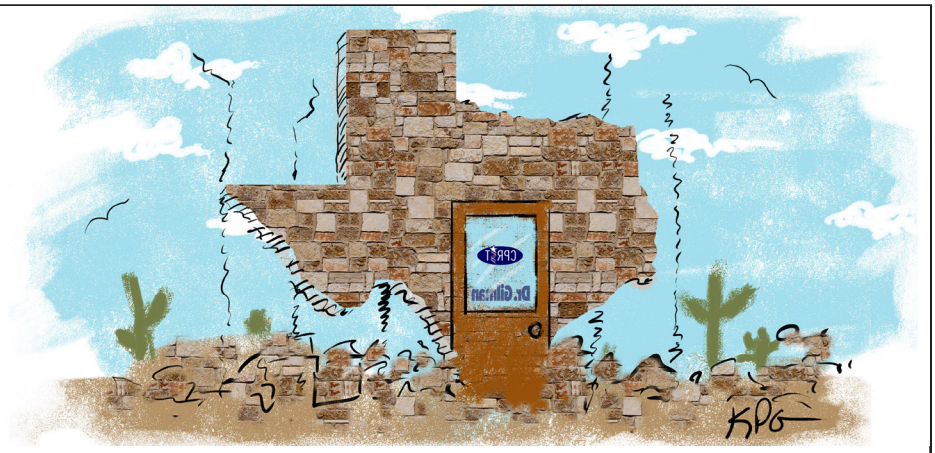
THE CANCER LETTER

Jan. 29, 2016 • www.cancerletter.com • Vol. 42 No. 4



Slamming the Door

How Al Gilman Taught Texas A Lesson in Science

This series re-examines the concurrent controversies at the Cancer Prevention and Research Institute of Texas and MD Anderson Cancer Center. This examination is possible in part because of new insight provided by Alfred Gilman, the Nobel laureate who served as the first scientific director of the state institution that distributes $300 million a year. Gilman died on Dec. 23, 2015.

Part I: The Hazard of Promising

By Paul Goldberg

Alfred Gilman's approach to distributing public funds wasn't particularly difficult to understand: he wanted to pay for the best science available. Period.

The pot of money entrusted to Gilman was vast. In 2007, Texas voters approved the largest investment in cancer research outside the federal government: $3 billion, to be spent over 10 years. By way of comparison, NCI grants going to Texas researchers and institutions added up to $240 million a year. CPRIT more than doubled that money. Only Texans were eligible to apply.

Gilman accepted the CPRIT job at age 68, because he thought that it would be a significant contribution to a major research effort, and a nice way to finish out a long career.

Gilman shared the 1994 Nobel Prize in Physiology or Medicine with Martin Rodbell for discoveries involving G-proteins, and served as the dean of the UT Southwestern medical school.

Since his life's research work was fundamental and not specifically focused on cancer, he needed to get to know more cancer people. His first call was to a friend—Phillip Sharp, a Nobel laureate himself and an institute

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How Al Gilman Taught Texas A Lesson in Science

(Continued from page 1)

professor at the Massachusetts Institute of Technology Koch Institute for Integrative Cancer Research.

Together, Gilman and Sharp recruited members of the CPRIT scientific council. Most of them were people Gilman didn't know. The members were the sort of people who could only be associated with a bona fide scientific peer review.

Planeloads of academics would come to Texas to review CPRIT scientific grants. Scientists who reviewed research proposals for the state-funded institute would later tell me that they had never served on a better peer review committee. For the first two-and-a-half years, the system worked smoothly.

There were no separate study sections for specific areas of research. The review committees were broadly constituted: basic, translational, clinical. There were no quotas for cancer type or research approach. There were no quotas based on geography. There were no quotas for science versus commercialization. The state law mandated that up to 10 percent of the funds were to be spent for evidence-based cancer prevention programs. The rest went to peer-reviewed science, including grants to companies, which were reviewed for both scientific quality and commercial potential.

Gilman walked into his office fully realizing that the job of CPRIT Chief Scientific Officer would entail working around bureaucratic absurdity and Texas-sized egos. But even being a seasoned academic politician, he could never have predicted that he would ultimately end up turning whistleblower in the name of defending of peer-reviewed science.

A year before his death from pancreatic cancer, Gilman sat down with me and provided a detailed account of his epic battle to protect public money from what he described as an arrogantly conceived, sloppily executed incursion. The stories of the ungluing of CPRIT and controversies at MD Anderson Cancer Center developed concurrently.

Some of these events have been described in The Cancer Letter before, but news stories seek to capture events as they unfold. Stepping back and enriching the narrative with greater insight can yield rich detail—and produce a different picture. My goal here is to present this material systematically, with the benefit of historical perspective—while incorporating Gilman's insight.

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Gilman had the demeanor of a curmudgeonly professor.

If he felt like presenting a six-pack of Budweiser to a student as a reward for the right answer, he did so. At one point, he compared his scientific council to World War II generals—on the Allied side, of course. A conversation with him was never brief and it was always a hoot.

At CPRIT, Gilman ended up fighting a war on many fronts.

There were attacks from a state legislator, who was seeking more research funds for his part of the state.

A number of institutions were objecting to the fact that UT Southwestern, the institution with which Gilman once helped run and where he kept office while at CPRIT, was getting more funds than anyone else.

The 11-member oversight committee provided no shield from political meddling. Indeed, Gilman used to say that only one of its 11 members knew that cancer was spelled with a "c." (That wise man would be Joseph Bailes, an oncologist.)

And, finally, there was a proposal for a $20 million biotech incubator that was going to be located at MD Anderson Cancer Center.

Through this proposal—and the role of Lynda Chin, a senior scientist and wife of that institution's president, Ronald DePinho—the problems at CPRIT merged with controversies over interactions between MD Anderson leadership and private industry. Gilman's resignation brought these controversies to the attention of scientists and the public.

"I built something I am proud of, and now it's being taken apart," Gilman said to me at the time. "I can't work

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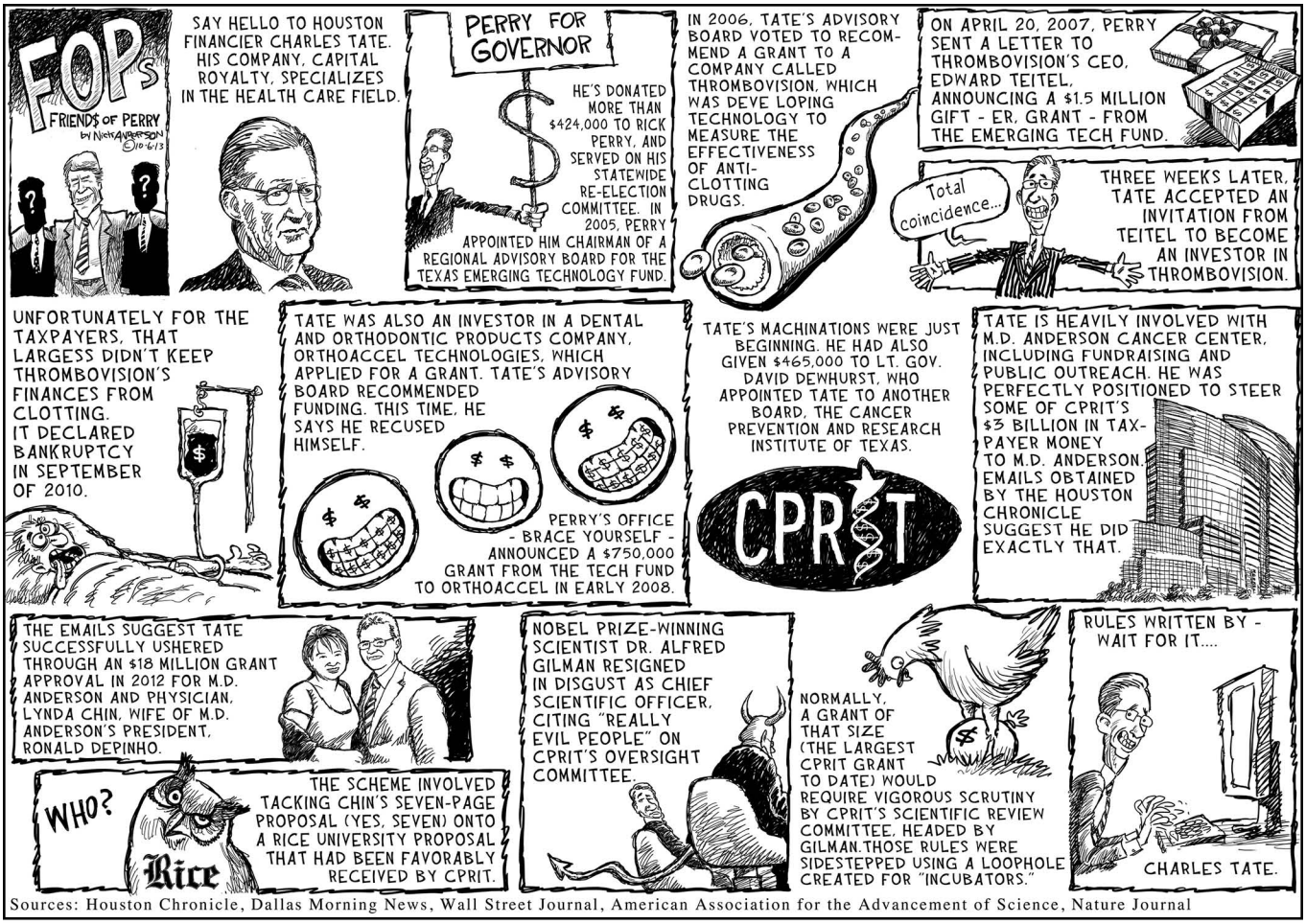
Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $420 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.



A cartoonist's view of what happened at CPRIT.
Reprinted with permission from the Houston Chronicle and Nick Anderson.

for people who are pushing their own interests at the expense of the interests of cancer patients."

Gilman was disappointed but not surprised.

"A wise and experienced friend said to me: 'This is always the way it works when you put a large amount of public money on the table. The vultures and the hyenas lie low for two or three years to see how the system really works. And then they come in for their feast.'"

The controversy made enough of an impact to inspire a cartoon by Nick Anderson, which appeared in the Houston Chronicle, and is reprinted above.

Gilman was wary of anything called "a moonshot." The metaphors of war and space travel were deceptive, he said.

"We have been guided by a few simple principles," Gilman and Sharp wrote in an opinion piece in the Houston Chronicle after they departed from CPRIT. "We were truthful about the complexity of cancer.

"To find cures, we must ponder dynamic cellular systems containing huge numbers of parts whose behaviors are governed by rules that have evolved over millions of years. We don't understand these systems in nearly enough detail to explain why and how they become dysfunctional. Progress in treating cancer requires rare and penetrating insights into deep pools of ignorance and translation of these insights into new therapies. It's pointless to push money at a problem—no matter how important it may be—if you lack insight for finding a solution.

"Texans deserve to hear the truth about cancer. They must understand that miracles will not happen in a short time. Progress will not be made by those who simply proclaim without explanation that they can do better than hundreds of skillfully staffed and well-financed pharmaceutical and biotechnology companies. Real progress requires the concerted high-quality efforts of basic, translational and clinical investigators from the academic community collaborating with counterparts from the private sector when appropriate."

Gilman believed that the only way to save CPRIT was to knock it down—to walk out the door, followed by the world's premier scientists, and slamming said door

as loudly as possible. Nothing less than that could create the urgency for Texas to re-create a clean peer-review system. Those who followed Gilman out still believe that this was the right thing to do.

His successor at CPRIT, Margaret Kripke, said in an interview that she basically reconstituted the review system Gilman had constructed (The Cancer Letter, Jan 6).

"I'm not sure resignation was necessary," Dan Fontaine, executive chief of staff at MD Anderson, said to me recently. "I'm not sure it required a resignation; I'm certainly not sure it required resignation of others. I think there could have been other avenues that would not have stirred the controversy, but at the same time that's the benefit of hindsight.

"Regardless of what the circumstances are, there's no question that CPRIT is in a very good place today and doing exactly what the voters wanted them to do. Secondarily, I think that the debate about the role of academic institutions and commercialization has not gone away. I think, as you well know, there's always going to be some differences in opinion about that," said Fontaine. An attorney, Fontaine is not an MD Anderson faculty member.

The MD Anderson project that contributed to the controversy went on without CPRIT support.

"I do believe, quite frankly, that when you look at the fact that there is a pipeline of some very promising therapeutics that we are moving through the Institute for Applied Cancer Science—there have been some spectacular strategic partnerships that we have put together with the pharmaceutical world because we have the capabilities of the Institute for Applied Cancer Science—I really think that four years hence, our commitment to bridging that gap between the discoveries in the academic world and products in the commercial world, which is what the Institute for Applied Cancer Science was designed to do. I think history is on our side on this one," Fontaine said.

"I think it's being proven out that we are on the right path. And I'm not sure that Dr. Gilman's resignation had anything to do with that at all, or the resignations of any of the scientific board. We went on without the CPRIT grant, and while I think all of the benefits of the Institute of Applied Cancer Science are yet to come, certainly there's some early successes in what we have been trying to do, partnered with our strategic industry ventures department, to really put together ways of accelerating discoveries into therapeutics and diagnostics."

Last year, Chin left MD Anderson to become the UT System's associate vice chancellor for health transformation and chief innovation officer for health affairs, based in Austin, and there are no plans to replace her as the scientific director of the cancer center's Institute for Applied Cancer Science, Fontaine said.

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By design and policy, the scientists who guided Gilman were from outside Texas.

This was an effort to keep intrastate academic rivalries from influencing the review process. Every member of every study section was from out of state as well.

With this set of conflicts managed, Gilman believed it was reasonable for him to run the review process from an office on the UT Southwestern campus in Dallas. He felt it was critical to remain in an academic environment. Besides, he was recused from the actual decisions about funding. These recommendations came from the study sections and the Scientific Review Council. Gilman had no vote, nor did he voice opinions about grants, save for reiterating what insiders called his mantra: "We want the best science."

The office in the medical school administration building was rented by CPRIT for his use. This was a nondescript place—just large enough for Gilman and an administrative assistant. There was also a small conference room with a videoconferencing hookup, which was used for monthly meetings of the Scientific Review Council.

Gilman was an academic's academic. A friend once joked that he is likely the only person ever named after a textbook. His father, Alfred Gilman, a well-known professor of pharmacology, was a co-author of the classic textbook The Pharmacological Basis of Therapeutics. The younger Gilman's middle name was chosen in honor of the book's other co-author, Louis Goodman.

Throughout his career, Gilman had never worked anywhere other than a biomedical research campus, including three medical schools and the National Institutes of Health.

By staying on campus, he could attend seminars and meet with long-time friends in their offices or at the faculty club.

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CPRIT's main office in Austin, a place Gilman rarely graced with his presence, seemed to have evolved a culture that was foreign to Gilman. The place was full of people whose stock in trade was politics.

It could be a tribute to Gilman that for the first two-and-a-half years of CPRIT's existence, I had little interaction with CPRIT. The peer review committees met, the place hummed along, and there was nothing for me to do, as a journalist. After things changed, my job was to pry the truth, or at least a coherent lie, out of bureaucrats who seemed to have three speeds: lying, stonewalling and an eagerness to please, in the hopes that I would go away. Some of these bureaucrats spoke as though they were on a mission from God to rid Texas from the scourge that is cancer.

Geographically isolated from the bureaucrats, Gilman drew on the expertise of top-tier cancer experts, the sort of people who would never let their names be associated with whitewashing a politically fixed giveaway of public funds in Texas or any place else.

They were:

• Clara Bloomfield, the William G. Pace III Professor of Cancer Research at Ohio State University.

• Sanjiv Sam Gambhir, the Virginia and D.K. Ludwig Professor in the department of radiology and bioengineering, chair of the department of radiology, director of the Molecular Imaging Program, and director of the Canary Center for Cancer Early Detection at Stanford University.

• Tyler Jacks, the David H. Koch Professor in the department of biology and director of the David H. Koch Institute for Integrative Cancer Research at MIT.

• William Kaelin, professor of medicine in the department of medical oncology at Harvard University and the Dana-Farber Cancer Institute.

• Richard Kolodner, professor of medicine and member of the Ludwig Institute for Cancer Research at the University of California, San Diego.

• Charles Sherr, chair of tumor cell biology, co-director of the Molecular Oncology Program, and Herrick Foundation Chair at St. Jude Children's Research Hospital.

• Everett Vokes, the John E. Ultmann Professor of Medicine and Radiation Oncology, and chair of the department of medicine at the University of Chicago Medical Center. (Vokes replaced David Johnson, who was impressed with CPRIT after brief service on the council, and was ultimately recruited from Vanderbilt to become chair of Internal Medicine at UT Southwestern.)

"Al knew many of us, although some better than others. In fact, as far as I'm concerned, he tried to recruit me to UTSW as a department chair many years ago," Sherr said to me recently. "As a council member, I was asked to appoint a review committee. Al said, "Just get 15 solid scientists who deeply understand cancer biology—the only caveats were that all must come from institutions outside of Texas and that no more than two of them could come from a single institution. I called 16 friends, of whom all but one agreed to serve on the Basic Science Review Committee that I would chair.

"Among the seven council members, we drafted over 100 scientists as CPRIT reviewers. We paid little attention to being politically correct—we just tried to get the very best people involved. Still, on this basis alone, my committee had national representation, and a virtually equal number of men and women. Despite the work, I think that CPRIT received some 850 applications at the get-go, and although we had to figure out how to parse them between committees at our very first meeting, the review process soon evolved to be very effective. Everyone wanted to ensure that the proposals got a fair reading, and council members 'traded' applications so that reviewers with appropriate expertise would be available. This was an adventure—the rules of the game were established on the fly."

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Gilman and his advisors weren't the sort of people who promise the cure. They had seen the sad results of overpromising, overstating and overselling. The best science was the only thing they could promise responsibly. It was possible and desirable that some of the basic knowledge bought with Texas taxpayers' money would lead to development of new therapies, but there could be no guarantees.

From his first day at CPRIT, Gilman urged state officials and politicians not to promise too much. To him, such promises were classic buffoonery, which people resort to in order to generate support and short-term infusions of cash. Basic science would be included in CPRIT's portfolio. You have to accept that you are building a foundation of knowledge from which great things will spring. Alas, you can't tell exactly when and where this is going to occur.

This doesn't mean that basic science produces no returns. Just ask an elderly person what her life expectancy was when she was born. She will have greatly exceeded it, and that's at least in part due to advances in medicine that have been driven by fundamental understanding.

When people started to discuss cancer as an

engineering problem, Gilman cringed. Engineering is a study of systems created by man, which presumably can be understood by man. Biology was created by evolution over hundreds of millions of years. The rules are incredibly complicated and dynamic.

Biology demands humility. Every time you think you understand it, something new comes along and hits you in the face.

Sixty-Nine Cancer Centers Urge HPV Vaccination

By Matthew Bin Han Ong

In an unprecedented move, 69 NCI-designated cancer centers have come together to advocate for HPV vaccination as a preventive measure against many HPV-related cancers.

"HPV vaccination is our best defense in stopping HPV infection in our youth and preventing HPV-related cancers in our communities," the centers said in a consensus statement published Jan. 27. "The HPV vaccine is cancer prevention."

According to a 2015 CDC report, only 40 percent of girls and 21 percent of boys in the U.S. are receiving the recommended three doses of the human papillomavirus vaccine. This falls far short of the HHS goal of 80 percent by the end of this decade. The goal is a part of the HHS Healthy People 2020 mission.

"Together we, the NCI-designated cancer centers, recognize these low rates of HPV-vaccination as a serious public health threat," the cancer centers said. "HPV vaccination represents a rare opportunity to prevent many cases of cancer that is tragically underused. As national leaders in cancer research and clinical care, we are compelled to jointly issue this call to action."

The effort stems from an NCI initiative in the 2014 fiscal year to fund research on HPV vaccination, focusing on the barriers to uptake as well as opportunities for encouraging immunization.

Eighteen competitive awards were made to academic cancer centers, which eventually formed a "consortium of interests," said Cynthia Vinson, a health science administrator for implementation science at the NCI Division of Cancer Control and Population Sciences.

"It was a one-year supplemental fund to the cancer centers, and the cancer centers themselves decided to organize meetings so that they could learn from each other," Vinson said to The Cancer Letter. "There were two meetings: the first one was held at Moffitt in January 2015, and then in November, MD Anderson hosted a meeting so that the cancer centers could come together to talk about what had happened during their one-year supplement."

This month, cancer centers across the country received invitations from MD Anderson President Ronald DePinho to support HPV vaccination.

This is the first time NCI-designated cancer centers have endorsed a joint statement on public health, said Ernest Hawk, vice president of cancer prevention and population sciences at MD Anderson.

"To me, the exciting thing is to see NCI-designated cancer centers come in together as a community to advocate for prevention and control, which is our best approach to the disease," Hawk said to The Cancer Letter. "That really hasn't happened, together, previously in this way, and that's the big news here. What you're seeing through this action and excitement that's generated in the cancer community is the idea of awakening these centers of excellence to another important component of their mission—this is advocacy on behalf of the public we serve.

"That's the most exciting form of advocacy. It's science-based, it's credible, and it's powerful, because it's not just this center or that center acting in isolation, but truly coming together. That's new and novel."

The 69 NCI-designated cancer centers urge parents and health care providers to "protect the health of our children" through these actions:

• "We encourage all parents and guardians to have their sons and daughters complete the three-dose HPV vaccine series before the 13th birthday, and complete the series as soon as possible in children aged 13 to 17. Parents and guardians should talk to their health care provider to learn more about HPV vaccines and their benefits.

• "We encourage young men (up to age 21) and young women (up to age 26), who were not vaccinated as preteens or teens, to complete the three-dose HPV vaccine series to protect themselves against HPV.

• "We encourage all health care providers to be advocates for cancer prevention by making strong recommendations for childhood HPV vaccination. We ask providers to join forces to educate parents/guardians and colleagues about the importance and benefits of HPV vaccination."

NCI officials say that while promoting HPV vaccination is a high priority, the institute does not endorse or promote specific guidelines.

"We are funding as much good science as we can to understand how to do it better," said Sarah Kobrin,

a behavioral research program director in the NCI Process of Care Research and Science of Research and Technology Branches. "We are enthusiastic about saving people from cervical and other HPV-related cancers. That's our goal, to generate the evidence.

"NCI doesn't make policy statements; we generate the evidence on which statements can be based. We're not policymakers, we no longer send guidelines as we did a couple of decades ago. That's a different time. It's just not our job."

NCI no longer participates in policymaking, because of controversy over breast cancer screening in the 1990s, said Otis Brawley, chief medical officer of the American Cancer Society and a former NCI cancer prevention expert.

"NCI has been like this since the early 90s, when they made a statement that breast cancer screening saves lives for women 50 and over," Brawley said to The Cancer Letter. "It was not a statement against screening women in their 40s, but [then-NCI Director Samuel] Broder got in trouble and said, 'Fine, we won't endorse anything, that way we can't get in trouble for endorsing things.'

"It was [then-Republican] Sen. Arlen Specter [of Pennsylvania], at that time, who threatened to cut the budget of the NCI. That's when NCI backed off and said, 'We're not going to do this anymore, save the money for all those R01s.'"

The American Cancer Society recommends HPV vaccination for girls ages 11 to 12, and as early as age 9. At this time, the society has no recommendation regarding the use of HPV vaccines in boys or men. The evidence for the use of HPV vaccines in males is being reviewed and updates to the society's recommendations will likely be published in 2016.

Coming Together

NCI's Kobrin said the NCI-designated cancer centers decided to work together, because they recognized an opportunity in cancer control.

"The fact that we are a cancer community working together to understand how to promote a vaccine is why there's so much interest," Kobrin said to The Cancer Letter. "It's a different area for us; it's not another cancer screening test as we have done for decades, it's not another prevention behavior. Immunization is a whole other world of medicine, and people who are familiar with cancer prevention and control research have needed to make linkages with immunization research communities.

"We've been fortunate to do that our CDC colleagues—they also are working with their cancer prevention people and their immunization people. It's understandable why the cancer community feels the need to gather together, because it's a new kind of topic for us."

While MD Anderson led the initiative, the credit belongs to all cancer centers, Hawk said.

"Moffitt, right at the inception, sponsored a collaborative meeting involving NCI, CDC, and these 18 centers to figure out how to do that work and to learn from one another," Hawk said. "And then, as it evolved over the course of the year, we thought, 'Wouldn't it be fantastic to come back together—these 18 original centers—but also invite all centers to the table to hear the results of these scans, so we could forge stronger ties across the cancer center community?'"

NCI-designated cancer centers operate independently of one another in most research areas, Hawk said.

"The centers of excellence do outstanding work in research, patient care, education, training, and some of them in cancer prevention and control, but they largely are funded as independent entities," Hawk said. "They largely do what they're funded to do; create excellence in those areas independent of one another. And then there are opportunities where they may come together around a particular topic such as NIH funding to sustain cancer research or the latest immunotherapy or something.

"So, whether it's cooperative groups or collaborations among centers, they take joint action and try to advance some aspects of their mission. But it really hadn't happened in cancer control, previously, to my knowledge, and that's the big opportunity that we saw.

"We invited everybody to the table—yes, it was MD Anderson-led, but it was certainly supported by all the centers—and we designed that meeting with the help of NCI, CDC and Moffitt, with the idea of putting together what have we learned and how can we work together."

Cancer control is a local issue requiring individual implementation strategies, Hawk said.

"What we've seen is, in every case, implementation of effective strategies require a local tailoring to the needs—that was one message coming out of the studies," Hawk said. "Health care providers, mainly family medicine physicians, pediatricians, may have been suggesting vaccination, but they weren't really advocating for vaccination, and so there's an opportunity to educate and try to motivate and support primary care physicians in their efforts to educate parents and move them towards vaccination."

Who Will Benefit?

The populations that stand to benefit most from HPV vaccination are those that are not currently being screened for cancer, NCI officials said.

"Generally speaking, it's the people who have the lowest access to routine health care, so the people who live far away, who don't have the money for good health insurance, who live in geographic areas where there are very few of the appropriate health care providers available for a community that's spread too thin," Kobrin said. "It's not a new story about health care access, it's those same people."

HPV vaccination is especially important for women who do not regularly screen for cervical cancer screening, Kobrin said.

"It's certainly true that we have a pretty effective cervical cancer screening system already in the United States, and we've succeeded in getting up to 80 or 85 percent of women to participate in cervical screening over their lifetimes in the U.S., which is the big reducer of cervical cancer diagnoses and death," Kobrin said. "But the remaining population of people persistently—and for decades we've been trying to understand; we can think who they are, but how to reach them has been an unresolved problem. Reaching them meaning, not talk to them, but actually get them to participate in screening.

"One of the challenges with screening is that you can't just do it once. Screening reduces mortality when it's a lifetime pattern of screening at the appropriate intervals, and so, from a public health perspective, it's most urgent for us to bring the vaccine to the communities that are not being well screened. And that's where the biggest opportunity for cervical cancer mortality reduction comes.

"A number of other cancers and diagnoses of the other cancers that can be HPV-related are increasing, so at this point, each year, as many non-cervical HPV-related cancers are diagnosed as cervical HPV-related cancers. And for none of those other cancers do we have any available screening test. So this primary prevention with the vaccine is really the right approach."

No one in the scientific community disagrees with HPV vaccination as a necessary public health measure, Kobrin said.

"There are no voices of dissent in the scientific community or medical community," Kobrin said. "Some pediatricians have expressed reservations talking to parents. They perceive that they might end up talking about sexual activity with parents of young children. Part of what CDC is doing, and we're trying to provide evidence to help them do, is teaching doctors how to make the recommendation just as they would for any other vaccine."

HPV vaccination rates have not kept up with other CDC vaccine recommendations, Vinson said.

"The reason why looking at HPV vaccination is so important is CDC has been tracking HPV vaccination data, and when guidelines come out, immunizations generally follow a trend where they're implemented rapidly for the population," Vinson said. "HPV hasn't followed the normal trend for other adolescent vaccine, so we're seeing a difference between HPV and the other adolescent vaccines."

Kobrin said CDC is "puzzled" by the behavior of the population in its uptake of the HPV vaccine.

"Two other recommendations for the same age groups—both recommended and approved about the same time—and the rates of uptake for the two gone straight up to the 75 to 85 percent rate, while within the same period of time, the HPV vaccine has been lagging," Kobrin said.

ACS's Brawley attributes the slow uptake to the cost of the vaccine as well as misperceptions about the vaccine's impact on youth sexual behavior.

"The HPV vaccine hasn't taken off in the U.S.—one, because it's expensive, and two, because many people are concerned they'll promote promiscuity," Brawley said.

"Literally, a large number of people who are against the HPV vaccine are against it because they view it as encouraging promiscuity. The truth is, the HPV vaccine has the tremendous ability to prevent a number of head-neck, cervical and anal cancers."

MD Anderson's Hawk said that the NCI-funded studies found that parents are still concerned about HPV vaccination as promoting promiscuity.

"That was an old concern, but now data has emerged since then showing that HPV vaccination really doesn't promote promiscuity," Hawk said. "It's an old wives' tale. There's an opportunity to move beyond that through effective public education.

"And of course, in isolated settings, there are individuals in the population that are still concerned about vaccine safety. However, those concerns aren't science-based so much as they are emotionally or individually based. That told us that there was an opportunity still in public education."

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NCI officials said researchers are working on identifying the efficacy of the vaccine in reducing cancer incidence.

"Efficacy of the vaccine in reducing infection rates is extremely well substantiated," Kobrin said, "However, it's a little too soon to be looking at cancer data, because the vaccine was approved in 2006, and we're talking about children.

"There are data on precancerous endpoints and there are data on infections and transmissions, for example, in Australia, they actually now have such good population level uptake that they have been able to document the decrease in infections.

"We don't have that kind of data and uptake, and it's soon to have actual cancer diagnosis outcomes because of that—girls who have been vaccinated at age 11 in 2006 and are not old enough even to have cervical cancer."

Public advocacy by NCI-designated cancer centers is important for encourage uptake of the HPV vaccine in their local communities, Vinson said.

"The cancer centers are uniquely poised, because of their expertise and their presence in their local community, to start pulling those things together," Vinson said. "We have a chance to potentially eliminate HPV-related cancers, and this is the first time that we have this opportunity."

PCORI Passes $1.2 Billion In Total Research Funding

The Patient-Centered Outcomes Research Institute approved $70 million for nine new patient-centered research projects focused on conditions including ductal carcinoma in situ, diabetes, chronic lung disease and migraines.

With these latest awards, PCORI has now approved or awarded more than $1.2 billion in research funding.

The newly approved studies will compare:

• Active surveillance versus traditional treatment options, such as surgery and radiation, for women diagnosed with DCIS.

• The effectiveness of two medications—roflumilast and azithromycin—commonly used to treat patients with chronic obstructive pulmonary disease.

• The effectiveness of different approaches involving community health workers, tailored education, and other means to help adults with serious mental illness quit smoking.

• The effectiveness of daily use of an inhaled corticosteroid versus symptom-based use for reducing asthma exacerbations in African American and Hispanic adults with asthma.

• The effectiveness of two approaches to help people manage their chronic migraines and reduce the risk medication overuse.

In addition, the PCORI Board of Governors approved $6.7 million in awards to three of the Clinical Data Research Networks that are members of PCORnet, PCORI's initiative to develop a national patient-centered clinical research network. The awards will help the recipients study the impact of population-targeted health policies and interventions on risks, complications and disparities related to type II diabetes.

Their projects will be part of the Natural Experiments Network, a joint effort of PCORI, the Centers for Disease Control and Prevention, and the National Institute of Diabetes and Digestive and Kidney Diseases.

The board also approved $5.2 million for a study that addresses PCORI's priority to fund research on improving healthcare systems. This study will determine whether encouraging text messages or working with diabetes wellness coaches is more effective at helping of African Americans with uncontrolled diabetes manage their conditions.

In addition, the board authorized an additional $3.8 million in funding for the ADAPTABLE trial, a PCORnet study that aims to identify the optimal dose of aspirin to prevent heart attacks and strokes in patients with heart disease. The funds will support expanded trial activities, including the participation of two additional CDRNs as well as recruiting patients with no Internet access, an important subpopulation given the study's reliance on digital tools.

In Brief

Mehta Named Deputy Director At Miami Cancer Institute

MINESH MEHTA joined **Miami Cancer Institute** at Baptist Health South Florida as deputy director and chief of radiation oncology.

Mehta comes to Baptist Health from the University of Maryland School of Medicine, where he served as medical director of the Maryland Proton Treatment Center in Baltimore—the area's first proton treatment center, which he helped to launch.

Mehta was also the university's associate director of clinical research in the Department of Radiation Oncology. Prior to his time at Maryland, he held academic, research and administrative leadership positions at Northwestern University and the University of Wisconsin, where he was appointed chairman of the medical school's Department of Human Oncology and led research studies, technology development and expansion at the University of Wisconsin Cancer Center. He also headed the university's brain tumor program for more than 15 years. At the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Mehta was co-director of the Radiation Oncology Residency Training Program.

The Miami Cancer Institute's new $430-million proton therapy facility, opening in 2016 and located on the Baptist Hospital of Miami campus, expects to treat its first patient with proton therapy in 2017.

CARMEN SOLÓRZANO was named chief of the Division of Surgical Oncology and Endocrine Surgery at **Vanderbilt University Medical Center**. Solórzano is a professor of Surgery and director of the Endocrine Surgery Center.

Solórzano joined the Vanderbilt faculty in 2010 and specializes in endocrine surgery, including neoplasms and cancers of the thyroid, parathyroid and adrenal glands, the pancreas and digestive system, as well as neuroendocrine tumors. She was selected following a national search that included more than 70 potential candidates, according to the center.

In addition to her current role at VUMC, Solórzano has served as chief of General Surgery at the Veterans Administration Hospital since 2012.

Solórzano previously served as assistant professor of surgery at the University of Miami, and later became chief of Endocrine Surgery. She has authored more than 100 publications, has lectured around the world and serves on the editorial boards for several journals.

JUDY KEEN was named director of scientific affairs of the **American Society for Radiation Oncology**.

Keen will work to develop and implement initiatives that promote clinical, translational and basic radiation research, with the ultimate goal of advancing both science and evidence-based patient care throughout the radiation oncology community—including managing various funding mechanisms offered by ASTRO, such as its junior faculty awards and seed grants, as well as finding and promoting opportunities from external funding agencies to share with ASTRO members.

Keen will also serve as ASTRO's primary scientific liaison to internal and external partners involved in biomedical research, including the ASTRO Science Council, federal agencies, other medical societies, coalitions, the biopharmaceutical industry, and policymakers.

Prior to joining ASTRO, Keen was director of research collaborations for the National Breast Cancer Coalition. Before NBCC, she worked at NCI, first as a health science analyst in the Office of Science Planning and Assessment, then as program director for the NIH Genotype Tissue Expression project within the Biorepository and Biospecimen Research Branch. The GTEx project included curating a collection of genomic and clinical data from more than 900 donors that was designed to explore genetic variability in humans and the changes that lead to disease.

Keen also spent several years as an assistant professor in the department of medicine at the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey.

TARA YATES was named director of communications of **the Wistar Institute**.

Yates comes to Wistar from Roswell Park Cancer Institute, where she was director of public affairs in the marketing department. While there, she led the public affairs team and managed internal, external and crisis communications, media relations, and web content for the comprehensive cancer center.

Yates also serves as vice-chair of the Public Affairs and Marketing Network, a professional organization of academically based comprehensive, clinical, basic and consortium cancer centers. PAMN works in close association with the NCI's Office of Media Relations and Public Affairs to further public awareness of cancer research, prevention, detection and treatment.

THE OVARIAN CANCER NATIONAL ALLIANCE and the **OVARIAN CANCER RESEARCH FUND** announced a merger, forming the **Ovarian Cancer Research Fund Alliance**. The new body will be the largest global organization dedicated to advancing ovarian cancer research.

"The Ovarian Cancer Research Fund Alliance believes we can gain more ground together, fighting disease through a 'one-stop shop' approach to research, advocacy, education and awareness," said OCRFA President and CEO Audra Moran. "The formation of OCRFA will propel ovarian cancer prevention and treatment forward at an accelerated pace."

Between the two organizations, nearly $70 million has been invested over the past 22 years in research grants to diagnose, treat and cure ovarian cancer.

"This merger will unite the ovarian cancer community under one strong voice. OCRFA is committed to continuing and expanding the many patient-centered programs begun by both the Ovarian Cancer National Alliance and Ovarian Cancer Research Fund in the past, including, the Ovarian Cancer National Conference, Survivors Teaching Students and Woman to Woman," said OCRFA Executive Vice President Calaneet Balas.

UC SAN DIEGO HEALTH selected **e+CancerCare**, a national operator of outpatient cancer care centers, to operate the UC San Diego Health - Chula Vista radiation oncology facility.

e+CancerCare will fully manage operations allowing affiliated physicians, UC San Diego faculty, nurses and staff. It will serve as the company's first center in California and its first collaboration with an academic health system.

The Chula Vista facility, which focuses on patients of Moores Cancer Center, includes patient navigators and clinical staff. Founded in 2002, e+CancerCare runs 22 centers in nine states, providing diagnostic testing, radiation oncology, medical oncology and ancillary services.

HARVARD BUSINESS SCHOOL's Health Care Initiative launched the **Precision Trials Challenge**, a competition to bring precision diagnostics and therapies to market more quickly.

"How can we develop business models that support the advancement of precision medicine? How can we get new therapies to market faster and at a lower cost? Our Precision Trials Challenge will help answer these questions by encouraging conversation and helping to put leading-edge ideas into practice," said professor Richard Hamermesh.

The challenge is accepting applications through March 13. A panel of judges will select one winner and two runners-up to share a $100,000 prize. The winner will be announced in April and have the opportunity to present at the 2016 Personalized Medicine Conference.

The Precision Trials Challenge is funded by the Kraft Endowment for Advancing Precision Medicine, established last fall by a $20 million gift from the Kraft Family Foundation under the leadership of Foundation president Robert K. Kraft.

Drugs and Targets

FDA Expands Opdivo-Yervoy Label with Accelerated Approval

FDA granted accelerated approval to a combination of Opdivo (nivolumab) and Yervoy (ipilimumab) for the treatment of patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma.

This approval expands the original indication for the Opdivo-Yervoy regimen for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma to include patients regardless of BRAF mutational status, based on data from the phase III CheckMate-067 trial, in which PFS and overall survival were co-primary endpoints. Opdivo is sponsored by Bristol-Myers Squibb.

FDA also expanded the use of Opdivo as a single-agent to include previously untreated BRAF mutation-positive advanced melanoma patients. The use of Opdivo as a single-agent in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma is approved under accelerated approval based on progression-free survival. Opdivo was approved by the FDA in November 2015, for use in previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma.

CheckMate-067 is a double-blind, randomized study that evaluated the Opdivo-Yervoy regimen or Opdivo monotherapy vs. Yervoy monotherapy in patients with previously untreated advanced melanoma.

The trial evaluated previously untreated patients, including both BRAF V600 mutant and wild-type advanced melanoma, and enrolled 945 patients who were randomized to receive the combination regimen (Opdivo 1 mg/kg plus Yervoy 3 mg/kg every 3 weeks for 4 doses followed by Opdivo 3 mg/kg every 2 weeks

thereafter; n=314), Opdivo monotherapy (Opdivo 3 mg/kg every 2 weeks; n=316) or Yervoy monotherapy (Yervoy 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks; n=315).

Patients were treated until progression or unacceptable toxic effects. The median duration of exposure was 2.8 months (range: 1 day to 18.8 months) for patients in the combination arm with a median of four doses (range: 1 to 39 for Opdivo; 1 to 4 for Yervoy), and 6.6 months (range: 1 day to 17.3 months) duration for the Opdivo monotherapy arm with a median of 15 doses (range: 1 to 38). The co-primary endpoints were PFS and OS; the study is ongoing and patients continue to be followed for OS.

Results from the trial demonstrated a statistically significant improvement in PFS in patients with advanced melanoma treated with the combination regimen ($p<0.0001$) and with Opdivo as a single-agent ($p<0.0001$) vs. Yervoy monotherapy.

Median PFS was 11.5 months (95% CI: 8.9-16.7) for the combination regimen and 6.9 months (95% CI: 4.3-9.5) for Opdivo monotherapy, compared to 2.9 months (95% CI: 2.8-3.4) for Yervoy alone.

The Opdivo-Yervoy regimen demonstrated a 58 percent reduction in the risk of disease progression vs. Yervoy (HR: 0.42; 95% CI: 0.34-0.51; $p<0.0001$), while Opdivo monotherapy demonstrated a 43 percent risk reduction vs. Yervoy monotherapy (HR: 0.57; 95% CI: 0.47-0.69; $p<0.0001$).

Opdivo is associated with immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryofetal toxicity.

FDA approved Halaven (eribulin mesylate) Injection for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen, following priority review.

The approval was based on the results of a phase III trial, Study 309, which demonstrated that previously treated liposarcoma patients who received Halaven (n=71) experienced a median overall survival of 15.6 months compared with 8.4 months for those who received dacarbazine (n=72) (HR 0.51; 95% CI: 0.35-0.75), making it the first single agent to demonstrate an OS benefit in this stage of the disease, according to the drug's sponsor, Eisai.

Median progression-free survival, the trial's secondary endpoint, was longer in patients with liposarcoma treated with Halaven than in those who received dacarbazine (2.9 vs. 1.7 months; HR 0.52; 95% CI: 0.35-0.78).

The adverse events seen in Study 309 were consistent with the known profile of Halaven. Serious side effects from treatment with Halaven may include neutropenia, peripheral neuropathy, embryo-fetal toxicity and QT prolongation.

First in the halichondrin class, Halaven is a microtubule dynamics inhibitor with a distinct binding profile.

Halaven is a synthetic analog of halichondrin B, a natural product that was isolated from the marine sponge Halichondria okadai. Based on in vitro studies, Halaven exerts its effect via a tubulin-based antimitotic mechanism, ultimately leading to apoptotic cell death after prolonged and irreversible mitotic blockage.

Halaven was first approved in the U.S. in November 2010 for patients with metastatic breast cancer who have received at least two chemotherapeutic regimens for the treatment of metastatic disease. Halaven was granted an FDA Orphan Drug Designation for soft tissue sarcoma in May 2012.

FDA approved Zepatier (elbasvir and grazoprevir) for the treatment of adult patients with chronic hepatitis C virus genotype 1 or 4 infection, with or without ribavirin, following priority review.

Zepatier is a once-daily combination tablet containing the NS5A inhibitor elbasvir (50 mg) and the NS3/4A protease inhibitor grazoprevir (100 mg). The FDA previously granted two Breakthrough Therapy designations to Zepatier, for the treatment of chronic HCV GT1 infection in patients with end stage renal disease on hemodialysis, and for the treatment of patients with chronic HCV GT4 infection.

Across multiple clinical studies, Zepatier achieved high rates of sustained virologic response ranging from 94 to 97 percent in GT1-infected patients, and 97 to 100 percent in GT4-infected patients, according to Merck, the therapy's sponsor. Sustained virologic response is defined as HCV RNA levels measuring less than the lower limit of quantification at 12 weeks after the cessation of treatment.

Zepatier was approved with a treatment duration of 12 or 16 weeks, depending on HCV genotype, prior treatment history and, for patients with GT1a infection, the presence of certain baseline NS5A polymorphisms. A 12-week, once-daily regimen is recommended for the vast majority of patients for whom Zepatier is indicated.