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NCI Advisors Approve Recompetition Of $132 Million Proteomic Network

By Kirsten Boyd Goldberg

In a hotly debated decision, an NCI advisory group approved the institute's plan to continue an extramural research program using mass spectrometry to discover biomarkers for cancer.

However, the NCI Board of Scientific Advisors mandated that the concept for the $132.5 million five-year program be rewritten and resubmitted to a subcommittee for final approval.

The project in question is a recompetition of grants for the Clinical Proteomic Technology Assessment for Cancer network. Five research teams were initially funded in 2006 under the first phase of the program to develop

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NCI News:

NCI Places Hold On Genentech Drug Trials, Citing Disagreement Over IP Provisions

By Paul Goldberg

NCI placed a hold on new studies of three Genentech cancer drugs, citing ongoing disagreement over intellectual property provisions of the standard cooperative research and development agreements used by the institute.

The hold on new studies was announced by the NCI Cancer Therapy Evaluation Program in an email to clinical investigators March 3. The hold affects Avastin (bevacizumab) and two new drug candidates, hedgehog pathway inhibitor GDC-0449 and Bcl-2 inhibitor ABT-263. All three drugs are sponsored by Genentech, a unit of Roche. ABT-263 is being co-developed by Genentech and Abbott Laboratories.

In the case of GDC-0449, NCI has sent out letters of intent, received replies, and has trials ready for investigators.

Sources familiar with the situation said the hold has been placed because persistent disagreement over IP rights is preventing the institute from completing the CRADAs with Genentech.

NCI has written a Federal Register notice that would allow it to solicit public comment on the IP provisions of standard CRADAs, but the notice has been awaiting NIH clearance since late 2009, sources said.

Genentech officials did not provide a response to a reporter's questions by deadline.

NCI has been in the middle of a controversy raging between

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BSA: Is Mass Spec Research Good Use Of TCGA Tissues?

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and standardize mass spectrometry technologies for biomarker studies.

Under the recompetition, NCI would fund six to eight U24 awards and issue contracts for a data coordinating center and the production of biospecimens and reagents.

As is its usual practice with review of NCI concepts for Requests for Applications, the BSA appointed a subcommittee to review the clinical proteomic concept. The subcommittee met twice with NCI staff, submitted four pages of questions, and received a 29-page response. But when the concept was presented at the board's March 8 meeting, the subcommittee members weren't satisfied.

BSA members expressed concern about NCI's plan—derived from a workshop last fall—to allow the network to use some of the highly-characterized human biospecimens collected by The Cancer Genome Atlas program. The network investigators would use mass spectrometry on these biospecimens "to define the proteins that drive from these genomic alterations compared with controls," according to the institute's concept statement.

The principal emphasis of the project was not precisely defined, board members noted. Was the research intended to foster discovery of biomarkers, technology development, or both?

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"We believe that this will be a paradigm-shifting program that will inform a lot of areas, not the least of which is proteomics," said NCI Deputy Director Anna Barker as she presented the concept to the board. "We are moving ahead in terms of the kind of science that will flow from this that is remarkably almost life-changing. We see this as a way to leverage the progress that we've made in proteomics, and to actually use TCGA and other genomic data to define where we might go in cancer proteomics, in terms of informing this space of molecular diagnostics.

"What is being piloted in the centers today, as we speak, and what the subcommittee will want to talk about, is, should we use this for biomarker discovery, or should we create nonbiased data that the community could use? And I think those are not necessarily mutually exclusive," Barker said. "The deliverables would be the credentialed biomarker candidates, and you could argue that they are biomarkers."

Later in her presentation, Barker said, "I don't think it's easy with this program to tell you what we are going to deliver exactly. I think we'll know a couple of years into this with our new centers whether this can actually be successful…. We will discover biomarkers. I think there's no question. We've got to decide, and that's the main question, whether this should be the main focus of the RFA or not."

Barker said the BSA subcommittee was involved in critiquing the proposed concept. "We were soundly beaten up, you'll be happy to know, by the subcommittee," Barker said. "They had lots and lots of questions. We had a great discussion. We answered, I think, all the questions."

Subcommittee's Questions

Three members of the subcommittee—Jean Wang, Bruce Stillman, and James Heath—said their questions weren't fully answered:

—**Jean Wang**, associate director of basic research at the Moores UCSD Cancer Center:

"It's still not clear to me, during next five years, what are the milestones or scientifically-driven goals of this so-called clinical biomarker discovery network. I want to emphasize 'clinical.' It's not clear to me if the proposed analysis of tissues being collected for TCGA, bringing those tissue samples into this particular mass-spec analysis—what is the overall goal? Is it to develop targeted assays? There has to be thoughtful discussion of which targets. You can find hundreds of papers, of the so-called whole-genome mass spec based cataloguing? That would be, to me, not a wise utilization of what

has been built. We need to develop the next frontier of biomarker discovery technology. What may that be? Are we going to limit that to mass spectrometry, or are we going to open that up?"

—**Bruce Stillman**, president and CEO of Cold Spring Harbor Laboratory:

"The project that was begun three-and-a-half years ago was a mass spectrometry-driven process. Then it was recognized that the technology was not up to speed. There were some very publicly visible attempts at using mass spectrometry for cancer diagnostics, and they turned out not to be vigorous enough and validated. So the consortium over past three-and-a-half years in this phase I has developed a series of developments which are not going to make the front page of any newspaper, but nonetheless, I think they are important. They have developed standard technologies. They have even worked with NIST and the FDA to help bring this technology into what might be acceptable down the road, and I think these are important contributions—the portability of various technologies across platforms.

"In my mind, the expectation was that this phase I would gear up to the stage when one would be able to apply it to clinical cancer. However, then came the concept that you have in front of you, and in my mind, the concept was ambiguous on those lines. It does mention biomarkers. But, as a result of a workshop that was held in November, the concept came from people attending that, that maybe you should link this to TCGA and use mass spec analysis on tumor samples, with the goal of being able to recognize proteomic differences between them. I have no doubt that that is possible. In fact, it's been demonstrated that it is possible. I have serious doubts about the reasons why that should be done. I don't believe that proteomic analysis is at the stage of doing tissues and to try and link it to The Cancer Genome Atlas, and in fact, I've mentioned this privately, that having had to defend publicly The Cancer Genome Atlas in the beginning, I don't feel comfortable in trying to link other technologies to it, just because they are looking around for something to do, which I see as being part of this.

"In the concept, it is stated that the assumption is that the genetic alterations that are present in somatic tissues in cancer are not going to be reflected in the proteome. I think that assumption is wrong. I think it is going against the fundamental principle of biology, of information transfer in biology, and if we're going to use phosphorylations of proteins as biomarkers or clinical biomarkers for cancer, I think we're on the wrong course. The TCGA is having a big impact on the cancer community and can inform on how to go about the search for biomarkers. I'm not in favor of having this group go on and analyze tissues as part of this, quote, pipeline to identify biomarkers.

"During the committee's discussions [with NCI staff] last week, we sent a bunch of questions, and there was a response. Twice, very explicitly in the response, it says the reissuance of the CPTC will not be a biomarker discovery or development program. So after that came, I was completely against this whole thing. However, since then, having had discussions with staff, I think they are more inclined to having it back on track as a biomarker discovery program. I still reservations about whether or not spectrometry is the sole technology for biomarker development; clearly, it's not. Clearly, having centers using mass spectrometry and knowing how to use it properly, which is very important, is going to be a key component of moving forward.

"I would be in favor of this only if the concept is rewritten so that the measurable goal is to develop biomarkers, and nothing else. I think they have had their time in technology development.

"The problem with mass spec versus the genome (sequencing) is that the technologies in the development of the genome sequencing are essentially exactly the same. There are different machines and different ways to do it, but it's basically the same technology for DNA sequencing. That has been driven by the Human Genome Project and the derivatives of that.

"Mass spectrometry, on the other hand—there are many, many different technologies in mass spectrometry, and there are many different companies providing machines, not all of them are interchangeable and overlap. So I don't think there is going to be a standard technology in mass spec in the near future. One company hasn't won, so to speak. If we can morph this into biomarker development using mass spectrometry, but not just that, then I would be in favor of it, because of the fundamental importance of the problem."

—**James Heath**, professor of chemistry, California Institute of Technology:

"From running my own program with a lot of people from a lot of different disciplines, having a patient on the end of the program has an incredible focusing effect, not just on translational medicine, but everything, from the fundamental science on. If you look at where this program has come over four years, mass spec, of all the analytical chemical techniques, has probably been the most rapidly advancing one over the past 15 years. It still has a lot of issues. I think making it portable at all, in terms of translatable across geographic

locations for systems as complex as tissues and blood, is a real achievement. But it still has a lot of problems.

"Right now, if you wanted to test some hypothesis—say it came out of The Cancer Genome Atlas, or say it came out of some other model system—in terms of measuring proteins to test, based on relatively incomplete biological knowledge, you might make a list of 50 or 100 proteins that you would want to measure to test a hypothesis based on the capacity and what you can do with Western blot analysis and ELISAs, you might pick the top three of those and you would have the project would fail, because picking the top three is not going to tell the story. A program like this does have the potential to pick the top 100 and be able to measure them in a preliminary stage. If that's the level of hypothesis, it's different from what we normally think of in terms of developing one gene, one protein type of hypothesis, but it's the level of hypothesis that's possible with this kind of a program. That said, this technology is still quite expensive, and that implies a need for technology development.

"There is a basis of chemical technologies that could be developed within this program that can be generically enabling of proteomics. So my conclusion is that without a patient and at least some level of hypothesis, although the freedom to take the hypothesis at a much broader level than one would normally have to do, I think this program has potential to lack focus. So I think you need to add that so that it has a strong focus.

"On the other hand, I think the technological hurdles to making this a reality and making it something that we can all imagine impacting, whether it's patients or science over the next decade, the technological hurdles are great. So this has to have a balance of the two of those. I do believe that this is a valid program going forward. I think it does probably have to be rewritten in a way that reflects a combination of patients and biological outcome driven science with technology development."

Appropriate Use of TCGA Samples?

BSA Chairman Richard Schilsky, professor of medicine and chief of the section of hematology and oncology, University of Chicago, asked Stillman whether it would be appropriate to use the valuable TCGA biospecimens for discovery of biomarkers with mass spectrometry.

STILLMAN: "Not having complete intimate knowledge of every biospecimen in TCGA, I am skeptical of that, and the reason is the following: TCGA spent a lot of time in standardizing and worrying about the uniformity of tissue samples designed for genome sequencing or RNA expression analysis, and that has been done. I think the products of the TCGA have reflected that. I think some of those tissues can be used for subsequent analysis for biomarker discovery, but I don't think just taking those and putting them through mass spec and looking at the thousands of proteins using multiple reaction monitoring, which is a technology that is being developed in mass spectrometry, I don't that that is going to necessarily complement TCGA nor help develop biomarkers.

"We are at the stage now where one really needs to develop hypotheses and link mass spectrometry with other technologies. We heard an example of that this morning in the nanotechnology area. If you couple nano detection with mass spectrometry, then you can potentially develop more sensitive detection methods, and they could go on to become validated biomarkers. For instance, one could use blood samples, other body fluids, urine, all sorts of things, for biomarker development, and those aren't in TCGA. So it's limiting this whole thing to doing proteomics on tumor tissue samples, although very good tumor tissue samples, but I don't think it should be limited like that."

"This Is Biomarker Discovery"

Responding to the comments of the subcommittee, Barker said the main focus of the project would be biomarker discovery.

"When you write a concept like this, you can't write everything down," she said. "When you actually go out to the community for a concept like this, you can't predict what the community is going to propose. The best you can do when you write an RFA is capture what we want and see how the community responds. This group has taken mass spec to a new level, and it is actually portable, it is in lots of clinical laboratories, and FDA is acting on these kinds of assays. Yes, it's expensive, but everything we do is expensive.

"As a starting technology, MRM mass spec is not a bad place to start. If you open this up to other technologies in the RFA, they will come in and I think you will see the growth of these technologies.

"This is biomarker discovery, clearly. We've got to do something like this, or I don't think the diagnostics world is going to go very far very fast. I don't see how the NCI can not have a major stake in proteomics. It's how we do it and where we focus this initiative, that seems to be the question on the table. I think it is a viable way to do biomarker discovery.

I think technology development is mandatory in this, and I think the centers would be judged as they come in based on their ability to do that. The academic centers will be more open to engaging here, because it's not just proteomics. You're going to have to have knowledge of genomics, computation, assay development, and especially technology development. These would be much more multidimentional centers, multidisciplinary centers, than the current proteomic centers. It will open it up much broader to the community, which I think would be a good thing."

SCHILSKY: "Most of the work done so far, I believe, has been done in fluid specimens, not tissue specimens. And if that's correct, could I just get clarification as to whether you all feel that the technology development that has been done thus far can be easily adapted or transferred from studies in serum and plasma to studies in tissue, keeping in mind in particular the fact that the TCGA tissue specimens are perhaps the most well-characterized and therefore most valuable tissue specimens ever collected, and probably we don't necessarily want to use them up for additional technology refinement before we start using them to get meaningful answers."

BARKER: "Let's go back to what TCGA is, Rich. TCGA is, what we are doing in robustly characterizing a statistically valid set of samples across all these technologies and all of these transcription levels is to say that genes that were implicated in cancer are real. In other words, those pathways as we define them and those subclasses are real. So whatever you decide to do with GBM as an example, if you follow the tissue acquisition strategies and you follow the procedures set in place and you have a statistical set of samples that are robust enough, in theory, you can bring samples in from TCGA, you can bring GBM samples in under those conditions, and do the assays."

SCHILSKY: "But the chances of those conditions being replicated in real world medical practice—"

BARKER: "I think, actually, no, I don't agree with that. If clinical medicine is going to be relevant in the future, and personalized medicine is going to happen, this has got to flow to the clinic. We're doing everything we can to make sure that happens, including caHUB [NCI's Cancer Human Biobank]. CaHUB will set standards in this regard, and I think it will work."

SCHILSKY: "Could you answer the question about whether or not the technologies that have been optimized for fluid are transferable to whole tissues?"

BARKER: "Yes, we believe they are."

Need For A Clinical Question?

BSA member Todd Golub, director of the cancer program at the Broad Institute of MIT and Harvard University, said NCI should stay involved in technology development. "Five years ago, there wasn't a platform for thinking about biomarker discovery in a serious way, and there wasn't a clear analytical path for sorting out whether you had a good approach or not," he said. "The group should be commended for making great progress.

"But now the question is, which this capability in hand, should you declare victory on technology development? I think there the answer is clearly 'No,' and it would be a mistake for NCI to pull out of technology investment entirely," Golub said. "But I think it would also be inappropriate to not think about applying today's technology to some important questions.

"All of these genomic studies involve some sort of comparison," he said. "In the case of the somatic genome, you're comparing the DNA sequence in the tumor to the patient's germline. So that makes it very easy to see what are the mutations, because if it's there in the tumor and not in the reference DNA, you know there's a variance, and it may or may not be biologically important. This is not the case for RNA profiling, or proteomic profiling.

"Given that, it makes it more important to have some question in mind at the time you are generating the data, and so that's why I have concerns about the idea of just generating the proteomic profiles of TCGA specimens, because in the absence of either a clinical question or a biological question in which to do some comparative analysis, I'm not sure that that data set would be maximally useful."

BSA member Don Listwin, founder and chairman of the Canary Foundation, said the field needs both research and technology development. "So far, undirected discovery doesn't work in proteomics," he said. "What has begun to work is the view toward validating things that have been discovered. Our teams are starting to get a sense that if you take a mouse model and a cell line and some blood and you do some things, you actually start finding some concurrent things.

"I think there is a technology development need here," Listwin said. "There are a lot of different stakeholders that can use this technology and then get their own clinical questions. I don't think this team should be trying to answer any particular questions. I am supportive of going forward."

BSA member Paul Allen, professor of pathology at Washington University School of Medicine, said he

agreed on the need for further technology development. "I'm in support of this moving forward, because I think this is what NCI has to do," he said. "This is exactly what we need to do to get this technology going and then being able to analyze whatever samples we wanted at whatever sensitivity, and also bring along the methodologies and the reagents."

Support for the Concept

BSA member Joe Gray, director of the Division of Life Sciences, Lawrence Berkeley National Laboratory, said he fully supported the recompetition. He submitted written comments because he wasn't able to attend the meeting. Schilsky read Gray's remarks:

"I support the renewal. I've been impressed over the last few years at the progress the CPTAC investigators have made in developing mass spectrometry, multireaction monitoring assays, and specific proteins to the point where they are reproducible and transferable between labs. I'm particularly enthusiastic about this technology, since I think it accords a highly multiplexible way to assess how -omic changes discovered by the TCGA project translate into changes at the protein level. While the genomic data give us valuable insights into the cellular mechanisms that drive tumorigenesis, proteins report in real time complementary information, such as the absence or presence of cancer cells, tumor type, and/or therapeutic responses. The challenge is accessing the relevant portion of the proteome. The CPTAC labs have demonstrated that MRM MS assays quantitatively measure any protein in blood an other body fluids, cells, or tissues, at mid-picogram per ml, a high microgram per ml levels, and with near-clinical grade performance. This capability allows analyses of the normal protein repertoire, and cancer-related changes at the amino acid sequence level, and including post-translational modifications. Unlike immunoassays, MRM MS approaches can be highly multiplexed.

"The CPTAC groups have already demonstrated high inter- and intra-lab assay reproducibility for MRM MS measurements approaching some plasma. Additionally, the methods are robust, economical, and amenable to wide dissemination. These assays have great potential for adoption by both research and clinical laboratories. Individual CPTAC labs have pushed this technology into the low picogram per ml detection range by adding affinity capture methods without diminishing their multiplexing capabilities for the basic research. Working together in a highly coordinated effort, five to 10 laboratories that are experienced in MRM MS could configure hundreds of these multiplexed assays, allowing researchers to interrogate a portion of the biologically relevant human proteome that has heretofore been inaccessible for study. Once developed, these methods could be widely distributed and used effectively by less experienced labs for numerous purposes.

"Like genomic technologies, the MS and separation methods that underpin the MRM assays are rapidly improving and evolving. I personally think a continuation of the proteomic initiative will be cost effective and will bring validated MRM MS assays to the community much faster than what would otherwise happen."

STILLMAN: "I agree 100 percent with Joe. However, for the people who are aficionados of mass spec, what he talked about is analyzing proteins that you know about. If you don't know about the proteins, you can't do what he just said.

"So this boils down to, if you know the proteins, or if you hypothesize what set of proteins you want to look at, you can use the mass spectrometry technology to analyze those. I agree with Jim that you should probably co-develop chemical technologies for affinity capture and all these other things along with it. If you do that, there's no doubt that can this technology can—whether it's portable enough, I don't know—detect proteins very sensitively, which ultimately could be biomarkers. If the RFA were written like that, I would support it. The RFA is not written like that—"

BARKER: "The RFA isn't written, Bruce, that's the concept."

STILLMAN: "Well the concept is not written like that, and that's why we're having such a hard time with this, and in fact, in the responses to the questions, it was said, 'No, this is not the goal. The goal is not to develop biomarkers.'

"If we can agree that the long term goal here is to develop biomarkers and not just, as implied in the response to our questions, to take tissue samples from TCGA and do mass spec on them, but to have real hypotheses about what out of TCGA might be biomarkers down the road—and I agree about technology development—I think we can all agree that this would be a good RFA, because I think everybody understands this is what's needed. The concept, and then the RFA, needs to be written so that it's not just doing on the proteome what has been done on the genome with tumor samples. You cannot do that."

NCI Director: Why Focus on Biomarkers?

JOHN NIEDERHUBER, NCI director: "Bruce, I don't understand why we have to take what I consider

an evolving technology and focus that on biomarkers. Yes, we may be lucky and develop biomarkers in this project, but I don't think that's where we are right now. I think where we are is trying to understand the catalogue of genomic defects in cancer and the cancer host microenviroment as well. And we're trying to translate that information into understanding functional biology. To me, I think a big step in that understanding of functional biology has to be understanding any of these genomic changes, how they affect proteins, the proteins that are produced as a result of these genomic changes. And in conjunction then with understanding the functional biology at the level of the cell, at the level of networks within the cell and outside the cell. That's kind of where we are right now. That's a long way from having a biomarker in my hand."

STILLMAN: "That's not what's written in the concept."

NIEDERHUBER: "But that's where we need to be investing the NCI's resources in terms of working in conjunction with the TCGA and other similar programs, to get us to an understanding of what does this mean, and then how can we apply it in terms of developing biomarkers, developing potential targets for the development of novel therapies."

BARKER: "As much as I hate to say this, I agree with Bruce. I think he's right in the sense that, what we really are talking about is biomarker discovery, and that is ultimately where this goes. This is a gap that the proteomics community has identified, and one that I think is important. It's one that is going to inform beyond diagnostics, it's going to inform cancer biology as well, because it is the functional space. If you don't like proteins, you love DNA, I don't care what you love, everybody loves something different in this community. This discussion sounds exactly like the discussion we had five years ago, because the proteome is still an evolving space for us, and I think we have to take our best shot here. I think we have to show leadership. I think, Bruce, too many great investigators have told us that we can use TCGA samples to ask good questions, and I think we should take that advice. I think it could be sharpened up and I think we could deliver a message that would be much clearer, that you would probably resonate with, because it is a stage of biomarker discover, but it's a lot of other things, too."

WANG: "What we couldn't determine in our teleconferences was the future direction, and I can identify three pieces: technology development, development of targeted quantitative analysis based on TCGA data, or random whole proteome profiling. What I've heard is, there is very strong support for technology development—we agree on that one. There is strong support for targeted assay development, because that's what phase I has done for us, and it would be great to pick hypothesis-driven biomarker clinical endpoint driven and make that a clear piece of this RFA. But this idea that we're just going to take this precious tissue and throw it on mass spec—I don't think there's support for this."

BARKER: "I don't think you're being fair, Jean. Nobody said they are going to take a whole tissue and throw it on mass spec. No."

WANG: "That's what we got from the discussion we had with staff."

BARKER: "No, no, no, no, no. What you got was a pipeline with a lot of real good science done with selecting which candidates."

WANG: "That's the piece that we are all concerned with—"

BARKER: "We can't predetermine everything. The community is going to have to help us to determine how you prioritize those candidates, and I've learned that from TCGA. What we think versus what they think, in real time, will be quite different, so we've got to give this concept enough flexibility that the community can ask good questions. I don't know that we can fashion it so that everybody loves it, but I think we can fashion it so that lots of people love it."

Calling The Question

SCHILSKY: "Jim has one other comment, and then I'm going to ask one of the subcommittee members to make a motion. See which one of you wants to race to the microphone to do that. Jim?"

HEATH: "It seems to me that we are actually arguing on the same thing. If you have the flexibility to make a broad enough hypothesis, then you have the flexibility to extract a protein regulatory network out of a sample that's going to lead to biomarkers. I don't see the discontinuity here. I think the issue is that, experimental space, especially here, is infinite. You don't want it to be infinite, you want it to be focused, or you're going to be lost. I think that's what we were struggling for. Amazingly enough, I think we as a subcommittee actually did come to consensus here, whether it sounded like that or not."

SCHILSKY: "That's good, because I'm not sure what the consensus was, but maybe we'll get one."

HEATH: "I would make the motion to pass this with the caveat that the RFA be reissued with more of a focus towards some biomarker type purpose."

BARKER: "I would think that would require coming back to the subcommittee."

HEATH: "Yes. I think we would be asking to see it again."

WANG: "That would be nice."

STILLMAN: "The proposal would be to conditionally approve the concept on the assumption that the concept will be rewritten to more clearly focus on the biomarker development with all of the things we discussed. If the subcommittee is comfortable with that, because we have been critics of it, then if the board is comfortable with that, then we move forward with approving the concept, which means NCI would move forward with developing the RFA."

SCHILSKY: "So let me just rephrase: If I understand correctly, the motion is to concur with reissuance, provided that the concept is revised to reflect a greater focus on biomarker development, and that the subcommittee have an opportunity to review and concur."

BAKER: "I think we are comfortable with that and I think we understand what they are asking for."

SCHILSKY: "If that motion is acceptable to committee members, can I have a second?"

PAULETTE GRAY, director of the NCI Division of Extramural Activities: "That means it doesn't have to come back to the full board."

SCHILSKY: "It does mean, though, that if the full board wishes to vote in the affirmative, you have to be comfortable with the notion that the subcommittee will give the final sign-off, because the full board will not see the revised RFA concept."

STILLMAN: "Three years after the RFA is issued, the full board will see the product of this, and we'll either like it or not."

BARKER: "Some of you will probably be applying for it, would be my guess."

SCHILSKY: "There's a motion on the floor, I'm not sure I heard a second. Is there a second?"

WANG: "I second it."

SCHILSKY: "Moved and seconded. Is there further discussion?"

BARKER: "I hope not."

* * *

The board voted unanimously in favor of the motion.

The full text of the concept statement is available at http://cancerletter.com/special-reports.

BSA approval of two other concepts will be reported in next week's issue of The Cancer Letter.

Disclosure:

St. Martin's Press Buys Rights To Book By Brawley, Goldberg

By the Editors

St. Martin's Press bought the rights to a non-fiction book that will be co-written by oncologist Otis Brawley and The Cancer Letter editor Paul Goldberg.

Brawley serves as chief medical officer of the American Cancer Society. However, the book is not an ACS project.

The working title is "What I Know, What I Don't Know, and What I Believe: A Doctor's Education." The book will present Brawley's perspective on the state of medicine, focusing on cancer treatment. The book was acquired by editor Nichole Argyres and is scheduled for publication next spring.

The project was cleared by the ACS ethics officer. The Cancer Letter will manage the conflict primarily through disclosure.

"This situation is challenging because The Cancer Letter is a two-reporter operation and the two reporters are a married couple," said Kirsten Goldberg, editor and publisher of The Cancer Letter. "We are a medical publication, and our readers are well-practiced in living with and interpreting disclosure."

In addition to publishing this story, The Cancer Letter will add a disclosure page to its website, and will add disclosure lines to stories that may be affected by this conflict. In the process of reporting such stories, disclosure will be made to sources prior to interviews.

The Cancer Letter asked three experts in conflicts of interest in medicine for advice in managing this conflict.

"The common way that these things are done is to post them on websites and whenever appropriate to make mention of them in printed materials," said Eric Campbell, associate professor at the Institute for Health Policy at Massachusetts General Hospital and Harvard Medical School. "It's commonplace among the docs who write books. The issue for you is you just have to avoid doing things that can be construed as outright promotion of your book."

Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania, advised that coverage of ACS be assigned to Kirsten Goldberg. While Kirsten, as a spouse, is affected by the financial conflict, she is not involved in the project.

"It might give you three percent more distance, but I'd take it," Caplan said. Disclosure should be

made prior to interviews in stories that may involve Brawley or ACS. "If someone is to say, 'That bastard Otis Brawley, he is the source of our aggravation,' you really don't want to be put in the position of saying, 'Oh, by the way, I am writing a book with him.' You want to have that up-front before anything like that would ever happen."

Gary Schwitzer, publisher of Health News Review, said the conflict can be managed through aggressive disclosure. "What you propose presents clear potential for conflict of interest," he said. "But you know that. And the very fact that you're seeking opinions from others is a healthy sign.

"You want to achieve two good things: continued publication of The Cancer Letter and the publication of this book. I, for one, think both are good things worth pursuing.

"With a Cancer Letter publication team of two—married at that—you can't just leave ACS-related issues to a co-worker. And you don't want to walk away from what you consider to be a terrific, eye-opening book project. So, how you manage this potential conflict and how you disclose it will be key.

"You will have to disclose your relationship with Dr. Brawley whenever you write about anything to do with him or the American Cancer Society—which will be quite often.

"You will have to prove to readers how you wrote independently and how you sought perspectives independent of Dr. Brawley. But, knowing you, I have no doubts about your ability to do this. And I doubt that most of your Cancer Letter readers have any doubts about that either. But you have to manage and disclose with people who don't know you in mind."

NCI News:

NCI's Federal Register Notice On CRADA IP Stalled In Review

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pharmaceutical companies and researchers, who are battling over intellectual property rights to discoveries that could be made in correlative research studies secondary to NCI-sponsored clinical trials.

Last summer, NCI responded to pressure from the industry by proposing a substantial change: if a drug company provided an experimental agent to a cooperative group trial, it would be entitled to a royalty-free commercial license to inventions stemming from studies of biomarkers stemming from that trial.

The proposal triggered objections from clinical researchers, who argued that granting these rights would diminish the incentives for university scientists to conduct biomarker research. Also, drug companies may be put in a position to squelch biomarker findings that would limit the use of their drugs (The Cancer Letter, Oct. 16, 2009).

Responding to objections from clinical researchers, NCI presented a reworked plan, which forms the foundation of the apparently stalled Federal Register notice (The Cancer Letter, Nov. 13, 2009).

The plan has the following features:

• Reverting to the current IP agreements, drug sponsors would get royalty-free worldwide non-exclusive licenses.

• Sponsors would receive a time-limited first option to negotiate an exclusive or co-exclusive royalty-bearing commercial agreement.

• If in the course of a clinical study scientists make an observation that a drug can be used for another indication, that indication would be subject to a royalty-free, worldwide non-exclusive commercial license.

While clinical trials cooperative groups and NCI's advisors were largely pleased with these revised CRADA provisions, it's not publicly known whether sponsors have found them acceptable as well.

NIH News:

Collins, Lander, Botstein Win Albany Prize In Medicine

FRANCIS COLLINS, NIH director, has been named a recipient of the Albany Medical Center Prize in Medicine and Biomedical Research for his leading role in mapping the human genome.

While accepting the honor, Collins declined his portion of the $500,000 prize in order to comply with government ethics rules.

Collins will share the honor with co-recipients Eric Lander, director of the Broad Institute at the Massachusetts Institute of Technology and Harvard University, and David Botstein, director of the Lewis-Sigler Institute for Integrative Genomics at Princeton University.

The prize was announced by James Barba, president and chief executive officer of Albany Medical Center and chairman of the National Selection Committee.

"These three scientists undoubtedly will hold a special place in the history of science and medicine as primary initiators of a profound revolution in human development," Barba said.