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Advisors Criticize A Biomarker Study Touted As High Priority For NCI And FDA

By Kirsten Boyd Goldberg

Members of the NCI Clinical Trials Advisory Committee appeared to be unimpressed by a $6 million study that institute officials described as a "paradigm shift" that would lead to development of guidelines for future trials to validate predictive biomarkers for cancer therapy.

The committee members at the July 11 meeting characterized the proposed trial as excessively expensive, too large, and lacking sufficient financial involvement from the companies sponsoring the biomarker tests. Also, the study would be unlikely to produce meaningful clinical benefit for patients, several members said.

However, at the end of the discussion, the group wasn't asked to vote. The presentation was an "informational presentation" only, said James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis.

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Appreciation:

"Quack-Buster" Saul Green Used Science To Debunk Alternative Medicine Claims

By Paul Goldberg

Saul Green, a cancer researcher who devoted the latter part of his career to challenging the claims made by practitioners of alternative medicine, died July 1.

Green was 82 and lived in Manhattan. He succumbed to multiple diseases, said his nephew Howard Ruben. According to friends, these included Parkinson's disease and prostate cancer.

Green was a member of an impromptu group of skeptics who call themselves "quack-busters." In that capacity, he challenged the scientific underpinnings of therapies that included homeopathy, coffee enemas, hydrazine sulfate, antineoplastons, immunoaugmentative therapy, shark cartilage, macrobiotic diets, and anti-oxidants.

"There is a tendency among scientists to behave as though we belong to some kind of fraternity," said Robert Park, a physics professor at the University of Maryland and the author of "Voodoo Science: The Road From Foolishness To Fraud." "We hesitate to come out and say, 'You are wrong.' Saul didn't look for ways to cushion that message. He was impassioned. He just wasn't tolerating bull shit."

People who knew Green well believed that his experiences in World War II strengthened his resolve to reject the ideological, the anti-scientific,

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Trial Would Seek To Validate EGFR FISH For Use Of Tarceva

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In the future, similar trials would be brought to the committee, Doroshow promised.

The phase III study in question would attempt to validate fluorescence in situ hybridization to test for the epidermal growth factor receptor gene and determine whether it is a predictive marker for clinical benefit from the EFGR inhibitor Tarceva (erlotinib), an agent sponsored by Genentech.

The trial would also evaluate the role of EGFR immunohistochemistry and EGFR mutational analysis as predictive markers for erlotinib, as well as the role of RAS mutations as a negative marker for erlotinib.

The study, led by the North Central Cancer Treatment Group, proposes to enroll 1,196 non-small cell lung cancer patients, stratify them according to whether they test positive or negative for EGFR FISH, then randomize each group to either erlotinib or Alimta (pemetrexed), a chemotherapy sponsored by Eli Lilly.

The trial has been described as a high-priority initiative by top NCI and FDA officials. NCCTG submitted an earlier version of the study to NCI around the time when the NCI-FDA Interagency Oncology Task Force was interested in moving forward with a biomarker validation trial. NCI staff presented the idea to the biomarkers working group of the interagency task force.

In March 2006, when John Niederhuber became acting NCI director, he asked Doroshow to develop a biomarker validation trial in NSCLC patients, Doroshow said to The Cancer Letter.

"What I was charged to do was to utilize one of the cooperative group studies under review for the development of a prospective biomarker validation trial, and we thought the NCCTG trial was an appropriate place to start," Doroshow said in an interview. "The idea was the vetted with the cooperative group chairs and the lung committee chairs, and there was a lot of interest in developing a new model for working prospectively with FDA. We are still learning how to do these types of trials. The decision to push ahead was made in spring of 2006. All of that came together last fall, and the commitment was made to go ahead with [the trial] long before the CTAC was in existence."

CTAC was formed last year to provide greater coordination and oversight of the institute's clinical trials program, but NCI has only recently completed the process the committee will use to prioritize trials, Doroshow said. "That's why there wasn't a vote at CTAC, because this was developed prior to that process, and it would have been difficult to go back," he said.

"I was actually very gratified by the discussion, because I think there was high level of engagement by members of the committee, which bodes well for the future of our ability to discuss these expensive studies," Doroshow said. "You had members who hadn't seen this. Were you to discuss this with many folks who helped develop it, you would get a variety of different opinions.

"This trial is a totally new model for NCI to work with FDA to develop these biomarker trials," Doroshow said. "This is really the first-in-class way of doing this. Perhaps the ultimate value of this is that if we are very good stewards of the biospecimens, they could be used for future biomarker studies."

The trial is expected to open this fall, Doroshow said. Patient recruitment is expected to take about four years.

Paradigm Shift

At the committee meeting, Doroshow said that the trial should be "paradigm shifting and should be coordinated with FDA and industry so that any result would have immediate impact on clinical practice, and furthermore, it might be utilized for future studies to develop guidelines for biomarker trials.

The trial has the support of the cooperative group chairmen, the Lung Cancer Intergroup, the Critical Path Institute, patient advocates, FDA, the NCI Cancer

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Therapy Evaluation Program, and "a variety of other lung cancer content experts," Doroshow said at the meeting.

One such expert, David Johnson, deputy director of the Vanderbilt-Ingram Cancer Center and a lung cancer specialist who represented the Eastern Cooperative Oncology Group in the design of the protocol, said the committee members' concerns were valid. "While well-intentioned, I am not sure this initiative is the most pressing research question out there at the moment," Johnson said to The Cancer Letter.

"I think we can all agree that biomarker development is a worthwhile endeavor, but I suspect the aims of the proposed trial could be achieved by being incorporated into other proposed or ongoing trials, including those being sponsored by industry," Johnson said. "There is an approved trial to be conducted within the SPORE program that has many of the same goals. It is to be done in first-line with erlotinib in 'unselected' patients who will have their biospecimens collected and assessed via multiple assays, including FISH, proteomic analysis, gene analysis, etc. Thus, this project is somewhat duplicative, albeit not an identical study.

"The question is, in this era of ever tightening research funds, do we have the luxury of doing two studies that are pretty much asking the same questions?"

Multiple smaller studies have suggested that patients with EGFR mutations appear to derive more benefit from erlotinib than patients with EGFR-negative tumors, said the study's principal investigator, Alex Adjei, senior vice president of clinical research and chairman of the department of medicine at Roswell Park Cancer Institute.

"It is unclear to us, if a patient has one of these markers, will they benefit from therapy?" Adjei said to the committee. "NCCTG came up with the idea of doing a prospective study to try to answer the question. What we set out to do was to validate EGFR FISH as a predictive marker for clinical benefit from EFGR inhibitor erlotinib."

The study is designed to have the 90 percent power to detect 50 percent improvement in progression-free survival favoring erlotinib in FISH-positive patients; 90 percent power to detect a 30 percent improvement in PFS favoring pemetrexed in FISH-negative patients; and greater than 90 percent power to detect interaction.

For overall survival with one more year follow-up, the study would have 78 percent power to detect a hazard ratio of 1.42 (42 percent improvement or 11.36 vs. 8 months in overall survival) in the FISH-positive subgroup in favor or erlotinib; and 94 percent power to detect a hazard ratio of 1.33 (33 percent improvement or 8 months vs. 6 months in overall survival) in the FISH-negative subgroup in favor of pemetrexed.

Tumor specimens will be collected by the Southwest Oncology Group and University of Colorado Lung Cancer SPORE. Additional per-case reimbursement of $2,104 has been proposed. Eli Lilly and Genentech are contributing the therapies, while the diagnostic companies will contribute their tests either in kind or with a price reduction.

Abbott and Vysis make the EGFR FISH test, which is not FDA approved. DAKO PharmDX makes the EFGR IHC test, approved by FDA for EGFR expression in colorectal carcinoma. Genzyme makes the tests for EGFR and RAS mutations, which are not yet FDA approved.

Other than the drugs and test kits, no additional funding is being provided by the companies, said Janet Dancey, of CTEP.

In discussion, the committee members questioned the study's endpoints, selection of patients, its cost, and lack of funding from the companies involved.

"What would you consider a success?" asked committee member Michael Link, chief of pediatric hematology/oncology at Stanford University School of Medicine. "You are comparing two things. The reasons that erlotinib may work or not work in this trial, according to the design, is that chemotherapy may better than you expected. But it doesn't rule out the fact that erlotinib may be very active. It just didn't reduce the hazard ratio as much as you anticipated, which could be for several reasons."

"We are trying to validate using a diagnostic test to determine what treatment our patients should have," NCI's Dancey said. "So a success here is in identifying that having the marker test done and then having the treatment selected based on that test result, that has been demonstrated to be the superior strategy—that is the successful outcome of this trial. We may not show that. We may show that erlotinib works best in all cases, or that chemotherapy works best in all cases, or that we may actually be able to define, based on the marker, a group of patients who benefits from one treatment rather than the other treatment. That goes to the magnitude of the benefit that is being targeted here. There has to be a justification for using the test. So prioritizing treatments based on marker results is a goal of this study."

Committee member James Abbruzzese, chairman of gastrointestinal medical oncology at M.D. Anderson Cancer Center, said he thought the study design was "the

most robust" of the possible designs for understanding the value of EGFR FISH. "But I wondered, given the background you presented and the overall goals to try to identify whether the FISH positivity will predict for activity, which seems to be the primary thing you are interested in, and given the duration and the numbers you are going to have to accrue, I wonder what would be lost by not including the patients that are EGFR FISH-negative, and just doing the randomization with the patients that are EGFR FISH-positive?" he asked. "That would make the study much smaller, but probably doesn't address the prognostic value of the test very well. Maybe that's something that could be compromised in the interests of trying to understand the predictive value of the test."

"This was a topic of great discussion," said Lisa McShane, an NCI statistician. "The choice was between this marker treatment interaction design versus what I call enrichment design. The arguments came down to a couple of points. One is, we already have results from the BR21 trial which suggested that erlotinib relative to placebo might have activity in everyone, so if we went with an enrichment design, we couldn't be guaranteed that those FISH-negative patients might have had some benefit, perhaps smaller. The other issue is that there are many different markers that people are interested in, and if we did an enrichment design, we could only answer the question about those markers in the context of the FISH-positive patients, and we didn't think that was very illuminating."

Committee member Daniel Sargent, director of cancer center statistics at Mayo Clinic, Rochester, who is involved in the proposed study, said the study wouldn't accrue faster by including only FISH-positive patients. "We have to screen everyone anyway to find the FISH-positives, and we would lose an important opportunity to test [FISH-negative samples] later," he said.

Just Wasting Time?

Committee member David Parkinson, senior vice president for oncology research and development at Biogen Idec, said the study should serve as the basis for approval of the FISH test. "Otherwise, we are just wasting time," he said. "I think everybody understands that the therapeutic question is not too interesting, and it will be even less interesting by the time the trial is done.

"As we go forward to design new studies for the future, the issue is, could we not come up with designs that somehow allow us to move the therapeutic field at the same time that we get insight into the diagnostic markers?" Parkinson asked. "Why not take lung cancer patients and then characterize in every way you can possibly currently, by saving specimens, their biology, and then in a fairly orderly way, as much as you can in a national program, begin to explore therapeutics and patients' biological character.

"One way to partly do that in this trial—you mentioned that the heterogeneity of therapies in patients who come off this trial, which they will fairly quickly, is going to be pretty great and the new agents are interesting enough that they may well affect survival," Parkinson said. "So why not forget the survival endpoint, because nobody believes that it is going to be that interesting to anybody, we've moved on. Or, create a series of phase II trials in a formal way to capture the patients who are well-characterized biologically so that we have information on patients after PFS.

"I just think that we sort of already know what the answer to this is, given the data we have seen," Parkinson said. "So shouldn't we be trying to use these kinds of resources—patients, diagnostic companies, interactions, highly trained professionals, some of whom are in this room—to really anticipate how the field is moving? Why not try to use this trial to really set the standard for the next generation of therapeutics and the next generation of diagnostics?"

Adjei said he could have could have completed and published four phase I studies in the time it has taken to develop the proposed validation study. "The hope is that the tissue and blood repository will allow us to test the subsequent questions that come up," he said. "The one unanswered question here is that we don't know whether having FISH-positive is actually a prognostic marker. We have a lot of ideas from prospective studies, without a lot of confidence, and it's dangerous to try to take these ideas and try to use them to treat our patients. At first blush it appears we know the answer, but when you actually go into the data and look at it, not really."

Committee member Joel Tepper, chairman of radiation oncology at University of North Carolina, Chapel Hill, said the cost of the trial could exceed the value of the information it would produce. "In some ways, we know a fair number of the answers to the questions being asked, and we are spending $6 million, or maybe more, to get a little bit of additional information that we know is not going to get a huge therapeutic impact," he said.

"You have powered this to look at, for the FISH-negative patients, a 16-day improvement in median survival," Tepper said. "How big is that? I think there is enough preliminary data to know it's not going to be

a huge impact on survival. There is enough data to set bounds on how much benefit you might get, and even in FISH-positive patients, it is powered to look at a six-week improvement in survival, 42 days.

"When we are talking about the limited resources available in NCI at the present time, how much dollars to we want to spend to answer that type of a question, with that type of benefit?" Tepper said. "I am not sure you can extrapolate it to something else that looks at EGFR from some other vantage point. So, I have concerns from the broader perspective of the $6 million expenditure."

Fred Hirsch, professor of medicine and pathology at University of Colorado Cancer Center, who presented background to the committee about EGFR FISH, said he disagreed with Tepper about the clinical importance of the study. "FISH-positive patients had a hazard ratio of 0.44 in the BR21 study and extended the median survival from six months to 21 months, which I think for this patient category is a significant prolongation of survival," he said. "There is another aspect of it, too, and that is what does FDA require for approving diagnostic tests? We need a prospective trial if we want to move forward to individualized therapy and if we want this test approved."

"I don't think we know the answer," Adjei said. "We forget that these data were prospective data from EGFR inhibitor vs. placebo. We don't know what happens if you put chemo in this group. In a disease that has poor outcomes like lung cancer, you can always argue about the magnitude of benefit when you convert it from a percentage to absolute months or days. If lung cancer docs could feel that they could take some test and improve outcomes by 50 percent, the feeling is that this would be a reasonable trial."

Committee member Peter Adamson, chief of clinical pharmacology and therapeutics at The Children's Hospital of Philadelphia, questioned the benefit of the trial for patients. "For 70 percent of the patients, therapeutic success is going to be 16 days [of improvement in median survival]," he said. "Is that the best question we can ask in 2007? A 16-day improvement?"

"The primary sample size is driven by the FISH-positives, where we want the 50 percent improvement," Sargent said. "The FISH-negatives go on trial anyway. So we are not looking for 16 days in FISH-negatives. We are looking for meaningful benefit of 50 percent in FISH-positives, so I don't think it's fair to focus on the 16 days, because it's a package."

ADAMSON: "There are no more important questions to ask in the FISH-negative group?"

ADJEI: "Yes, that is correct. The fact is that interactions in mutations may come up. The study wasn't powered to specifically answer these questions."

MCSHANE: "Success here will be defined as success in showing the marker is useful for identifying patients who then go on erlotinib. Even in the negative group, if outcome is the same, you still have a success if you identify the positive group who benefit in a clinically meaningful way by getting erlotinib."

SANDRA HORNING, professor of medicine, Stanford Comprehensive Cancer Center: "Given that is the definition of success, and it seems like Abbott/Vysis would have a lot to gain from a positive study, what is the reason for not trying to pair that together to help defray the cost by partnering to them? It just seems obvious to me."

RICHARD PAZDUR, director, FDA Division of Oncology Drug Products: "I would like to underscore that, because I think that points to a problem not only in this trial, but other trials that we see. I would like to make it quite clear that I am speaking as Richard Pazdur, private citizen, rather than FDA employee.

"There is a financial interest that would benefit from this trial being done. This is an example of many other trials we see being done at government expense, that will result in registration trials either supplements or primary registration trials. We, as U.S. taxpayers, are not given any breaks when these drugs get approved and we have to pay for them.

"Let's face it: these drugs are some of the most expensive drugs and cause a great deal of concern about our Medicare budget. So I would like to emphasize that we need to pay attention, when we go into these public-private partnerships, about what will be the eventual costs of these drugs and also what will be the reimbursement issues, especially when the entire development program or a significant portion of it is sponsored by the U.S. taxpayer.

"It's really not fair to pay for the development of the drug substantially and then at the rear end, pay for it with Medicare dollars, at what many people consider exorbitant prices."

TEPPER: "I suspect that virtually all of these patients are going to get both drugs eventually, and how much it is going to affect actual treatment and put patients onto a better treatment they wouldn't get is very much suspect, in this setting. If you didn't treat FISH-negative patients, you would substantially decrease the cost."

DOROSHOW: "We are going to have to go on. I think that this is a wonderful discussion and you are

going to have a chance to do this many times, I hope, and actually have major decision-making input into further trials as we move forward."

KIRBY BLAND, deputy director, University of Alabama at Birmingham Comprehensive Cancer Center: "Pardon me, Jim, do we vote today, or do we defer?"

DOROSHOW: "This presentation was an informational presentation, but you can be assured that going forward there will be vote on any trial of this nature that is presented to this committee."

Appreciation:

Green Criticized NIH Foray Into Alternative Medicine

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and the expedient. A tailor's son from Washington Heights, Green trained in Louisiana and California for the invasion of the Philippines, but ended up in Europe, disembarking in time for the Battle of the Bulge. In the barracks, Green was given the nickname "Stretch," likely because he stood at well over six feet.

In late April 1945, as a mortar man with Company G of the 86th Infantry Division, Stretch Green was accompanying a small group of U.S. tanks that encountered one of the subcamps of the concentration camp Dachau.

"I don't suppose we were even supposed to smash into the place, but we did," recalled Emil Johansen, a machine-gunner who was with Green that day. "We knocked the front gates of the thing down, and as we were knocking the front gate down, the Krauts were going out the back one."

The soldiers knew nothing about the existence of concentration camps and were unprepared for what they saw. "We were pretty young, the grass was pretty green," said Fred Carlson, a fellow mortar man and another of Green's lifelong friends. "We didn't know much of what was going on, and none of us were officers or had any chance to check things out with the higher-ups. We were just dogfaces."

"As soon as we saw what the hell it was, we were not happy," Johansen recalled. "We wanted to get the hell out of there. All we got was a bunch of starving skeletons. Those poor devils were not happy people. They were pretty gaunt, and wearing those stupid prison uniforms."

The tanks stayed outside, and some of the GIs fanned out through the camp. "Saul got on a Jeep and drove around the whole place," said Johansen. "He was taking pictures." Also, Green was able to speak Yiddish with the inmates.

"What we saw was so bad, that most of us were vomiting all over the place," Johansen said.

The outraged GIs shot the Nazis who remained. "The few that we found, they weren't there when we left," Johansen said. After a short time, the tanks received an order to get out immediately, and a second lieutenant showed up to confiscate Green's camera. "We finally ran him off, threatening to shoot him," Johansen said, but Green's film and the camera were taken.

On the way out, the GIs dumped out their rations, leaving them for the inmates.

"Saul had a sense of right and wrong," said Wallace Sampson, a fellow quack-buster and a retired hematologist and oncologist and emeritus clinical professor at Stanford University. "He made it the guiding principle of his life. It was very important for him to be true. He was a true friend. Never double-crossed anybody, never told fibs for any reason at all. He was righteous, and he put it to good use. You could trace it back to the war, or you could just trace it back to the way he was born. Maybe he was genetically built that way."

Green's anger was hard to miss.

"That's Saul: any form of injustice was an outrage to him, beginning from the injustice he saw in the Nazi camps, and moving on to the injustice he saw in medicine," said Shannon Brownlee, formerly a reporter with U.S. News & World Report, who met Green when she was reporting a story about alternative medicine. "There is a continuum: it's okay to do things to people in the name of some 'higher good.'"

Green earned a semester's worth of college credits before going off to basic training. After the war, he got a degree in biology from the City College of New York, and went to the State University of Iowa, where he received a Ph.D. in biochemistry, microbiology, organic chemistry, and immunology.

He was hired by Cornell Medical School in 1954, and by Memorial Sloan-Kettering Cancer Center five years later.

In the 1950s, Green focused on the biologic characteristics of oxidation. "He published a paper showing that EDTA [an agent used in chelation therapy] in the presence of vitamin C was a highly oxidizing material," said Sampson.

Sampson, who teaches a medical school course in scientific examination of claims of alternative healers, said that he uses a 1957 paper by Green and the late Abraham Mazur, of City College, that demonstrates that antioxidants can promote oxidization of tissue. "So far

as I know, it was the first demonstration of a reducing agent acting as an oxidant," Sampson said. "That's where this whole thing about pro-oxidant qualities of ascorbic acid came from."

In the 1960s, Green focused on tumor necrosis factor. He identified TNF in the circulating blood of normal mice as well as demonstrating its presence in normal human blood, which he called normal human globulin, said Harrold Wanebo, professor of surgery at Boston University and Brown University, who worked with Green at Memorial in the late 1970s.

The substance Green discovered could kill tumor cells, Wanebo said. "Saul considered that the cellular death occurring in the tumor cells was a natural self-destruction process, which would now be called apoptosis," he said. "Saul was ahead of his time by 30 years in describing this process."

Colleagues say that Green clashed regularly with Lloyd Old, his supervisor at Memorial, who directed the TNF work. In 1982, Green was denied reappointment, and soon after that became involved in scientific examination of alternative medicine.

At first, Green found work as a scientific director under an NCI grant that sought to create a complete listing and analysis of alternative and nutritional therapies. The project, directed by Grace Powers Monaco, a lawyer and patient advocate, and Beth Barnett, a psychologist and a computer expert, was intended to separate promising therapies from quackery.

Green was the perfect man for the job. Alternative practitioners often borrowed terminology from mainstream immunology, routinely claiming that their therapies boosted the immune system and enabled the body to fight cancer. These claims were often made without understanding of the underlying biology.

After the database was completed, it was taken over by the American Cancer Society, which failed to maintain it. Green's quack-busting continued, albeit without compensation. He became a freelance defender of public health and integrity of science.

Writing for the Journal of the American Medical Association, he critiqued the antioneoplaston therapy by the Houston practitioner Stanislaw Burzynski, the immunoaugmentative therapy by Lawrence Burton, and the Gerson cancer therapy, which included coffee enemas and diet.

"What Saul and a few other people know how to do is how to dig out the basic science and find out just where these people's claims are wrong on a very basic level," Sampson said. "It's not enough just to say that they don't have proof. You have to show that it couldn't possibly be true, because the physics and the chemistry are such that it couldn't possibly work that way. He was a master at this."

The work is thankless. "It doesn't pay anything, nobody is particularly interested in it, but it's worth doing on its own, because it has to be done," Sampson said. "He was lucky to get his two or three papers published in JAMA, but then they stopped, because someone decided that they didn't want any more."

During that period, Green slammed NCI for its attempt to test Burzynski's antineoplastons. He slammed NIH for establishing the Center for Alternative Medicine. He ridiculed Sen. Tom Harkin (D-Iowa), the man who forced NIH to look into alternative medicine, for his claim that he had cured his allergies by swallowing 250 pills of bee pollen.

Also, Green offered scientific guidance to prosecutors and government agencies whenever they sought to impose sanctions on alternative practitioners, and he provided boxes full of documents—as well as jugular-ripping quotes—to reporters he respected. Calling Green when you had less than an hour to spare was a bad idea.

Every time his papers were published or his pronouncements appeared in the press, Green received abusive phone calls and threats.

Green loved threats. "That gave him the resolve to go on," said Monaco.

He wasn't an inviting target for assailants. He worked out, had more combat experience than an average thug, and wore a big leather jacket that made him look armed and dangerous. Overall, he had the appearance and mannerisms that reminded Monaco of the actor Sean Connery.

Monaco knew that there were two sides to Green: the heroic mortar man fighting the forces of evil, and the lonely scientist whose phone didn't ring nearly enough.

Periodically, Green called friends to announce solemnly that he had reached the end of the road. His work was clearly for naught, and since no one cared, he would simply throw in the towel. "The hell with them," he said, referring to humanity.

Some dismissed these calls as cyclical mood fluctuations, but Monaco was more compassionate. "You are too dumb-headed about this," she would say. "You just do not get the fact that what you are doing now is going to live forever. Whether we are here or not, those words live forever. The analysis lives forever, and people in the future are going to be grateful for that. So, stop being such a crybaby and go back to work."

Generously Yiddishized English was Green's language of choice, and whether you were a gentile or a Jew, if Green liked you, he called you *bubee*, a term of endearment. Wanebo, who is part Norwegian and part Irish, was a *bubee*, as was this reporter.

In the Army, Stretch Green "always had something funny to say, something clever to say," said his friend Johansen, a retired geophysicist who lives near New Orleans. As a quack-buster, Green was beyond funny. His humor and his fury became one and the same.

Consider a letter to the editor published in the Nov. 5, 1993, issue of The Cancer Letter. In the opening, Green posed a series of methodological questions about an NIH-funded study of the impact of "intercessory prayer" on health outcomes:

"Did the study section that evaluated that application ask [the investigator] whose God would the prayers be offered to? Would it be Allah? Jehovah? Jesus? Buddha? Who would write the prayers? How would the investigator prevent the controls from praying secretly? Would sinners be included in or excluded from the experimental and control groups? What published evidence indicates this investigation has a rational basis?"

Dispensing with God, Green aimed his proverbial mortar at Harkin, the pollen-popping appropriator who directed NIH to set up what was then the Office of Alternative Medicine:

"Fifteen minutes with a child's encyclopedia turned up some fascinating facts about bee pollen. Pollen collected from bees comes from the hairs on their hindquarters.

"It consists of 40 percent plant carbohydrate, 5 percent plant fat and 5 percent plant protein. The remaining 50 percent is fungus, bacteria, insect body parts and hairs, mites and bee fecal material. Since Sen. Harkin's allergies were cured by this mixture, isn't it the duty of OAM to fund a 'rigorous scientific research project' to identify the component in the mixture that cured Harkin?

"It is entirely conceivable that the active ingredient was the bee fecal material. After all, goat feces are used in Ayurvedic medications (OAM funded this modality with two grants.) Americans who suffer from allergies should demand that Harkin, [then OAM Director Joseph] Jacobs and OAM take immediate steps to find out whether feeding bee shit to the public would be more healthful than the bull shit they are currently dishing out."

Green is survived by a sister, Edith Ruben of Cherry Hill, NJ.

In the Cancer Centers:

M.D. Anderson, AU Beirut Sign Collaboration Agreement

M. D. ANDERSON Cancer Center and American University of Beirut signed a formal agreement to collaborate on their mutual missions for cancer prevention, education, research and patient care in the U.S., the Middle East and globally, said **John Mendelsohn**, president of M. D. Anderson, and **Nadim Cortas**, dean of the AUB Medical Center. The relationship between the institutions developed, in part, from the efforts of AUB alumni who hold leadership positions at M. D. Anderson. They have facilitated a share-and-learn strategy between the institutions through a basic and translational oncologic research fellowship program at M. D. Anderson, which has trained more than 50 junior faculty and fellows from AUBMC and other facilities in Lebanon. At the outset, the collaboration will focus on increasing training and education opportunities for medical residents and fellows in leukemia, radiation oncology, neuro-oncology and infectious diseases. The institutions also will work to implement, at AUBMC, the multidisciplinary research-driven patient care model practiced at M. D. Anderson in leukemia and stem cell transplantation. Special attention will be directed to breast cancer and the health of women in the Middle East, which M. D. Anderson committed to as a member the U.S.-Middle East Partnership for Breast Cancer Awareness and Research. . . . **MICHAEL ZALUTSKY**, professor of radiology and biomedical engineering at Duke Comprehensive Medical Center, received the 2007 Paul C. Aebersold Award for outstanding achievement in basic nuclear medicine science. He was recognized for his work in using molecular targeting in cancer, said **Martin Sandler**, president of the Society of Nuclear Medicine. His areas of contribution also include radionuclide production, radiochemistry and radiation biology.

Funding Opportunities:

RFA-MH-08-040: Methods of Statistical Analysis of DNA Sequence Data for Studies Relating Variation to Disease. R01. Letters of Intent Receipt Date: Aug. 20; Application Receipt Date: Sept. 20. Inquiries: Lisa Brooks, 301-435-5544; lisa.brooks@nih.gov.

RFP S07117: Communications Program for Clinical Proteomics Technology. Response Due Date: July 26. Full text: http://www.fbodaily.com/archive/2007/07-July/13-Jul-2007/FBO-01339173.htm.

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