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Advisors Reject NCI's $89 Million Plan For Proteomics As Too Much, Too Soon

By Kirsten Boyd Goldberg

An advisory committee March 8 rejected an NCI plan to spend $89 million on proteomics research.

The Board of Scientific Advisors in effect determined that the science of proteomics is too tentative to warrant a five-year mega-program and voted 13-9 against approval.

The Institute sought to support the development of technologies and reagents, standards for data collection and analysis, and a biospecimen repository.

After killing the proposal, the BSA, in a 12-10 vote, urged Institute

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Zvi Fuks Of MSKCC Arrested On Charges Of Securities Fraud Related To ImClone Stock

By Paul Goldberg

Federal agents March 9 arrested Zvi Fuks, chairman of the department of radiation oncology at Memorial Sloan-Kettering Cancer Center, charging him with securities fraud and conspiracy to commit securities fraud.

The charges stem from a sale of $5.357 million worth of stock of ImClone Systems Inc. on Dec. 27, 2001, one day before the company received a Refusal to File letter on the monoclonal antibody Erbitux from FDA.

According to the criminal complaint filed in the U.S. District Court for the Southern District of New York, Fuks received the news of the RTF letter from a friend and Waksal's business associate Sabina "Sonia" Ben-Yehuda, who is facing the same charges related to her sale of $73,453 worth of ImClone stock.

Fuks was a friend of ImClone founder Samuel Waksal and a member of the company's scientific advisory board. A recent book about ImClone described 68-year-old Fuks as the "matchmaker" who brought together Waksal and John Mendelsohn, the co-inventor of C225, the agent now marketed as Erbitux.

Ben-Yehuda held a job at Scientia, a holding company started by Waksal. Though she had no formal connection to ImClone, she was on the company computer system and carried a company cell phone.

The Securities and Exchange Commission filed a separate civil complaint against Fuks and Ben-Yehuda. According to court documents, the charges were based on Waksal's testimony before a grand jury in early

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BSA Urges Proof Of Principle Before Large Investment

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officials to work with a subcommittee of the board to salvage a few pieces of the program.

"Before we move on to big science, the standard is to expect proof of concept," BSA member Jane Weeks, associate professor of health policy and management at Dana-Farber Cancer Institute, said at board's meeting. "I just don't see it here. Our experience with serum markers as screening tests has been horribly disappointing, and … terribly costly in dollars and suffering for patients."

Defending the proposal, NCI Director Andrew von Eschenbach said the cost represented "three-tenths of one percent" of the Institute's anticipated appropriations over five years. "I believe this is an opportunity for NCI to position itself at the forefront of a leadership effort," he said. "If we had this in place a few years ago, many of the problems and frustrations that we are dealing with right now may not quite have occurred, because we would have been able to preempt them, and not lead the public to think that we had the answer to cancer in our hands."

Von Eschenbach's acknowledgment that NCI may have overstated the promise of proteomics came on the same day that the Institute's leading proteomics researcher, Lance Liotta, and his FDA collaborator Emanuel Petricoin, announced their decision to move to George Mason University (see story, page 11).

If von Eschenbach's recent statements are an indication, he has been a believer in proteomics in general and in Liotta's and Petricoin's work in particular.

In a public television documentary that aired in the Washington area last week, von Eschenbach cited the ovarian cancer work as an example of scientific advances that, he claimed, would make it possible to achieve his goal of ending "suffering and death" associated with cancer within the next 10 years.

"One drop of blood, a laser, a mass spectrometer, a sophisticated computer, and we can be able to pick up the signature of very, very early ovarian cancer in women at a time when the disease is almost uniformly curable as opposed to what unfortunately happens today when we find it in most patients at a time when it's uniformly fatal," von Eschenbach said on the program "Senso Reports."

In this statement, von Eschenbach appears to refer to a commercial product, a test for ovarian cancer developed by Correlogic Systems Inc. The reference to a "drop of blood" was widely used by Correlogic, the company that was working with Liotta and Petricoin through a Cooperative Research and Development Agreement.

Correlogic is prevented by FDA from marketing the diagnostic.

According to the television station WETA, the interview with von Eschenbach was taped in late January, a year after FDA first blocked Correlogic from marketing its product. The agency contends that the company's software is a medical device that requires approval to establish safety and effectiveness.

BSA members said proteomics researchers haven't been able to reproduce each other's results, or, for that matter, their own. Therefore, the positive results of many studies may be due to chance or observational bias.

An article in the Feb. 16 issue of the Journal of the National Cancer Institute supports the board's view. Statisticians from M.D. Anderson Cancer Center and Baylor College of Medicine said their analysis of Liotta and Petricoin's data published in papers and released publicly on a Web site
found that the ovarian cancer test "results in classifications that are no better than chance."

"Our analysis reveals that the pattern that enabled successful classification is biologically implausible and that the method, properly applied, does not classify the data accurately," wrote the researchers, Keith Baggerly, Jeffrey Morris, Sarah Edmonson, and Kevin Coombes. "We conclude that the reproducibility of the proteomic profiling has yet to be established."

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Liotta and Petricoin replied that the statistical analysis drew "inappropriate conclusions," because the data the Baggerly paper analyzed "are experimental research study sets that were never part of any clinical 'test.'"

Nevertheless, in a commentary in the same issue of JNCI, David Ransohoff, professor of medicine at University of North Carolina, Chapel Hill, wrote, "The question about whether the approach of discovery-based serum proteomics can accurately and reliably diagnose ovarian cancer—or any cancer—has not been resolved."

Ransohoff elaborated on his concerns in a two-hour "mini-symposium" on proteomics the BSA held March 7. Since proteins tend to be unstable, unlike DNA mutations, everything done to a protein in the lab could affect the outcome, Ransohoff said. He recommended that NCI start on a small scale. "Demonstrating proof of principle in a study where everything is very tightly controlled will help us figure out whether the general approach is worthwhile," he said.

NCI officials didn't conceal their disappointment with the BSA's decision. "We spent two and a half years on this," said Anna Barker, NCI deputy director for advanced technologies and strategic partnerships. "We talked to a little over 1,000 investigators."

BSA Chairman Robert Young, president of Fox Chase Cancer Center, said he was confident the proposal could be revised to satisfy the board's concerns. "I don't personally believe that the majority of the Board of Scientific Advisors wishes the NCI not to explore, in an accelerated fashion, the issue of the potential applicability of proteomics," he said in response to Barker's lament. "What I think you heard is, they are not comfortable with this proposal."

"Empowering the Science of Proteomics"

The NCI proposal, titled "Clinical Proteomic Technologies Consortia: Empowering the Science of Proteomics," described a five-part program of grants, contracts, and small business set-asides. The proposed initiatives and their funding were as follows:

—Clinical Proteomic Technology Assessment Cores, $39. 4 million over five years for five U24 cooperative agreement awards to establish research groups to optimize mass spectrometry and related technology platforms, develop protocols, and generate data.

—Clinical Proteomic Reagents Core, $7.8 million over three years for "multiple" contracts and small business research awards to develop standard reagents and peptide antibodies, develop labeling and production methods, and distribute these resources to investigators.

—Clinical Specimen and Data Collection for Technical Application, $15.8 million over three years, one U01 cooperative agreement, to collect and annotate clinical biospecimens for proteomic analysis, standardize collection protocols, and optimize protein sample collection and fractionation techniques.

—Clinical Proteomic Data Analysis and Computational Resources, $5.1 million over five years, three to five R01 grants, for development of algorithms and analysis methods for proteomic measurements, and analytical software to support algorithm development.

—Clinical Proteomic Technology Development, $9 million over three years for three to four R01 and R21/33 grants, and $12 million over three years for three to four small business research contracts, to support new protein separation, capture, detection, and measurement technologies, improve mass spectrometry, and integrate proteomics with other advanced technologies such as biosensors, nanotechnology, and imaging.

The program would be led by a management council of the consortia investigators and NCI program managers.

"This Is Kind of Big Science"

To bolster its proposal before the BSA, NCI arranged a "mini-symposium," bringing in scientists to discuss their proteomics work.

Last year, Institute officials discovered the hazard of asking the board to approve a large program without providing substantial scientific background. The BSA tabled a $186-million nanotechnology proposal and criticized NCI officials for not giving them enough time or information to properly evaluate it (**The Cancer Letter**, July 2, 2004). A BSA subcommittee and NCI staff revised the proposal, cutting its funding by $42 million, and the board approved it (**The Cancer Letter**, July 16, 2004).

For the proteomics proposal, NCI provided materials ahead of time, arranged the symposium, and worked with a BSA subcommittee for about two months prior to the meeting. The preparation didn't appear to help the Institute make its case.

At the symposium March 7, BSA Chairman Young asked the scientists to address three issues of concern to the subcommittee:

—"The issue of reproducibility of the applications of these techniques, both inter-institutional as well as intra-institutional reproducibility, which has been a

serious obstacle to date.

—"The issue of statistical overfitting, which is undoubtedly addressable, but presents a new conceptual obstacle when one considers the kinds of sizes of comparative groups that exist in these kinds of studies.

—"Despite the technical and scientific underpinnings of this strategy, most of these comparisons turn out to be observational in character, and, therefore, the issue of bias is a serious obstacle to clinical application. Not bias on the part of investigators, or not so much bias for those issues that we understand, but rather, those biases that are inadvertent when we assemble these groups."

Young said the board didn't need to be convinced of the promise of proteomics.

"I don't believe there is anyone around this table who doesn't believe that early diagnosis and biomarkers for initial onset of disease would be a transforming commodity if we had it," Young said. "So I don't think we have to be convinced of the theoretical underpinnings of why this concept is exciting. Rather, we are going to have to labor with some of the existing obstacles and see how the proposals that the NCI presents us tomorrow address some of those."

Leland Hartwell, president and director of the Fred Hutchinson Cancer Research Center, began the symposium with the justification for NCI taking a "bigger science approach" to proteomics.

"This is a project about enabling protein biomarker discovery that is motivated on my part by the impact it would have on early detection," said Hartwell, who has advocated an NCI-funded proteomics program in lectures over the past year (**The Cancer Letter**, April 9, 2004).

"That's not the only justification," he said. "The first applications of any new biomarkers will be in stratifying patients for the choice of their treatment, will be looking at therapeutic response with more targeted therapies, and looking at disease recurrence where we have very high risk and early detection could be important. There, the performance doesn't need to be as demanding as it is for screening a population for early detection.

"The discovery of protein biomarkers is currently the limiting thing," Hartwell said. "If we had them, we could use them, we could validate them. We don't have them. Why don't we have them? I think the reason we don't have them is that we have not applied the current existing technology capable of analyzing proteins in the proper scale.

"The whole point of the project that's before you is to take existing current technology and enable it for protein biomarker discovery," he said. "It's not talking about what we hope will happen with technology development. It's talking about taking machines that any one of you could buy, for about $300,000, and apply it in an empowered way. If we did that, we could increase the rate of protein biomarker discovery by at least two orders of magnitude. That may not be saying a lot, because it's close to zero at the present time. Still, I think a lot could happen.

"It's like the genome project in 1988, when individual laboratories were sequencing small pieces of DNA with poor quality control," Hartwell said. "If we had just allowed that to continue and hope that the genome would have emerged, it never would have. What was needed was a highly systematic, comprehensive, coordinated effort that imposed quality control standards, and that's what got the job done. It was not technology development. It was automation.

"This is kind of big science," Hartwell said.

Hartwell is part of a seven-institution research group that receives $5 million a year from the Entertainment Industry Foundation to conduct breast cancer research. Four of the institutions are working on proteomics, he said.

Hartwell worked with NCI for more than two years to help develop the proteomics proposal, NCI's Barker said.

Besides Hartwell and Ransohoff, three proteomics researchers addressed the BSA: Richard Caprioli, director of the Mass Spectrometry Research Center at Vanderbilt University School of Medicine; Richard Smith, a Batelle Fellow at Pacific Northwest National Laboratory; and Joshua LaBaer, director of the Institute of Proteomics at Harvard Medical School.

"Looking for a Black Cat in a Dark Room"

When the board began discussion of the NCI proposal on March 8, Young said the previous day's scientific presentations hadn't addressed the problems.

"The issues of reproducibility, statistical overfitting, and observational bias were not substantially addressed in any of the presentations that look place yesterday, except perhaps to enhance many individuals' concerns about those issues," he said to the BSA.

Barker acknowledged the problems with the science.

"It's very hard to reproduce this data," she said in introducing the proposal. "We don't have standards,

because we don't have data that lends itself to developing standards yet. We don't have the reagents. We don't know how to collect the biospecimens and produce the kind of reproducibility that's required. We don't have the data analysis tools, and even if we did, we're not sure what questions to ask.

"This is not quite looking for a black cat in a dark room, but it's certainly the way we are characterizing it. It's possible that we are looking for a black cat in a dark room.

"The other thing we've heard is that this requires a systems approach," Barker said. "We can't all live in our respective cottages and hope to solve this problem. We need to network existing programs. We need to build new infrastructure."

To develop the proposal, NCI analyzed its current grants portfolio, reviewed 364 papers on proteomics written since 2002, and held several workshops with investigators, Barker said.

"We think we did our homework on this."

Biorepository Raises Objections

BSA member Joe Gray, director of the Division of Life Sciences, Lawrence Berkeley National Laboratory and chairman of the subcommittee that reviewed the proposal, said he was "very enthusiastic" about the program.

"My enthusiasm comes from having experienced what's gone on in the microarray universe, and I think that the cottage industry approach that has been applied in the microarray world hasn't served us particularly well," he said. "We really do need to have a larger, well-considered approach to developing some of these pretty powerful technologies."

However, Gray said the proposed biorepository raised questions. "We don't actually know what's important in collecting tissues," he said. "My main concern is in terms of front-loading [funding for] the biospecimen collection, is that the best way to launch into this?"

BARKER: "We have not built in money for maintenance of any of our biorepositories. They all have a finite lifespan and they all are going to have to be maintained. This is an area where NCI is going to have to suck it up and realize that if we created these resources, we are going to have to sustain them. We have been discussing this as part of our biospecimen investigation, but right now, we have not built in long-range support for these kinds of things. We have not chosen to build in long-range support for this. That's probably not a great idea."

VON ESCHENBACH: "This is occurring in a larger issue we are addressing across the institute around biorepositories. We are already spending a huge amount of money in the creation and support of biorepositories for various and sundry initiatives and places. We need to bring the biorepository question to a head from the point of view of standards, and that is flowing out of a lot of work that was done in the National Biorepository [Network] blueprint and the RAND report. We hired and brought Carolyn Compton in, because Carolyn is driving the exact kinds of questions, including, do we even know whether the anesthesia a person is given before that specimen is taken out may in fact be altering the expression of the things we think we are measuring.

"We are trying to … get quality standards across all the biorepositories. That is a significant effort."

BARKER: "We put in three years [of funding], because we want to sunset this initiative in five years, and we should have it sufficiently developed to sunset in five years. But the same question will sit out there, how do we want to sustain this biorepository, or have we by that point distributed it into the right technology centers so it becomes self-sustainable."

GRAY: "Sorry to belabor this, but it's still a bit unclear to me. It seems to me that one opportunity for this biorepository is to address the issues… just raised, namely, what is the impact of anesthesia, and this biorepository would have to capture some of the heterogeneity to allow us to explore those issues. Is that's what's intended?"

BARKER: "Our hope is to get as many good ideas from the community as we can and then build this repository to be the absolutely state-of-the-art for proteomics."

Proof of Principle Before Big Science

BSA member Weeks said she was "troubled by several things" about the proposed program.

"As a non-laboratory scientist, I was dazzled by the toys we saw [at the mini-symposium] yesterday," Weeks said. "They were very cool, really exciting, but I'm having trouble putting into a big picture exactly what it is that we are trying to accomplish here. I'm confused about what the goals of this project are. There is a lot reference in the materials and the presentations yesterday about the potential for an early screening test for cancer and how that would revolutionize care of the disease, and I completely agree with that.

"There is also some suggestion about having a test to more quickly assess response to therapy as a potential outcome of this. I'm considerably less enthusiastic about

that. If you ask me where that falls on the list of priorities for spending taxpayer dollars, it would pretty low down. I'd rather invest every last penny in new treatments than in assessing response to treatments that all of us are not terribly happy with.

"The third sort of subterranean issue here is that, somehow, better characterizing these proteins would help in understanding fundamental biology. I'm a little fuzzy about exactly what that connection is, and I think more thought on that issue would be helpful.

"So we're sort of left with the implicit compelling rationale here being the development of a screening test. I can be enthusiastic about that.

"However, if the goal is to develop a screening test, the optimal biorepository would be specimens of patients who have clinically undetected disease. It may not be operative specimens, it may not be patients with advanced disease, because the characteristic abnormalities in patients in whom we intend to use this may be quite different in early disease and late disease.

"Whether that's the only thing we do or not, I don't know, and I defer to the basic scientists on that. I would argue that we need considerably more clarity about the goals.

"The second issue is the scale of the project. Dr. Ransohoff made a terribly important point yesterday. In addition to the issues about chance and bias, he repeatedly pointed out that we're missing proof of concept, and that concerns me. I think that before we move on to big science, the standard is to expect proof of concept. I'm troubled by the analogies to the Human Genome Project, where there clearly was proof of concept before the massive engineering came in. I just don't see it here. Our experience with serum markers as screening tests has been horribly disappointing, and not only disappointing, terribly costly in dollars and suffering for patients. So I think we need to be very careful about not getting ahead of the science.

"Finally, I think it's useful to distinguish between the need for standardization--which is extremely clear here, and I'm very supportive of the components of this that look to standardize the science going on in the field--and the need for big science. They are not the same thing. You can push the field toward standardization without massively investing in developing a technology whose value is not yet proven."

BARKER: "Let me start with the first issue. The intention was never to design a transparent system to develop only a screening test. This is an infrastructure proposal to actually develop the capability to underpin early diagnosis, but also this will actually inform drug discovery [and] clinical trials management in terms of stratification of patients. This will inform all the issues that are across that discovery, development, delivery paradigm. There was an emphasis on early detection when we started this concept development, and I think it is one of our best hopes for eliminating suffering and death due to cancer, but I think there are a lot of other issues in there.

"I don't think there is a belief on anybody's part that there's going to be a test for cancer. I wish there were. Personally and professionally, I wish there were. But I think that is a misconception. We think that's very important in terms of developing not only diagnostics, but also other parts of the system."

VON ESCHENBACH: "I appreciate the fact that we may not have been clear in the sense of exactly what all the specific goals are in terms of how they are laid out, but I think there has been a conceptual framework that recognizes that, as we create this trunk and as we go down some of these branches, we don't know yet what the full extent of that branch is going to be and how far that is going to take us, but we believe that … proteomics can take us down a branch to early diagnosis, take us down a branch of being able to monitor therapy. What this is intended to do is to provide a very disciplined, very systematic way of exploring those branches, rather than trying to play with the leaves and then figure out whether they actually fit onto the tree. Does that help?"

WEEKS: "It does…. The standardization and very structured approach I really applaud. My emphasizing the potential uses has to do with the fact that you're a little beyond the trunk here. For example, the emphasis on a biorepository of specimens for patients with advanced disease is probably the wrong strategy for some uses of that trunk. I'm just urging a little more thought about where the trunk ends and where the branches begin."

BARKER: "I think that's a very good point…. Our goal here for this project is to try to see what we can do with serum eventually. To get to your question, Jane, which I thought was a good one, what will we have when we're done with this? I wish we asked this question about everything we fund here, because we've asked this question hard about this. We will have an infrastructure and systems to support the derivation of answers that we need to address the issues that Bob has raised, and we also will have a flexible system. If those roads don't look that promising, we can stop.

"We will have some optimization of current

technology. That's moving very quickly. We have very good people working in this area, if we can only tie them together, I think we could actually get the optimization. With the database, we can encourage the R01 groups to get engaged here.

"Ultimately, the question is going to be asked, as it was asked about the genome, is how are we going to systematically do this? Without the infrastructure to develop even asking the question, I don't think we are going to be there for another 10 or 15 years….

"I don't think it is big science. It might set the stage for big science. We can't undertake big science without something like this."

Who Drives The Bus?

BSA member Christopher Logothetis, chairman of genitourinary medical oncology, M.D. Anderson Cancer Center, said the program would need strong management.

"I think the analogy to the genome is apropos, because we've learned that the early lack of investment in informatics and standardization is costly. We're in complete agreement that we need to invest a lot in standardization. The need for reagents are applicable beyond this project and that would be important.

"The bigger issue, in my mind, is the management issue and the structure. The difference with the genome is that we have a relatively finite frontier, but here we don't even know the borders of this concept. We don't know what the frontiers are, we don't know how to pursue it. We are in this field without a compass. All our findings are exciting. So in order to retain some sense of direction, this is going to need some kind of inspired management. If Lee is right, and this is at the center of everything we are going to do for the next generation of science, there needs to be some thought to integrating it throughout, in this management, so we don't create a proteome silo at the end of this.

"Milestones can be established, but that comes in conflict with the desire to diffuse this throughout the community. It's not just having technocrats, but some inspired leadership over the management team to make them evolve and become part of the fabric of cancer investigation, as opposed to a proteome silo. I don't know how to do that, but I didn't see that satisfied in the organization, because the way the management was described, it was described as a technocratic tool.

"You need to think about who needs to sit and drive this bus. It can't be chemists alone, it can't be clinicians alone, and it can't be pathologists. It almost needs a philosopher to oversee it."

VON ESCHENBACH: "Some of you may be aware that there has been this larger issue at the [National Cancer Advisory Board] that Lee Hartwell referred to, the Lander-Hartwell committee, that has been looking at these issues and has come forward with a report that addresses both biomarkers and the cancer genome project. Included in that report is a recommendation for the creation of an oversight committee at the NCI from the external community."

"I Like Proteomics, But…"

BSA member Tom Curran, chairman of developmental neurobiology, St. Jude Children's Research Hospital, said the field isn't ready for a big proteomics project.

"I should confess, I like proteomics. I use proteomics. I was using 2-D gels to scan the genome in the early '80s. We identified very interesting proteins and spent many years afterwards working on those proteins. But I'm concerned that the big issue here is that it's not ready for this kind of massive roll-out and establishment of what is essentially a large infrastructure. It's very key when you put together an infrastructure that you place the right bets. I'm concerned that we don't know enough yet to place the right bets.

"Perhaps we were all taken by the over-promises of some of these human proteomics screening technologies that in the early days looked marvelous—SELDI techniques and others come to mind. But, logically, I have a problem with a generic approach to cancer identification using serum proteomics. What we've learned about cancer in the last several decades is the heterogeneity that's based in the genome.

"What I don't see in this proposal is what Lee mentioned yesterday, is that one must integrate genomic approaches based on RNA and DNA together with proteomic approaches to truly identify markers that may be very specific to unique cancer types, and by taking that generic approach, we may miss the markers that may, in the end, look at different signatures for subsets of tumors that would respond differentially to therapy.

"So the issue is, are we ready to do this right now? I don't think that mass spec will ever be a high-throughput screening technology. I think it's a great discovery tool, and some of the science you heard about yesterday was truly marvelous, but it has to evolve into a simple, reproducible assay that may be based on new technologies that we don't yet know right now.

"I do appreciate that there are many aspects of the proposal that are very positive. I'm a little concerned that, in a sense, everything is being done at once. So, for

example, the isolation of good endpoints, reagents for validation, … in advance of coming up with signatures that could then be validated. In a sense, you have to define these markers early on, if you are going to go back and query into this mass of proteomics…

"The technology investments, absolutely I agree with. In fact, you already invest in these kinds of technologies…. The informatics and computational analysis is simply not up to scratch right now. We don't have standards. Absolutely, you should be investing in that area.

"I'm very worried about making a large bet right now on what is really a small part of this evolving field. When it comes to proteins, not all proteins are equal. We have wonderful generic statements in the document that says, 'proteins are important for cancer.' Well, I hope so, since proteins are essential for life, they are important for everything. But the question is, which proteins?...

"It's not like DNA. A great deal of discovery research needs to be made before you are ready to roll this out.

"I worry about over-promising to the public. Saying, OK, we will have in a relatively short period of time, a quick-screen assay, you can come into your local clinic, we'll run a mass spec on you and tell you what you need to stop the cancers that are harbored within your body.

"I am somewhat conflicted in that the field definitely needs support. The science is very strong, there are points of the proposal that we should absolutely go ahead with. But in the current climate, I'm worried about the cost-benefit of building a large infrastructure that may come at the expense of the innovations that would make that infrastructure irrelevant."

GREG DOWNING, director of the NCI Office of Technology and Industrial Relations: "I think we have taken a fair amount of responsibility in looking at our past experiences in over-promising. Going back to Jane's point, proof of concept for what? I don't think there is any element in this plan that says that this is about testing, that this is going to identify the next serum marker for pancreatic cancer. Certainly, there are lot of steps that need to go through that, there are no shortcuts in the biology proposed here. We are trying to broaden the resources necessary to enable the discovery."

PAULA KIM, BSA member and a consultant: "There is a combination of science we are looking at, but we're also looking at systems. That's where part of the really hard decision needs to be made… If we don't have the system and the mechanism and the structure, it really doesn't matter what the science is, because it won't work."

ELLEN SIGAL, BSA member and chairman, Friends of Cancer Research: "I'm very enthusiastic on this project. I think it's essential that we do this and NCI take the leadership on this, for lots of different reasons. Number one is, we clearly have a cottage industry, we really need to get our hands on it. Science is a bit hard. You talk about philosophy, I talk about hard. It's never perfect, and I think that's really important. We need standardization, we need integration, we need focus. I think if we don't do this now, we'll never do it. The field is emerging, we have to get our hands on it. This really does need strong management and it needs clinicians involved in it in a very strong way up front."

SHELTON EARP, BSA member and director, University of North Carolina Lineberger Comprehensive Cancer Center: "We really need proof of principle. We have wonderful animal models and we know when they are going to get cancer and when they don't. Second point, biospecimens. We are in an era of tight money, and I think we need to integrate rather than separate. There are 50-60 SPOREs, there are 8-10 EDRN locations, and I don't see why, with supplements bringing them together, they couldn't form the biorepository in a much less expensive way, and they would be integrated into the SPOREs."

BARKER: "That's a good point and we've thought about that. That's a distinct possibility."

GRAY: "Back to the way in which this project has been framed, and it has been framed primarily targeted on the serum proteome, and for that I agree that proof of concept is at some level missing. But, biology functions through the proteome and there is no lack of proof of concept that proteomic function is important. Ninety percent of what's proposed in this concept will lift all boats in terms of helping us to understand how biology performs."

LOGOTHETIS: "The challenge is the serum. I would, in rolling this out, focus on tissue with established disease. There's no need for proof of concept that proteins are important, but proof of concept that interrogating these at a tissue level will inform you, does need some level of confidence, at least with the present technology."

"Three-Tenths of One Percent"

Von Eschenbach said NCI is faced with "the need and the opportunity to take bold steps without being absolutely, 100 percent certain, as to where all those roads ultimately are going to lead."

The program would have oversight from NCI,

extramural investigators, and the BSA. "We're not going to simply launch this and hope good things will happen. This will be managed very aggressively," von Eschenbach said.

"We know that it's a significant investment, but putting it into context, over the period of time that this initiative is proposed, NCI will spend about somewhere in the range of $25 billion," he said. "This is an $89 million investment over that period. It's three-tenths of one percent of what we will spend over the next five years."

NCI will spend $200 million on the National Lung Screening Trial to compare CT scans to chest x-rays, he said. "You made that courageous investment, knowing that there were larger questions that would ultimately be addressed, including the fact that it was creating a precious biorepository of lung cancer," he said to the board.

"So, we do make significant investments. We make them not based on the cost, but based on the return on investment. I believe that three-tenths of one percent of our budget over the next five years, with the kind of management, with the kind of structure, with the kind of leadership both from this board and the external community, we will guide and direct this effort to provide standards, to provide a discipline, and as Joe pointed out, create an environment in which all ships can rise.

"I believe this is an opportunity for NCI to position itself at the forefront of a leadership effort. We don't know where it will lead, but we know one thing: if we don't provide the discipline now, if we don't provide the leadership now, the likelihood is that it will lead to even more chaos than we currently have. If we had this in place a few years ago, many of the problems and frustrations that we are dealing with right now may not quite have occurred, because we would have been able to preempt them, and not lead the public to think that we had the answer to cancer in our hands."

YOUNG: "One clarification, however, is that while this represents an extremely small percentage of your entire budget, as you have pointed out repeatedly, an enormous percentage of your budget is non-discretionary or not under your control. So we're working in the same way Congress does."

VON ESCHENBACH: "I hope I didn't say that. Every dollar is under our control, but not in the sense that you can immediately change how you are spending that dollar in the next 10 minutes. The fact of the matter is, we have commitments in place, and we will be transitioning those commitments to new commitments…. I have been trying to make the case that most of the dollars that we have, have been committed by previous years' initiatives, and we have to work aggressively in long-range planning for that."

Motion To Approve, Minus Biorepository

BSA member David Alberts, director of the Arizona Cancer Center, made a motion to approve the proteomics concept, except for the $15-million biospecimen repository.

"I like David's motion," said BSA member Richard Schilsky, associate dean for clinical research in the Biological Sciences Division at University of Chicago, and chairman of Cancer and Leukemia Group B. "There are many structures supported by NCI right now that collect biospecimens of various sorts. One could enable the collection of specimens for this initiative by competitive supplements to existing grants."

Barker said adding to existing grants could save between $1 million to $5 million. "You are going to have to put some money into this, folks," she said. "You can't get these samples for nothing.'

BSA member William Kaelin Jr., a Howard Hughes investigator at Dana-Farber Cancer Institute, said he would vote against the motion, because proteomics hasn't proven better than other emerging technologies that compete on a "level playing field" for NCI grants. "Now we are about to give proteomics most favored nation status, just like a few months ago, we gave nanotechnology most favored nation status, and three months from now, maybe something else," he said.

"I think if we are going to take that leap, it should be based on what I've heard several times today: show me the proof of concept experiment that says you have reached that point where it warrants this sort of investment. I'm willing to believe that proteomics is going to be the answer, but I'm willing to believe a lot of other things that we haven't talked about are going to be the answer. Furthermore, there are a number of companies that we haven't talked about today that were founded based on proteomics, founded on business models to deliver biomarkers and new targets, and as far as I know, they're not doing incredibly well."

"I applaud the need for standardization, even somewhat excited about toolkits that might come out of this initiative, but I don't think otherwise that it warrants our support."

WEEKS: "I was going to say essentially the same thing. I'm going to vote 'no' and hope that the next motion will be to defer and to ask for a rewrite of this that addresses the issues that have been raised around

the table, over and above the biorepository issue, which there is an easy fix for that—take it out. I'm not sure that's the best fix, frankly. It's appropriately integrated into the document and simply ripping it out has ripple effects that I think should be thought through, in addition to some of the larger issues that have been raised around the table."

The board voted 13-9 to defeat the motion for concept approval.

NCI: "We Need Direction"

Weeks made a motion to table the proposal and ask NCI and the board subcommittee to rewrite it.

MARK CLANTON, NCI deputy director for cancer care delivery systems: "I'm not so sure senior staff has enough direction to rewrite this along the lines of discussion. I think it's important to outline very precisely which issues you want addressed in terms of a rewrite."

BARKER: "I want to reiterate what Mark said. We spent two and a half years on this. We talked to a little over 1,000 investigators. If we know how to design this, let's design it, but we need direction on this in terms of what the BSA feels is sustainable or supportable."

YOUNG: "Certainly the subcommittee has spent already a good deal of time. As you can tell, there is a spectrum of opinion in the subcommittee that goes all the way from 'hooray' to 'boo,' and I suspect that offers you a rigorous nucleus to begin to explore these things in detail. Furthermore, I would suggest that a good deal of specific input has already been placed back in terms of the discussion. You heard a great deal of interest in the concept that perhaps animal model focuses initially could unravel some of the basic pieces that need to be in place before we expand substantially to the roll-out that's been proposed.

"So, I think the BSA is certainly willing to work with the NCI through this subcommittee to provide you with the input with what its concerns were and to help craft a document that everybody feels will advance the pace of this science."

BARKER: "I think, Bob, the concern is that with a diverse group like this--it's been invaluable to hear this--but I think we've heard everything from, design this around population science, clinical science, the management issues. I think it is a proposal that had a lot of thought, so I think we would need a little more direction, particularly around the issues such as which of these resources are critical, what do we think about this in terms of how it should be coordinated or managed. Those kinds of things would be helpful to us in terms of re-crafting this, so that if you go around and ask everybody about why they voted the way voted, you know, where you stand on an issue depends on where you sit. Several people here sit in certain areas and they want to see those addressed. What we want to do with the community is to address those issues but also provide what we think the community can best use at this time."

YOUNG: "Anna, let me say it a different way. Based on my experience with this body when it has run into things like this in the past, when it seems pretty clear that NCI is interested in doing something and the BSA is equally interested in doing something, that continued discussion and continued reworking causes a proposal to come back which is subsequently approved.

"I don't personally believe that the majority of the BSA wishes the NCI not to explore, in an accelerated fashion, the issue of the potential applicability of proteomics. What I think you heard is, they're not comfortable with this proposal, and they said some of the reasons why. I suspect that you will always get differences of opinion around this table with everything we put on the table, but I think there is common ground here. I would have a great deal of confidence in the subcommittee, which as you can see, runs the spectrum of attitudes about this, to be able to work with you to convey the kinds of concerns that would make this body more comfortable with the proposal."

BARKER: "We will certainly meet with the committee and have a go at that."

A Last-Minute Maneuver

In the final moments, two supporters of the NCI plan—Sigal and Hoda Anton-Culver, chief of epidemiology at University of California, Irvine—made last-ditch efforts to deliver a positive outcome for the Institute.

First, Sigal suggested that the board approve the proposal, subject to a rewrite by NCI and the subcommittee, thereby making the conclusion less negative.

However, Weeks' motion to table the proposal had parliamentary precedent and would have required withdrawal or defeat. Weeks declined to withdraw her motion, and the board voted 12-10 to approve it.

At this point, Anton-Culver tried a bigger gamble.

"Can I make a motion to approve the concept in general?" she suggested.

"No, you cannot," Young replied.

Paul Goldberg contributed to this report.

Liotta, Petricoin To Move To George Mason University

By Paul Goldberg

Lance Liotta and Emanuel Petricoin, two researchers whose work shaped NCI's proteomics programs, are moving to George Mason University where they will co-direct a new Center for Proteomics and Molecular Medicine.

Last May, Liotta and Petricoin were brought before a House subcommittee that investigated conflicts of interest at NIH (**The Cancer Letter**, May 21, 2004).

Liotta supervised a technology transfer program with a Maryland company while accepting consulting fees from its competitor. The case convinced NIH Director Elias Zerhouni that intramural scientists should not be allowed to consult for the industry (**The Cancer Letter**, June 25, 2004).

Both Liotta and Petricoin had permissions to consult.

Earlier this week, the Los Angeles Times reported that Liotta was one of several NIH employees whose cases were referred to the HHS Office of the Inspector General.

Liotta, 57, and Petricoin, 40, started their collaboration in 1997. Their work led to an interagency agreement between NCI and FDA to develop and test proteomics technologies.

"These appointments add a new dimension to George Mason's research agenda and bring new opportunities to expand our activities," unversity President Alan Merten said in a press release. "We are excited that Drs. Liotta and Petricoin are joining us in our mission to build a research program of national prominence."

Liotta and Petricoin will be working in the Life Sciences division of George Mason's College of Arts and Sciences at the university's Prince William Campus. The university has no teaching hospital, but has a research collaboration with Inova Health System.

"It was a very hard decision to make, but I couldn't pass up the exciting opportunity offered by GMU," Liotta wrote in a March 7 email to colleagues at NCI. "The newly created GMU center will synergize with the world-class GMU expertise in mathematics, engineering, life sciences and nanotechnology, combined with the access to renowned clinical expertise provided by the GMU partnership with [Inova]. The mission of the center will be to accelerate the transition of basic science discoveries in the world of proteomics to innovative clinical research and patient-tailored medicine."

Fuks Faces Charges On Sale Of $5.357 Mil. In ImClone Stock

(Continued from page 1)

February. Fuks and Ben-Yehuda are facing prison terms of up to 15 years and maximum fines of the greater of $1.25 million or twice the gross gain from the trades. They pleaded not guilty to the charges.

"It is a sad day, but Dr. Fuks is not guilty, and he will be vindicated," said Joel Cohen, an attorney with Stroock & Stroock & Lavan, who represents Fuks.

The government's case appears to turn on Waksal's testimony.

Waksal, who is serving an 87-month prison sentence for securities fraud, told the grand jury that on Dec. 27, 2001, in the midst of his own efforts to unload ImClone stock, he called Ben-Yehuda, who was in Israel, and advised her to sell ImClone stock.

According to court documents, Waksal also asked Ben-Yehuda to warn Fuks, who was in New York. Waksal and Fuks didn't exchange telephone calls.

Documents show that investigators started probing the stock sales three years ago, but while they had documentation from stock trades as well as Waksal's telephone logs, they apparently could make no allegations about reasons for the trades.

Shortly after Waksal was arrested in June 2002, federal investigators interviewed him about the trades, but his answers weren't damaging to Fuks and Ben-Yehuda. However, making a court-ordered appearance before a grand jury on Feb. 2, Waksal changed his story, stating that he had tipped off Ben-Yehuda after learning in advance about the FDA decision.

"Waksal admitted in the grand jury that he had not been truthful in the interview when he answered those questions, and stated that he understood that, as a result, he had no expectation of receiving a reduced sentence or any benefit as a result of his testimony before the grand jury," the criminal complaint states.

Fuks's attorney Cohen questioned Waksal's credibility. "Dr. Fuks is a distinguished doctor," Cohen said. "Sam Waksal is a convicted perjurer who has testified under oath to the exact opposite to what he now falsely alleges."

The fact that the ImClone case remains active and producing criminal charges is almost as surprising as Waksal's willingness to testify against Fuks, the scientist who helped him to make connections at Memorial and who introduced him to Mendelsohn.

"Waksal and Fuks were old friends and business partners," said Alex Prud'homme, author of "The Cell

Game," a recently published book about ImClone. "Ben-Yehuda worked at Scientia and was a contact for him in Israel. It's surprising that Waksal turned on them, but, then, he has burned almost everybody he has ever known—including his family, and friends like Martha Stewart. The FBI and SEC must be holding a Damoclean Sword over his head, and I doubt the investigation will end here. The question is: who will be next?"

Waksal told the grand jury he had known Fuks since about 1974, and he met Ben-Yehuda in about 1998. Subsequently, Ben-Yehuda became executive vice president for business development of Scientia. Fuks was a member of that company's medical advisory board. According to Prud'homme's book, Scientia shareholders included Waksal family members, Martha Stewart, Mendelsohn, and ImClone investor Carl Icahn.

"Ben-Yehuda and Fuks had a very close personal relationship," Waksal told the grand jury. According to the criminal complaint, "in December 2001, Waksal discussed with Fuks concerns expressed by the FDA about ImClone's Erbitux [application]."

In the early morning of Dec. 27, 2001, Waksal called Ben-Yehuda and said that ImClone would likely receive an RTF. "Ben-Yehuda asked Waksal whether she should sell her ImClone stock; whether she should call a Swiss individual who handled securities transactions for her and for Waksal; whether she should buy put contracts (options contracts that give the holder the right to sell stock at a specified price in the future); and whether she should inform Fuks of this information," the complaint states.

"Waksal told Ben-Yehuda that she should inform Fuks," the document continues. "Waksal subsequently spoke to Fuks, who informed Waksal that he had sold all of his ImClone stock after speaking with Ben-Yehuda, and thanked Waksal for making sure that Ben-Yehuda was taken care of.

"In January 2002, Waksal met with Ben-Yehuda, who informed Waksal that Fuks was worried because he had been contacted by the FBI. Waksal stated that Fuks should not worry because Fuks had not spoken directly to Waksal. Ben-Yehuda replied that she was worried because Fuks had spoken to her and sold stock based on the information that she provided to Fuks about what was going to happen with the Erbitux BLA.

"Subsequently, Waksal had a conversation with Ben-Yehuda, who stated that she and Fuks were worried because they were aware Waksal was under investigation and had concerns about what Waksal might say. Ben-Yehuda asked whether Waksal was going to protect her and Fuks. Waksal replied that he would.

"After Waksal was arrested in June 2002, Waksal had a conversation with Ben-Yehuda, in which Ben-Yehuda stated to Waksal that Fuks was very concerned about what Waksal might say to the authorities. Waksal told her not to worry."

By selling their shares the day before the bad news caused a drop in the price of ImClone stock, Fuks avoided a loss of $1.214 million, while Ben-Yehuda avoided a $18,700 loss, the complaint states.

Officials at Memorial declined to comment.

Fuks is credited with developing precise radiation delivery techniques, including three-dimensional conformal radiation therapy.

Ben Yehuda's name flashed briefly in the ImClone scandal, at the Oct. 10, 2002, hearing of the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce.

"[Who] was Sonia Ben-Yehuda?" Rep. James Greenwood (R-Pa.), then chairman of the subcommittee asked Harlan Waksal, Samuel's brother, who at the time was ImClone president and CEO.

WAKSAL: "I believe she is a friend of Sam Waksal's."

GREENWOOD: "Okay… Sonia Ben-Yehuda was not an employee at ImClone, and yet ImClone has produced records of a cell phone paid by ImClone, but used by Ms. Ben-Yehuda in addition to e-mails have been produced showing Ms. Ben-Yehuda as being on the ImClone e-mail system. Can you explain why a non-employee at ImClone would have use of an ImClone cell phone and have access to internal ImClone e-mail?"

WAKSAL: "I know nothing about this."

GREENWOOD: "Do you know—so you don't even know if it is still the case that that—that these things are happening?"

WAKSAL: "I do know that it came to my attention that she had been on ImClone's e-mail system. It was brought to my attention by the systems people."

GREENWOOD: "When was that?"

WAKSAL. "That was about, I guess, three or four weeks ago. And from what I understand, she is—and I can't—I really would have to get back with you, but I do not believe she is on the system."

GREENWOOD: "Did she receive any other benefits or compensation from the company, that you were aware of?"

WAKSAL: "She was not involved with ImClone Systems."

GREENWOOD: "But that was not exactly my question."

WAKSAL: "Not to my knowledge, sir."

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