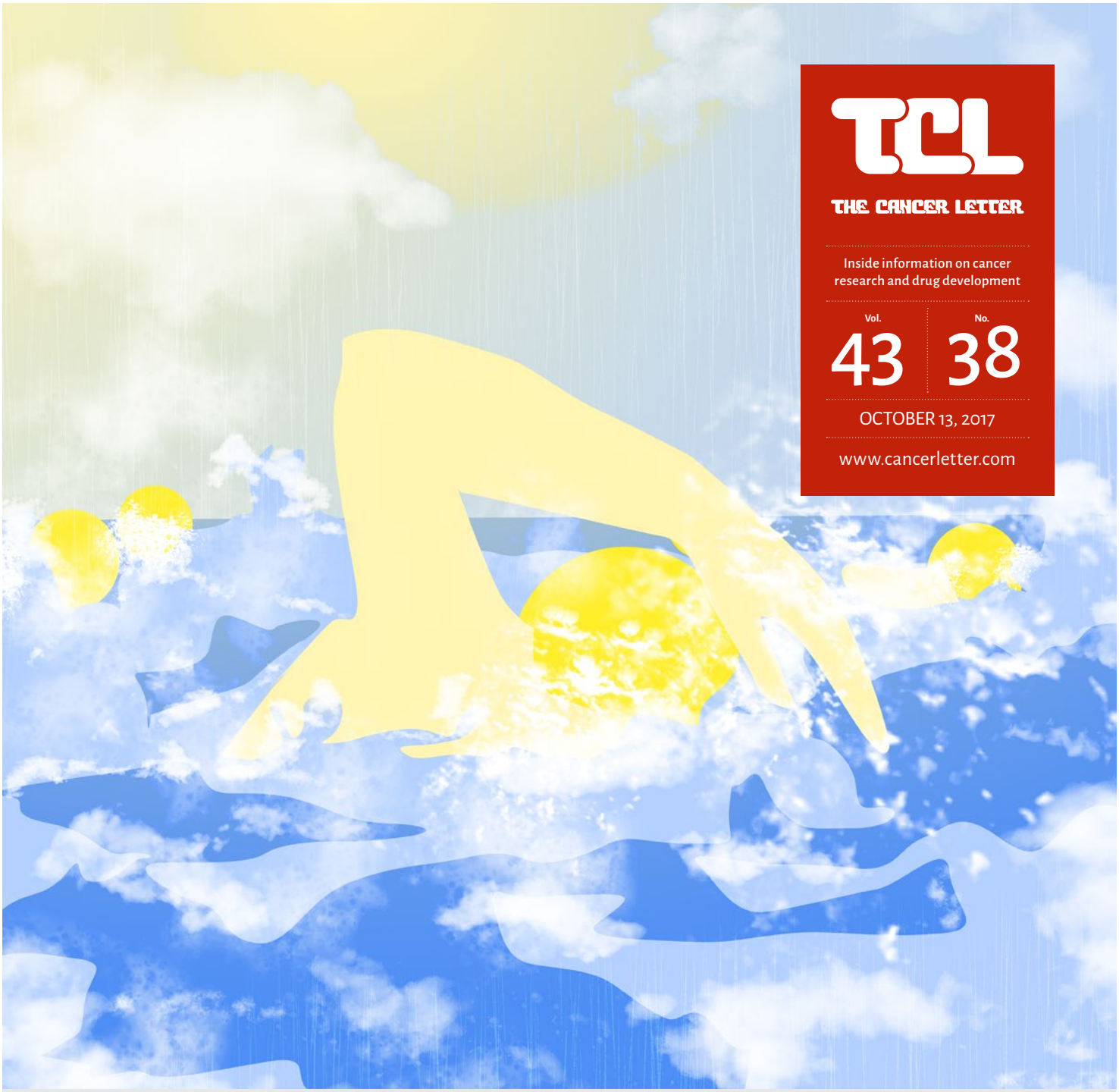

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Inside information on cancer research and drug development

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FDA: THE DEVELOPMENT OF SITE-AGNOSTIC INDICATIONS CALLS FOR DEVELOPMENT OF SPONSOR-AGNOSTIC DIAGNOSTICS

By Paul Goldberg

Earlier this year, when FDA approved Merck's PD-1 inhibitor Keytruda (pembrolizumab) for "site-agnostic" indications, it raised new questions that will likely shape the future of oncology:

In indications that are defined by biomarkers, will diagnostics in effect create a bundle containing the drug and the assay, driving the patients to a particular drug? Or will these diagnostics allow patients to be tested for a range of therapies?

In other words, is it possible to develop companion diagnostics in manner that is "sponsor-agnostic"?

This cluster of fundamental technological and policy questions is just starting to be formulated as the field adjusts to the future where indications may be defined by molecular characteristics of agents, as opposed to tumor sites.

Earlier this week, a group of top oncology officials at FDA published a "perspective" piece in the New England Journal of Medicine, in which they laid out the agency's concerns about a future where companion diagnostics are tied to specific drugs:

"Although sponsors have conventionally focused on the development of a drug, the strategy of pursuing site-agnostic indications must focus on both drug and biomarker development. For a biomarker-defined indication, multiple drugs may be developed by various commercial sponsors. The establishment of some new disease-indication–defining biomarkers (e.g., tumor mutation burden as a predictor of response to immunotherapy) may require a more collaborative approach than conventional drug development. If a biomarker will, in essence, define the disease indication, then it should be developed through the collaboration of multiple stakeholders including commercial sponsors, device manufacturers, academia, and patients."

The Cancer Letter asked the lead author of the piece, Steven Lemery, associate director, Division of Oncology Products 2, to address questions that have surfaced since Keytruda's approval.

The practice of medicine is evolving in the direction of testing, Lemery said. "Standard treatment guidelines in the US already recommend testing all patients with colorectal cancer for MSI-H or dMMR," he said. "Ultimately, whether all patients with metastatic colorectal cancer should be tested would be considered a practice of medicine decision, which the FDA, in general, doesn't regulate. Nevertheless, we believe that the community will adopt testing given the paucity of treatments for refractory metastatic colorectal cancer."

A conversation with Lemery appears on page 11.

Eric Rubin, vice president, global clinical oncology at Merck Research Laboratories, said development of the indication was the result of many conversations with FDA.

"When [FDA officials] saw these data, they were really helping us to figure out what exactly would we need to give them for them to be able to sign off on a tissue-agnostic approval, and so it really was a collaborative effort once the data started to come in, and once we had the breakthrough status from them," Rubin said to The Cancer Letter.

A conversation with Rubin appears on page 16.

The NEJM paper stems from Keytuda's approval for microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumors.

The indication—and the trial—resulted from a hunch.

Luis Diaz, a cancer geneticist who at the time was at the Johns Hopkins University School of Medicine, decided to test the role MSI-H or dMMR might play in determining response to PD-1 therapy for colorectal cancer.

Merck gave the Hopkins team the drug, and a relatively small charity called Swim Across America paid for the clinical trial that led to the indication. Diaz has since been named head of the Division of Solid Tumor Oncology in the Department of Medicine at Memorial Sloan Kettering Cancer Center.

Thus, the understanding of the biological rationale for using this entire class of drugs and the approval of the first-ever site-agnostic indication is a classic story of a group of academics deploying elegant science to verify a hypothesis.

A story about the genesis of the indication appears on page 5.

Keytruda's site-agnostic indication received an accelerated approval on May 23. Technically, the drug isn't approved for all solid tumors. The indication notes specific prior therapies for MSI-H or dMMR colorectal cancer on the basis of the patient population studied and in the context of multiple approved drugs for metastatic colorectal cancer.

Patients need to be tested if they wish to find out whether their tumors have MSI-H or dMMR characteristics. If they do, there is a strong possibility that they would get an excellent response to treatment. Alas, the percentage of patients who have these disease characteristics is small.

When resections are performed, about 30 percent of endometrial cancers, 20 percent of colon or gastric cancer, and less than 5 percent for most other tumor types have MSI-H or dMMR characteristics. In the metastatic setting, the incidence is about 5 percent for colorectal cancer.

The Lemery et al. NEJM perspective piece and the Q&A published here represent the agency's first detailed public statement on the significance of the site-agnostic approval as well as its implications for diagnostics in oncology.

The Keytruda Supplemental New Drug Application didn't go to the FDA Oncologic Drugs Advisory Committee. Had it gone to ODAC, discussion would have needed to focus on the data presented to support the accelerated approval, and only a part of the conversation would have needed to be devoted to companion diagnostics.

As it stands, MSI-H or dMMR status is routinely measured by immunohistochemistry, polymerase chain reaction or next generation sequencing.

"In this supplemental application, the identification of MSI-H or dMMR was prospectively determined in 135 of 149 patients using local laboratory–developed tests for these biomarkers," FDA officials said in the perspective piece.

FDA had the capacity to mandate the development of a companion diagnostic as part of an application, but that would have added at least a year to the process. Instead, the agency asked Merck to develop the companion diagnostic as a post-approval commitment.

Now, as a consequence of this approval, the field has to confront a series of questions:

Should all patients with metastatic colon cancer be tested for MSI-H or dMMR? Should this be limited to the metastatic setting, or colon cancers, or, for that matter, solid tumors? Perhaps one could also ask whether the era of a single-analyte test is now over, which would likely make the question of what is to be done with laboratory-developed tests (a.k.a. home brews) more manageable for FDA.

Drugs that target PD-1 and PD-L1 provide an excellent setting for addressing these questions in part because these agents work across disease sites and because the pharmaceutical industry has mounted an unprecedented push to develop these drugs (The Cancer Letter, Oct. 7, 2016).

On Oct. 12, 11 pharmaceutical companies as well as NIH and NCI formed a consortium that would seek to develop biomarkers—including biomarker tests—for use in immunotherapy. The enterprise, which will have a budget of $215 million, is being launched under the auspices of the Cancer Moonshot.

A story on the consortium appears on page 8.

The genesis of the first site-agnostic indication

By Paul Goldberg

When he was at Johns Hopkins, there was nothing whatsoever noteworthy about Luis Diaz wandering into Bert Vogelstein's office.

Usually, an idea—sometimes even a good idea—was involved.

The idea Diaz brought in one day five years ago was clearly one of the good ones:

"I said, 'Bert, I think I know how these things work,'" Diaz said. The "things" Diaz was referring to were PD-1 and PD-L1 drugs, also known as checkpoint inhibitors. "They respond in melanoma and lung cancer, and I think it's high mutation."

It might then follow that microsatellite instability-high colorectal cancers would be more likely to respond to checkpoint inhibitors. This might apply to hereditary MSI-H, found in the Lynch syndrome, the molecular basis for which Vogelstein helped define, as well as sporadic MSI-H. Vogelstein is the Clayton Professor of Oncology and Pathology and director of the Ludwig Center for Cancer Genetics and Therapeutics at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

Luis Diaz, then at Johns Hopkins, had a hunch that resulted in the first site-agnostic approval in history.

A clinical trial in the MSI-H or dMMR population could thus provide a treatment option for a subset of colorectal cancer patients—and it could predict which patients are likely to benefit from these drugs in other sites. Perhaps, this could lay the groundwork for a site-agnostic indication.

This conversation between Diaz and Vogelstein took place two years before approval of the Merck drug Keytruda (pembrolizumab) and the Bristol-Myers Squibb drug Opdivo (nivolumab). The Hopkins group set out to get a checkpoint inhibitor—any one of them.

Hallway conversations were useful, too.

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At first, Drew Pardoll, director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy and co-director of the Cancer Immunology Program at Hopkins, told Diaz that checkpoint inhibitors didn't seem to be working in colorectal cancer.

However, later, a good, strong response showed up.

"I said, 'Check it for MSI-high,' and it was MSI-high," Diaz said.

"Bert and I wanted to run this trial, but we didn't necessarily have the money, we didn't have the compound, and we didn't have anyone to write the protocol and start running it," Diaz said. "We didn't care which drug we got. Nothing is exactly the same, but they are doing the same behavior. All vodkas do the same thing, but they are not the same. All of them will do the same thing—they will block PD-1. There may be subtle differences."

To find the money for the trial, Diaz approached Swim Across America, a charity that stages swim meets to fund cancer research. The proceeds from the Baltimore event go to Hopkins. Swim Across America was already funding Diaz's lab.

"We like doing high-risk, high-reward projects, the ones where there is a potential for a breakthrough, but where there is just no funding for it. We seek those out," Rob Butcher said to The Cancer Letter. "Our money plays a major role in paying for clinical trials, where dollars are just not available and insurance is not willing to cover it. That's a sweet spot for us, and that's where we like to be—in the bench research to clinical trials space."

Swim Across America is a small and frugal operation. Headquartered in a 700-square-foot office in Charlotte, NC, it pays $1,400 a month in rent, and has four full-time employees and one part-time employee.

"We don't spend money on television advertising, we don't spend money on radio and billboards. We don't spend money on lobbying firms in Washington, D.C., and all those things that would pull on our ability to pay for research and clinical trials," Butcher said.

Swim Across America CEO Rob Butcher: looking for high-risk, high reward projects.

This year, Swim Across America expects to raise $7 million and give out about $5 million in grants, Butcher said. Earlier this week, it received a $3 million commitment from Merck, and the charity expects to use these funds to start additional swims.

Swim Across America is adamant on one point: all of its money must go to research. It refuses to pay indirect costs.

Diaz estimates that the Hopkins group received over $500,000 for a small phase II study. The PI was Dung Le, an associate professor of oncology at the Johns Hopkins University School of Medicine. Since the study focused on a rare population, other institutions had to be brought in. Usually, per-patient research costs can be in the $30,000 range.

The money from Swim Across America covered $7,500. The rest had to come from other funds.

"We get the drug from Merck, we write the protocol, and we start enrolling patients, and these patients are doing miraculously well. The tumors are melting away," Diaz said. "These were people who were treatment-refractory. One was hospice-bound.

"Things don't work a lot. When something works, it's unbelievable!"

Diaz has since moved to become head of the Division of Solid Tumor Oncology in the Department of Medicine at Memorial Sloan Kettering Cancer Center.

The first batch of results, published in NEJM in June 2015, showed that the therapy was working.

The study published in NEJM enrolled 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency. Of this number, 12 patients had MSI-H and 25 didn't. "About 90 percent of those who had MSI-H got disease control, and all

but two of them are alive," Diaz said. "All others progressed rapidly.

"It was a genetic dichotomy. Over the next 12 months we saw a similar response in all the tumor types."

The cohort was later enriched to include more patients and 12 tumor types, and the results were published in Science in July 2017.

Patients were accrued at Hopkins as well as Stanford University, University of Pittsburgh Cancer Institute, Providence Cancer Center of Portland, OR, and Ohio State University. Ohio State was brought in when Vogelstein contacted Albert de la Chapelle, one of the collaborators on the Lynch Syndrome work.

"Literally, I saw for the first time in my career, the Lazarus effect," said Richard Goldberg, a GI oncologist who at the time was the physician-in-chief at The Ohio State University Comprehensive Cancer Center, and who has since become director of West Virginia University Cancer Institute.

"There was a particular patient that I had who was referred to me by my colleagues at Mayo," Goldberg said. "She had Lynch Syndrome. She had exhausted conventional therapy, she came in in a wheelchair, she just had her femur pinned, and when you examined her, she had masses in her neck, and breasts, and abdomen that you could feel. She was so depressed, she could barely hold a conversation. Here is the 26-year-old who is dying of advanced cancer.

"I treated her, and within a couple of months she was completely normal, and she is in theater and she went back to dancing—from dead to dancing."

Elizabeth Carner, Goldberg's patient, was diagnosed at 25, and was in the original cohort in the trial. Her brain metastasis was shown in the Science paper.

"I was faded when I met Dr. Goldberg," Carner said to The Cancer Letter. "I didn't have any energy, I was in a wheelchair, probably freaked my family out. I was having episodes where I was throwing up masses of blood. It was so bad that a local hospital told my parents that I probably had six weeks to live."

Elizabeth Carner was near death three years ago. Last summer, she danced in a theater production.

Improvement seemed slow, but it was definitely happening, Carner said to The Cancer Letter. "I started the trial in February, and by April I was on crutches, and I needed the wheelchair only because I tired easily," Carner said.

"Beth Carner is in complete remission three years after starting therapy and one year after stopping it," Goldberg said. "For patients with advanced solid tumors that is extraordinary in two ways:

"First, the fact that she went into CR. Second, the fact that the disease has not come back despite being off treatment for a year. That is a situation that I have never seen in my 34 years as an oncologist."

"This is a 'feel-good' story in so many ways," Goldberg said. "It is good for the patients like Beth, the science which it advanced, the researchers who were rewarded by seeing patients go from near dead to dancing, the swimmers and their supporters who funded it with their money and their muscle power stroke by stroke—and the drug company. Seldom do all the spheres align like this but when they do it is a beautiful thing, really an epiphany."

Now 28, Carner is back in community theater, working as a stage manager at a in Rockford, IL. Before her diagnosis, she had returned from an internship in stage managing at Cincinnati Playhouse in the Park. She was also a performer and part of the backstage crew.

Last summer, she danced in a production of "Beauty and the Beast."

"I have generally a somewhat twisted, dry sense of humor anyway, but it seems to have increased after this whole ordeal," Carner said. "It helped a lot to have a sense of humor, just to realize that you have to make light of a lot of really bad situations."

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NIH announces immunotherapy consortium with 11 companies to support Cancer Moonshot goals

By Matthew Bin Han Ong

As part of NCI's ongoing Cancer Moonshot program, the institute, NIH and 11 biopharmaceutical companies launched a five-year public-private research collaboration Oct. 12 designed to advance new immunotherapy treatments.

The $215 million consortium, the Partnership for Accelerating Cancer Therapies, will be managed by the Foundation for the National Institutes of Health. Initially, PACT will focus on efforts to identify, develop, and validate robust biomarkers that show promise in the clinic.

"We know today's announcement is part of an effort that President Trump is deeply devoted to—advancing life-saving cures for deadly diseases," Eric Hargan, the newly appointed acting secretary of the Department of Health and Human Services, said at the rollout at the National Press Club. "It's a special honor to be here in my first public appearance as acting secretary, because the HHS's role in advancing medical research is a cherished important part of the nation, and today is a major step forward."

This is likely the first time the current administration has issued a public endorsement of the Beau Biden Cancer Moonshot, an Obama-era White House initiative led by former Vice President Joe Biden that culminated in the formation of the FDA Oncology Center of Excellence and authorization of $1.8 million in new funding over seven years for cancer research via the 21st Century Cures Act.

PACT is modeled after another five-year consortium, the Accelerating Medicines Partnership, which was established in 2014 between NIH, FDA, and 10 industry partners to identify and validate promising biological targets for therapeutics.

"NIH does the basic scientific research, like identifying which biomarkers make patients well-suited for certain treatments, while the private sector helps develop the actual grants and brings them to market," Hargan said.

NCI is contributing about three quarters of the funding for the partnership, up to $160 million. The remaining quarter—$55 million—is calculated as $1 million per participating company per year for the duration of the partnership. This is well below the percentage of funding from industry for AMP, which comes up to a little over a third of the total budget of $187.2 million.

PACT's 11 partners are: AbbVie, Amgen, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb, Celgene Corp., Genentech, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceutical Companies of Johnson & Johsnon, Novartis Institutes for Biomedical Research, and Pfizer.

NIH Director Francis Collins, who insiders say had to negotiate more government investment and agree to accept lower investment from industry partners in order to bring them to the table, said the effort is nevertheless fruitful, since 11 companies agreed to play.

"I don't think there should be a formula," Collins said to The Cancer Letter. "I think we, like any group that is trying to put a partnership together, are trying to figure out who can contribute what. The NCI, thanks to the Cancer Moonshot, already had a plan to do a fair amount of the work that is now going to be a part of PACT, so it's entirely reasonable that they do so with this $160 million.

"With the companies, we had to kind of figure out where is the sweet spot between setting the bar so high that nobody could play and setting it so low that we're wasting our resources and opportunities—and where we landed, which got the maximum total contribution of millions of dollars every year for five years. That was not an easy sell, may I say, but as you saw, we ended up with 11 participants. I think that's pretty good."

Although government funds for PACT—via regular appropriations—will be channeled through NCI, insiders say the consortium will be run by consensus and shared governance between the institute, NIH, and industry partners. Going into the collaboration, as well as in the early phases, the onus is on NIH and NCI to convince industry partners that the institute will provide the biomarkers that could be translated into immunotherapies, insiders say.

PACT will facilitate systematic and uniform clinical testing of biomarkers to advance understanding of the mechanisms of response and resistance to cancer therapy. The research conducted under the partnership will also integrate immune and other related oncology biomarkers into clinical trials by defining a set of standardized biomarkers to be tested across a variety of studies.

This aproach will allow for consistent generation of data, uniform and harmonized assays to support data reproducibility, comparability of data across trials, and discovery and validation of new biomarkers for immunotherapy and related combinations.

"With the Cancer Moonshot, we actually have involvement with several other institutes and we have an immunotherapy program, which we are doing jointly with the National Institute of Allergy and Infectious Diseases," NCI Acting Director Douglas Lowy said at the press conference. "For PACT itself, that is not happening, but we certainly talk very regularly with colleagues where their expertise is relevant. Where we are focused particularly with our colleagues at NIAID is trying to understand side effects and what to do to try to overcome them."

While one of Biden's stated goals for the Cancer Moonshot, going forward, aims to address the costs of cancer drugs, drug pricing will not be a focus for this collaboration with 11 pharmaceutical companies with large portfolios in oncology.

"The question of pricing and combinations is relevant for payers, patients, and for industry to find the right solution," said Thomas Hudson, vice president of oncology discovery and early development at AbbVie. "At this point, the consortium is not really discussing about what the pricing would be, but I do think that we're all driven by trying to find, again, the best value drug or the best value combinations—the ones that are going to give a very deep response to some patients, and avoiding drugs for patients who are not going to respond.

"So, in a way, this higher-precision medicine, this ability to predict responders or not, is part of that answer, and one which we hear a lot from payers that the ability to be able to predict who's going to respond to a drug and who's not going to respond, is very helpful," Hudson said at the press conference. "Moving to an area of personalized medicine, which allows us to, again, only direct costs where you expect there will be benefits, where there's value, is something that we all discussed. But I don't think the consortium itself will be discussing prices."

A systematic approach like PACT will help bring immunotherapies to more people and more types of cancers, and speed up the process, Collins said.

"Well, I think this is a significant day. These kinds of partnerships can be enormously complicated to put together," Collins said. "There are various phases you go through from an initial exploration about whether there's an opportunity to then trying to get down to the nitty-gritty of exactly where is the sweet spot of that combination of scientific and resource contributions that makes the most sense. Then, once one has developed that kind of a plan, it really comes down to, 'OK, who's in?'

"I want to express sincere thanks to the 11 companies who decided they were in. That is a commitment of their resources, their time, and they are not only saying they're going to take part—they're committing their talents of senior scientists in their companies to be part of this going forward. This is going to be an adventure. I don't think any of us know how it's going to turn out, but it's exactly the right thing to do at this moment of exceptional potential."

Q & A

Lemery spoke with
Paul Goldberg, editor and
publisher of The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Lemery: "We saw consistent evidence of the drug's response in multiple tumor types"

> This represents a shift from the strict disease site orientation—where we previously only approved drugs based on the original location of the tumor—to an indication that is site-agnostic.

Steven Lemery
Associate director
Division of Oncology Products 2, FDA Office of Hematology and Oncology Products

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The application for approval of Keytruda (pembrolizumab) was based on internal discussions within FDA as well as working "proactively with the sponsor to submit this application," said Steven Lemery, associate director, Division of Oncology Products 2, FDA Office of Hematology and Oncology Products.

The agency decided against taking the application to the Oncologic Drugs Advisory Committee, Lemery said.

"For this approval, 1) we saw consistent evidence of the drug's response in multiple tumor types 2) the underlying science for how to target this biomarker was demonstrated, and 3) patients with this genetic feature (MSI-H and mismatch-repair deficiency) had a lack of approved therapeutic options available," he said. "Furthermore, pembrolizumab had already been approved for multiple other cancer indications; therefore, sufficient safety data already existed as well as an understanding of the efficacy of this class of checkpoint inhibitors."

However, the agency decided to write a "perspective" piece in the New England Journal of Medicine "to help explain our rationale in what was a first-of-its-kind drug approval and outline what we see as challenges and opportunities to this approach moving forward," he said.

Lemery spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

What's the significance of the accelerated approval of pembrolizumab?

Steven Lemery: This is the first time the FDA has approved a cancer treatment based on a biomarker without regard to the tumor's histology or tumor site. This represents a shift from the strict disease site orientation—where we previously only approved drugs based on the original location of the tumor—to an indication that is site-agnostic.

The agency took this action after the data showed consistent responses in several different tumor types, especially in patients who had no other treatment options and for which separate stand-alone drug development programs for each tumor type would not be feasible or appropriate.

Approving this indication expedited access of this therapy to patients with a high unmet medical need.

I have always thought that when new, important scientific or regulatory issues surface, you take them to ODAC, to create public discussion, even if clinically there are no profound dilemmas. Why did you decide against taking the application for the site-agnostic approval of pembrolizumab to ODAC? And why did you decide to write the perspective piece for NEJM?

SL: Decisions regarding whether to take drugs to an advisory committee are complex; however, drugs that require a thorough discussion regarding risks and benefits may be recommended for discussion in an advisory committee.

Not all drugs subject to a new regulatory issue are discussed at an ODAC. In some cases, important new regulatory issues are discussed internally with CDER management. We had these internal discussions prior to the submission of this application and worked proactively with the sponsor to submit this application.

This was the first time that data in an NDA or BLA was submitted to the agency supporting a tissue-agnostic approval. For this approval, 1) we saw consistent evidence of the drug's response in multiple tumor types 2) the underlying science for how to target this biomarker was demonstrated, and 3) patients with this genetic feature (MSI-H and mismatch-repair deficiency) had a lack of approved therapeutic options available.

Furthermore, pembrolizumab had already been approved for multiple other cancer indications; therefore, sufficient safety data already existed as well as an understanding of the efficacy of this class of checkpoint inhibitors.

This approval has received significant interest from the oncology community and general public. We wrote the NEJM Perspective to help explain our rationale in what was a first-of-its-kind drug approval and outline what we see as challenges and opportunities to this approach moving forward.

You note in the perspective piece that the indication was approved without an FDA-approved companion diagnostic. Is the development of the companion diagnostic one of the conditions of converting an accelerated approval to a full approval?

SL: No. We did not believe that such a requirement could be supported based on our interpretation of the accelerated approval recommendations. Nevertheless, the sponsor agreed to two post-marketing commitments to support the development of a companion diagnostic to detect MSI-H and a companion diagnostic to detect dMMR. FDA has taken this approach

with other drugs (e.g., crizotinib for ROS-1-positive lung cancer).

As part of the accelerated approval requirements, Merck will provide data to verify and describe the response rate and response duration in more than 400 patients, including children, with different tumor types.

Do you actually need a new companion diagnostic? Why not use PCR, NGS or IHC? People have been using those tests. Does it have to be a new companion diagnostic, or would standards for use of existing modalities suffice?

SL: The goal is to ensure the availability of tests that can accurately and reliably identify patients with MSI-H and dMMR to facilitate the safe and effective use of pembrolizumab. FDA would be open to reviewing data from currently available PCR or NGS tests for MSI-H or IHC for dMMR as companion diagnostic tests for use with pembrolizumab.

Should testing be mandated for all patients with metastatic colon cancer, even though only 3 to 5 percent of them would be eligible for this treatment?

SL: Standard treatment guidelines in the US already recommend testing all patients with colorectal cancer for MSI-H or dMMR. Ultimately, whether all patients with metastatic colorectal cancer should be tested would be considered a practice of medicine decision, which the FDA, in general, doesn't regulate. Nevertheless, we believe that the community will adopt testing, given the paucity of treatments for refractory metastatic colorectal cancer.

Is this the first time that single-arm confirmatory trials have been mandated by the agency? Why is that appropriate in this setting? Is there a way to extrapolate from this decision?

SL: Single-arm trials have supported regular approval for other drugs. Randomized trials have not been required for many drugs intended to treat patients with HIV. Similarly, examples where the FDA has granted regular approval of drugs for solid tumors based on response rate include crizotinib for ROS-1-positive lung cancer and vismodegib and sonidegib for advanced basal cell carcinoma.

The FDA approved avelumab for Merkel cell carcinoma based on response rate with a requirement to further study avelumab in single arm trials. Generally, accelerated approvals require sponsors to perform randomized trials after approval; however, given the limited number of patients and the unprecedented effects on response rate and response duration in refractory diseases such as MSI-H or dMMR endometrial cancer, biliary cancer, or pancreatic cancer, randomized trials were not believed to be feasible.

Response rates can be assessed in nonrandomized trials because, in general, tumors do not decrease in size in the absence of therapy. As indicated above, durable response rates have led to both accelerated and regular approvals.

What's your vision for using this approach in pediatrics?

SL: For the MSI-H/dMMR approval, FDA extended the indication to pediatric patients on the basis of the scientific rationale (based on tumor mutation burden) and based on the establishment of a reasonably safe dose in other pediatric clinical trials. FDA previously approved pembrolizumab for children with classical Hodgkin's lymphoma.

Where possible, we support this approach and line of thinking for pediatric approvals provided safety and efficacy can be established. Although we do not expect a large number of pediatric patients to have MSI-H/dMMR cancers, older adolescents with Lynch syndrome and younger children with congenital mismatch repair deficiency can develop life-threatening cancers.

In immunotherapy, we are seeing multiple drugs that are basically similar. Is it fair to say that the agency is trying to get the industry to develop companion diagnostics that would work for these entire classes of drugs, regardless of sponsors? Perhaps "sponsor-agnostic" could be the term to use—I just coined it, I think. How is the idea of a sponsor-agnostic diagnostic being received by the industry?

SL: The diagnostic devices should be accurate and reliable. Microsatellite instability can be identified through different testing platforms.

There are advantages to the development of different testing platforms, especially if each can measure the same disease state.

The challenge that you have identified is when sponsors develop platforms that identify different disease states or patient populations (e.g., for PD-

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L1). A lab is unlikely to test patients using multiple tests even though a patient may be eligible for treatment with multiple different drugs in the same class.

A sponsor-agnostic diagnostic test has not been developed for PD-L1; however, for tissue-agnostic trials, getting buy-in for the new definition of a disease state or indication will be more important.

Otherwise each sponsor will, in-essence, be defining a different disease state based on a test rather than on biology.

Do you anticipate future approvals of this nature?

SL: While we cannot speculate on future approvals, generally speaking it is important to note that a site-agnostic approach may not be appropriate for all types of biomarkers or drugs that target specific biomarkers, because not all tumor types will respond in the same way to targeted therapies.

For example, certain drugs that target BRAF or MEK have been shown to be effective for BRAF-mutant melanoma and lung cancer, but have appeared inactive as single agents for the treatment of BRAF-mutant colorectal cancer.

In addition, there may be challenges in developing site-agnostic clinical trials in untreated patients who have other available effective treatments.

As with the pembrolizumab approval, the data supporting future site-agnostic treatments will be dependent on the specific drug and on the specific characteristics of the biomarker and tumor type combination.

Q & A

Rubin spoke with
Paul Goldberg, editor and
publisher of The Cancer Letter.

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CONVERSATION WITH THE CANCER LETTER

Rubin: FDA helped Merck figure out how to channel science into regulatory approval

"We do a limited number of investigator-initiated studies for drugs that are not approved. If there's a compelling scientific rationale and it's something that fits into our overall scheme of development, we will do that."

Eric Rubin
Vice president
Global Clinical Oncology, Merck Research Laboratories

The idea that led to the site-agnostic indication for Keytruda (pembrolizumab) came from the academic oncologists, who ended up defining the biologic mechanism of activity of this class of drugs.

When FDA got involved, it took an activist stance, coming up with regulatory ideas to match the elegance of science.

"When they saw these data, they were really helping us to figure out what exactly we would provide for them to be able to sign off on a tissue-agnostic approval, and so it really was a collaborative effort once the data started to come in, and once we had the breakthrough status from them," said Eric Rubin, vice president, Global Clinical Oncology, Merck Research Laboratories. "I would say it really is a nice example of collaboration of academia, FDA, and industry."

Rubin spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

I believe that in December 2012, the Hopkins folks came to you and asked for the drug, and you gave them the drug. What was the decision like on Merck's side, whether to give a drug?

Eric Rubin: This was before Keytruda had been approved. I would say, we do a limited number of investigator-initiated studies for drugs that are not approved.

If there's a compelling scientific rationale and it's something that fits into our overall scheme of development, we will do that. There were a limited number of such studies back at that time that we were providing drugs for. Sometimes we provide funding. This was one of them that, of course, has become a great success story.

In this case, for you, the decision must have been a very difficult one--that's two years before approval. You probably had a fairly limited amount of the drug. There is risk exposure that comes with these studies. It couldn't have been a trivial decision for you.

ER: I think that's right. As I mentioned, we don't approve a lot of these, but this had a compelling scientific rationale.

It originally was not a large study, so we did feel that we had sufficient drug supply to support it beyond the other studies that we were doing.

What seems to be so fascinating is that the study shows how these drugs, the whole category of drugs, works. It seems like they just sort of stumbled across it... Is that is correct?

ER: Well, I think there's actually quite a body of data supporting the idea, and of course Bert Vogelstein [the Clayton Professor of Oncology and Pathology and director of the Ludwig Center for Cancer Genetics and Therapeutics at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center] has had a long, as I'm sure you know, long history of understanding the causes of colon cancer. He was one of the co-identifiers of mismatched repair gene mutations that lead to hereditary polyposis syndromes.

So, he's been working on this for a long time, and I think the idea that high mutation rates would confer sensitivity to checkpoint inhibitors has also gone on for a while. It even goes back to Steve Rosenberg [chief of the NCI Surgery Branch], who was trying to identify these so-called neo-antigens that come from mutated genes in cancer. I think it was pretty sound.

It was, again, one of the reasons we felt that this was something worth supporting. It was based on really good science.

But I think one of the things I'll comment on that I think is very interesting about it, is there have been prior small numbers of colon cancer patients who'd been treated with anti-PD-1 agents, and the responses were pretty much zero, and so the idea was, early on, that it really wasn't going to work in colon cancer, as a monotherapy.

One of the striking things that came out of this was if you actually select for the 5 percent to 10 percent of patients with colon cancer who carry these mutations, you go from a 0 percent response rate to a 50 percent or higher response rate.

That was really, I think, one of the amazing early stories for this. And the second part, where Hopkins also had data for early on, was that if you extended this beyond colon cancer, you saw similar types of high response rates.

Although the prevalence there tends to drop. In certain cancers, you're down to the one percent range of patients who have this MSI-H genotype.

Well, if it's 5 percent of cancers worldwide–that's probably an estimated about what, half a million people worldwide–that are candidates for this treatment. That would be one of the largest cancers out there. No? Am I wrong?

ER: I have to look at the calculations. I think what we surmised through this calculation a while ago, is that it's not a small number, but if you look at it, for example, compared to newly-diagnosed lung cancer, at least right now, I don't think it's that close to that, for example. But it's not a trivial number, that's true.

Right. And you ended up getting an indication out of this, which must be quite fabulous to see.

ER: Yes. We look for innovative ways to develop drugs, and this is, of course, really, quite an innovative one.

I know you're going to talk to Dr. [Richard] Pazdur, [director of the FDA Oncology Center of Excellence] and his colleagues, and I have to give them a lot of credit for this.

When they saw these data, they were really helping us to figure out what exactly we would provide for them to be able to sign off on a tissue-agnostic approval, and so it really was a collaborative effort once the data started to come in, and once we had the breakthrough status from them.

What are your thoughts on the New England Journal "perspective" piece that was just published? What do you think about the way to deal with the issue of companion diagnostic?

ER: Yeah. This is a good one. Under the leadership of Dr. Pazdur, they showed some flexibility. If we had had to develop a commercial FDA-approved test as part of the enrollment criteria for these studies, it probably would have delayed the study initiation for a year or more.

It just takes that long to find a diagnostic partner. We don't have a diagnostic company at Merck, so we partner with diagnostic companies, and it really tacks on a year or more of development if you have to start the studies with the commercial-ready test.

I think, you know as was pointed out, these MSI-H tests, or dMMR tests, have been around for years.

Even though they are not FDA-approved, they have validation, and so that was again, one of the discussions we had with the FDA—the acceptance that the enrollment could be based on these tests.

But, again, the feeling was that because it is something that will likely be widely used, there was a request for us, as a post-marketing commitment, to come back with and submit some FDA-approved tests.

As you may have seen, there are actually two of those that we have to submit. One is based on a protein-based test for detecting MSI-H, and then the other is a PCR-based test that looks at microsatellite instability in certain loci, and so we were asked to submit, for FDA approval, both of those kinds of tests.

Is it possible to do this in a way that is–I think I might be the one who coined the phrase "sponsor-agnostic"–way?

ER: Yes. There's a lot of interest in that. Part of this comes from the experience recently with one of the other companion diagnostics in the field, which is the PD-L1 immunohistochemistry test.

I don't know how familiar you are with that, but FDA became aware a couple of years ago that each company was developing its own IHC test, in some cases with a different diagnostic company, and potentially different cutoffs, and this, of course, can create a lot of confusion.

It actually spawned what was called the blueprint effort, where drug companies and diagnostic companies got together to try to come up with at least some information that physicians and patients could use to understand how the tests compare, and that was published recently. So, there's an interest, moving forward, to try to prevent that type of scenario as you allude.

Actually, I think the end paragraph in that New England Journal of Medicine paper was really all about that.

That's probably the whole reason they did the paper.

ER: I think it's probably two. I think they want to chronicle the thinking behind it, behind the first tissue-agnostic diagnostic tool, but I think they're pointing out that in particular, tumor mutational burden, which is really a very logical next step beyond MSI-H.

MSI-H is one way to get to a high tumor mutational burden. There are others, and so the feeling is that we're actually missing patients who might benefit from these drugs by only looking at the MSI-Hs, and so there are a variety of companies, including us, who are working on the set of measurements, looking at a tumor mutation burden type of assay, and that's what is alluded to in that last paragraph, where I think there's going to be a desire to try to harmonize on that before each company develops their own test with its own particular cutoff.

So, it's back to what you said, which is I do think the FDA would like to have a sponsor-agnostic approach toward biomarkers that are going to be used across the PD-1/PD-L1 class.

If we were to go back to the development of this indication for one moment, the part that I found really interesting was the way the Hopkins team raised money for the clinical trials. They went to Swim Across America. I didn't even know Swim Across America could do something like this, and they actually put the money together and did the trials. Were you following on that?

ER: I can't say I know that much about them, but I think Swim Across America's actually been a pretty long-standing supporter of Hopkins, is my sense. I don't know if you're talking to any of the Hopkins folks, but...

Oh, I am! I spoke with the Swim Across America, I thought it was really interesting.

ER: Okay, all right, yeah. I think they've been a supporter of Hopkins in general, and I think this was one of the ... To me, that was where this was coming from, that they like support Hopkins science and this made a lot of sense to them as well.

Very nice story, I agree.

Is there anything we've missed?

ER: I consider myself very lucky to have been a part of this. I'm a medical oncologist by background, and much of my career has been in academia. I came to Merck about ten years ago, and it really is incredibly gratifying to be part of something like this, and I would say it really is a nice example of collaboration of academia, FDA, and industry.

To me, it's just a great example of a success story. I'm sure we've covered that, but to me it's worth emphasizing.

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Nine researchers receive the 2017 NIH Director's New Innovator Award for cancer-related discoveries

NIH announced 55 recipients of the NIH Director's New Innovator Award, which supports exceptionally creative early career investigators who propose innovative, high-impact projects.

The NIH Director's New Innovator Award is part of the Common Fund's High-Risk, High-Reward Research program, which was created to accelerate the pace of biomedical discoveries by supporting exceptionally creative scientists with highly innovative research.

Established in 2007, the award supports highly innovative research from promising early stage investigators—researchers who are within 10 years of completing their terminal research degree or clinical residency and who have not yet received substantial NIH support.

Of the 55 recipients, nine researchers were recognized for cancer-related discoveries:

Ishan Barman, Ph.D.

Johns Hopkins University
Project Title: Spectroscopy Assisted Mechano-Chemical Phenotype Recognition Nanoscope

Ishan Barman is an assistant professor in the Department of Mechanical Engineering at the Johns Hopkins University with a joint appointment in Sidney Kimmel Comprehensive Cancer Center. He graduated from Indian Institute of Technology (Kharagpur) and then moved to Massachusetts Institute of Technology (MIT) for his Ph.D., where he investigated transdermal blood analyte monitoring using vibrational spectroscopy in the laboratory of Michael Feld. Following a postdoctoral stint at the Laser Biomedical Research Center at MIT, Barman established his independent group at the Johns Hopkins University in 2014.

By combining optical spectroscopy, chemical imaging and nanoplasmonics, the Barman lab develops non-invasive approaches in which structural and molecular data converge to provide integrated insight into disease mechanisms.

In addition to the NIH Director's New Innovator Award, Barman has received the Outstanding Young Engineer award from the Maryland Academy of Sciences and the Dr. Horace Furumoto Innovations Young Investigator Award from the American Society for Laser Medicine and Surgery (ASLMS).

Kivanc Birsoy, Ph.D.

The Rockefeller University
Project Title: Dissecting Tumor Metabolic Heterogeneity In Vivo

Kivanc received his Ph.D. from the Rockefeller University in 2009, where he studied molecular genetics of obesity in the laboratory of Jeffrey Friedman. In 2010, he joined the laboratory of David Sabatini at the Whitehead Institute of Massachusetts Institute of Technology (MIT).

There, he combined forward genetics and metabolomics approaches to understand how different cancer types rewire their metabolism to adapt nutrient deprived environments. He also used similar approaches to study how mitochondrial dysfunction influences cellular metabolism. In 2015, Kivanc joined the Rockefeller faculty as an Assistant Professor.

He is a recipient of NIH Career Transition Award, Irma Hirschl/Monique Weill-Caulier Trusts Award, Sidney Kimmel Cancer Foundation Scholar Award and AACR NextGen for Transformative Cancer Research Award. He has recently been named a March of Dimes Basil O'Connor and Searle Scholar.

Jessica Blackburn, Ph.D.

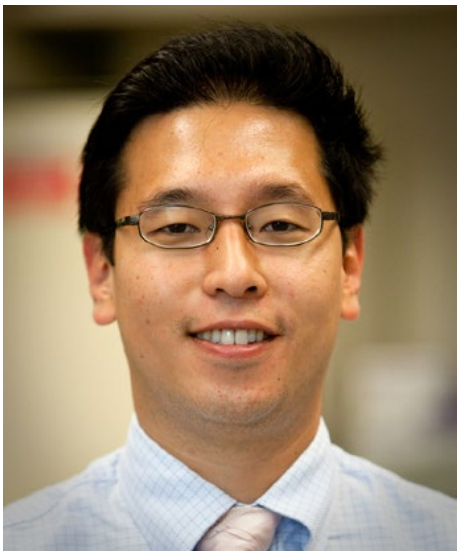
University of Kentucky
Project Title: Harnessing Single Cell Technology to Define Self-Renewal in Normal and Malignant Stem Cells

Jessica is an assistant professor in the Department of Molecular and Cellular Biochemistry and a member of the Markey Cancer Center at the University of Kentucky.

She received her B.S. from Centre College in Danville KY, and Ph.D. in Biochemistry from the Geisel School of Medicine at Dartmouth, where she identified new roles for matrix metalloproteases as signaling molecules in cancer. During her post-doctoral fellowship at Harvard Medical School, Jessica used zebrafish models to dissect heterogeneity within tumors and identified new mechanisms of leukemia relapse.

Jessica's own lab continues to leverage zebrafish model systems to understand how pediatric cancers develop and relapse, with the goal of identifying new molecular targets for these diseases. Jessica was the recipient of the NIH Pathway to Independence Award in 2014, and receives support from the V Foundation for Cancer Research and St. Baldrick's Childhood Cancer Research Foundation.

Jaehyuk Choi, M.D., Ph.D.



Northwestern University Feinberg School of Medicine
Project Title: Identifying Mechanisms Governing T Cell Diversity

Jaehyuk Choi is the Ruth K. Freinkel Assistant Professor in the Department of Dermatology and the Department of Biochemistry and Molecular Genetics at the Northwestern University Feinberg School of Medicine in Chicago, IL.

He received his A.B. in Biochemistry from Harvard and his M.D. Ph.D. degrees from the Yale School of Medicine. After clinical training in dermatology at Yale, he conducted his post-doctoral training first in functional genomics in Tian Xu's lab and later in Richard Lifton's lab where he employed next generation sequencing approaches to improve our understanding of the genetic basis of cutaneous T cell lymphoma and related diseases.

He is the recipient of the National Science Scholar Award, the AAD Young Investigator of the Year Award, the Leukemia Research Foundation New Investigator Award, and the Doris Duke-Damon Runyon Clinical Investigator Award.

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Greg M. Delgoffe, Ph.D.

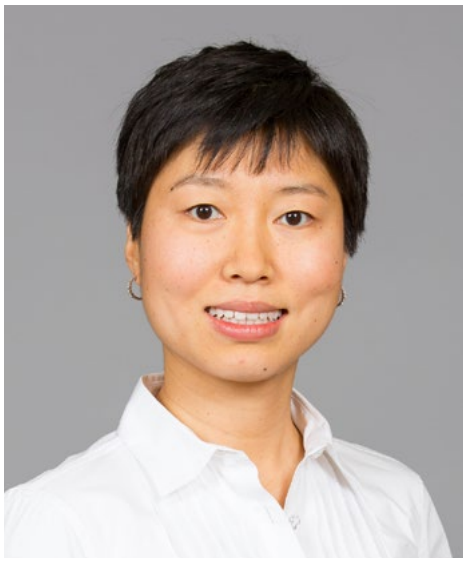
University of Pittsburgh School of Medicine
Project Title: Exploring and Exploiting Metabolic Plasticity in Regulatory T Cells

Delgoffe graduated with a Bachelor of Science from Western Michigan University prior to completing Ph.D training with Jonathan Powell at Johns Hopkins University School of Medicine.

He completing postdoctoral training with Dario Vignali at St. Jude Children's Research Hospital and started his lab in 2014 at the University of Pittsburgh in the Tumor Microenvironment Center. Delgoffe's research focuses on how the altered metabolic environment of cancer can affect the infiltration and activity of immune cells, and how these alterations can impact the efficacy of immunotherapy.

His NIA project focuses on immunosuppressive regulatory T cells, which display a phenotype of metabolic plasticity that allows them to thrive in nutrient poor microenvironments.

Lingyin Li, Ph.D.



Stanford University School of Medicine
Project Title: Chemical Biology of Innate Immunity for Treating Cancer and Autoimmunity

Lingyin Li is an assistant professor in the Department of Biochemistry and the ChEM-H Institute at Stanford University. Her lab uses chemical biology to uncover biochemical mechanisms in innate immunity and, in parallel, develop therapeutic hypotheses and lead compounds.

She received a B.En. from School of Chemistry and Materials Science at University of Science and Technology of China. She went on to obtain a Ph.D. in Chemistry from University of Wisconsin-Madison and trained with Laura Kiessling in chemical biology.

For her postdoctoral training, she worked with Timothy Mitchison at Harvard Medical School on cancer biology and innate immunology. She is the recipient of a Jane Coffin Childs Fellowship, a Pathway to Independence Award from the NIH, and a Baxter Faculty Scholarship.

Eleni Linos, M.D., Dr.P.H.

University of California San Francisco
Project Title: Targeted Advertising for Cancer Prevention

Eleni Linos is dually trained in public health and dermatology. After medical school at Cambridge and Oxford Universities in the UK, she completed a master's and a doctorate degree in Epidemiology at Harvard, where she gained substantial quantitative skills analyzing large cohort study data.

She completed Dermatology residency at Stanford, before joining the faculty at UCSF. Her training and clinical experience motivated her to think broadly about ways to tackle the growing problem of skin cancer—both by developing innovative prevention strategies and by improving the care patients receive. Her current work aims to radically shift our approach to disease prevention using online advertising, social media and smartphone technology.

Neville E. Sanjana, Ph.D.

New York Genome Center and New York University
Project Title: In Situ Functional Genomics to Understand Transcriptional Regulation
Grant ID: DP2-HG-010099

Neville Sanjana is a core faculty member at the New York Genome Center, and an assistant professor of Biology at New York University and of Neuroscience and Physiology at NYU School of Medicine.

Utilizing new technologies for large-scale DNA synthesis and gene editing, Sanjana has developed pooled screening approaches for functional genomics and applied them to gene regulation, cancer evolution and metastasis, drug resistance, cancer immunotherapy, neurodevelopmental disorders and synthetic biology.

Recent work in the Sanjana Lab is focused on creating new genome engineering tools to pinpoint functional elements in the noncoding genome and decipher their regulatory logic. Sanjana was previously a Simons Postdoctoral Fellow in Feng Zhang's lab at the Broad Institute and MIT, obtained a Ph.D. in Brain and Cognitive Sciences from MIT with Sebastian Seung, and holds a B.S. in Symbolic Systems and a B.A. in English Literature from Stanford University.

He is a recipient of the Kimmel Scholar Award, the Melanoma Research Alliance Young Investigator Award, the NIH Pathway to Independence Award, and the Paul Allen Institute for Brain Science Next Generation Leader Award.

Andrea Schietinger, Ph.D.

Memorial Sloan Kettering Cancer Center
Project Title: Spatiotemporal Regulation of T Cell Fate Decisions in Cancer

Andrea Schietinger is an assistant member in the Immunology Program at Memorial Sloan Kettering Cancer Center. Her research group investigates the regulatory mechanisms underlying tumor-specific T cell dysfunction in developing solid tumors.

Andrea received her degree in pharmacology from the University of Hamburg, Germany, before going on to do her Ph.D. with Dr. Hans Schreiber at the University of Chicago, where she studied how aberrant glycosylation of wildtype proteins in cancer cells creates tumor-specific neoantigens.

As a CRI Irvington postdoctoral fellow in Philip Greenberg's lab at the University of Washington in Seattle, she defined the molecular programs needed for self-reactive T cells to maintain self-tolerance. In addition to the NIH Director's New Innovator Award, Andrea is a Josie Robertson Investigator, a recipient of the NIH Pathway to Independence Award, the William and Ella Owens Foundation Award, and the V Foundation Scholars Award.

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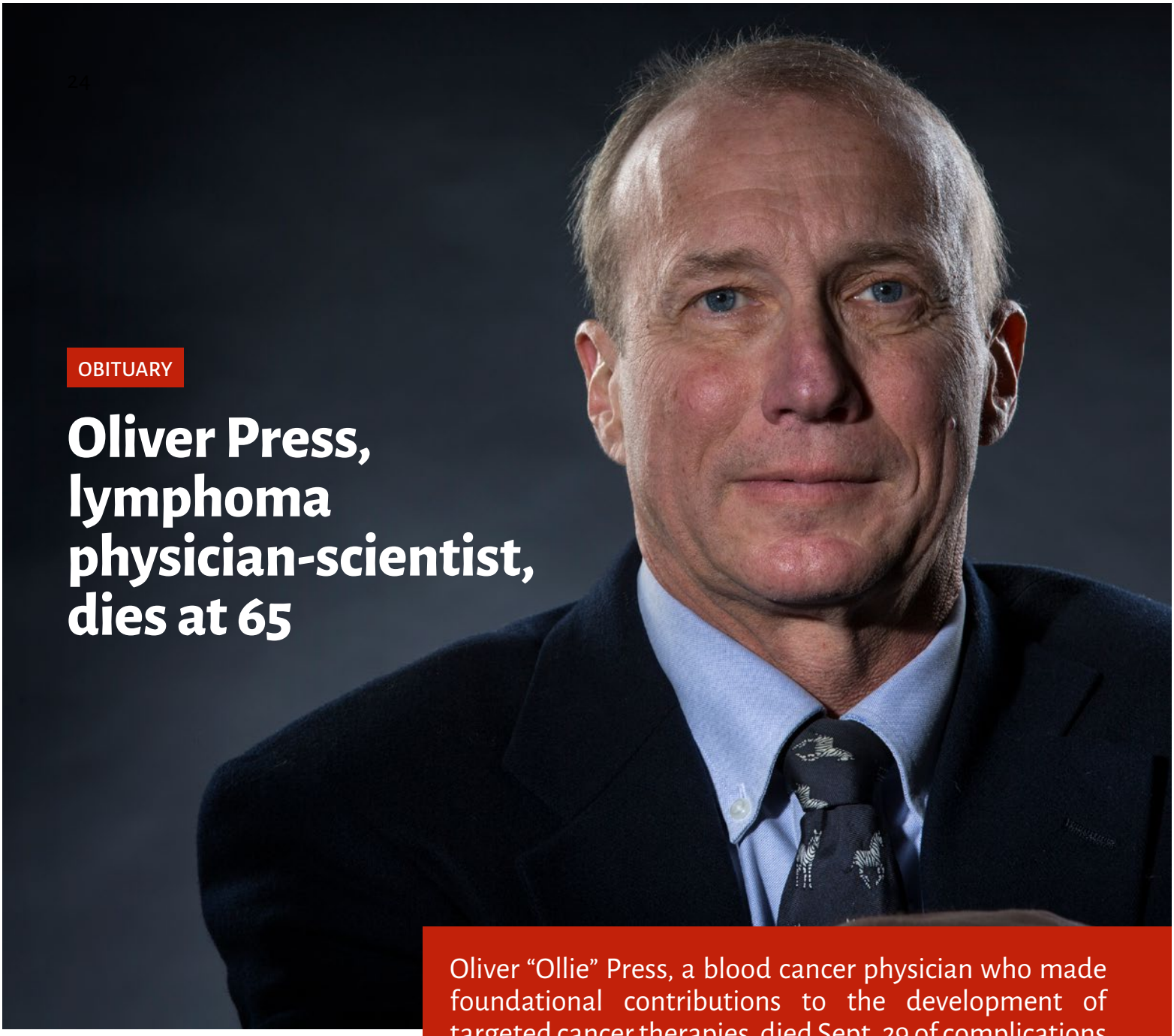

OBITUARY

Oliver Press, lymphoma physician-scientist, dies at 65

Oliver "Ollie" Press, a blood cancer physician who made foundational contributions to the development of targeted cancer therapies, died Sept. 29 of complications from glioma. He was 65.

Press was best known for his impact on the development of radioimmunotherapies. His scientific impact spans the research spectrum, from fundamental science to large-scale clinical trials.

"Ollie was an extraordinary physician-scientist and leader of [Fred Hutchinson Cancer Research Center's] Clinical Research Division [from 2013-2016]. He was an early pioneer in the use of monoclonal antibodies to target radionuclides to tumors, always keeping the immediate needs of cancer patients foremost in his translational science," said Gary Gilliland, president and director of Fred Hutch. "Perhaps most importantly, he was a truly remarkable mentor—his legacy and his work will live on through his many trainees. He will be dearly missed but will remain an inspiration and role model to us all."

Press was diagnosed with brain cancer in 2015. At the time of his death, he held the first David and Patricia Giuliani/Oliver Press Endowed Chair in Cancer Research at Fred Hutch and had been a faculty member in the Clinical Research Division since 1986. He also held the Hutch's Dr. Penny E. Petersen Me-

morial Chair for Lymphoma Research from 2001 to 2016. He maintained a joint appointment at the University of Washington, where he was a professor of medicine and adjunct professor of bioengineering.

"I think his impact is extraordinary. His impact is in science, in clinical care and in education," said UW Medicine CEO Paul Ramsey in a previously unpublished interview with Fred Hutch News Service, several months before Press' death. "In everything he does, he shows he's a leader by being a role model: He does the work as well as leads the work."

Press chaired the Scientific Advisory Board for the Lymphoma Research Foundation and co-chaired the NCI Lymphoma Steering Committee, which guides the design of national clinical trials for lymphoma, many of which he led. Appointed acting senior vice president and acting director of the Hutch's largest research division in 2013, Press continued to serve in this role for more than three years, throughout his treatment for cancer, until a permanent new leader, Nancy Davidson, took the helm Dec. 1, 2016.

"I had never met Ollie before I came to Seattle. From the moment I met him it was immediately apparent that Ollie was everything that one could hope for—a highly skilled and caring physician, an innovative and visionary cancer researcher, a talented administrative leader and an exceptional mentor for so many—including me as a newcomer," said Davidson, senior vice president and director of the Hutch's Clinical Research Division, director of medical oncology at UW Medicine and executive director and president of Seattle Cancer Care Alliance, where Press treated patients. "I am fortunate indeed to follow in his footsteps at Fred Hutch, UW and SCCA as we work toward a world without cancer. He will be sorely missed by his many patients and all members of the SCCA."

Press' cancer radioimmunotherapy research, which began when he was a fellow at Fred Hutch in the 1980s, played a pivotal role in the strategy's eventual FDA approval in the early 2000s. Clinical trials he led combining radioimmunotherapy and blood stem cell transplant have demonstrated some of the best long-term outcomes ever seen in certain kinds of blood cancers. Hundreds of patients have received radioimmunotherapy products created in his research labs, Press estimated in an interview earlier this year.

"From the moment I met him it was immediately apparent that Ollie was everything that one could hope for—a highly skilled and caring physician, an innovative and visionary cancer researcher, a talented administrative leader and an exceptional mentor for so many—including me as a newcomer."

– Nancy Davidson

Press was frustrated that radioimmunotherapy has had relatively low uptake in clinical practice, even though it can be a source of cures for many patients. Throughout his career, Press led the development of new technologies that he hoped would help to increase the strategy's uptake. For example, a new class of low-wavelength radioactive compounds he was investigating, called alpha-emitters, would make the procedure possible in an outpatient setting, obviating the need for specialized radiation-safe facilities that patients can typically only find at major academic medical centers.

Another new strategy he was developing, called pre-targeted radioimmunotherapy, would make the therapy even more specific to tumors, further reducing unwanted effects on healthy tissue.

Press has also made fundamental contributions to other targeted blood cancer therapies. As a fellow, he led the first trial of an antibody specifically aimed at a molecule called CD20 on certain immune cells called B cells that can become cancerous in leukemias and lymphomas. That trial in lymphoma, published in 1987, was the first to demonstrate the feasibility of targeting this molecule with an antibody to treat cancers; today, CD20-targeted antibody-based drugs are a mainstay of treatment for blood malignancies.

More recently, Press, with his mentee Brian Till, developed a genetically engineered immune-cell therapy targeting CD20, which is launching in its first-in-human trial this fall for patients with difficult non-Hodgkin lymphomas. This trial is one of the first in the world to aim these genetically engineered cells, called CAR T cells, at this target.

These projects are all now being carried on by junior researchers he mentored, to whom Press transitioned his research after he went on medical leave this January.

Press was born and raised in St. Louis. As an undergraduate at Stanford University, Press considered careers in herpetology and marine biology before settling on medicine.

> He was an early pioneer in the use of monoclonal antibodies to target radionuclides to tumors, always keeping the immediate needs of cancer patients foremost in his translational science. Perhaps most importantly, he was a truly remarkable mentor—his legacy and his work will live on through his many trainees. He will be dearly missed but will remain an inspiration and role model to us all.
>
> *– Gary Gilliland*

Press mentored 72 people at all stages of their careers. For 15 years, Press was associate director of the University of Washington's M.D./Ph.D. training program and, from 2014 until 2017, led the Fred Hutch/University of Washington Cancer Consortium's training program for new oncologists.

In February 2017, Fred Hutch unveiled the Oliver 'Ollie' W. Press Award for Extraordinary Mentorship, which was created by Press' colleagues to honor his impact on patients and on cancer research. Press also received the Excellence in Mentorship Award from the UW Department of Medicine in 2016. UW recently established the Oliver W. Press ARCS Foundation Endowed Fellowship ("The Ollie") to support M.D./Ph.D. students in the UW/Fred Hutch Medical Scientist Training Program.

And after brain surgery one Friday in October 2015 to remove a tumor that had been diagnosed just days before, he was back at work on Monday; he had patients scheduled in the clinic and he couldn't imagine cancelling on them.

Press received the inaugural Oliver W. Press Distinguished MSTP Alumnus Award from UW; the Research Visionary Champion Award from the Washington/Alaska chapter of the Leukemia & Lymphoma Society; a Gold Award for Achievement in Medical Research from Seattle Business Magazine; and several awards from the Lymphoma Research Foundation, including the organization's Distinguished Service Award, which was bestowed on him jointly with his wife in the days before his death. He has also appeared on local and national "top doctor" lists nearly two dozen times. Press will be posthumously awarded the SAAS Foundation for Medical Research's John Ultmann Award for Contributions to Lymphoma Research in October and the American Society of Hematology's 2017 Mentor Award in December.

He is survived by his wife of 38 years, Nancy Press, who collaborated with him behind the scenes on his research since the earliest years of their marriage, doing everything from flushing marrow from mouse bones to editing grant applications and, since 2006, serving in an official capacity as his lab's research administrator.

The couple has two children, attorney Michael Press of Boston and geneticist Maximilian Press of Seattle. Other surviving family members include Press' mother, Martha Press, of St. Louis; his brother, Michael Press, a breast cancer pathologist at the University of Southern California; and sister, Washington University cancer nurse Barbara Press. Press' father, Oliver H. Press, a former high school teacher, died in 1996.

Memorial gifts may be made to the Oliver W. Press ARCS Foundation Endowed Fellowship ("The Ollie") and the Oliver "Ollie" W. Press Award for Extraordinary Mentorship.

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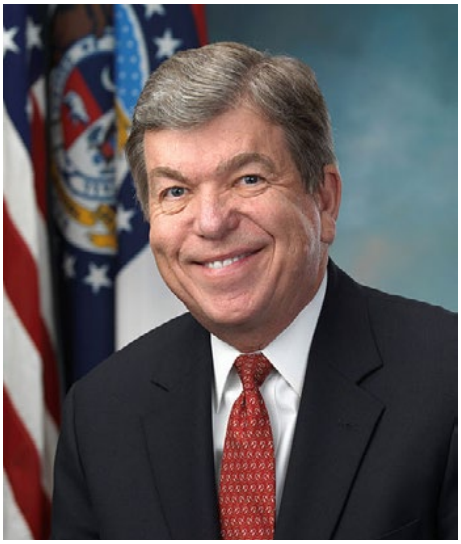
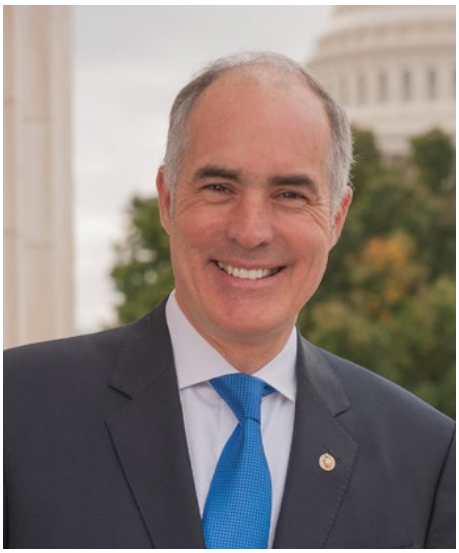
IN BRIEF

Carl June, Sens. Blunt and Casey to receive AACI awards

The 2017 AACI Distinguished Scientist Award will be presented to Carl June.





Sens. Roy Blunt (R-MO) and Bob Casey (D-PA) will receive the 2017 AACI Public Service Award at the Association of American Cancer Institutes' annual meeting, Oct. 15–17, in Washington.

June is director of translational research at the Abramson Cancer Center of the University of Pennsylvania, director of the Parker Institute for Cancer Immunotherapy and the Center for Cellular Immunotherapies, and Richard W. Vague Professor in immunotherapy, department of pathology and laboratory medicine, Perelman School of Medicine at the University of Pennsylvania.

In 2011, June's research team published findings which represented the first successful and sustained demonstration of the use of gene transfer therapy to treat cancer. On Oct. 16, he will deliver a talk on his ongoing work and the implications of the FDA's recent approval of gene transfer therapy to treat cancer.

Blunt is chairman of the Senate Committee on Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies. Casey is a member of the Senate Committee on Health, Education, Labor, and Pensions.

NCCN Radiation Therapy Compendium provides recommendations for 41 disease sites

NCCN announced the release of the Radiation Therapy Compendium that includes information designed to support clinical decision-making around the use of radiation therapy in patients with cancer.

The content is based directly on the NCCN Clinical Practice Guidelines in Oncology, and compiles every reference to radiation therapy across the 41 Guidelines referencing RT.

The NCCN Radiation Therapy Compendium includes a full complement of radiation therapy recommendations found in the current NCCN Guidelines, including specific treatment modalities such as 2D/3D conformal external beam radiation therapy, intensity modulated radiation therapy, intra-operative radiation therapy, stereotactic radiosurgery/stereotactic body radiotherapy/stereotactic ablative body radiotherapy, image-guided radiation therapy, low dose-rate/high dose-rate brachytherapy, radioisotope, and particle therapy.

NCCN first announced the launch of the Radiation Therapy Compendium during the Annual Conference in March. At the time, NCCN released a

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preliminary version of the Compendium featuring 24 cancer types. The newly completed version now contains all 41 disease sites that are currently being treated using radiation therapy.

The complete NCCN Library of Compendia also includes:

- NCCN Drugs & Biologics Compendium contains authoritative, scientifically derived information designed to support decision-making about the appropriate use of drugs and biologics in patients with cancer. The NCCN Compendium is recognized by public and private insurers alike, including CMS and UnitedHealthcare as an authoritative reference for oncology coverage policy.

- NCCN Biomarkers Compendium contains information designed to support decision-making around the use of biomarker testing in patients with cancer.

- NCCN Imaging Appropriate Use Criteria include recommendations pertaining to cancer screening, diagnosis, staging, treatment response assessment, follow-up, and surveillance to support clinical decision-making for patients with cancer. In 2016, NCCN was recognized by Centers for Medicare & Medicaid Services (CMS) as a qualified provider-led entity for creation of imaging AUC.

The compendium is available free-of-charge through March 2018.

The Lung Cancer Research Foundation and Free to Breathe announce Merger

The Lung Cancer Research Foundation and Free to Breathe announced a merger to make an even greater impact on closing the funding gap for lung cancer research. The New York State Attorney General approved the required merger documentation on Sept. 30.

The Lung Cancer Research Foundation name will be retained to best reflect the combined entity's shared mission.

Both the Lung Cancer Research Foundation and Free to Breathe have a long history of funding innovative, high-reward research across the spectrum of basic, clinical, and translational research with the potential to extend survival and improve quality of life for people with lung cancer. The newly expanded organization has funded a cumulative 332 grants, totaling more than $32 million, the highest amount of funding provided by a lung cancer research organization to date.

"By coming together, we can build upon the momentum we have established separately to expand our Scientific Grant Program and increase funding for lung cancer research," said Nancy Sanford, executive director of the Lung Cancer Research Foundation.

In addition to funding lung cancer research, the merged organization will focus on lung cancer awareness and education programs. The merged entity will also continue to host public events across the country. Free to Breathe's nationwide series of annual run/walk and yoga events will continue as the Free to Breathe Event Series.

Founded in 2005, the Lung Cancer Research Foundation funds novel lung cancer research that might otherwise go unfunded. Through its Scientific Grant Program, the Lung Cancer Research Foundation provides critical seed funding to U.S. and international investigators with groundbreaking ideas, helping establish proof of concept evidence to pave the way for additional funding.

Free to Breathe was founded in 2001 and focuses on funding lung cancer research, providing lung cancer education, and promoting advocacy and awareness. The organization develops lung cancer educational materials and provides them free of charge to patients, caregivers and healthcare professionals. Educating patients empowers them to make the best and most informed decisions about their treatment and care.

$2.4M grant aids exploration of social media to reduce indoor tanning behavior

A five-year, $2.4 million grant (R01CA218068) from the NCI awarded to Rutgers Cancer Institute of New Jersey behavioral scientist Jerod Stapleton, will support the development and testing of a novel behavioral intervention delivered through the social media site Facebook to reduce high-

risk indoor tanning behaviors among young women.

"There are well-publicized dangers of excessive exposure to ultraviolet radiation for the purposes of tanning, whether sunbathing outdoors or the use of indoor tanning beds. Tanning has been associated with increased risk of all types of skin cancer, including the deadly melanoma," said Stapleton, who is part of Rutgers Cancer Institute's Population Science Program and an assistant professor of medicine at Rutgers Robert Wood Johnson Medical School. "The 2014 Surgeon General's Call to Action to Prevent Skin Cancer report identified a critical research gap related to an absence of interventions that target high-risk indoor tanners and address underlying motives for tanning. It is for that reason we need to further explore this topic."

Stapleton and colleagues will refine existing intervention content from preliminary intervention studies conducted by their group. They will then conduct a trial of the new content in a sample of 400 young women who engage in indoor tanning.

Through a private group function on Facebook, participants will have an opportunity to interact with one another on content tailored toward addressing the underlying motives of indoor tanning rather than on the risks of the practice. For instance, content will focus on reducing the perceived pressure to be tan, reducing the value placed on tanning and promoting positive body image.

Investigators are looking to show that participants in the intervention will report less indoor tanning at a six-month follow-up period than those who take part in a control group. They also will examine psychosocial mediators of the intervention effects.

An estimated one in ten of all new U.S. cases of melanoma is directly attributable to indoor tanning, according to 2014 research (Wehner MR, Chren MM, Nameth D, et al., JAMA Dermatol.) that analyzed existing studies of tanning risks. Most concerning, notes Stapleton, are estimates from a 2013 study (Guy GP, et al., JAMA Internal Med.) that found nearly one in five young adult white females engage in high-risk indoor tanning, which is defined as using indoor tanning beds at least ten times a year. "If effective, the low-cost intervention we are exploring could be widely disseminated and would have the potential to help reverse concerning melanoma trends observed among young women," he said.

FDA awards 15 grants for clinical trials to stimulate product development for rare diseases

The FDA said it has awarded 15 new clinical trial research grants totaling more than $22 million over the next four years to boost the development of products for patients with rare diseases. These new grants were awarded to principal investigators from academia and industry across the country.

The FDA awarded the grants through the Orphan Products Clinical Trials Grants Program, funded by Congressional appropriations, to encourage clinical development of drugs, biologics, medical devices, or medical foods for use in rare diseases. The grants are intended for clinical studies evaluating the safety and effectiveness of products that could either result in, or substantially contribute to, the FDA approval of products targeted to rare diseases.

Approximately 33 percent of the new grant awards fund studies to accelerate cancer research by enrolling patients with rare forms of cancer. Sixty percent of these studies target devastating forms of brain and peripheral nervous system cancers, including glioblastoma and anaplastic astrocytoma. One study recruits children as young as one year old with a particularly aggressive form of neuroblastoma.

Other studies span a broad range of diseases and address unmet needs like treating hyperphagia in Prader-Willi syndrome, a genetic disease that primarily affects children, and idiopathic osteoporosis in premenopausal women. Two studies recruit patients with unmet need in sickle cell disease. In addition, one study evaluates a new combination of existing antibiotics to treat pulmonary tuberculosis, including multidrug-resistant TB. TB is a leading killer of HIV-positive patients, and, though not as common in the United States, one-third of the world's population is infected with TB.

A total of 76 grant applications were received for this fiscal year, with a funding rate of 20 percent. The grant recipients for fiscal year 2017 are the following:

- AADi, LLC (Pacific Palisades, California), Neil Desai, phase II Study of ABI-009 for the Treatment of Advanced Perivascular Epithelioid Cell Tumors — about $2 million over four years
- Albert Einstein College of Medicine (Bronx, New York), Caterina Minniti, phase II Study of Topical Sodium Nitrite for the Treatment of patients with Sickle Cell Disease & Leg Ulcers — about $2 million over four years
- Albert Einstein College of Medicine (Bronx, New York), Eric Hollander, phase II Study of Oxytocin for the Treatment of Hyperphagia in Prader-Willi Syndrome — about $1.5 million over three years
- Alkeus Pharmaceuticals, Inc. (Cambridge, Massachusetts), Leonide Saad, phase II Study of ALK-001 for

the Treatment of Stargardt Disease — about $250,000 over one year

- CereNova, LLC (Durham, North Carolina), Daniel Laskowitz, phase IIA Study of CN-105 for the Treatment of Intracerebral Hemorrhage — about $1 million over two years

- Columbia University Medical Center (New York), Elizabeth Shane, phase II Study of Teriparatide for the Treatment of Idiopathic Osteoporosis in Premenopausal Women — about $1.9 million over four years

- Columbia University Medical Center (New York), Gulam Manji, phase II Study of PLX3397 + Sirolimus for the Treatment of Malignant Peripheral Nerve Sheath Tumors — $2 million over four years

- Dana-Farber Cancer Institute (Boston), Steven Dubois, phase I Study of dual PI3K/BRD4 Inhibitor SF1126 for the Treatment of Neuroblastoma — $750,000 over three years

- Duke University (Durham, North Carolina), Allan Kirk, phase II Study of Belatacept, Alemtuzumab, and Sirolimus in Renal Transplantation — about $1 million over three years

- Johns Hopkins University (Baltimore), Susan Dorman, phase IIa Study of Rifampin, Merrem and Augmentin for the Treatment of Pulmonary Tuberculosis — about $2 million over four years

- New York Medical College (Valhalla, New York), Mitchell Cairo, phase II Defibrotide for the Prevention of Complications in High-Risk Sickle Cell Disease Patients Following Allogeneic Stem Cell Transplantation — about $1.75 million over four years

- Protalex, Inc (Florham Park, New Jersey), Richard Francovitch, phase I/II Study of PRTX-100 for the Treatment of Immune Thrombocytopenia — about $500,000 over two years

- Sloan-Kettering Institute for Cancer Research (New York), Ping Chi, phase II Study of MEK162 & Imatinib for the Treatment of Gastrointestinal Stromal Tumors — $2 million over four years

- Tocagen Inc. (San Diego), Asha Das, phase II/III Study of Toca 511 +Toca FC versus SOC in Recurrent Glioblastoma and Anaplastic Astrocytoma — $2 million over four years

- University of California, San Francisco (San Francisco), Marshall Stoller, phase II Study of Lipoic Acid for the Treatment of Cystine Nephrolithiasis — about $2 million over four years

Since its creation in 1983, the Orphan Products Clinical Trials Grants Program has provided more than $390 million to fund more than 600 new clinical studies. At least 60 grants have supported the marketing approval of more than 55 orphan products. Three of the studies funded by this grants program supported product approvals in 2016 alone, including treatments for aortic wall injury in patients with coarctation of the aorta and severe hepatic veno-occlusive disease (also known as sinusoidal obstructive syndrome).

DRUGS & TARGETS

FDA grants priority review for Lilly's Verzenio (abemaciclib) for advanced breast cancer

Eli Lilly and Co. said FDA has granted Priority Review designation for its New Drug Application for Verzenio (abemaciclib), a cyclin-dependent kinase (CDK) 4 & 6 inhibitor.

The NDA was based upon the positive interim results from MONARCH 3, a study of abemaciclib in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

The results were presented at the European Society for Medical Oncology 2017 Congress, and recently published in the Journal of Clinical Oncology

Priority Review aims to expedite the review of applications for drugs that, if approved, would represent a significant advance in treatment. With Priority Review of a new drug, the FDA's goal is to take action within eight months of receiving an application, compared with the standard review timeframe of 12 months.

Boehringer Ingelheim's Gilotrif granted Priority Review

Boehringer Ingelheim said the supplemental New Drug Application for Gilotrif (afatinib) has been accepted for filing and granted Priority Review by FDA. The application for Gilotrif is currently under review for first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor exon 21 (L861Q), G719X, or S768I substitution mutations as detected by an FDA-approved test.

Gilotrif is approved in the U.S., EU (Giotrif), and many other markets for the first-line treatment of patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) mutations, and squamous cell carcinoma of the lung whose disease has progressed after treatment with platinum-based chemotherapy.

The submission is based on a meta-analysis of three clinical trials from the LUX-Lung clinical trial program that examined the efficacy of Gilotrif in patients whose tumors have uncommon EGFR mutations. The efficacy outcomes evaluated in the study included: objective response, disease control, duration of response, progression-free survival, and overall survival.

Uncommon mutations, which include L861Q, G719X, or S7681, represent less than 10 percent of the EGFR mutations found in NSCLC patients and are associated with poor prognosis and survival.

Priority Review designation is granted to applications for drugs that the FDA has determined have the potential to provide significant improvements in the safety or effectiveness of the treatment, diagnosis or prevention of serious conditions compared to available therapies. Under Priority Review, FDA typically takes action within six months of receiving a supplemental application, rather than 10 months, which is the standard review timeframe.

Janssen submits NDA for apalutamide in non-metastatic castration-resistant prostate cancer

Janssen Biotech Inc. said it has submitted a New Drug Application to the FDA for apalutamide, an investigational, next generation oral androgen receptor inhibitor for men with non-metastatic castration-resistant prostate cancer. Currently, there are no FDA approved treatments for patients with non-metastatic CRPC.

This submission is based on phase III data from the pivotal ARN-509-003 (SPARTAN) clinical trial, which assessed the safety and efficacy of apalutamide versus placebo, in patients with non-metastatic CRPC who have a rapidly rising prostate specific antigen despite receiving continuous androgen deprivation therapy. Patients with non-metastatic CRPC with a rapidly rising PSA are at high risk for developing metastatic disease. The primary endpoint of this study was metastasis free survival. The SPARTAN study results will be presented at a future medical meeting.

FDA clears first 7T MRI device

FDA has cleared the first seven tesla (7T) magnetic resonance imaging device, more than doubling the static magnetic field strength available for use in the U.S.

The Magentom Terra is the first 7T MRI system cleared for clinical use in the United States.

"The overall image quality of MRI improves with higher magnetic field strength," said Robert Ochs, director of the Division of Radiological Health in the FDA Center for Devices and Radiological Health. "The added field strength allows for better visualization of smaller structures and subtle pathologies that may improve disease diagnosis."

FDA reviewed the Magnetom Terra through the 510(k) premarket clearance pathway. A 510(k) is a premarket submission made to the FDA to demonstrate that a new device is substantially equivalent to a legally marketed predicate device.

FDA based its clearance on comparison to a predicate device and acquisition of sample clinical images. The agency reviewed the safety of the radiofrequency subsystem through computational modeling, simulations and rigorous experimental validation. The manufacturer also provided data from a comparative study of 35 healthy patients that compared images of the patients using the 7T device and images using the 3T device. Board-certified radiologists reviewed the images and confirmed that the images acquired on the 7T device were of diagnostic quality and, in some cases, an improvement over imaging at the 3T.

The Magnetom Terra is for patients who weigh more than 66 pounds, and is limited to examinations of the extremities.

The FDA granted clearance of Magnetom Terra system to Siemens Medical Solutions Inc.