THE CANCER LETTER

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NCI Makes Plans for Moonshot Dollars

By Paul Goldberg

At a meeting of the NCI Board of Scientific Advisors March 29, NCI officials had good news to report:

• The appropriations are increasing, with bipartisan support to boot.

• The White House "moonshot" initiative on cancer is bringing new money and new urgency to the institute's work.

The cancer program has seen many aggressive mandates and has made many big promises, and it's worthwhile to remember this current initiative is being launched by an administration that is concluding its term.

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AVEO Execs Face Fraud Charges from SEC; Company to Pay $4 Million to Settle

By Paul Goldberg

The Securities and Exchange Commission March 29 announced fraud charges against AVEO Pharmaceuticals Inc., a biotechnology company, and three of its former executives.

SEC said the company agreed to pay a $4 million penalty to settle the charges without admitting or denying the allegations.

The agency said it is continuing to pursue its case against three of AVEO's former officers: CEO Tuan Ha-Ngoc, Chief Financial Officer David Johnston, and Chief Medical Officer William Slichenmyer.

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In Brief

Singer, Kibbe Named Acting NCI Deputy Directors

DINAH SINGER and **WARREN KIBBE** were named acting deputy directors of NCI.

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NCI Plans for Moonshot Dollars

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The resources being placed on the table will flow through the relatively simple bureaucratic machinery that will be largely housed within NCI.

The institute is about to announce the members of a "blue ribbon" panel that will guide its moonshot efforts.

Though initial funding is relatively modest by comparison with the overall federal spending on biomedical research, the moonshot is shaping up as a broad-based research and public health initiative.

The administration's $1 billion proposal establishes a game plan for how the funds will be spent: the moonshot initiative will begin with $195 million in cancer research at NIH in fiscal 2016, according to the White House.

The budget for the 2017 fiscal year proposes to allocate $755 million in mandatory funds for new cancer-related research activities—$680 million for NIH and $75 million for FDA. The remaining $50 million is expected to fund Centers of Excellence in the Departments of Defense and Veterans Affairs. (The Cancer Letter, Feb. 12.)

"The overall goal is to accelerate progress in cancer, including prevention and screening, to go from cutting-edge basic research, all the way to greater uptake of the standard of care," Lowy said to BSA. "It's to encourage cooperation and breaking down siloes, both in and between academia, government and the private sector, and the overriding importance of data sharing."

Lowy said the new money will speed up progress.

"Needless to say, the proposed amount of money is just a small proportion of what the NCI has," Lowy said. "In addition, there's a lot of additional investment in cancer research. So this is just on top of what's already being done. We are going to try to coordinate the rest of the research so that putting them together, we will be able to make faster progress.

"The money allocated or being proposed for the initiative by itself is not going to change things overall, because although it's a lot of money, relative to all the other investment, it's relatively small."

In June, NCI will provide greater detail on the Genomic Data Commons, which will enable the sharing of annotated patient-level clinical and cancer genomic data.

"One of the charges in the president's memo establishing the cancer initiative was to try to accelerate research so that what would normally have been done in a decade could be done in five years," said Dinah Singer, director of the NCI Division of Cancer Biology, who was recently named NCI acting deputy director. Warren Kibbe, director of the NCI Center for Biomedical Informatics and Information Technology, was also named acting deputy director.

Likely, NCI would be able to move quickly to distribute the money.

For example, the moonshot will include an "exceptional opportunities fund."

"This fund is slated to have up to $100 million in it, and the idea is if new and exciting ideas emerge…, that fund could be used in a very rapid way to support various groups to pursue the research in that area," Singer said. "One could imagine, for instance, launching challenges that would be open to the broader community that could be relatively quickly funded."

The following are excerpted presentations by Lowy, Singer and James Doroshow, NCI deputy director and director of the NCI Division of Cancer Treatment and Diagnosis:

LOWY: There is the potential for continuing increases in federal cancer research funding, and for NIH funding, and it's important that this funding is frequently coordinated with private funding efforts. For example, today there's going to be an announcement of a $125 million donation by former New York City Mayor Bloomberg and Sidney Kimmel and others to Johns Hopkins, and this is just one area of private philanthropy making private contributions for cancer research.

For FY16, the NCI received about $265 million in a total increase—$70 million was for the president's Precision Medicine Initiative in oncology, and we have gone over the elements of that effort previously.

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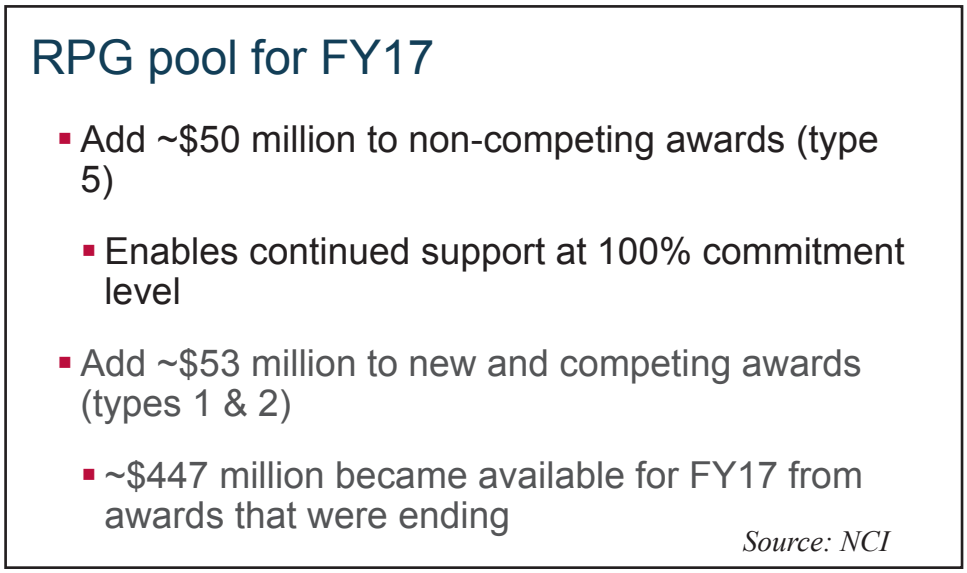
As I mentioned, Jim will say a little bit about a couple of areas. And $195 million was for non-PMI oncology activities.

I just want to focus on one aspect for the current fiscal year. We are adding about $50 million to the non-competing awards, the Type 5 awards, because that enables us to continue support at the 100 percent commitment level. In addition, we are adding about $53 million for the new and competing awards—those are the type 1 and type 2 awards. The rationale for that is that about $447 million became available for FY16 from the awards that were ending. So we are supplementing that with $53 million, so that when it comes to these awards, we will be at approximately the $500 million level.



[Consider] the funding for the NCI for the last almost 20 years. There have been substantial changes. The increase in FY16, note that this is really just keeping pace with inflation. But there's a substantial increase proposed for FY17 of $680 million for the NCI by the president's budget. And this would go ahead of inflation and get us at about the same purchasing power as 2000-2001, sort of in the middle of the doubling.

I'd like to turn now to the vice president's cancer initiative, of which there has been a fair amount written, but not too many specifics up to now.

The overall goal is to accelerate progress in cancer, including prevention and screening, to go from cutting-edge basic research, all the way to greater uptake of the standard of care. It's to encourage cooperation and breaking down siloes, both in and between academia, government and the private sector, and the overriding importance of data sharing.

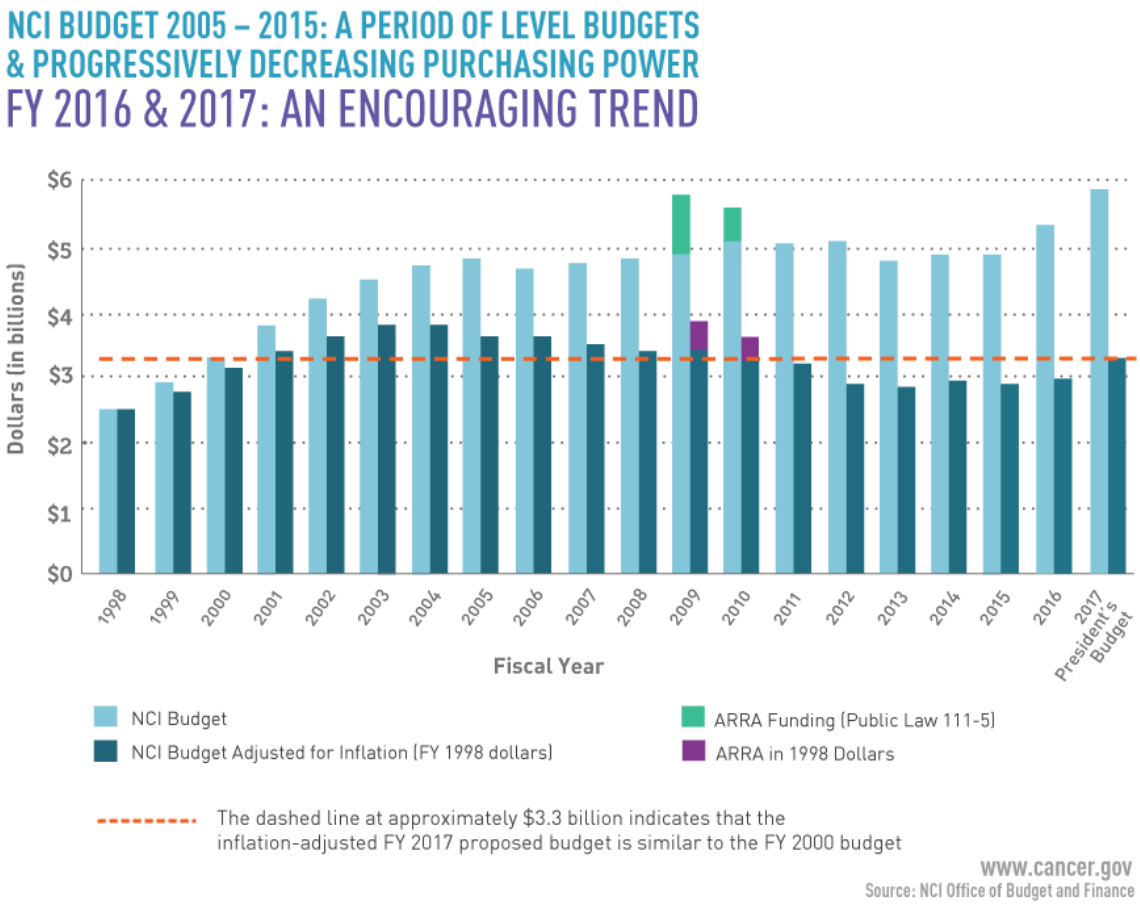
In June, NCI is going public with the Genomic Data Commons, and this will enable annotated patient-level clinical data, and omics—and as you will hear when Warren [Kibbe] talks about it in more detail in June, there will be an opportunity for others who wish to contribute such information to the genomic data commons, that it will be able to accommodate that. This information will be publicly available to the scientific community.

Many people are aware that the vice president's initiative is referred to as the moonshot, and there has been a certain amount of controversy about what that implies. During a visit of the vice president to the University of Pennsylvania Abramson Cancer Center in January—these are two quotes, just so that he understands that this is not going to be a single magic bullet, or landing on a particular crater on the moon, that is going to take care of everything. He says, we're talking about prevention, early detection, "I'm convinced that we can get answers and come up with game-changing treatments and get them to people who need them. We have the opportunity to fundamentally change the trajectory."

The scientific proposal is going to be vetted by the blue ribbon panel, which we hope will be announced in the very near future, perhaps this week, this will be an evaluation of the current proposal and their recommendations which will be made to the NCAB may or may not look like what I am discussing now.

One of the proposals is to develop preventive interventions, such as vaccines against infectious and non-infections targets. These different proposals take advantage of recent technological innovation, and try to apply these advances in different areas of cancer research. The one area is with the [Epstein-Barr virus] vaccine—we had the presentation from Jeff Cohen [chief of the Laboratory of Infectious Diseases and the Medical Virology Section at the National Institute of Allergy and Infectious Diseases] back in December—but also trying to think about immunological approaches to deal with precancers or early invasive cancer that might be able to be targeted when there are not—to molecular abnormalities, that have nothing to do with infections.

[Other proposals to] develop screening tests with



bodily fluids, and there has been a lot of publicity about blood, but also urine, saliva, and other fluids. There have been enormous improvements in sensitivity and specificity particularly with identifying nucleic acids, which are currently being used to monitor recurrence of cancer, etc., but there is some potential to use this as a screening test. And then increased uptake of standard of care for prevention screening, as well as for treatment.

[Proposals in] cancer treatment, in clinical and preclinical work, to increase immunotherapy trials and combination therapy trials, increase patient participation in clinical trials, develop new treatments for pediatric cancer, develop a drug formulary for many companies, but that formulary would be at NCI to facilitate the study of combination therapy and other activities, and Jim will talk about that during his remarks.

And, importantly, to expand the omics analyses of tumor cells and stromal cells for patients and also to include clinical annotation that would be far better than what has been available through TCGA.

And then some other areas, as I mentioned, increasing preclinical vaccines and cancer immunotherapies, increase basic research, especially in immunology, and to develop exceptional opportunities fund for new opportunities in cancer research.

I'd now like to turn the discussion over to Dinah, and she will continue to talk about the vice president's initiative.

SINGER: The cancer initiative was announced by President Obama in his State of the Union message back in January. The idea was to accelerate progress in cancer. And it really is to extend all the way from basic research in cancer through translational and clinical and also access to care. So it is a very broad-spectrum initiative that is intended to really affect patients.

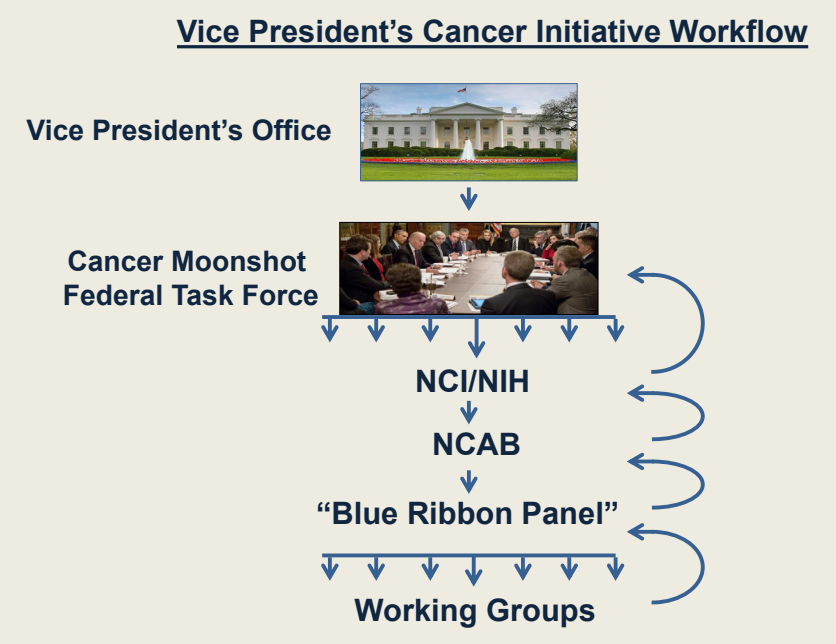
Specifically, it's also going to encourage greater coordination and collaboration. There's a sense in the White House of siloes that exist within academia and within government and within the private sector, and between them all. One of the goals is to break down those siloes and finally to enhance data sharing, which Doug also alluded to a little bit.

To give you an idea of how this whole initiative is structured, the presidential memo that established this initiative places this leadership directly in the White House, with the vice president, in his office.

Derived from that is a federal task force for the

cancer moonshot, which includes the NCI and the NIH, and, within the presidential memo, creates a blue ribbon panel, which is a working group of the NCAB, and authorizes the blue ribbon panel to form working groups to further pursue the science to make recommendations back to the blue ribbon panel—which will report back to the NCAB, which will report back to the NCI director, who, through the NIH, will report back to the federal task force the recommendations for the scientific opportunities.

The federal task force met here back in February. It was attended not only by Vice President Biden but also by President Obama—and it might not be immediately apparent, but the leaders of the free world were looking to Doug for advice.



The task force consists of about 13 federal agencies. This is only a partial listing. The vice president is chair. The secretary of HHS is on the task force, representatives for NCI—you've already saw Doug—Jim was actually there, but he wasn't in that picture; he's also in another one. They were also looking to Jim for leadership.

NIH, FDA is represented; Commerce and the Patent and Trademark Office is involved; the Department of Defense and the Veterans Administration; the Department of Energy, and NSF, and a few others are all part of this task force.

Reflecting on the goals of the moonshot initiative, the specific identified goals of the task force again are to accelerate our understanding of cancer, its prevention, early detection, treatment and cure—importantly to support greater access to research data and computational capabilities.

Improving patient access to care is another important component of the moonshot mission. To identify and address any barriers and to consider any ways to expedite considered reforms and to identify opportunities to develop public-private partnerships to increase coordination of the federal government's efforts with the private sector as appropriate. Obviously the first two bullets are where NCI has the greatest responsibility.

The task force will also be looking at ways to improve patient access and care. The FDA is already starting to think about ways to reduce regulatory barriers. And Francis Collins has already tried to establish some new public-private partnerships in this arena.

One of the attempts to progress the cancer research that was specifically mentioned in the president's memo was the establishment of a blue ribbon panel, which is going to be a working group of the NCAB, and the goal or the charge of the blue ribbon panel is to provide expert advice on the vision and proposed scientific goals and implementation of the national cancer moonshot. Importantly the panel is authorized to recommend other cancer research activities to enhance this effort.

As Doug mentioned the roster of the panel has not been released yet officially, but we anticipate that it's not going to be more than about 20 people, which is really not enough to provide all the scientific expertise that would be needed to really provide or identify the various important opportunities and gaps that should be addressed through this cancer initiative.

The panel is authorized to establish working groups, and we anticipate that this will be one of the first actions of the panel, focused on the various scientific themes that the panel thinks are going to be of critical importance to pursue and provide feedback and recommendations.

In the original proposal that went to the White House, these areas were identified, Doug went through the science in many of these, and we anticipate that these will be among the areas that the working groups will be asked to evaluate, so again: cancer and prevention vaccine development, not only for infectious agents, but also for the non-infectious agent vaccines; detection is going to be a critically important component of the effort; cancer immunotherapy and combination therapy; genomic analysis of tumor and surrounding cells, I think

Blue Ribbon Panel Timeline

April/May 2016

- **Blue Ribbon Panel (BRP) discussion of its charge and organize working groups**
- **Working groups generate a series of recommendations**
- **NCI staff incorporate recommendations into draft reports**

June/July 2016

- **BRP discusses and edits Working Groups recommendations**
- **Working groups finalize their recommendations**
- **NCI staff finalize individual Working Group reports and integrate them into a single coherent report**

July/August 2016

- **BRP report circulated, edited, finalized and sent to the NCAB**
- **NCAB discusses the BRP report and make recommendations to the NCI**

August/October 2016

- **NCI prepares FOA concepts for approval and publication**

January/March 2017

- **Receipt date for applications responding to FOAs**

June/July 2017

- **Review of applications**
- **Funding of awards**

with an important emphasis on the surrounding cells, but also on the stromal components and secreted factors. Enhanced data sharing has been a topic of discussion here and beyond, and I think will be a major focus that Warren will talk about. New approaches to pediatric cancer, understanding the underlying molecular bases, and new therapeutic options, and the exceptional opportunities fund.

This fund is slated to have up to $100 million in it, and the idea is if new and exciting ideas emerge from all of these considerations, that fund could be used in a very rapid way to support various groups to pursue the research in that area. One could imagine, for instance, launching challenges that would be open to the broader community that could be relatively quickly funded.

Now, critical to a successful accomplishment, the identification of scientific goals is trying to get as much input from the broader scientific community, the patient and the advocacy community, and the public at large. We've begun to formulate a strategy for scientific outreach, with the goal of providing the public and experts who are not engaged in the blue ribbon panel or in the working groups with ways to submit their ideas or proposals, and also to try to increase the public's participation and engage the broader public in the development of scientific opportunities.

And so the approaches that are being considered are an online idea repository, where people would post their proposals for new ideas—also we'd be willing to accept new ideas by email. We'd have workshops in a variety of different areas.

There's going to be representation of the NCI at various professional meetings including AACR and ASCO. And we also hope to have some of the blue ribbon panel meetings open to the public, as well as the working group, so we hope in that way to not only receive information but also to be very transparent in the [deliberations] of the panel and the working groups.

One of the charges in the president's memo establishing the cancer initiative was to try to accelerate research so that what would normally have been done in a decade could be done in five years. Accordingly, there's a very aggressive timeline for the blue ribbon panel to complete its work. What we are hoping is that

by the August-October 2016 timeframe we will already be preparing FOA concepts that will be brought here for approval and then publication with the goal of actually funding awards in the summer of 2017.

DOROSHOW: One of the aspects of the moonshot activities builds on something that's not really terribly expensive in dollars, but is expensive in terms of time, regulatory effort and interactions that need to be established.

Many of you know, I've talked a little about how we have a timeline for the development of the MATCH trial, and the length of time that it took to develop the formulary for the drugs involved in that study—roughly two years of negotiations with a large number of pharma companies that was reflected in a study that will reopen in a month or two with 24 different drug arms.

But all of those agreements, all the CRADAs, clinical trials agreements etc., are all related to a single clinical trial. And over the same two years, maybe longer timeframe, I've had many discussions—not only with folks around this table, but with many of the NCI cancer center directors—about how we could potentially help them to enhance their own precision medicine activities at their own centers.

Many months ago, actually, even before the moonshot activities got off the ground, but certainly catalyzed thereafter, we've begun trying to develop a process of developing a virtual drug formulary that we could make available for studies at individual NCI-designated cancer centers, and other centers that could hold their own in investigator-initiated INDs, but where we would serve to distribute drugs which is a relatively costly process—do some overall quality control and facilitate the IP arrangements with a large number of companies.

I can tell you that we've spoken to a number of companies so far, and have had a number of calls scheduled for the next several weeks, and pretty much the response has been positive. Always the details are the issue, but we hope to have a large meeting at ASCO with many pharma companies there because we want to be able to provide as many drugs as possible to all of your centers for all the studies that you would all like to do, whether they're supported by NCI grants or your own philanthropic or other kinds of funds.

I know especially for combination studies, utilizing drugs from two different companies—as well as for preclinical activities, but primarily for clinical trials, this has been a major limiting issue that has made it difficult for centers around the country to carry through their mission.

We hope to roll this out as part of the moonshot activity. One of the encouraging parts of this is that we have strong support from the vice president's office. He is certainly willing to interact with pharmaceutical companies to try to facilitate access to these compounds for such trials.

So, more later—it's certainly something that is in process—but we would love to have, by the end of the year, something that we can announce to you.

Let me give you a little bit of update on the precision medicine activities, because you will be seeing—both at the June meeting and at subsequent meetings—RFAs that come to you that are in response to the funding from the precision medicine in oncology activities.

The first of these will be in the area of immunotherapy. We were very fortunate to have a large workshop toward the end of January—very well attended, with outstanding presentations that generated a plethora of ideas. The only issue will be how much money we have to carry forward these ideas.

Just to give you broad brushstrokes, because of course you will see the details: but there was a lot of support for trying to fund more in the way of basic immunotherapy, in the R01 space.

There was significant interest in the NCI trying to support further development and pilot activities in the T cell adoptive immunotherapy, which is a very expensive undertaking, as you all know. And then I think the largest amount of support was for us to work with the immunotherapy community to figure out how we could develop platforms to take the clinical trials that we're supporting—not just to do more trials that companies might be interested in doing, but rather to have the kinds of correlative science translational support to really understand inpatient materials, biopsies, pretreatment biopsies and the like and circulating cells, and the pharmacodynamic effects and molecular effects of these compounds are in the context of both tumor and stromal cells.

And that's an expensive undertaking, but there are organizations, many of them at your institutions, well poised to facilitate the fairly large spectrum of immunotherapy trials that the NCI supports now, without that kind of basic scientific translational scientific underpinning that we would hope to be able to utilize some of these funds to carry forward. And you will hear more about this at the next meeting.

There are other activities related to PMO that are in the process of development. We're having a workshop

on Thursday about patient-derived xenografts. You will almost certainly see FOAs related to that activity, but with respect not to phase, but to the associated development of the NCI's PDX repository.

I'm happy to tell you that it's very likely that, come July or so, we will be open for business in terms of starting to distribute the first cell lines and models that we will make available at very modest cost—very well-characterized models.

Our website will go live—and you'll all get notice of this; this is not something that will be under the radar. We are all working very hard to make sure that we have enough material to supply your investigators when this goes live in July.

AVEO Execs Face Fraud Charges

(Continued from page 1)

In court documents, SEC said that AVEO didn't disclose the extent of the agency's concern about tivozanib in public statements to investors. Specifically, the company didn't disclose that FDA staff had recommended a new clinical trial to address the concerns about patient death rates during the first clinical trial, the complaint states.

Months later, when FDA made a public statement that it had recommended an additional clinical trial, the company's stock price dropped by nearly a third. The trial was never conducted and the drug wasn't approved.

The complaint, filed at the U.S. District Court for the District of Massachusetts, is posted here as a PDF. The document draws on AVEO internal documents to demonstrate the insider's view of the tivozanib development program.

Court documents don't mention any of the company's board members, and focus entirely on AVEO's former executives—what they knew, and when they knew it.

AVEO's co-founders include Ronald DePinho, now president of MD Anderson Cancer Center, and his wife Lynda Chin, formerly a senior scientist at MD Anderson.

After coming to MD Anderson, DePinho continued to serve on AVEO's board of directors and Chin served on the company's scientific advisory board. DePinho has since stepped off the board, and the company, which is trading below $1 per share, appears to no longer have a scientific advisory board.

In May 2012, DePinho caused considerable controversy by recommending AVEO's stock during an appearance on a CNBC program. This recommendation got him named as a defendant in the initial version of shareholders' suit, which is currently on appeal. Neither the episode nor his name figure in the SEC complaint.

Documents from the shareholders' litigation are available on The Cancer Letter website.

MD Anderson officials declined to comment on the SEC action and AVEO's settlement with the agency.

The SEC complaint reads:

"On May 11, 2012, AVEO officials met with FDA staff to discuss the results of the clinical trial and to discuss the anticipated filing of a New Drug Application for Tivo. At the May 11, 2012, pre-NDA meeting, FDA staff told AVEO they were concerned about results from TIVO-1 [phase III trial] that showed that, while Tivo seemed to be slowing the progression of the disease, patients taking Tivo were dying sooner than patients taking the other study drug. The FDA staff recommended that AVEO conduct a second large, randomized clinical trial to address these concerns. Conducting a clinical trial for an experimental drug such as Tivo is expensive and time-consuming. AVEO estimated the cost of such an additional trial at more than $80 million, and estimated that it would take approximately three years. AVEO had already invested a similar amount of time and money in TIVO-1.

"Although AVEO informed investors that FDA staff had raised concerns about death rates for patients taking Tivo, defendants concealed from investors the depths of the FDA staffs concerns and, in particular, the fact that FDA staff had recommended a second full clinical trial to address those concerns. AVEO adhered to a corporate communications strategy that emphasized AVEO's data analysis efforts, while downplaying the possibility of further, preapproval trials."

Key Date in SEC Complaint: May 11, 2012

A week after AVEO's pre-NDA meeting, on May 18, 2012, DePinho appeared on Closing Bell with Maria Bartiromo, a CNBC television program, and described tivozanib as a "very effective drug that has a superior safety profile," that constitutes "massive advances in our ability to really do something about a disease that has long been very refractory."

Soon after making this statement, DePinho was contacted by The Cancer Letter. He immediately apologized, stating that his position as a state employee makes it inappropriate for him to recommend stocks.

At the same time, AVEO officials said to The Cancer Letter that DePinho wasn't speaking for the

Tradeoffs

Source: SEC complaint

Approach	Pro	Con
Stay the course, start an additional OS trial	Maintains potential for on-time launch	High Risk of RTF or Non-approval
Proceed in EU, Delay in US until 2nd OS trial complete	Reduces Risk in US	Lose 3 years of US revenue
Delay WW until 2nd trial complete	Reduces Risk WW	Lose 3 years of WW revenue

An AVEO executive's summary of options open after a disastrous pre-NDA meeting with FDA.

company when he appeared on the television program. (The Cancer Letter, June 1, 2012). Indeed, he appeared on the program in his roles as a scientist and president of MD Anderson, and on that trip to the CNBC studios in New York he was accompanied by MD Anderson employees.

Contacted by The Cancer Letter a year later in 2013, as details of the tivozanib controversy continued to emerge, DePinho said he wasn't aware of FDA's views on the approvability of tivozanib when he appeared on CNBC. "I was not involved with the discussions with FDA. I suggest you contact AVEO." (The Cancer Letter, May 10, 2013.)

The Cancer Letter originally relied on Texas sources who said that AVEO's pre-NDA meeting occurred on May 12, 2012. The SEC complaint corrects the record: the pre-NDA meeting occurred on May 11, but its results were discussed with the AVEO executive team on May 12, 2012.

Records obtained by The Cancer Letter show that on May 7, 2012, or 11 days before DePinho offered this stock tip—Chin traveled to the Boston area to take part in a meeting of AVEO's scientific advisory board as it prepared to present clinical data to FDA (The Cancer Letter, Sept. 13, 2013).

The agenda for the May 7 meeting of the AVEO scientific advisory board, which was obtained by The Cancer Letter, consisted of three items; "Discussion of TIVO-1" was one of them. TIVO-1 compared tivozanib with sorafenib in 517 patients with advanced renal cell carcinoma.

"I did attend the May 7, 2012, AVEO Scientific Advisory Board meeting," Chin said in an email, responding to questions from The Cancer Letter in 2013. "Due to SAB confidentiality requirements, I am unable to disclose confidential or proprietary AVEO information; you may wish to contact AVEO for further information."

Chin said she didn't discuss the details with DePinho after returning from the SAB meeting.

According to the SEC complaint, the AVEO scientific advisors could have been briefed only on the company's interpretation of clinical data. The FDA interpretation of these results—including the statement that a new clinical trial would be required—would be given to the company four days later.

According to the SEC complaint, May 30—12 days after DePinho's appearance on CNBC—the company produced a PowerPoint presentation intended for board members.

The presentation stated that, according to FDA staff, "when one randomized trial is used to support registration, all endpoints must be consistent," that it is "[p]roblematic for FDA to approve a drug if OS trends in the wrong direction, despite positive PFS, even if there is a good reason for the OS trend," and that it would be "in the sponsor's best interest to start another randomized trial, in a population relevant to the US," and that "[o]verall survival is a key safety endpoint."

Internal Documents

According to the SEC complaint, AVEO's chief medical officer, Slichenmyer, attended the contentious pre-NDA meeting with FDA. Officials from Astellas Pharma, a partner on developing tivozanib, were also present.

FDA's official minutes, which were given to the company, read:

"The Agency expressed concern about the adverse trend in overall survival. Further discussion of these findings will be required at the time of filing and if the application is filed they will be a review issue that could affect approvability. FDA recommended that the sponsor conduct a second adequately powered randomized trial in a population comparable to that in the US. FDA also recommended that the sponsor conduct the final analysis of overall survival in the current trial. The Sponsor noted they plan to submit exploratory analyses in the NDA."

The problem was non-trivial: there were more deaths on the tivozanib arm.

The AVEO team tried to suggest that the patients taking tivozanib in the crossover trial were dying earlier because they were only receiving one therapy instead of two. FDA officials said that a well-designed trial would be needed to rule out an alternative explanation: that tivozanib patients were dying from the drug's toxicity.

"After leaving the meeting, beginning on his flight back to Boston, Slichenmyer prepared a PowerPoint presentation summarizing the pre-NDA meeting and laying out three options for AVEO to consider," the complaint states.

AVEO's executive committee met the next day, Saturday, May 12, 2012, and saw a slide that presented the three options: (1) Stay the course, ignoring FDA's recommendations; (2) proceed in Europe, but delay U.S. launch; or (3) delay worldwide launch.

The slide appears on page 9.

Soon after the pre-NDA meeting, AVEO drilled into the existing OS data in an effort to show that the OS results were a product of some patients having taken one drug, while others took two.

The company also started work on a second large-scale, randomized trial, to be called TIVO-2, which was projected to cost at least $83 million.

In July 2012, AVEO requested a meeting with FDA. As it requested the meeting, AVEO said that it "will conduct an additional randomized as recommended by the Agency at the pre-NDA meeting." A draft of a protocol for TIVO-2 was included.

AVEO proposed that TIVO-2 be initiated by the first quarter of 2013. "Does the Agency agree that the timing and design of the study...are consistent with the Agency's thoughts regarding an additional RCC study mentioned in the pre-NDA meeting?" the AVEO document asked.

On Aug. 29, 2012, FDA staff responded in writing to AVEO's request. In response to AVEO's question about the timing and design of the study, FDA staff said no:

"The FDA has significant concerns regarding the trial design described in your meeting package," the agency said. The proposed TIVO-2 design wouldn't adequately measure OS, given that "the primary concern of the current proposed NDA submission is the negative trend in [overall] survival."

Two days later, AVEO cancelled the meeting it had requested, writing to the FDA staff that, "[u]pon thorough review, AVEO believes it is not necessary to proceed with this meeting."

According to the complaint, this unconventional approval strategy disappointed Astellas. In an email to Slichenmyer, Johnston and others, the Astellas head of medical oncology wrote:

"The FDA did not provide a direct response on the question of timing for this study...This raises the possibility that this [additional] trial might be required before approval. These issues are directly relevant to the timing and probability for approval of the RCC indication and therefore necessitate discussion and deeper understanding with the FDA as soon as possible.

"[W]e find it highly unusual for a sponsor to cancel a scheduled Type A meeting with the FDA when the preliminary responses from the FDA indicate lack of agreement with the strategies proposed and 'significant concerns' with a Phase 3 study design. The approach taken by AVEO may decrease the risk of an acceptance for filing by the FDA which could also impact the probability of successful applications in other regions such as Europe."

A month later, on Sept. 28, 2012, AVEO filed the tivozanib NDA, which included the final OS results, which had worsened slightly for tivozanib since the pre-NDA meeting, the complaint states.

In March 2013, AVEO submitted a revised TIVO-2 protocol, and asked for a meeting with FDA to discuss the protocol. Here, the company asked whether the study could be conducted as part of a "postmarketing commitment or requirement."

The FDA staff said no, and that a survival deficit is too important a concern to be addressed after approval: "[We] encourage you to design the trial properly as soon as possible," the agency said. "The design, conduct, and results of this trial will determine whether this one additional trial will be sufficient for approval purposes."

What the Public Heard

The complaint provides these examples of the company executives' alleged failure to disclose what they were told by FDA:

"• On Aug. 2, 2012, AVEO issued a press release that referenced the FDA's 'concern regarding the [overall survival] trend' from TIVO-1. The press release stated that AVEO would be doing 'additional analyses' to address the FDA's concerns, but omitted any reference to the FDA staffs recommendation to conduct another trial or AVEO's ongoing work designing TIVO-2.

"• In a conference call with investors the same day, consistent with AVEO's communications strategy, Slichenmyer falsely stated that he could not 'speculate' on what the FDA might want in the future as far as additional studies. Slichenmyer did not need to 'speculate,' because he knew that FDA staff had recommended an additional clinical trial and that failure to complete such a clinical trial could jeopardize Tivo's approval prospects."

According to the SEC complaint:

• AVEO raised $53 million in a public offering of its stock in January 2013 while failing to disclose that the FDA staff had explicitly recommended during a May 2012 meeting that AVEO conduct an additional clinical trial for tivozanib.

• AVEO and its officers understood that the FDA's concerns were serious and an additional clinical trial is an expensive and time-consuming proposition. While AVEO went so far as to design a second trial and present trial designs to the FDA, it was never conducted.

• In corporate communications, AVEO and its officers suggested that they intended to satisfy the FDA by presenting new analyses of the data that had been gathered in the previous clinical trial. In doing so, AVEO concealed the FDA staff's level of concern about tivozanib's impact on patient survival and the recommendation that AVEO conduct a second clinical trial.

• Ha-Ngoc and Johnston knowingly approved and certified a press release and public filings that failed to disclose the FDA staff's recommendation for an additional clinical trial.

Johnston also made public statements during investor conferences suggesting the FDA staff had asked only for an explanation of the survival results. In reality, the FDA staff had recommended a second trial.

• Slichenmyer misled investors in an investor conference call when he falsely stated he could not "speculate" on what the FDA "might be thinking" and "might want [AVEO] to do in the future." He actually knew that the FDA staff had recommended an additional trial, the complaint says.

"We allege that AVEO and its executives hid from investors the reality of their communications with the FDA on Tivozanib while suggesting they had identified a simpler route to FDA approval," Paul Levenson, director of the SEC's regional office in Boston, said in a statement.

"Companies must be forthcoming about their communications with regulators so investors can make informed investment decisions while knowing what challenges may lay ahead."

The $4 million settlement with AVEO is subject to court approval. The SEC is seeking disgorgement against Ha-Ngoc, Johnston, and Slichenmyer, plus interest and penalties, as well as permanent injunctions and officer-and-director bars.

The Tivozanib Timeline

December 2008, May 2009

End-of-phase II meetings between AVEO Pharmaceuticals Inc. and FDA result in agreement concerning the design of the phase III trial of tivozanib for advanced renal cell carcinoma.

During the December 2008 meeting, the agency and AVEO discuss several study designs and FDA states that "a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive may be considered for regulatory decision."

FDA also states that "a statistically significant improvement in OS is not required for regulatory approval, but a pre-specified OS analysis plan is still helpful in the regulatory decision making process."

In the May 2009 meeting, the agency and AVEO discuss the final phase III protocol. Crossover design is not discussed and is not included in the phase III study itself (a later protocol added the crossover). See the FDA briefing documents for ODAC.

According to clinicaltrials.gov, the study's estimated completion date—defined as final collection date for primary outcome measure—is December 2011.

June 9, 2011

Ronald DePinho, co-founder of AVEO and member of the company's board of directors, is named president of MD Anderson Cancer Center.

His wife, Lynda Chin, an AVEO co-founder, joins MD Anderson as a senior scientist.

April 16, 2012

AVEO says the TIVO-1 pivotal trial demonstrates tivozanib's safety and efficacy. In a press release, William Slichenmyer, the company's chief medical officer, states: "We believe that the efficacy and safety profile consistently demonstrated by tivozanib and recently validated in our phase III TIVO-1 trial represent an important step forward in the treatment of patients who have advanced RCC. We are pleased with the opportunity to collaborate with tivozanib study investigators on publishing these positive phase II data in the Journal of Clinical Oncology, and look forward to advancing our work with our global partners at Astellas to bring tivozanib to patients who can benefit from this therapy."

April 20, 2012

DePinho asks for a waiver from the UT System to allow him to stay involved in commercial activities. The waiver would cover his service on the board of AVEO (The Cancer Letter, Oct. 26, 2012).

May 7, 2012

AVEO holds a meeting of its Scientific Advisory Board. The results of tivozanib trial are on the agenda.

May 11, 2012

At the pre-NDA meeting, FDA officials say the agency "expressed concern about the adverse trend in overall survival in the single phase III trial and recommended that the sponsor conduct a second adequately powered randomized trial in a population comparable to that in the U.S."

According to the SEC's March 2016 complaint, the final analysis of overall survival showed a trend toward a detrimental effect on OS with tivozanib; HR=1.25, p=0.11. Median OS was 28.8 months in the tivozanib arm and 29.3 months in the sorafenib arm. See the FDA briefing documents for ODAC.

May 12, 2012

AVEO's executive committee discusses the previous day's meeting with FDA, and considers the following options: (1) Stay the course, ignoring FDA's recommendations; (2) proceed in Europe, but delay U.S. launch; or (3) delay worldwide launch, as seen on a slide produced by AVEO Chief Medical Officer Slichenmyer. Pros and cons are listed for each.

May 16, 2012

An AVEO press release states that "overall survival data are not yet mature." The press release reports progression-free survival data: "Based on independent radiological reviews, tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 11.9 months compared to a median PFS of 9.1 months for sorafenib in the overall (Intent To Treat) study population (HR=0.797, 95% CI 0.639–0.993; P=0.042). Objective response rate for tivozanib was 33 percent compared to 23 percent for sorafenib. The efficacy advantage of tivozanib over sorafenib was consistent across subgroups in the study."

May 18, 2012

DePinho—who, at the time, was on the AVEO board of directors—appears on the CNBC program "Closing Bell with Maria Bartiromo." He recommends investment in the company and its drug, stating that AVEO "has utilized, has exploited science-driven drug discovery, and it's about to announce, or has announced already publicly, and will present in detail at ASCO, a very effective drug that has a superior safety profile for renal cell cancer, a major unmet need. So these are massive advances in our ability to really do something about a disease that has long been very refractory."

The appearance is posted on the CNBC website, and a transcript can be downloaded from The Cancer Letter.

DePinho and his family hold 590,440 shares in AVEO, company filings show. For three days preceding DePinho's appearance on CNBC, AVEO's stock price had been falling, trading at $11.28 per share just before DePinho goes on camera. The DePinhos' holdings are worth $6.66 million.

May 30, 2012

According to the SEC's March 2016 complaint, the company produced a PowerPoint presentation intended for board members May 30, 2012.

The presentation stated that, according to FDA staff, "when one randomized trial is used to support registration, all endpoints must be consistent," that it is "[p]roblematic for FDA to approve a drug if OS trends in the wrong direction, despite positive PFS, even if there is a good reason for the OS trend," and that it would be "in the sponsor's best interest to start another randomized trial, in a population relevant to the US," and that "[o]verall survival is a key safety endpoint."

June 1, 2012

Contacted by The Cancer Letter, DePinho apologizes for praising AVEO stock on the CNBC program. Offering investment advice is inconsistent with his position as an employee of the state of Texas (The Cancer Letter, June 1, 2012). Following DePinho's appearance, the share price started to climb back up, trading at about $12.73 when the market closed on May 31, making the DePinho holdings worth about $7.5 million. The company states that DePinho was not speaking on its behalf.

June 2, 2012

At the annual meeting of the American Society of Clinical Oncology, Robert Motzer, an attending physician on the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center and the principal investigator on the study, presents the TIVO-1 data. He says the overall survival data would be presented at a later date.

July 2012

AVEO requests a second pre-NDA meeting with FDA officials, saying that it "will conduct an additional randomized as recommended by the Agency at the pre-NDA meeting," and included a draft protocol for the $83 million TIVO-2 study.

AVEO proposed that TIVO-2 be initiated by the first quarter of 2013.

Aug. 2, 2012

AVEO acknowledges the survival deficit. A press release contains a "regulatory update," which states:

"The FDA has expressed concern regarding the OS trend in the TIVO-1 trial and has said that it will review these findings at the time of the NDA filing as well as during the review of the NDA. AVEO is conducting additional analyses to be included in the NDA submission that demonstrate that the OS data from TIVO-1 are consistent with improved clinical outcomes in RCC patients receiving more than one line of therapy; analyses that the company believes will directly address this issue. AVEO is continuing to work toward submitting the NDA by end of the third quarter; however, there is a chance that the additional OS analyses may cause the submission to move into the fourth quarter."

Aug. 31, 2012

AVEO cancels its request for a second pre-NDA meeting with FDA officials, after the agency expressed "significant concerns regarding the trial design" for the proposed TIVO-2 study

The proposed TIVO-2 design wouldn't adequately measure OS, given that "the primary concern of the current proposed NDA submission is the negative trend in [overall] survival," the agency said.

AVEO cancelled the meeting it had requested, writing to the FDA staff that, "[u]pon thorough review, AVEO believes it is not necessary to proceed with this meeting."

Sept. 28, 2012

AVEO submits an application for tivozanib for the treatment of advanced renal cell carcinoma. According to a press release, the application is supported by a single phase III trial, a randomized phase II trial, and an extension/crossover study.

Oct. 10, 2012

DePinho receives a waiver, which enables him to continue to serve on the AVEO board of directors (The Cancer Letter, Oct. 26, 2012). The waiver requires him to place the stocks of AVEO and other firms in a blind trust.

Dec. 20, 2012

AVEO announces that DePinho would step off the board effective Dec. 31, 2012. His wife, Chin, continues to serve on the company's scientific advisory board.

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May 2, 2013

ODAC votes 13:1 against approval of tivozanib, concurring with the agency that a deficit in overall survival on the experimental arm is unacceptable (The Cancer Letter, May 3). Post-ODAC, the company is trading at just above around $2.50, which means that if the DePinho holdings in AVEO remained the same, they would be worth less than $1.5 million.

June 10, 2013

FDA formally rejects AVEO's application for tivozanib in the treatment of patients with advanced renal cell carcinoma.

FDA stated that the inconsistent progression-free survival and overall survival results and imbalance in post-study treatments make the TIVO-1 results uninterpretable and inconclusive when making a risk-benefit assessment necessary for drug approval, and recommended that AVEO conduct an additional clinical study to support approval of tivozanib for the treatment of advanced RCC. The FDA also stated that the proposed dissolution acceptance criterion was not supported by the provided dissolution data, and would need to be updated and resubmitted.

March 29, 2016

The SEC files charges against AVEO Pharmaceuticals and three of its former executives, saying that AVEO did not disclose the extent of the agency's concern about tivozanib in public statements to investors.

Specifically, the complaint said that the company didn't disclose that FDA staff had recommended a new clinical trial to address the concerns about patient death rates during the first clinical trial, the complaint states.

SEC said the company agreed to pay a $4 million penalty to settle the charges without admitting or denying the allegations.

The SEC is seeking disgorgement against Ha-Ngoc, Johnston, and Slichenmyer, plus interest and penalties, as well as permanent injunctions and officer-and-director bars.

Schools of Public Health: Moonshot Undervalues Prevention

Over 70 deans and directors of public health programs and institutes signed a letter March 21 asking the White House for to prioritize federal investments in public health and cancer prevention.

The letter, addressed to Vice President Joe Biden, urges the administration to "pay careful attention to the balance between treatment and prevention-related investments."

The letter comes from the Association of Schools and Programs of Public Health and includes signatories from Yale School of Public Health, the New York Medical College, Harvard T.H. Chan School of Public Health, Johns Hopkins Bloomberg School of Public Health and University of California, Berkeley School of Public Health.

Biden is leading the National Cancer Moonshot Program, a $1 billion initiative aimed at doubling the progress of cancer research over the next five years. The program would allot $195 million to NIH in fiscal 2016, according to Obama's budget proposal (The Cancer Letter, Feb. 12).

The fiscal 2017 budget proposes to allocate $755 million in mandatory funds for new cancer-related research activities—$680 million for NIH and $75 million for FDA. The remaining $50 million is expected to fund Centers of Excellence at the Departments of Defense and Veterans Affairs.

The public health deans say they "strongly support" the moonshot.

"We are concerned, however, that the initiative may be undervaluing the vital role that public health and prevention have played—and must continue to play—in reducing cancer incidence and mortality," the March 21 letter states. "Investments in public health and cancer prevention can make an enormous impact on reducing cancer incidence and mortality and should be a priority of the Cancer Moonshot initiative."

A PDF of the letter is posted here.

In Brief

Singer, Kibbe Named NCI Acting Deputy Directors

(Continued from page 1)

Singer serves as the director of the NCI Division of Cancer Biology and head of the Molecular Regulation Section of the Experimental Immunology Branch. Kibbe is the director of the NCI Center for Biomedical Informatics and Information Technology.

"Dinah Singer is going to have major responsibility for coordinating the proposals, etc., with the blue ribbon panel and setting up other aspects of the vice president's initiative," Lowy said at a virtual meeting of the NCAB. "Warren has been an absolutely key member down at the White House meetings and elsewhere. We think his expertise and commitment are second to none in this area," he continued.

Singer has served as the director of the Division of Cancer Biology since 1999. She serves on a number of scientific and advisory boards, is a member of the American Association of Immunologists and the American Association of Cancer Researchers, and has served as a senior science officer at the Howard Hughes Medical Institute.

Singer's research is focused on the regulatory networks governing transcription and the interplay of promoter elements and transcription complexes that establish appropriate regulation of gene expression across diverse cellular and tissue environments.

In recent studies, Singer and her team discovered that BRD4, a bromodomain family member currently being tested as a therapeutic target in cancer and autoimmune diseases, is a RNA polymerase II kinase essential for transcription. Studies demonstrated that BRD4 plays a critical role in regulating the early steps of transcription initiation, both through its direct phosphorylation of RNA polymerase II and its interactions with other components of the transcription machinery, including TAF7.

Prior to joining NCI, Kibbe had been at Northwestern University for more than 20 years, and was most recently a professor of Health and Biomedical Informatics in the Feinberg School of Medicine and the director of cancer informatics and CIO for the Robert H. Lurie Comprehensive Cancer Center.

Kibbe is an active member of the open biomedical ontologies community, part of the Gene Ontology Consortium, was a member of the CTSA Ontology Working Group, and was a founder of the open source Human Disease Ontology. Kibbe was the co-principal investigator of the NIH-funded Dictyostelium Model Organism Database dictyBase.

PETER PAUL YU was named physician-in-chief of the **Hartford HealthCare Cancer Institute.**

Yu, a medical oncologist and hematologist, comes to Hartford HealthCare from Palo Alto Medical Foundation in California, where he has worked since 1989. Since 2008, he has served as the organization's director of cancer research.

In 2015, Yu served as president of the American Society of Clinical Oncology.

"We are enormously pleased to have someone of Dr. Yu's stature and ability join us to lead the clinical direction of our Institute. His vast expertise and passion for excellence made him the clear and ideal choice," said Elliot Joseph, president and CEO of Hartford HealthCare.

Yu has served as a research fellow and associate at Memorial Sloan Kettering Cancer Center. His experience makes him well-suited to oversee the Hartford HealthCare Cancer Institute's membership in the MSK Cancer Alliance, said Donna Handley, vice president of operations for the cancer institute.

The Hartford HealthCare Cancer Institute is a charter member of the Memorial Sloan Kettering Cancer Alliance, and Yu will serve as the alliance's director of health informatics. In that capacity, he will report to Jose Baselga, MSK's physician-in-chief and chief medical officer.

GREG SIMON was named executive director of the **national moonshot cancer initiative** by Vice President Joe Biden.

Previously, he helped start the charity FasterCures in 2003. In 2009, he became senior vice president for patient engagement at Pfizer. Most recently, he was chief executive of Poliwogg, a financial services company. Simon was diagnosed with leukemia in 2014 and was treated at Memorial Sloan Kettering Cancer Center.

JOHNS HOPKINS UNIVERSITY launched the **Bloomberg-Kimmel Institute for Cancer Immunotherapy**, with $125 million in donations.

The institute was founded with two $50 million donations, one from former New York City mayor Michael Bloomberg, and one from philanthropist Sidney Kimmel. An additional $25 million was raised from other supporters.

Drew Pardoll will serve as the institute's

inaugural director. Pardoll is co-director of the Cancer Immunology and Hematopoiesis Program and a professor of oncology at Johns Hopkins. He is also the s Seraph Professor of Oncology, Medicine, Pathology and Molecular Biology and Genetics.

For over 20 years, Pardoll has studied molecular aspects of dendritic cell biology and immune regulation, particularly related to mechanisms by which cancer cells evade elimination by the immune system. He helped produce a number of immunotherapies, including GVAX cancer vaccines and Listeria monocytogenes-based cancer vaccines. He has also served on the editorial board of the Journal of the National Cancer Institute and Cancer Cell.

Bloomberg is a 1964 graduate of Johns Hopkins University and was chairman of its board of trustees from 1996 to 2002. He has given more than $1.2 billion to the university and the Johns Hopkins Health System since graduating.

Since 2001, Kimmel has contributed $157 million, and Johns Hopkins has named its cancer center after him. Kimmel also has given an additional $2.4 million to support 12 young cancer scientists at Johns Hopkins as part of his national Kimmel Scholars Program.

HYUNDAI HOPE ON WHEELS announced four $1 million grants to Children's Oncology Group institutions: The Children's Hospital of Philadelphia, Dana-Farber Cancer Institute, Fred Hutchison Cancer Research Center and the University of Florida.

Through the Hyundai Quantum Grant, each institution will receive $250,000 per year over the course of four years to fund their research on pediatric cancers. The winning proposals will help advance new immunotherapies and therapeutic strategies for the most high-risk childhood cancers, including acute myeloid leukemia and medulloblastoma tumors.

The grant winners are: **Richard Aplenc**, of The Children's Hospital of Philadelphia; **Loren Walensky**, of Dana-Farber; **Soheil Meshinchi** and **Marie Bleakley**, of Fred Hutch; and **Duane Mitchell**, of the University of Florida.

This year marks the organization's 18th year, with a total of $115 million donated.

"The Hyundai Quantum is a terrific grant. Outside the NIH, this is one of the largest grants available to pediatric cancer researchers. This is a significant amount of money and it will provide researchers the time and funding they need to drive real advances in the field. We applaud Hyundai for its leadership," said Crystal Mackall, former head of the NCI pediatric cancer division and current associate director of the Stanford Cancer Institute and HHOW committee reviewer.

MD ANDERSON CANCER CENTER and **TESARO Inc**. announced a collaboration to discover and develop small molecule product candidates against immuno-oncology targets, through the cancer center's Institute for Applied Cancer Science.

Under the agreement, TESARO will receive exclusive worldwide rights to develop and commercialize any small molecule product candidates that result from this collaboration. MD Anderson will be responsible for conducting research activities aimed at identifying clinical candidates with defined characteristics targeting certain immuno-oncology targets. TESARO will fund research, development, and commercialization expenses for this collaboration. Additional terms of this agreement were not disclosed. The TESARO collaboration is IACS's first to specifically focus on small molecule drug discovery, according to MD Anderson.

Drugs and Targets

FDA Publishes Draft Guidance On Biosimilar Product Labeling

FDA published a draft guidance of recommendations for biosimilar product labeling.

Based on a demonstration of biosimilarity, biosimilar product labeling should include a description of the clinical data that supported safety and efficacy of the reference product as described in the FDA-approved product labeling for the reference product, the agency said.

"FDA recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The relevant data and information from the reference product labeling that should be incorporated into the biosimilar product labeling will depend on whether the applicant is seeking approval for all conditions of use (e.g., indication(s), dosing regimen(s)) or fewer than all conditions of use of the reference product for the biosimilar product," the guidance said.

The guidance also included sections on approaches to content presentation and product identification, as well as recommendations on updating product labeling.

A PDF of the draft guidance can be found here.

FDA also published a blog post regarding their perspective on biosimilar product labeling.

"For the Full Prescribing Information, we recommend that biosimilar product labeling incorporates relevant data and information from the FDA-approved labeling for the reference product, along with any appropriate modifications specific to the biosimilar product. Note that a biosimilar product is not required to have the same labeling as its reference product, and so biosimilar product labeling may differ from the reference product labeling for a variety of reasons. For example, a biosimilar applicant may seek licensure for fewer than all of the indications for which the reference product is approved, and this difference would be reflected in product labeling," wrote Leah Christl, associate director for therapeutic biologics and lead of the Therapeutic Biologics and Biosimilars Staff in the FDA CDER Office of New Drugs.

The Notice of Availability will post the week of April 4 in the Federal Register and will provide information on how to submit comments on this draft guidance, FDA said.

FDA approved Defitelio (defibrotide sodium) to treat adults and children who develop hepatic veno-occlusive disease with additional kidney or lung abnormalities after hematopoietic stem cell transplantation. This is the first FDA-approved therapy for treatment of severe hepatic VOD. Hepatic VOD can occur in patients who receive chemotherapy and HSCT.

The efficacy of Defitelio was investigated in 528 patients treated in three studies: two prospective clinical trials and an expanded access study. The patients enrolled in all three studies had a diagnosis of hepatic VOD with liver or kidney abnormalities after HSCT.

In the three studies, 38 to 45 percent of patients treated with Defitelio were alive 100 days after HSCT. Based on published reports and analyses of patient-level data, the expected survival rates 100 days after HSCT would be 21 to 31 percent for patients with severe hepatic VOD who received only supportive care or interventions other than Defitelio.

The most common side effects of Defitelio include abnormally low blood pressure, diarrhea, vomiting, nausea and nosebleeds. Serious potential side effects of Defitelio that were identified include bleeding and allergic reactions. Defitelio should not be used in patients who are having bleeding complications or who are taking blood thinners or other medicines that reduce the body's ability to form clots.

The FDA previously granted Defitelio priority review and an orphan drug designation. Defitelio is marketed by Jazz Pharmaceuticals.

FDA granted orphan drug designation for Iomab-B, a radioimmunotherapeutic that conditions relapsed and refractory acute myeloid leukemia patients for a hematopoietic stem cell transplant. Actinium Pharmaceuticals Inc., iomab-B's sponsor, plans to begin a phase III trial in 150 relapsed and refractory AML patients over the age of 55.

Iomab-B is a radioimmunoconjugate consisting of BC8, a novel murine monoclonal antibody, and iodine-131 radioisotope. BC8 has been developed by the Fred Hutchinson Cancer Research Center to target CD45, a pan-leukocytic antigen widely expressed on white blood cells.

This antigen makes BC8 potentially useful in targeting white blood cells in preparation for hematopoietic stem cell transplantation in a number of blood cancer indications, including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, Non-Hodgkin lymphomas and multiple myeloma. When labeled with radioactive isotopes, BC8 carries radioactivity directly to the site of cancerous growth and bone marrow while avoiding effects of radiation on most healthy tissues.