THE CANCER LETTER

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Betting on Biotech

Wall Street Analyst Who Sounded Alarm Over Prostate Cancer Drug Provenge In JNCI Settles with SEC Over Shorting Dendreon Stock

By Paul Goldberg

The lead author of a paper that argued that the prostate cancer immunotherapy Provenge endangered lives of cancer patients has entered a settlement agreement with the Securities and Exchange Commission.

The agreement states that Marie Huber, an analyst at a hedge fund, had prepared and anonymously circulated a paper about Provenge (sipuleucel-T) at a time when her put options in Dendreon Inc., the drug's sponsor, were about to expire.

Huber subsequently expanded her arguments as the lead author of a 2012 paper in JNCI. Disclosure that accompanied that paper stated that Huber holds no position in the company, but stops short of disclosing that she had shorted the stock 18 months earlier. JNCI requires disclosure of relevant conflicts for a period of 36 months prior to submission.

(Continued to page 2)

An Earmark in the Making?

NCI Urged to Boost Gastric Cancer Funding

By Matthew Bin Han Ong

A group of members of both chambers of Congress is urging NCI to increase funding for research in gastric cancers—the latest in a string of advocacy initiatives to carve out fiscal support for specific diseases.

"Deadly gastric cancer is on the rise in young people," reads a Nov. 26 letter from five members of the Senate. "Gastric cancer receives by far the lowest amount of research funding for the common cancers at NCI, at only $12 million in 2012. That amounts to only 0.4 percent of the entire NCI FY 2012 budget for common cancer research."

The letter, addressed to NCI Director Harold Varmus, is a response to Varmus's reply to an earlier letter from members of the House of Representatives.

(Continued to page 7)

In Brief

Johnson to Leave NCI Office of Communications

LENORA JOHNSON was named director of health education, communications, and science policy at the **National Heart Lung and Blood Institute**. Johnson will be leaving her job as director of the NCI Office of Communications and Education. Johnson will be leaving NCI Dec. 13.

Johnson has served as OCE director for over seven years.

(Continued to page 10)

Analyst who Published in JNCI Enters Agreement with SEC

(Continued from page 1)

In the agreement with SEC dated Nov. 27, Huber admitted no guilt, but agreed to pay a $25,000 fine and accepted a six-month suspension from participating in securities trading activities.

Her associate, Jess Jones, who played a supporting role in distribution of the document, also signed the agreement with SEC and was subjected to the same penalties.

More than anything, the story of Provenge, an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castration resistant prostate cancer, points to fluidity of the boundaries between the investment community, academia and advocacy groups.

Since March 29, 2007, the day the Provenge application was first considered by the FDA Cellular, Tissue and Gene Therapies Advisory Committee, these interests—in both the pro-Provenge and anti-Provenge camps—clashed ferociously (The Cancer Letter, April 13, 2007; April 27, 2007; May 4, 2007).

During the drug's colorful history, the most unseemly behavior came from the pro-Provenge forces, a loose conglomeration of self-described patients and investors.

Many of these individuals—derided as "Dendreonites" and "Provengeans" by people who didn't share their zeal—congregated on the Investor Village forum, whipping themselves into frenzy of enthusiasm for Provenge and vitriol toward skeptics.

At one point, death threats were made against doctors and scientists who advised FDA to delay approval until data from a randomized trial became available.

Money was collected on Investor Village to sue FDA, and unsuccessful efforts were made to seize computers from The Cancer Letter as part of discovery in that suit. An Ohio judge ultimately fined the plaintiff for using invalid subpoenas and engaging in behavior that was meant to harass this publication (The Cancer Letter, Dec. 9, 2010).

Dendreon wasn't involved in these activities and was at times their target.

Now, Huber's agreement with SEC and her failure to make disclosure to JNCI suggests that neither side was well-behaved. (This would be doubly disappointing if the hypothesis she puts forth in the JNCI paper is valid.)

And, after all that steam was expended, Provenge has failed to become the blockbuster drug its boosters envisioned.

Provenge hit the market in 2010 with the price tag of over $90,000, almost double what was then the going price of a cancer drug. Other pricey cancer therapies at that time clustered around $50,000 for a year of treatment.

Now, Provenge is getting competition from other therapies, primarily the Johnson & Johnson oral drug Zytiga (abiraterone acetate), which was approved for castration-resistant prostate cancer.

Today Dendreon's stock is trading at around $3 a share. In late-April 2010, just before Provenge hit the market, the company's shares were trading at over $54.

Now, the scientists who conducted the phase III clinical trial that led to Provenge's approval are about to ask JNCI to retract the paper, arguing that the behavior described in the SEC settlement is inseparable from the paper ultimately published by the journal.

"The Huber paper published by the JNCI is a sad example of how financial interests have subverted the scientific process," said Eric Small, co-director of the Urologic Cancer Service and director of urologic oncology research at the University of California San Francisco, is a co-author of a New England Journal of Medicine paper that Huber disputed in JNCI.

Philip Kantoff, the lead author on the NEJM paper that summarized the results of the Provenge pivotal trial, said the SEC disclosure provides grounds for retraction of Huber's paper.

Kantoff, chair of the executive committee for clinical research and vice chair of Department of

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Medical Oncology, Solid Tumor Oncology at Dana-Farber Cancer Institute, said he isn't surprised by this latest twist in the story of Provenge.

"Provenge has been one of the most polarizing therapies," Kantoff said. "I think the reason for that goes deep into the history of immunotherapy, the believers vs. the non-believers. There was some amount of charlatanism, some amount of poor science that went into it, leading to a general disbelief that it actually would work eventually.

"The flip side of it were people who were strong believers in it who wanted it to be the answer to cancer."

An Alternative Explanation

Though an advisory committee voted to approve Provenge in 2007, FDA decided that the company's application was flawed and that a well-conducted phase III trial would be needed to support approval.

This delay so profoundly angered the Dendreonites that scientists who expressed skepticism received death threats. Howard Scher, chief of the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center, and Maha Hussain, associate director for clinical research at the University of Michigan Comprehensive Cancer Center, had to attend the 2007 annual meeting of the American Society of Clinical Oncology in the company of armed bodyguards.

Nonetheless, Dendreon completed a large randomized, controlled trial, IMPACT, announcing its results in a press release in April 2009, claiming a four-month survival advantage. FDA approved the agent on April 29, 2010 (The Cancer Letter, April 30, 2010) and NEJM published the results on July 29, 2010.

After reviewing the FDA approval documents, Huber concluded that the Provenge pivotal trial was fundamentally wrong.

Patients on the experimental arm lived longer than those on control arm because patients who got placebo received significantly fewer T-cells than Provenge arm patients. She believed that placebo patients received about one-third of their cells back, which caused them to die sooner.

In June 2010, she started work on a report titled "Provenge Ph III Trials – The Alternative Explanation of Survival Results."

Huber, who at this writing is 35, was employed as an analyst at a hedge fund. She has a Bachelor's degree in biochemistry and a Master's degree in Bioscience Enterprise from Cambridge University. She is not a registered adviser and doesn't hold any securities licenses, SEC documents state.

Wall Street analyst and JNCI author Marie Huber.
Source: www.theprovengetrials.org

Her resumé, available on her website, states that between 2007 and 2011 Huber was an analyst with New York-based P. Schoenfeld Asset Management.

Documents suggest that Huber believed that the market would soon recognize the flaws that she believed marred the Provenge pivotal trial.

Between June 17 and July 12, 2010, Huber purchased $125,431 in July Dendreon put options and $110,627 in August put options.

"Huber also purchased put options in her mother's account, and shared her analysis with friends and family who subsequently traded in Dendreon securities," the agreement with SEC states.

According to the agreement, Huber didn't receive approval for these trades, as required by her fund's trading policies. Jones, who gambled a lower sum, similarly didn't obtain approval from his fund.

The July put options were set to expire July 17, 2010, and had strike prices ranging from $10 to $30. All of the put options were "out-of-the-money," and most of them had strike prices of $25 or less.

Dendreon common stock was selling in the low to mid $30s.

This was a gutsy move. Put options that aren't exercised become worthless.

On June 30, 2010, the Centers for Medicare & Medicaid Services launched a national coverage analysis for Provenge, and requested public comment.

According to SEC documents, Huber encouraged

her hedge fund to submit the report she prepared on Provenge to CMS. Though anyone can submit a public comment to a government agency, hedge funds generally do not.

"As the July 17, 2010, put option expiration date neared, respondents were concerned that HFA-A was not going to submit the report to the CMS website prior to the expiration of their put options," the agreement states. "As a result, Respondents arranged to disseminate the Alternative Explanation on their own prior to option expiration."

On July 12, 2010, Huber gave Jones a flash drive which contained documents relating to the alternative explanation, including copies of the alternative explanation, a distribution list of email addresses, and a version of the email text that Jones subsequently used to disseminate the report.

Documents state that on July 14, 2010, Jones created an email account using the name Jonathan White and Dendreon's ticker symbol DNDN (jon.white.dndn@gmail.com) and sent emails attaching the alternative explanation to more than 450 email addresses from a distribution list that Huber had provided.

Most of the email recipients were affiliated with the medical and pharmaceutical industries, documents state.

The report that was attached to the "Jonathan White" emails, as well as Huber's agreement with the SEC, are both posted on The Cancer Letter website.

The letter read:

Dear Colleague,

The document attached...was written by a group of scientists and physicians whose concern for their safety has forced them into hiding. In it they postulate a design flaw in the Provenge Ph III trials with potentially profound implications. Those who previously voiced legitimate scientific concerns regarding this drug had their lives threatened, were forced to employ body-guards and have been traumatized into silence.

Every dissenting voice is squashed. This fear extended to the FDA reviewers, who stated if it doesn't get approved this time, there will be bloodshed. It is our constitutional right to express our opinions. If money and power can scare dissenters into silence, it is a sad day indeed for our nation and for humankind.

I call upon you to read this argument and make your own independent, critical assessment of its merits. If you see the merit of the concerns it voices, I call upon you to express those views to the FDA and CMS (Leslye Fitterman, PHD; Leslye.fitterman3@cms.hhs.gov) who have been trusted with the power of protecting the American public.

In my personal opinion (and that of select esteemed colleagues) that a legitimate concern has been raised, which is that the immune cells that are explicitly removed from placebo patients in the Provenge trials could have significantly compromised these patients and their ability to fight their cancer. This possibility must be explored as an alternative explanation for these trial results, because if it is right, it implies that Provenge treatment is harmful to patients because of all the immune cells that are lost during this treatment, and not prolonging life at all!

If any of you reach the same independent assessment of this piece as I do, it is our moral obligation to have a voices heard and demand this matter is investigated. We must stand up against those that wish to use the power of the sword to threaten legitimate scientific discourse and concern for patient safety. We cannot allow the big money invested in this drug to feed on the fear and desperation of cancer patients and their families to co-opt their voice to silence those very people that are trying to protect them.

Sincerely,

A concerned physician, scientist and citizen.

P.S. Scientific progress since 1999, when the FDA agreed to the design of these trials, has significantly increased our understanding of immune aging. Now that we know that the aged immune system cannot replace lost cells in the way that the youthful immune system can, we should identify the possible mistakes of our earlier ignorance. We infected thousands of people with HIV and hepatitis C through blood infusions before we discovered that these are blood-bourn pathogens. We gave thalidomide to thousands of pregnant women before we understood that this was causing birth defects. We used epo to drive hemoglobin levels to unhealthy levels until we learned that this is harmful. We make mistakes, and scientific progress reveals those mistakes. The sooner we rectify earlier mistakes, the sooner we curtail the unintentional harm we are causing.

Stock Price Drops, But Not Enough

On July 14, 2010, Dendreon shares closed at $33.99 on volume of 4,042,300. On July 15, 2010, after the "Jonathan White" emails were sent, Dendreon shares fell 7.2 percent intraday ($31.54) and closed down 4.5 percent ($32.45).

According to the agreement, trading volume on July 15 was 9,084,700, nearly double the average volume for the three trading days before and after July 15. That day, Huber sold 376 July put option contracts with strike prices of $27 and $30 for total proceeds of $2,841.

However, Huber and Jones "suffered significant trading losses because the vast majority of their put option contracts remained unsold or unexercised because they were so far 'out-of-the-money,'" the agreement states.

According to documents, on July 14, Huber told her boss at her hedge fund that there had been a leak of the alternative explanation, and that she didn't know who leaked it. Since the document was now in public domain, she urged her boss to submit the document to CMS as public comment.

The fund's outside counsel submitted the alternative explanation to CMS on behalf of an unidentified client, and CMS posted the report on its website as part of the public comments. It's legal for a hedge fund to submit comments to CMS. However, such actions are unusual. An anonymous comment from a hedge fund is all the more unusual.

While it's appropriate for analysts to peruse publicly available data, such as FDA releases, SEC states that "the text of the July 14 'Jonathan White' emails omitted to state material facts.

"The emails stated that the Alternative Explanation was 'written by a group of scientists and physicians' and was signed 'a concerned physician, scientist and citizen.' These statements were materially misleading because the respondents were hedge fund analysts who held Dendreon put option contracts that were about to expire. These facts were material because investors would have considered the identity, motive, and financial self-interest of respondents important to assessing the report and any decision to buy or sell the securities of Dendreon."

From "Jonathan White" to JNCI

Contacted by The Cancer Letter, Huber responded with a statement, which was forwarded through her attorneys:

"I have agreed to a settlement with the SEC and I look forward to putting this issue behind me. I stand by the rigor of my scientific analysis and I shall continue to follow-up on the concerns that I expressed with regard to Provenge in the article published in JNCI in 2012.

"My primary motivation has always been the well-being of patients and the safety and effectiveness of this treatment. The accuracy of my research and conclusions are not an issue in the SEC settlement; neither my findings on Provenge submitted to CMS in July 2010, nor the concerns set forth by my co-authors and me in the JNCI article were contested by the SEC.

"Since first submitting the article to the JNCI in 2011, I have had no financial interest in the fate of Provenge. With this settlement complete, I look forward to moving forward with my life and career."

The JNCI paper gave Huber's argument something it lacked: scientific oomph. By the time she submitted the paper, she was no longer employed by the hedge fund.

She was working with three academic colleagues: Chris Parker, senior lecturer and honorary consultant in clinical oncology and prostate cancer translational research at the Institute of Cancer Research and the Royal Marsden, UK; Peter Iversen, professor of urology at Rigshospitalet, in Copenhagen; and Laura Haynes, then of the Trudeau Institute, of Saranac Lake, N.Y.

"I'm aware of the development, which of course is very disturbing," Iversen said in an email to The Cancer Letter. "I am a co-author on the manuscript above. Apparently the first author, Marie Huber, have had an extremely unfortunate potential conflict of interest, which was unknown to me. However, I stand completely behind the arguments and concerns expressed, and questions asked, in the article. The content of the article remains an accurate reflection of my personal concerns about the IMPACT trial."

"It's very peculiar how academics got into this discussion along with someone who was working in a hedge fund," Kantoff said to The Cancer Letter. "When that whole hypothesis came out, I asked a lot of expert immunologists and transplant physicians whether there is any potential validity to the contention that leukapheresis could be harmful, and I couldn't find amongst a bunch of experts that there was anything that could potentially be harmful from it. I think this is purely conjecture not based on sound data."

Revisiting the COI Disclosures

The JNCI instructions to authors state:

"Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the sponsor of the work that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so."

In a separate section, authors are urged to "report other relationships or activities that readers could perceive to have influenced or that give the appearance of potentially influencing, what you wrote in the submitted work."

In the disclosure form, a copy of which was obtained by The Cancer Letter, Huber stated that she has no conflicts to report, and added the following comment:

"I was previously employed by a registered investment advisor (until March 2011). Neither I, nor my former employer, has (or will have prior to publication), any financial interest in securities, either long or short, which may be influenced by the publication of this manuscript."

On her website, www.theprovengetrials.org, Huber wrote that after leaving the hedge fund she continued to pursue the Provenge controversy.

Huber wrote that "neither I, nor my former employer, has any financial interest in the fate of Provenge."

Huber's description of her evolving interest in Provenge offers a glimpse at the manner in which analysts approach scientific inquiry:

"Unfortunately there was very little evidence publicly available to support the mechanism proposed by Dendreon. Provenge didn't appear to affect disease progression and there was no published evidence of tumor killing. With most drugs I had previously researched, my comfort in their efficacy was based on studies, which provided evidence for the molecular and cellular mechanisms behind the outcomes being tested in trials. Because of this, the available evidence of Provenge's efficacy came entirely from survival results of its phase III trials.

"A complicated history of changing endpoints and enrollment criteria, had left the trials with several design flaws. But the FDA had approved these changes, and since most of the flaws would probably result in relatively small biases, they needed to be weighed against the robust statistical significance of the 4.1 month survival benefit the trials had shown. I knew, however, that the FDA had access to significantly more data than the public, and so, when the FDA approved Provenge on April 29, 2010, I was fascinated to discover what data and analyses had been available to them to provide insights into the drug's mechanism.

"Typically within 2-6 months after the FDA approves a new therapy, it posts a large set of its internal documents related to that approval on its website. And so it was that on June 9, I was able to begin scanning through these, and came across the confusing age data, which sparked my curiosity to dig deeper. Within days, the alternative explanation for the trial results became apparent, and in the weeks and months that followed, I spoke (under confidentiality agreements) with dozens of immunologists, immune aging experts, urologists and oncologists to solicit their opinions and see if there was any flaw in its logic or evidence against its plausibility that would justify dismissing it. While I heard many proposals for such counter-arguments, none of these held up to scrutiny.

"The story of the remainder of 2010 is long and complex, because my employer, for many very good reasons which I understood, did not want me to express and defend my concerns in public while I was still employed by the firm. Thus, in January 2011, I quit my job (a great job, with great healthcare benefits and a boss who was, and continues to be, a friend) in order to pursue the publication of the paper detailing the alternative explanation."

It's not publicly known how SEC became aware of the put options Huber purchased in 2010 or how it came to examine her role in writing the email blast on alternative explanations of the Provenge clinical trial. However, the JNCI paper was likely an invitation to scrutiny.

Huber's agreement with SEC describes the paper as "a version of the Alternative Explanation," which was "subsequently published in the Journal of the National Cancer Institute."

The agreement states that the findings do not address Huber's hypothesis.

A Dilemma for JNCI

Usually, a journal's remedy for an author's failure to disclose a relevant conflict of interest is mild: a correction.

However, in this case, the authors of the NEJM paper summarizing the IMPACT trial told The Cancer Letter that they intend to seek retraction of the Huber paper.

Charles Drake, associate professor immunology, urology and oncology and Johns Hopkins Kimmel Cancer Center, said the Huber paper should be retracted.

"I think the motivation was insincere," Drake said.

The paper should be retracted because of the now acknowledged connection between the anonymous email and the article in a peer-reviewed journal.

The link between the email and the JNCI paper was immediately obvious. "Everybody either got it or passed it around," he said.

"And when the article came out, that email, which seemed a little bit suspicious, had actually led to a paper. And the question is, who had actually written the email, who had written the article?"

Kantoff agrees.

"To say, 'Oops, she didn't disclose; she should disclose now,' is, to me, not sufficient. I think it places into tremendous question the whole hypothesis that they bring forward that is made into an article that's based on no data," Kantoff said. "It's based on 'This is what we think.'

"It's one thing to write a letter to the editor saying, 'We think this,' but they made this into an article, and it was co-authored by someone who is in a hedge fund, along with two academics, coming up with a non-scientific piece. And when I tried to rebut it, we were allowed to write a letter to the editor.

"I think JNCI handled it very poorly, and I would like to see retraction of the article."

JNCI editors said they haven't had the time to formulate a response.

"We are aware of the SEC settlement and are reviewing the relevant publications," JNCI Editor-in-Chief Carmen Allegra said in an email to The Cancer Letter.

An Earmark in the Making?

Group Wants NCI to Increase Gastric Cancer Research Funding

(Continued from page 1)

"We ask you to increase the federal research for stomach cancer in order to stem these dangerous trends," the Senate letter states.

The letter from the senators, as well as the July 22 letter from 39 House members, was the result of lobbying efforts by Debbie's Dream Foundation, an advocacy group focused on stomach cancer founded in 2009.

"We met with a number of representatives and we got tremendous interest from the members of Congress who talked to their constituents who are facing this," DDF Advocacy Committee Chair Kristin Fitzgerald said to The Cancer Letter. "We particularly want to advocate that stomach cancer is rising in young people—it had primarily been a disease of older people in the past, but that trend is really changing."

The Senate letter was signed by: Sens. Mark Kirk (R-Ill.), Sherrod Brown (D-Ohio), Robert Menendez (D-N.J.), Marco Rubio (R-Fla.), and Brian Schatz (D-Hawaii).

Jon Retzlaff, managing director of science policy and government affairs at the American Association for Cancer Research, said earmarking for specific diseases is harmful to research.

"Because of the broad scope of the AACR, we are very concerned about all of the more than 200 different types of cancer," Retzlaff said to The Cancer Letter. "In fact, in 2013, more than 580,350 Americans will

die from one of these more than 200 types of cancer.

"Therefore, while we can certainly understand and appreciate the interest and need for advocacy groups to draw attention to their particular disease, we also don't believe earmarking for one particular type of cancer is advisable, especially when so much of the funding from NIH and NCI is in vital discovery research, which benefits all diseases.

"In addition, there are also scientific opportunities that exist today to conduct research on many of the different pathways that are implicated in numerous cancers."

A similar campaign launched by the Pancreatic Cancer Action Network in 2012 resulted in a bill that required NCI to develop scientific frameworks for "recalcitrant" cancers (The Cancer Letter, Aug. 3, 2012).

At the time, the political momentum made outside critics—as well as some NIH and NCI officials—cringe at the prospect of interest groups competing for Congressional earmarks that would be doled out based on severity of disease and the advocates' ability to mobilize political clout.

Ultimately, Congress passed a watered-down version of the bill. The initial text of the bill threatened to touch off a "disease Olympics" and dilute NCI's authority to set research strategy, critics said (The Cancer Letter, Jan. 4).

Measures targeting specific diseases are a slippery slope, Varmus said at the time.

"One thing that I would very much object to that was part of the original bill is an effort to take decision-making about grant-making out of the hands of the NCI and putting it in the hands of advocacy groups, not just because inherently it's wrong, but very quickly, every other advocacy group would say, 'I want that too!' And then we have chaos."

So far, DDF's advocacy hasn't resulted in a legislative directive from Congress.

"I think that we have not yet determined where our strategy will proceed once we hear back from NCI," Fitzgerald said. "I think that's entirely going to depend on their response."

The House letter cites estimates from the American Cancer Society: 21,600 new cases of gastric cancer will be diagnosed in 2013, and 10,990 men and women will die from the disease within the year. At stage IV, the five-year survival rate for gastric cancer is 4 percent.

In responding to the letter, Varmus said the expected frequency of gastric cancer in 2013 represents a substantial decrease compared to over 80 years ago.

"Since 1930, the age-adjusted mortality rate from this cancer has decreased by more than 80 percent and incidence by more than 50 percent in the past 30 years," Varmus wrote in a letter dated Aug. 23. "However, as you noted in your letter, recent data from an NCI epidemiology study has suggested an increase in the incidence of diffuse gastric cancer in U.S. whites 25-39 years of age, although gastric cancer continues to arise far more frequently in older age groups.

"At this time, it remains to be determined if this observed increase, derived form a retrospective analysis of a relatively small number of cases, will be confirmed in additional studies and, if it is, what factors may account for the increase," Varmus wrote.

The letters are posted on The Cancer Letter website.

Neither Congress nor DDF have suggested a target figure for gastric cancer research, according to Fitzgerald.

NCI's breast cancer program received over $600 million in 2012, and NCI's funding for pancreatic cancer is about $105 million, according to the institute's portfolio.

"I hesitate to make comparisons to other diseases in terms of that," Fitzgerald said. "Congress is very careful about putting numbers in any kind of research. However, there has been language in the appropriations bills reports for several years in a row asking that NCI dedicate resources and attention to this issue.

"Now, unfortunately, it's hard to control the appropriations bills becoming law."

Fitzgerald said her organization would consider every avenue of support.

"I will expect that our advocacy will continue until we are able to make progress on this disease," Fitzgerald said. "I am hopeful that, given the severity of this disease and the young age of the people that are being diagnosed with stomach cancer, that that would help to make the case for the importance of the research that will stem the tide."

A former congressional staffer, Fitzgerald joined DDF after her husband died of stage IV gastric cancer in 2009 at 37 years old, eight months after being diagnosed.

"I am going to be an optimist with continued advocacy," Fitzgerald said.

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Varmus: TCGA Data is Available to Researchers

The various forms of gastric cancer are being evaluated as part of The Cancer Genome Atlas—a comprehensive sequencing, characterization and analysis of the genomic changes of more than 20 types of cancer.

TCGA is a joint effort of NCI and the National Human Genome Research Institute.

According to Varmus, more than 300 gastric tumors are being analyzed by TCGA, with more cases being added in the near future.

"The first publication concerning gastric cancer from the TCGA network should appear in the next six months, and will include analysis of all major subtypes of gastric cancer," Varmus wrote in his reply to the House letter. "Preliminary analysis suggests that the current definition of gastric cancer subtypes by histology is imprecise and can be refined by analysis of the tumor genome, and that gastric cancers have a number of recurrent oncogenic abnormalities, some of which are restricted to particular gastric cancer subtypes.

"Importantly, several of these genetic abnormalities may be amenable to testing candidate inhibitors for therapeutic intervention in the near future."

The completed data from TCGA gastric cancer samples are available to researchers for analysis.

"NCI has made access to this data a priority by funding the development of web sites that allow researchers to search for genetic alterations in any cancer studied by TCGA," Varmus wrote. "For example, researchers can use one cancer genomics portal to identify mutations in any particular gene of interest or determine the association between genetic abnormalities and clinical outcome."

However, the impact of TCGA on gastric cancer will be minimal without efforts by the NCI to assist researchers in utilizing the genomic data, lawmakers said.

"Very little foundational research data exists for gastric cancer; thus, gastric cancer researchers are greatly in need of federal assistance to ensure that promising gene candidates identified in TCGA research are able to be investigated to make progress in this field," the members of Congress wrote. "Though the TCGA information will be available on the cancer genomics portal, researchers need funding in order to develop the research data necessary to apply and receive NCI research grants."

DDF and its constituents want to see a return on federal investment in TCGA, Fitzgerald said.

"Think of the money Congress has spent on the TCGA analysis," Fitzgerald said to The Cancer Letter. "Enormous amounts of money have been spent to create this data, so we've got an investment there in creating this data.

"I think those at NCI would need to really seriously evaluate what kinds of funding that would be necessary in order to see that investment reach fruition. What we are asking is for their assistance to ensure that it does reach fruition."

DDF: Gastric Cancer Funding is "Affirmative Action"

Asked whether DDF's efforts would potentially erode NCI's peer review process and ability to set research strategy, Fitzgerald said the group's mission is more about leveling the playing field and getting the small players in.

"For example, if you have a lot of money and you have a lot of foundational research, you can draft a grant application that will get funded because you can show the potential for scientific discovery based on your previous research," Fitzgerald said. "You have the funding to make further investigation to prove those discovery potentials, and you can get a successful grant research application funded.

"The current situation works for folks like that.

"In the past, as a country, we have said, 'Gosh, everybody's trying to get into college. But gosh, only the people that really have the ACT prep and all these things are able to get in.'

"Well, then we made affirmative action and we said, 'OK, some groups are having a harder time getting in, well, let's help those groups so that we're able to make an equal playing field, whether or not you have the same degree of resources going in.'

"That would be my parallel here."

Increasing funding for lower-incidence cancers such as stomach cancer is therefore, a "process question," Fitzgerald said.

"I think that takes away from it this idea that you are pitting one cancer against another, or advocating that one particular cancer gets one thing versus another," she said. "I think that we have some of these smaller cancers that don't have that foundational research knowledge, that don't have those foundation dollars, that don't have those grant dollars, and that, nonetheless, really want to make potential progress in these diseases, and patients are waiting for them to make that same degree of progress."

The future of gastric cancers depends on the creation of an attractive, well-funded research market, Fitzgerald said.

"When you have this disparity in situations for

researchers in one area, and not others, researchers are more apt to go towards the areas where it's going to be easier to get resources," Fitzgerald said.

"And so we are not looking at just what happens with this data, and what research and progress comes from that, it's who even goes into the field, which will determine the data and the research 20 years from now."

Fitzgerald said she understands that NCI's budget has been flat for years, and that sequestration reduces funds for cancer research. DDF is advocating for NCI's overall budget to be increased to $5.24 billion in fiscal 2014—about $460 million above current funding levels.

"I don't, by any stretch of the imagination, suggest that it's easy to make these kinds of decisions, particularly when you are in a situation where your funding is being cut," Fitzgerald said.

"Nonetheless, as a country and as an institution, we have a responsibility to each of our patients who is facing cancer to make progress."

In Brief

Johnson to Move to NHLBI, Leaving NCI Communications

(Continued from page 1)

"While this is a tremendous opportunity for her, Lenora's departure is a huge loss for the Institute," John Czajkowski, NCI deputy director for management, wrote in a recent memo to the staff.

Nelvis Castro was appointed acting director of OCE. Also during the transition, **Peter Garrett** will join NCI as senior advisor for communications to NCI Director Harold Varmus.

Garrett is the director of communications and public affairs at HHS Office of the National Coordinator for Health Information Technology. He replaces **Rick Borchelt** who left for the Department of Energy Office of Science in August.

NCI spends more than any other NIH institute on public relations and education activities, and Johnson's office has been undergoing unprecedented scrutiny and budget cuts.

The Cancer Letter published a series of stories on the NCI spending on PR and education, and the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce launched an investigation.

NCI spent $46.2 million on these activities in fiscal 2012. However, Varmus has cut the budget by about 15 percent this year, as part of his response to sequestration, and is expected to cut another 15 percent in fiscal 2014, bringing the budget down to about $30 million a year.

The NHLBI budget for PR and education was around $10 million in fiscal 2012.

A Series by The Cancer Letter
On the Cost of Cancer Communications

- Dec. 7, 2012: "Is $45 Million Too Much to Spend on PR? NCAB Panel Weighs NCI Communications Budget"
- Feb. 1: "NCI Ends Brash Foray Into the News Business—Emails Tell the Story of the NCI Cancer Bulletin"
- March 1: "NCI Spent $381.2 Million on PR from 2006 to 2012, Vastly Outspending Other NIH, FDA Units"
- March 15: "Nature Editorial Criticizes NCI PR spending"
- June 14: "FASEB: Focus on Research Funding, Not PR"
- July 12: "NIH Spent $181.3 Million on PR Last Year; House Probe Prompts Analysis of Spending."

ADRIENNE LANG, vice president for executive operations at **MD Anderson Cancer Center**, is stepping down from her position. The resignation was announced in an email from MD Anderson President **Ronald DePinho**. Her last day will be Dec. 31.

Lang served as interim senior vice president for institutional advancement, and as DePinho's chief of staff since his arrival.

She joined MD Anderson in 1998 as assistant director of governmental relations, and also served as chief of staff for John Mendelsohn, who was president of the center from 1999 to 2011.

"Her strong relationships with The University of Texas System Board of Regents and officers, as well as the MD Anderson Board of Visitors, have been invaluable to me," wrote DePinho.

MICHAEL FOLEY was selected to lead the **Tri-Institutional Therapeutics Discovery Institute Inc.**, a collaboration of Weill Cornell Medical College, The Rockefeller University, and Memorial Sloan-Kettering Cancer Center, which will focus on early-stage drug discovery.

Foley will be the Sanders Director of Tri-I TDI,

and director of its Sanders Innovation and Education Initiative, in recognition of the $15 million gift from Lewis and Ali Sanders to help establish the Institute.

He is scientific co-founder of four companies and one academic institute, and has placed 12 single-agent or combination drugs into clinical development. He was most recently director of the chemical biology platform at the Broad Institute of Harvard and MIT. He also worked at Bristol-Myers Squibb and GlaxoSmithKline.

The institute was formally launched in October and formed its first collaboration with Takeda Pharmaceutical Company Ltd. to develop small-molecule drugs.

THE AMERICAN ASSOCIATION FOR CANCER RESEARCH announced that **Beti Thompson** will present the fourth annual AACR Distinguished Lecture on Cancer Health Disparities, funded by Susan G. Komen.

Thompson, associate program head and associate director for health disparities research in the Cancer Prevention Program of Fred Hutchinson Cancer Research Center, will deliver her lecture Dec. 6, during the opening plenary session of the AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved.

Thompson is being recognized for her key role in developing one of the nation's pre-eminent programs in cancer health disparities, and for her research in the design and implementation of community approaches to reducing cancer health disparities in minority and other underserved populations.

In her lecture, she will discuss lack of access to care in terms of cancer prevention behavior among Hispanic populations. She will examine community-based, participatory research initiatives and the effect of such programs on increasing colorectal cancer screenings.

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FDA News

FDA Expands Nexavar Indication To Include Thyroid Cancer

FDA approved a supplemental new drug application for Nexavar tablets (sorafenib) for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment. The expansion of Nexavar's label was approved following a priority review by the FDA.

The approval was based on the results of the DECISION trial, an international, multicenter, placebo-controlled study.

A total of 417 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma refractory to radioactive iodine treatment were randomized to receive 400 mg of oral sorafenib twice daily (n=207) or matching placebo (n=210). Metastases were present in 96 percent of the patients: lungs in 86 percent, lymph nodes in 51 percent, and bone in 27 percent.

Sorafenib significantly extended progression-free survival, the study's primary endpoint. The median PFS was 10.8 months (95% CI 9.1-12.9) among patients treated with sorafenib compared to 5.8 months (95% CI 5.3-7.8) among patients receiving placebo (HR=0.59 [95% CI, 0.46, 0.76]; p<0.001).

Nexavar is approved in the U.S. for the treatment of patients with unresectable hepatocellular carcinoma, patients with advanced renal cell carcinoma and patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment.

Nexavar is thought to inhibit both the tumor cell and tumor vasculature. In in vitro studies, Nexavar has been shown to inhibit multiple kinases thought to be involved in both cell proliferation and angiogenesis, including Raf kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B, KIT, FLT-3 and RET.

Nexavar is co-developed by Bayer HealthCare and Onyx Pharmaceuticals Inc., an Amgen subsidiary.

FDA granted 510(k) clearance to an estrogen receptor image analysis and digital read application for breast cancer. The Companion Algorithm ER (SP1)1 image analysis algorithm is used with the iScan Coreo scanner running Virtuoso2 software, and is developed by Ventana Medical Systems Inc., a member of the Roche Group.

There are two intended uses: first, clinical use

of the software algorithm to semi-quantify the ER biomarker; and digital read, or clearance to manually read and score the ER biomarker using a computer monitor, in lieu of a microscope. The pathologist will be able to digitally view a slide on a computer monitor, assign a score, and then sign out the case with a diagnosis or opinion, with or without the assistance of an image analysis algorithm.

Along with the Companion Algorithm ER (SP1) image analysis software, the full breast panel includes HER2 (4B5), PR (1E2), Ki-67 (30-9) and p53 (DO-7) image analysis algorithms along with their accompanying Ventana IHC assays.

FDA approved the Aptima HPV 16 18/45 genotype assay for use on the Panther system. Both are produced by Hologic Inc. The Aptima HPV 16 18/45 genotype assay uses ThinPrep liquid cytology specimens, and is intended to be tested from the same sample that has already received Aptima HPV assay positive results.

In patients 21 years and older with atypical squamous cells of undetermined significance cervical cytology results, the assay can be used to test samples from women with Aptima HPV assay positive results to assess the presence or absence of high-risk HPV genotypes 16, 18 and/or 45. The results of this test are not intended to prevent women from proceeding to colposcopy.

In patients 30 years and older, the assay can be used to test samples from women with Aptima HPV assay positive results. The assay results will be used in combination with cervical cytology to assess the presence or absence of high-risk HPV genotypes 16, 18 and/or 45.

The assay is the first FDA-approved test for genotyping human papillomavirus types 16, 18 and/or 45.

Although HPV genotype 45 is fairly uncommon, identified in only 0.4 percent of women with normal cytology, data indicates that it is the third most common HPV genotype in invasive cancer.

The assay received FDA approval on the Hologic Tigris high-throughput system in October 2012.

FDA granted Priority Review to ramucirumab as a single-agent treatment for advanced gastric cancer following disease progression after initial chemotherapy.

Priority Review status means that the FDA's goal is to take action within eight months of a completed filing. Eli Lilly and Company, the drug's sponsor, anticipates agency action on this application in the second quarter of 2014.

The application was based on data from REGARD, a global, randomized, double-blind phase III study of ramucirumab plus best supportive care compared to placebo plus best supportive care as a treatment in patients with advanced gastric cancer, including adenocarcinomas of the gastro-esophageal junction, following progression after initial chemotherapy.

Lilly also studied ramucirumab in combination with paclitaxel for the treatment of advanced gastric cancer in its phase III RAINBOW trial.

The combination-therapy ramucirumab data from that trial will be the basis for separate regulatory applications. Lilly expects top-line results from three additional phase III trials of ramucirumab, one each in colorectal, hepatocellular and lung cancer, in 2014.

Ramucirumab is a human, receptor-targeted antibody that specifically blocks the vascular endothelial growth factor receptor 2 and inhibits downstream signaling involved in the formation and maintenance of aberrant blood vessels that supply blood to tumors.

FDA and the European Medicines Agency granted orphan drug designation to IMAB362 for the treatment of pancreatic cancer. IMAB362 is a monoclonal antibody currently in phase IIb clinical trial in gastroesophageal cancer.

Orphan drug designation is given to investigational new drugs that are under development for the treatment of life-threatening or very serious diseases that affect fewer than 200,000 patients in the U.S. or less than 5 in 10,000 individuals across Europe.

IMAB362 is a monoclonal antibody selectively binding to the tight junction protein CLDN18.2, which is expressed in approximately 60 percent of primary and metastatic pancreatic cancers. CLDN18.2 is also expressed in up to 80 percent of gastroesophageal cancers as well as in other solid tumors. However, CLDN18.2 is absent from the vast majority of healthy tissues.

IMAB362 is being developed by Ganymed Pharmaceuticals AG.