomized trials with the I-ELCAP data originated with Henschke and her supporters.

The characteristics of the eight people who died after declining care puzzled skeptics since Oct. 26, 2006, when the claim appeared in the I-ELCAP paper in NEJM. The controversial paper stated that "all eight untreated patients died within five years of diagnosis," but didn't cite the cause of these patients' death (The Cancer Letter, Nov. 3, 2006).

While the eight patients—called the Henschke Eight by the skeptics—are far from a substitute for a control group, their deaths were cited as an argument that the early disease found via the I-ELCAP protocol was clinically relevant. Altogether, the study screened 31,567 current and former smokers.

The cause of death of the Henschke Eight appeared in a response to letters to the editor published in the Feb. 15, 2007, issue of NEJM. "All eight patients with untreated stage I disease died of lung cancer within 5 years after screening," Henschke and a colleague wrote. Thus, technically, the cause of death was not part of a peer-reviewed article.

Subsequently, the number of subjects who refused treatment increased, reaching 13, as noted in the January edition of Chabner's journal, The Oncologist. That article doesn't explain when additional subjects were enrolled or how their cause of death was determined.

In the letter to the editor published online by NEJM on July 30, Henschke acknowledged that of the eight patients, "only three had a pathological diagnosis of

stage I lung cancer."

"Another four had stage I disease confirmed on CT, but further workup was delayed despite repeated promptings, and pathological diagnosis was made only after the cancer had progressed to stage IV," she wrote. "The remaining patient had a solitary nodule on baseline CT that grew at a rate consistent with primary lung cancer, refused biopsy and treatment, and died of lung cancer 6 months after the last CT showing lung cancer.

"Thus, all eight patients died from lung cancer within 5 years after their actual or potential diagnosis during stage I," she wrote. "Since, however, pathological diagnosis of lung cancer was required by the [I-ELCAP] investigators, I should have classified four of the eight patients as having stage IV lung cancer and the remaining patient who had not received a pathological diagnosis during stage I as having an interim diagnosis. The remaining 483 patients received an antemortem pathological diagnosis of their lung cancer. Thus, the correct number of patients who were untreated and had a diagnosis of stage I lung cancer is 3, not 8, and the total number of patients who had clinical stage I lung cancer is 407, not 412."

The letter also claimed that one of the 38 I-ELCAP sites had violated the trial's enrollment criteria. However, Henschke wrote that the results remain basically unchanged.

Peter Bach, a pulmonologist and outcomes researcher at Memorial Sloan-Kettering Cancer Center, said Henschke's letter essentially invalidates the only comparator provided in the I-ELCAP study were invalid.

"The conclusions of the I-ELCAP study were based entirely on a comparison between the outcome of treated and untreated subjects with screen-detected stage I lung cancer," Bach said. "The authors originally claimed that the patients with screen-detected stage I cancer who were treated had great survival, while those with stage I cancer who were untreated, and thus the comparison group, died rapidly (all within five years)."

Bach is the author of a JAMA paper showing that CT screening of current and former smokers may lead to overdiagnosis and, therefore, harm.

"Their argument is essentially that screening may be beneficial because the outcomes of people with screen-detected cancer is markedly better when they are treated than when they are not treated," Bach said. "This letter, which should probably be a correction, basically retracts the data for the comparison group, in that the PI reports that despite the original paper, and the multiple follow-up publications from the same investigators, there were never eight untreated patients.

"There were only three untreated patients. The other five had metastatic disease at diagnosis (four patients) or were diagnosed post-mortem (one patient) and clearly should not have been included as subjects with stage I disease. To be frank, I always thought that the study was underpowered for its conclusions.

"For instance, there was only one person in follow-up at 10 years, yet the investigators emphasized the 10-year survival, rather than some earlier time point that was better estimated. I also thought that their comparator was too small when it had only eight patients in it. Now that we know that five of the patients didn't belong in it at all, I think the remaining comparison group made up of three whole subjects is entirely meaningless."

FDA News:

FDA Caps Advisors' Holdings To $50,000 In Firms Affected By Committee Meetings

FDA is instituting a cap of $50,000 as the maximum personal financial interest an expert serving on an agency advisory committee may have in all companies that may be affected by a particular meeting.

In final guidances issued Aug. 4, the agency also made changes in voting procedures and in the processes for disclosing information pertaining both to advisory committee members and to specific matters considered at advisory committee meetings.

Most of the changes will go into effect immediately, and all are expected to be fully implemented within 120 days. The documents are posted at http://www.fda.gov/oc/advisory/.

Two of the guidance documents address FDA's processes for evaluating and disclosing information about potential conflicts of interest and FDA waivers allowing participation in advisory committee meetings. Prior to each meeting, advisory committee members are screened by FDA staff to determine whether they have a potential financial conflict of interest, such as grants, stock holdings and contracts with a company that would be affected by the committee's recommendations.

If an advisor's personal financial interest is greater than $50,000, he or she will not be allowed to participate in that meeting. If less than $50,000, FDA officials may, in certain situations, grant a waiver, but will do so only if they determine that there is an essential need for the advisor's particular expertise. Waivers, which include a description of the advisor's personal financial interest

and why the need for the expertise was essential, will be posted on the FDA's web site in advance of the meeting.

Another change addresses the public availability of briefing materials, the background information provided to advisory committee members in advance of a meeting. FDA intends to post briefing materials given to advisory committee members prior to a meeting on the FDA's web site at least 48 hours before the meeting is scheduled to occur. The guidance document provides details on preparing and submitting documents to FDA for inclusion in the briefing materials, and also recommends a timetable that sponsors should follow when submitting such documents.

The agency also issued recommendations addressing the way that advisory committees will vote on questions, so as to avoid the perception of any manipulation of votes. It is recommended that advisory committees use a process of simultaneous voting, in which all members vote at once. Previously, advisory committees sometimes voted sequentially, with the committee chair calling on each member individually and asking them to announce their vote aloud. Simultaneous voting avoids "voting momentum" in which some voters may be influenced, even subconsciously, by the votes of those who precede them. The agency also recommends that the results of votes be announced immediately in the meeting, and FDA intends to post on the FDA website a list indicating how each member voted. Any posted list will be part of the permanent record of the meeting.

FDA also proposed new criteria to clarify when the agency should refer a matter to an advisory committee. In some instances FDA is required by law to refer a matter to an advisory committee. In other instances, FDA would consider these new criteria when deciding whether to refer a matter to an advisory committee. The draft guidance being published for public comment is designed to make FDA's advisory committee process more predictable and transparent.

* * *

FDA has begun to offer a two-year fellowship program aimed at attracting scientists, engineers, and health professionals to the agency, the FDA Commissioner's Fellowship Program.

Applicants are being considered for the first entering class of the program, which begins in October. The agency is seeking physicians, microbiologists, chemists, statisticians, pharmacists, biomedical engineers, nutritionists, veterinarians and other science professionals. Further information: http://www.fda.gov/commissionersfellowships/program.html.

NCI News:

NCI Offers Cancer Prevention Fellowship Program

The Cancer Prevention Fellowship Program at NCI is accepting applications for 2009 Fellows from now through Sept. 1.

The program provides training toward an M.P.H. degree at an accredited university during the first year, followed by mentored research with investigators at the NCI. Opportunities for research cut across a wide range of methodologies: basic science laboratory studies, clinical studies, epidemiologic studies, community intervention trials, studies of the biological and social aspects of behavior, policy studies, and research on the ethics of prevention.

The CPFP provides competitive stipends, paid health insurance, reimbursement for moving expenses, and a travel allowance to attend scholarly meetings or training. The typical duration in the CPFP is four years (year 1: master's degree; years 2-4: NCI Summer Curriculum in Cancer Prevention and mentored research).

To be eligible, applicants must possess an M.D., Ph.D., J.D., or other doctoral degree in a related discipline (e.g., epidemiology, biostatistics, ethics, philosophy, or the biomedical, nutritional, public health, social, or behavioral sciences) or must be enrolled in an accredited doctoral degree program and fulfill all degree requirements by June 22, 2009. Applicants must also be U.S. citizens or permanent residents.

For further information: http://cancer.gov/prevention/pob or contact cpfpcoordinator@mail.nih.gov.

Funding Opportunities:

RFA-HG-08-008: Revolutionary Genome Sequencing Technologies-The $1000 Genome. R01. Letters of Intent Receipt Date: Sept. 22. Application Due Date: Oct. 22. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-HG-08-008.html. Inquiries: Jeffery Schloss, 301-496-7531; schlossj@exchange.nih.gov.

RFA-HG-08-009: Revolutionary Genome Sequencing Technologies-The $1000 Genome. R21. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-HG-08-009.html.

RFA-HG-08-010: Revolutionary Genome Sequencing Technologies-The $1000 Genome. SBIR R43/R44. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-HG-08-010.html.

RFA-HG-08-011: Revolutionary Genome Sequencing Technologies-The $1000 Genome. STTR R41/42. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-HG-08-011.html.

PAR-08-212: Methodology and Measurement in the Behavioral and Social Sciences. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-212.html. Inquiries: Bryce Reeve, 301-594-6574; reeveb@mail.nih.gov.

PAR-08-213: Methodology and Measurement in the Behavioral and Social Sciences. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-213.html.

PAR-08-214: Methodology and Measurement in the Behavioral and Social Sciences. R03. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-214.html.

PA-08-220: Investigational Nutrigenetic Studies for Cancer Prevention. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-220.html. Inquiries: Nancy Emenaker, 301-496-0116; emenaken@mail.nih.gov.

PA-08-221: Investigational Nutrigenetic Studies for Cancer Prevention. R21. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-221.html.

PA-08-226: Ruth L. Kirschstein National Research Service Award Institutional Research Training Grants. T32. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-226.html. Inquiries: Lester Gorelic, 301-496-8580; gorelicl@mail.nih.gov.

PA-08-227: Ruth L. Kirschstein National Research Service Award Institutional Research Training Grants. T35. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-08-227.html.

PAR-08-223: Fogarty International Research Collaboration-Behavioral and Social Sciences Research Award. R03. Application Submission/Receipt Date: Sept. 29; Sept. 29, 2009; and Sept. 29, 2010. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-223.html. Inquiries: Michele Bloch, 301-496-8584; blochm@mail.nih.gov.

PAR-08-224: Using Systems Science Methodologies to Protect and Improve Population Health. R21. Letters of Intent Receipt Date: Sept. 16. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-224.html. Inquiries: Stephen Marcus, 301-594-7934; sm311j@nih.gov.

PAR-08-225: Quantitative Imaging for Evaluation of Responses to Cancer Therapies. U01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-225.html. Inquiries: Robert Nordstrom, 301-4496-3428: nordstrr@mail.nih.gov.

RFP N02-CM-91000-16: Cancer Therapy Evaluation Program's Informatics and Computer Support. Full text: http://www.fbodaily.com/archive/2008/07-July/05-Jul-2008/FBO-01607476.htm. Inquiries: Annmarie Keane, 301-435-3814, ak155a@nih.gov.

RFP N02-CM-87021-17: Collection and Taxonomy of Shallow Water Marine Organisms. Full text: http://www.fbodaily.com/archive/2008/08-August/07-Aug-2008/FBO-01631517.htm. Inquiries: Andrea Spinelli, 301-228-4228; as833z@nih.gov.

American Cancer Society

MEN2 Thyroid Cancer Consortium

Research Scholar, Mentored Research Scholar and Postdoctoral Fellows

A Request for Applications

The American Cancer Society announces this **Request for Applications** for the **American Cancer Society MEN2 Thyroid Cancer Consortium.** Up to seven (7) **Research Scholar** and/or **Mentored Research Scholar** grants and up to five (5) **Postdoctoral Fellow** grants will be awarded. The Consortium will be led by a single renowned senior scientist who will be awarded the American Cancer Society MEN2 Thyroid Cancer Professorship and act as leader for the overall program (details at links below). Appropriate areas of investigation include, but are not limited to: understanding consequences of *RET* mutations, molecular events underlying the development of MEN2-related tumors, improved animal models of MEN2, new screening and monitoring tools, new imaging approaches, and new pharmacologic and other strategies to blunt the effects of *RET* mutations.

Individuals applying for a **Research Scholar Grant** must have an independent research or faculty position and be within six years of their first independent research or faculty appointment at the time of application. These grants will be awarded for up to $200,000 a year, direct costs, for 5 years. **Mentored Research Scholar Grants** will be awarded to junior faculty members with a doctoral degree in a clinical or cancer control research discipline (e.g., M.D., and/or Ph.D.) that are within the first four years of a full time faculty appointment or equivalent, and have no more than 4 years of postdoctoral research experience immediately prior to their faculty appointment. The successful applicant is expected to transition into a career as an independent investigator. Awards are for up to five years and for up to $135,000 per year direct costs.

Applicants for **Postdoctoral Fellowships** must have obtained their doctoral degree prior to activation of the fellowship. Awards are for three years with progressive stipends of $40,000, $42,000, and $44,000 per year, plus a $4,000 per year institutional allowance. Individuals who have held a PhD or MD for more than 4 years at the time of application are not eligible. **Deadline**: Complete applications are due by October 15, 2008. Funding will begin July 1, 2009. For information regarding funding policies or to obtain an application, go to https://proposalcentral.altum.com or refer to the ACS website at www.cancer.org/research: select *Funding Opportunities* followed by Index of Grants, scroll down to *Special Initiatives* and select the appropriate RFA for MEN2 Thyroid Cancer. For inquiries, contact Charles Saxe, PhD at (404) 929-6919 (charles.saxe@cancer.org).

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