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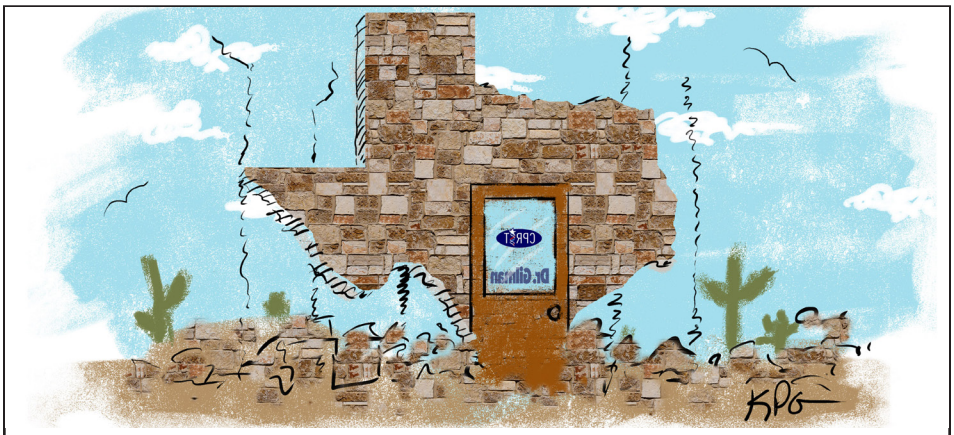

Slamming the Door

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, a 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 of the series appeared last week.

Part II: Cancer's Butt

By Paul Goldberg

CPRIT's review process appeared to have become a major annoyance to those who wanted to redraft the criteria for dispensing the princely sum of $300 million a year. Texas geography and Texas politics did matter—a lot.

The cross-state competition between MD Anderson Cancer Center and UT Southwestern Medical Center proved to be especially important.

MD Anderson has long been a clinical powerhouse, the kind of place you go with a complicated cancer. If it ramped up its basic science, the cancer center would be better positioned to understand the origins of cancer and make more fundamental contributions to treatment of cancers, including discovering useful drug candidates and moving them from the bench to the clinic.

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White House Promises $1 Billion for Cancer

By Matthew Bin Han Ong

The White House announced a $1 billion initiative Feb. 1 to jumpstart the national cancer moonshot program—an ambitious proposal first announced by President Barack Obama during his final State of the Union address.

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Slamming the Door, Part II: Cancer's Butt

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The place is rich with doctors you would want to treat your mother, but none of its faculty members had won the Nobel Prize. The UT Southwestern faculty of the Dallas institution included five Nobel laureates. And year after year, MD Anderson would trail UT Southwestern in the number of CPRIT grants

In 2011, the oncopolitical map of Texas was to be redrawn.

MD Anderson was recruiting a new president, and the job of MD Anderson president doesn't open often. Over the preceding 70 years, the institution has had three presidents: R. Lee Clark (1946-1978); Charles LeMaistre (1978-1996), and John Mendelsohn (1996-2011).

The regents were considering two leading candidates. Raymond DuBois, the MD Anderson provost, was an inside candidate who understood how a structure as complex as MD Anderson functioned. In 2007, DuBois surprised oncology insiders by leaving the job of director of the Vanderbilt Ingram Cancer Center to become the MD Anderson provost.

Observers pointed out that DuBois, whose name is pronounced in the Anglo rather than the French manner, is a native Texan. He was born in the farming and ranching town of Runge, around 75 miles southeast of San Antonio. Surely, DuBois, an expert in colon cancer, was given assurances that he would get a good shot at becoming the next president of MD Anderson, observers presumed.

Since his duties as provost were to promote the center's academic mission, DuBois kept his hand on MD Anderson's money spigots. His principal mission was to boost the center's basic research programs. Others pointed out that DuBois is not a predator. He is uniformly described as a nice guy, who doesn't begin his mornings by determining whose career he would gut by sunset. Could someone like that be entrusted to run MD Anderson?

The second candidate was Cheryl Willman, director of the University of New Mexico Cancer Center, whose work is focused on leukemia. Willman is a solid administrator who has run her cancer center since 1999.

Another candidate, Brian Druker, co-developer of the drug Gleevec, which made it possible to control chronic myelogenous leukemia, bowed out early. According to knowledgeable sources, Druker, director of the University of Oregon Knight Cancer Institute, a place much smaller than MD Anderson, had one meeting with the search committee.

Asked how he would approach the job, Druker told the committee that during the first years he would want to engage the faculty in developing a strategic plan. After all, MD Anderson is a complex, functioning structure that has to be handled with care.

Druker noted that MD Anderson is extraordinarily highly regarded for its clinical research and that he would want to make sure that it remained well-supported and even enhanced to do precision medicine trials.

In addition, the level of science supporting pre-clinical and clinical studies needed to be strengthened, and it would be incumbent upon the new president to look for opportunities to ensure this happened.

In the job interview, Druker emphasized his enormous respect for the institution and said that any changes he would make would be in an effort to further increase its reputation and impact.

Ultimately, Druker decided to stay in Oregon, building a billion-dollar program focused on the molecular characteristics of cancer in order to treat diseases before they become lethal (The Cancer Letter, Aug. 1, 2014).

Later, I would obtain a copy of an email in which Kenneth Shine, then the UT System executive vice chancellor for health affairs and head of the search committee, announced Druker's decision not to pursue the job:

"I am sorry to report that after extensive discussions with his wife, Brian Druker has withdrawn from our search. The principal issue revolved around the need to be the public face of MDACC and the needs of his three children and family, which he felt would suffer

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from these obligations as well as other duties of the President. I discussed several options in this regard with him, but to no avail. I would propose to continue with three candidates."

Many cancer centers are run by chief executives who are basic scientists. However, the UT System requires that the presidents of its health organizations have MD degrees. This would make sense at Anderson, a huge clinical enterprise. The help-wanted ad posted by the UT System read:

"MD Anderson's next President will be a licensed physician possessing an M.D. degree with at least five years of experience practicing medicine; distinction in scholarship and practice; present a strong scientific background; a substantial commitment to patient care, education, and research; management experience appropriate to overseeing a $3.2 billion enterprise of 17,000 employees; and will convey well-established leadership, communications, and interpersonal skills along with a genuine passion for MD Anderson's mission to treat and eliminate cancer."

The regents quickly focused on a Harvard power couple: Ronald DePinho, a scientist focused on drug development, and his wife Lynda Chin, a genomic scientist. DePinho was vying for the job of president and Chin was being recruited to serve in a senior scientific position.

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On May 11, 2011, a colleague, Todd Ackerman, called me from the Houston Chronicle.

"Have you ever heard of Ronald DePinho?" he asked. The name didn't ring a bell.

I searched my memory. I searched my emails. I searched the documents on my computer. All I could see was that DePinho was a subscriber to The Cancer Letter.

"No. Definitely not. Of course, this doesn't mean anything. I guess it can mean only that the regents chose to give the job to someone less well known, someone younger. It could be the right thing to do; probably is. After all, the guy is from Harvard."

Then I pilfered a line from Woody Allen: "That said, Harvard makes mistakes. Henry Kissinger taught there." I should stop using that line.

I made a call or two and learned that DePinho was, in fact, very well known in basic science circles.

I couldn't see how I could possibly contribute to coverage of selection of the next president of MD Anderson. Unlike Todd, I didn't understand the mechanics of the UT Board of Regents, didn't have the sources I'd need to get the bearings straight. I hate being beaten, but at least I had an excuse: I didn't have boots on the ground. And it helped that I like and respect Todd.

To see what I was missing, I looked back at Todd's coverage, zeroing in on a juicy tidbit: DePinho had been a guest on Colbert Report. I found the segment.

It was hilarious. DePinho was a suit-wearing gray-haired guy, a perfect foil for Colbert, also a suit-wearing guy.

Colbert invited DePinho to discuss the finding that it was possible to reverse aging in genetically engineered mice. To explain this, Colbert brought out a massive, plush model of a chromosome. The thing was large and, in an exaggerated way, phallic. This set the tone for the conversation.

DePinho remained unflappable as Colbert massaged his preposterous "chromosome," noting that the tip—the telomere—was its most sensitive part. DePinho seemed to be channeling his discomfort into comedy. Was this intentional on DePinho's part? Was it accidental? Where is it written that humor has to be intentional to be genuine?

Whatever it was, it worked. At one point, DePinho started tearing off pieces from the red telomere to demonstrate what happens when we age. As the level of discourse spiraled downward, I started to think that DePinho will be a fun center director to cover.

I called some friends at Harvard, who told me that DePinho had an aggressive style and was certain to ruffle some feathers. I learned that DePinho and Chin worked so closely together that at Harvard they were nicknamed DeChinho.

Also, I learned that some folks in Cambridge put together a betting pool, stratifying predictions of how long DePinho would last at MD Anderson. Moving aggressively isn't necessarily a bad thing, I thought. The guy had to be cool.

DePinho's board certification is in internal medicine. In 1998, he moved to Harvard from the Albert Einstein College of Medicine in New York, yet he was still licensed to practice medicine in New York. He appeared to have seen no need to get a medical license in Massachusetts, and records showed that, similarly, he had no license to practice in Texas.

DePinho focused on applying genomic leads to selecting compounds for future drug development. One of the drugs he helped select for testing—tivozanib—was going through the final phase of clinical testing. Having a drug in phase III trials represents the penultimate bragging rights for a cancer doctor. The ultimate bragging rights, of course, would be having

the drug approved and used for the benefit of patients.

The company that was co-developing tivozanib—AVEO Pharmaceuticals Inc.—had been started by DePinho and Chin.

On May 11, 2011, the day he was chosen to lead MD Anderson, AVEO was trading at about $17 a share, which meant that the 626,000 shares owned by the DePinho family were worth more than $10.6 million. FDA approval would be certain to push the stock value even higher.

DePinho and Chin were involved in other companies, too, though none were as close to payday.

Tivozanib was licensed from a Japanese company. AVEO's and DePinho's expertise was said to be in relying on technology for *choosing* drugs rationally, taking the guesswork out of drug approval. This technology could be applied equally to making new compounds and unlocking the potential of existing compounds.

As they considered DePinho's candidacy, the regents had little reason to doubt that tivozanib would work. Ron was confident and, after all, the drug was chosen rationally, based on emerging science.

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Later, I would obtain a copy of DePinho's application letter. The letter, addressed to Kenneth Shine, the UT System executive vice chancellor for health affairs and head of the search committee, was informative, even illuminating.

"MD Anderson's next leader must continue to nurture its strong programs in clinical care, while building world-leading multidisciplinary teams that are focused on the basic mechanisms of cancer and driving such science toward clinical endpoints," DePinho wrote. "In this broad context, I wish to convey that I appreciate the challenges facing the institution with a budget of $3B where the majority of its operating budget derives from patient care, yet facing health care reform, reductions in state budgets, and contracting NCI pay-lines—the latter impacting not only finances, but also weighing heavily on the psychology of our next generation."

There is a lot to unpack here.

MD Anderson's engine—clinical revenues—has to grow, or at least remain the same. On top of that, new money has to be found to finance a massive expansion into basic science. While the opportunities around it withered, MD Anderson would have to grow. Some other funding opportunities were needed; philanthropy, CPRIT, and pharmaceutical companies would have to play a role in this growth.

The letter was also a reminder about the impossible feats directors of large cancer centers are expected to perform.

In addition to being a world-class scientist, the president of MD Anderson had to be the chief administrator of a $3 billion health system. The job required a scientific vision and an administrative prowess that somehow had to produce a coherent multi-year strategy.

The psychology component is fascinating, too. DePinho seems to be suggesting that during these difficult times, physicians and scientists need to be given a glimmer of hope.

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DePinho and Chin had a flashier sales pitch than DuBois and Willman.

While DuBois and Willman were solid scientists and experienced administrators, DePinho and Chin were experts in "personalized" medicine, genomics, the science that seeks to bring the right drug to the right patient, even engineering unique cures intended for just one patient.

As interviews continued, the couple promised to make MD Anderson into a very well-funded institution by inviting in the pharmaceutical industry and making it easier to develop drugs.

An entire unit—an institute—would be created for the purpose of finding and rapidly testing compounds. Some of these compounds would come from MD Anderson researchers. Others would be brought in by the industry.

The institute would, in effect, represent a hybrid of academia and industry. The place would be operated by Chin. And how could you dispute that DePinho and Chin understood what makes the industry tick? They were founders of several companies and had a multi-million-dollar portfolio to show for it.

In a nutshell, this pair would link academia with industry, finding new cures, and bringing millions—perhaps even billions—in new funds to MD Anderson.

On May 11, 2011, the UT System Board of Regents met in closed session to interview the three candidates, DuBois, Willman and DePinho.

Candidates came in one by one, and one by one they left.

Then the decision was announced: the job would go to DePinho.

In a statement announcing the selection, Regents'

Chairman Gene Powell praised DePinho as "a distinguished scientist and proven administrator capable of leading the nation's premiere comprehensive cancer center, UT MD Anderson."

While it was technically okay to call DePinho an "administrator," the program he ran—the Belfer Institute for Applied Cancer Science—was minute by comparison with MD Anderson.

According to DePinho's application letter, over a decade, Belfer secured $100 million in grants, $50 million in donations, and another $50 million in corporate alliances. By way of comparison, MD Anderson is a massive enterprise that employs nearly 19,000 people, occupies 11.5 million square feet of space and has the revenues in excess of $3 billion.

Chin would also join the faculty of MD Anderson, the UT System announced that day. Chin received her medical degree from the Albert Einstein College of Medicine and her research interest is in cancer genomics and cancer biology. She worked with her husband at Dana-Farber, too, as the scientific director of the Belfer Institute for Applied Cancer Science. She was also a professor of dermatology at the Harvard Medical School and department of medical oncology at Dana-Farber Cancer Institute.

As a basic scientist placed in control of a massive clinical enterprise, would DePinho understand what MD Anderson clinicians do? Would he understand the complexity of clinical trials? How would his wife and collaborator fit into the delicate political fabric of the state institution? Would DePinho have the humility to acknowledge that there are things—vast areas, in fact—where he knows next to nothing? Would he have the wisdom to ask questions, to delegate? Would he choose the right people to guide him?

These were vitally important questions, because MD Anderson is a huge operation that has a very small profit margin. It looked like Ron and Lynda landed very lucrative positions, even for a couple whose AVEO stock was worth more than $10 million. DePinho's compensation for the first year was $1.8 million, and Chin's $813,000.

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By the time Ron DePinho and Lynda Chin appeared on the scene, CPRIT spent over $670.7 million on research within the state and on helping recruit scientists from the outside.

Altogether, $489.6 million went to academic research, $111.4 million went to commercialization, and $69.7 million went to prevention. (Research on prevention came from the research budget.)

DePinho and Chin could impress the UT System Board of Regents, the MD Anderson Board of Visitors, but Gilman's crew would give them their due; no more, no less.

In October 2011, DePinho addressed the Board of Visitors:

"In this decade, the cancer genome atlas will provide scientists with the list of genes that are mutated in cancer.

"With the complete list of mutated genes in hand, we will make use of our newfound ability in functional genomics to silence specific genes at will. We can see if the extinction of a mutated gene causes the cancer cell to die. We anticipate that there will be several hundred genes playing critical roles in cancer and our goal will be to identify every one of these rogue genes. It is important to appreciate that going after a single target will not lead to cure. Cancer DNA is highly unstable, allowing for emergence of resistance. Thus, the key to success will be to determine which combination of targets will need to be co-extinguished in order to elicit durable responses, i.e., cure. This is key—there is no single magic bullet.

"With that list of key drivers, we can genetically engineer perfect models of human cancer. Test drug and drug combinations. Needed are combination strategies – designed to co-extinguish multiple cooperative targets as well as harness the power of the immune system to eliminate every last cancer cell in the body.

"Once drugs are in hand, we need sophisticated mouse model systems to enable testing of combinations prior to clinical testing, and we need a clinical trial design that incorporates the genotyping to select tumors with those targets. This is the future of treatment at MD Anderson.

"Cancer is not simply about treating advanced cancers. It is also critical that we develop robust preventive strategies that will quell the largely unknown processes responsible for causing cancer in the first place. If we can understand these processes, then we can monitor them and control them. Here, there are exciting advances in our understanding of the underlying circuitry of aging—given that age is the most important risk factor for cancer, such molecular insights are

providing new therapeutic points of attack to reverse the aging process and diminish the incidence of age-related diseases. These are historic times indeed.

"Early detection is another important area, providing an enormous opportunity to impact on the cancer problem in the near term. There is a revolution in serum proteomics and imaging that will enable us to diagnose cancers at much earlier stages where the chance for cure is greatest. This is good news. However, these advances will fuel new challenges in the accurate management of these early stage cancers. Witness the impact of PSA testing in prostate cancer. Today, this nation spends from $500 million to $1 billion in unnecessary interventions because we do not have the molecular markers needed to identify which 15 percent of the 220,000 cases will go on to die of the disease. It is estimated that for every life saved, we treat close to 50 men.

"To accomplish our moon shot, full knowledge and powerful technology will not be enough. We need new organizational constructs as well.

"The current drug discovery and development ecosystem is not optimally configured to systematically drive discoveries to clinical endpoints that make a difference in patient's lives. Historically, discovery in academia has created new biotech companies that, in turn, fuel the pipeline for large pharma who have the capital and commercial abilities to move assets into mainstream use.

"This ecosystem has a 95 percent failure rate in cancer drug development with 56 percent of failure occurring in late stage testing. Huge cost. It is my view that a major cause of these failures rests on the inability of the biotech industry to conduct the deep analyses needed to validate targets and drugs at the preclinical stage.

"And the situation has gotten worse with the near-collapse of the biotech industry which will translate into fewer assets for pharma to buy in the years ahead.

"Academia has been and will continue to be a caldron for innovation but I believe that it must also be further optimized organizationally to drive discoveries into effective drugs in the clinic.

"A new organizational construct is needed that will systematically validate targets, develop drugs against those targets, test them in sophisticated models and bring them forward to the private sector."

Gilman, who was deeply involved in drug discovery and commercialization (he was also on the board of Eli Lilly & Co.), didn't share DePinho's outrage about the high failure rate of drugs in late-stage trials of cancer drugs. "Depending on his definitions, this is no different from all other areas of drug discovery," Gilman said to me. "And of course many of those failures are because of uncommon adverse events that can only be discovered in later stages of human trials.

"In my view, a lot of the problem is biotech companies running poorly controlled phase II studies so they get the results they need to get more funding and get the stock price up. Many are not interested in actually getting a drug. They are more interested in a profitable strategy for early exit."

At the time, DePinho's ideas about the "new organizational construct" seemed intriguing. Was he really suggesting building something reminiscent of a pharmaceutical company within MD Anderson?

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The words "the cure" seemed to have flashed in DePinho's early remarks. According to the Chronicle, On May 11, in his post-selection comments, on May 11, 2011, DePinho said:

"We're now positioned to make an assault on a disease that's truly dreaded worldwide. I give you my word that I will give it my all to keep (M.D. Anderson) the world-class (institution) it is and bring the best science to make it reach its ultimate potential—nothing less than curing the disease."

In November, 2011 two months after he moved to Houston from Dana-Farber Cancer Institute, at a fundraising event in San Antonio, the researcher, who is also a martial arts expert, pledged on camera to "kick cancer's butt. (The Cancer Letter, Oct. 12, 2012).

I bounced this statement off Gilman.

"Are you sure he said 'cancer's butt' and not 'cancer's butts'?" Gilman asked. "Had he said butts, I would have found it less problematic."

Cancer, after all, is an uncounted multitude of diseases, and if you insist on taking the anthropomorphic route, you would be required to give each of them a separate butt, Gilman explained.

They don't give out Nobel Prizes for nothing.

White House Promises $1 Billion For National Cancer Moonshot

(Continued from page 1)

Vice President Joe Biden, whose son Beau died of brain cancer in May 2015 at age 46, is leading the program, which aims to achieve a decade's worth of progress within the next five years.

The $1 billion announcement establishes a game plan for how the funds will be spent: the moonshot initiative will begin with $195 million in cancer research at NIH in fiscal 2016, according to the White House. The fiscal 2017 budget will propose to allocate $755 million in mandatory funds for new cancer-related research activities—$680 million for NIH and $75 million for FDA. The remaining $50 million is expected to go to the Departments of Defense and the Veterans Affairs through funding Centers of Excellence.

Further details on the funding are expected to become available Feb. 9 when the president's budget proposal is released.

The $75 million infusion for FDA includes a proposal to create a new Oncology of Center of Excellence.

According to the White House: "The FDA will develop a virtual Oncology Center of Excellence to leverage the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, and devices. This center will expedite the development of novel combination products and support an integrated approach in:

• "Evaluating products for the prevention, screening, diagnosis, and treatment of cancer;

• "Supporting the continued development of companion diagnostic tests, and the use of combinations of drugs, biologics and devices to treat cancer; and

• "Developing and promoting the use of methods created through the science of precision medicine."

In an October 2015 editorial, Ellen Sigal, chair and founder of Friends for Cancer Research, called on Congress to update FDA's structure to better reflect 21st century science.

"By investing in the FDA, and through the creation of a new Center of Excellence of Oncology, the administration has taken a significant step that we hope will enhance the FDA's ability to execute their vital role in translating scientific discovery into new therapies for patients," Sigal said in a statement Feb. 1.

The FDA Centers of Excellence would improve coordination between FDA medical product centers, Sigal said. The centers would also facilitate and expedite the development of novel combination products, support integrated product evaluation, and promote precision medicine methods.

The moonshot's priorities include promoting enhanced data sharing, which involves pooling together oncology bioinformatics data banks and making that data more accessible and interoperable across research platforms (The Cancer Letter, Jan. 22).

"Almost every cancer center keeps a database of information—genetic history, medical records, and tissue banks—that might hold the key to improving certain cancer therapies," Biden wrote in a blog post Jan. 27.

"Allowing researchers and oncologists to tap into this treasure trove of information is absolutely vital to speeding up the pace of progress toward a cure. If we ensure this data is interoperable and accessible for scientists, researchers, and physicians, the consensus is that we can absolutely speed up research advances, improve patient care, and get ourselves closer to a cure."

On Feb. 1, Obama and Biden convened a working group, officially called the White House Cancer Moonshot Task Force, which consists of the heads of the executive branch departments, agencies and offices, including the HHS, NIH, NCI and the Department of Defense, among others. The task force members will oversee the execution of the program, with funding and administrative support from NIH.

The task force is charged with reaching out to external stakeholders to produce a detailed set of findings and recommendations to: "(a) accelerate our understanding of cancer, and its prevention, early detection, treatment, and cure; (b) improve patient access and care; (c) support greater access to new research, data, and computational capabilities; (d) encourage development of cancer treatments; (e) identify and address any unnecessary regulatory barriers and consider ways to expedite administrative reforms; (f) ensure optimal investment of Federal resources; and (g) identify opportunities to develop public-private partnerships and increase coordination of the Federal Government's efforts with the private sector, as appropriate."

Input will be critical to the success of the moonshot, NIH Director Francis Collins said.

"There was a lot of energy in the room—the kind that comes with a shared desire to make a positive difference in people's lives and the awareness that the United States has the brainpower and determination to do it," said Collins Feb. 2, referring to the first meeting of the task force which was presided over by the president and vice president. "We are, indeed, a nation of innovators."

"The administration also released the first details of the initiative, calling for $680 million in NIH's

FY2017 budget to support seven scientific areas ripe for advancement.

"To share the news, the National Cancer Institute Acting Director Dr. Doug Lowy and I fielded many questions from the public during a Twitter chat using #CancerMoonshot, where it was apparent that we weren't the only ones excited about the effort.

"One of the most-asked questions was how can people get involved to help shape the initiative. To be clear, stakeholder input will be critical to the success of the National Cancer Moonshot and there will be numerous opportunities in the coming months to share your ideas and input. I encourage you to sign up for updates on the NCI Cancer Moonshot web page to stay apprised of the latest developments."

Standing Ready

The new infusion of funds comes at a crucial point in cancer research, the American Society of Clinical Oncology said.

"With the current explosion of new cancer science, diagnostic tests, and treatments, there is no better time for this bold commitment to reduce the human suffering and loss of life that cancer inflicts on millions of Americans each year," ASCO said in a statement. "ASCO applauds the president for taking this important step toward making the 'moonshot' vision a reality and for outlining a comprehensive approach to speed advances in cancer prevention, diagnosis and treatment that addresses critically important issues, such as patient access to care, federal funding, and information technology and interoperability of electronic health records.

"ASCO stands ready to offer its full support to the 'moonshot' initiative and looks forward to working with Vice President Biden as he leads this unparalleled and essential effort to accelerate the rate of progress in the fight against cancer."

ASCO, along with the American Association for Cancer Research and other oncology organizations, has been in meetings with Biden to discuss the evolution of bioinformatics and other goals for the moonshot program.

"The AACR very much appreciates the Obama administration's continued commitment to providing significant federal funding increases in the fight against cancer, and we look forward to next week's release of the president's budget for additional and more specific information," said AACR CEO Margaret Foti.

"The AACR, and its 35,000 laboratory researchers, physician-scientists, other healthcare professionals, and patient advocates who constitute our membership, stands ready to work with Vice President Biden's 'Cancer Moonshot Task Force' to provide valuable insights and creative thinking about how to further reduce cancer incidence and mortality."

In 2015, members of Congress from both parties have acted in support of biomedical research, said Mary Woolley, president and CEO of Research!America.

"The president told Majority Leader [Mitch] McConnell and Speaker [Paul] Ryan that assuring resources for research, cancer in particular, is one of his five priorities for working across the aisle this year," Woolley said. "His FY17 budget proposal—scheduled for release next Tuesday—will reportedly request additional dedicated funding for the moonshot and for combating substance abuse.

"There is every reason to be optimistic, but we can't take anything for granted."

A recent public opinion survey by Research!America showed that 50 percent of Americans favor a tax increase to fund cancer research. Thirty-eight percent disagree and an additional 12 percent are not sure.

Two-thirds of Democrats, 67 percent, and more than a third of both Republicans (at 38 percent) and independents (39 percent) support a tax increase, and support is particularly strong among Americans ages 18 to 49.

Of those who favor a tax increase, more than half (57 percent) say they are willing to pay up to $50 per year in taxes (60 percent of Republicans, 58 percent of independents and 54 percent of Democrats) and 28 percent are willing to pay even more. This finding applies across all age groups.

"Americans understand that we must turbo-charge our investments in cancer research in order to make significant headway in our battle against this insidious disease," Woolley said. "Our new survey finding illustrates that individuals across the political spectrum view the 'moonshot' initiative as an all hands on deck endeavor that is worthy of taxpayer support.

"With significant advances in immunotherapy and genomics, it is incumbent upon candidates and elected officials to tell potential voters whether they support increased funding for research to find cures for cancer and other diseases," Woolley said. "It's time to put research to work to find solutions and cure what ails us; we call on all policymakers and those who aspire to be, to speak out for and act to make research for health a number one national priority.

"We urge President Obama to include sufficient funds to support the 'moonshot' initiative in his FY17 budget proposal."

Capitol Hill

FDA Releases New Opioid Plan As Senators Stall Robert Califf's Confirmation as Commissioner

By Conor Hale

Robert Califf, the nominee to serve as the next FDA commissioner, and other FDA leaders called for a broad plan to reassess the agency's approach to prescription opioid medications. The move comes as Senators block a vote on his confirmation for the top post.

Sen. Edward Markey (D-Mass.) and Democratic presidential candidate Sen. Bernie Sanders of Vermont have both placed procedural holds on Califf's confirmation, citing the agency's policies and methods for approving opioids, as well as Califf's financial ties to the pharmaceutical industry.

A third hold was placed by Sen. Lisa Murkowski (R-Alaska), over the agency's plans to enforce the labeling of genetically modified salmon. Califf, currently the FDA's deputy commissioner on medical products and tobacco, received a unanimous vote in his favor from the Senate Health, Education, Labor and Pensions Committee in January.

Markey called for "immediate reforms to the agency's approval process for opioid painkillers, which are fueling a prescription drug and heroin overdose crisis that led to 47,000 deaths, including more than 1,300 in Massachusetts, in 2014."

"I share Sen. Markey's concerns that the FDA must change the way it approaches addiction. Too many Americans are dying from what has become an opioid epidemic," Sanders said in a statement. "I also strongly believe that at a time when millions of Americans cannot afford to purchase the prescription drugs they require, we need a leader at the FDA who is prepared to stand up to the drug companies. We need someone who will work to substantially lower drug prices, implement rules to safely import brand-name drugs from Canada and hold companies accountable who defraud our government."

The agency's plan will focus on policies "aimed at reversing the epidemic, while still providing patients in pain access to effective relief," according to a statement from FDA.

The FDA plans to re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public health effects, and convene an advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties. The agency said it also plans to consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved.

Markey originally blocked Califf's nomination following the FDA's decision to approve pediatric OxyContin in August 2015 without convening an advisory committee to examine the issue.

"While people in every community across the country are dying every day from opioid overdoses, the FDA continues to operate as if safety just means the right dose when it should include all the dangers of these painkillers," said Markey Jan. 25. "Expert after expert has warned about the real world dangers of abuse of and dependence on these new supercharged opioid painkillers, but the FDA has willfully blinded itself to the warning signs. The FDA needs to commit to shift the way it approaches and evaluates addiction before I can support Dr. Califf's nomination."

In a letter to HHS Secretary Sylvia Burwell in December 2015, Markey said the hold would stand until the pediatric approval for OxyContin was rescinded, and until an advisory committee reconsiders the indication.

Markey has also pointed to the agency's 2014 approvals of Targiniq ER and Hysingla, two extended release opioid analgesics, made without consulting its advisory committees—as well as the 2012 case of Zohydro ER, which was approved contrary to an 11-2 vote against recommendations for approval by the FDA's Anesthetic and Analgesic Drug Products Advisory Committee.

"We are five percent of the world's population but consume 80 percent of the world's supply of Oxycodone. We need to stop the over-prescription of pain medication that is fueling this crisis and ensure that all prescribers are required to receive education in responsible prescribing practices," Markey said.

Earlier this week FDA said it also plans to develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to the extended-release/long-acting opioid analgesics labeling that is currently required; update its Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements; expand access to, and encourage the development of, abuse-deterrent formulations of opioid products; and improve access to naloxone and medication-assisted treatment options for patients

with opioid use disorders; and support better pain management options, including alternative treatments.

Previously, FDA asked the National Academy of Medicine to help develop a framework for opioid review, approval and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse and abuse. The FDA also plans to strengthen requirements for drug companies to generate postmarket data on the long-term impact of using extended-release opioids.

"In addition, the FDA will convene independent advisory committees made up of physicians and other experts when considering for approval any new opioid drugs that do not contain abuse-deterrent properties. The FDA will also convene a meeting of its standing Pediatric Advisory Committee to make recommendations regarding a framework for pediatric opioid labeling and use of opioid pain medications in the pediatric population," the agency said in its statement.

"We are determined to help defeat this epidemic through a science-based and continuously evolving approach," Califf said. "This plan contains real measures this agency can take to make a difference in the lives of so many people who are struggling under the weight of this terrible crisis."

Nancy Goodman, of Kids v Cancer, supported the FDA's plans, such as including a pediatric advisory committee for pediatric opioid labeling.

"I applaud the FDA and Dr. Robert Califf for taking a giant step toward addressing the opioid epidemic that is affecting our country's youth," said Goodman, Kids v Cancer executive director.

Robert Piniewski, of People Against Childhood Cancer, said: "I lost my son, AJ, to childhood cancer and can assure you that struggles with pain management are very real. I'm encouraged by the FDA taking this step to help children with cancer with pain management while still addressing the opioid epidemic."

Markey said the FDA's olive-branch proposal falls short of what's needed.

"To its credit, the FDA has agreed to my request to reassess the way it considers the risks of addiction and misuse when it evaluates the safety of new opioids," Markey said in a statement Feb. 4. "While this is a good start, even more is required to ensure the FDA's approval process protects Americans from the dangers of opioid painkillers." Markey said the FDA's proposed plans would still not guarantee advisory panels for approving drugs like Hysingla and Targiniq.

"By refusing to convene advisory committees to inform all of its opioid approval decisions, the FDA continues to ignore outside experts who could help stem the tide of tragic deaths and overdoses plaguing the country," he said.

"Until the FDA commits to convene advisory committees of outside experts for all its opioid approval decisions, I will continue my hold on Dr. Califf's nomination."

In Brief

Lonial Named Head of Winship Hematology and Oncology

SAGAR LONIAL was named chair of the Department of Hematology and Medical Oncology at **Emory University School of Medicine** and **Winship Cancer Institute**.

Lonial currently serves as Winship's chief medical officer and as professor of hematology and medical oncology. He previously held the position of department executive vice chair. Lonial assumes this role vacated by Fadlo Khuri, who became president of American University of Beirut.

Lonial has worked in the field of immunotherapy and oncology since joining Emory in 1997 for his fellowship. His most recent research focuses on combinations of novel agents as therapy for myeloma and development of new targets and treatment strategies for high-risk myeloma. He was principal investigator on two large studies of novel monoclonal antibodies. The research team he developed has contributed to all the major drug approvals in myeloma over the past decade, and he is currently leading a global genome sequencing study in newly diagnosed myeloma.

"We are very excited that Sagar Lonial will take the helm of the largest oncology-related department at Emory," says Walter Curran, Jr., Winship's executive director. "By assuming this leadership position, he will play a key role in attracting and mentoring the best and brightest faculty within the department and Winship."

Lonial serves on the editorial board of the Journal of Clinical Oncology, Leukemia, and is the myeloma editor for Clinical Lymphoma, Myeloma, and Leukemia. He is the secretary for the International Myeloma Society, on the scientific advisory board for the International Myeloma Foundation, and serves as steering committee chair for the Multiple Myeloma Research Consortium.

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STAND UP TO CANCER CANADA announced a four-year cancer stem cell dream team focused on brain cancer in children and adults.

Researchers will receive CA$11.7 million, or approximately $8.4 million USD, in funding from Stand Up To Cancer Canada, Genome Canada, Canadian Institutes of Health Research, Cancer Stem Cell Consortium, and the Ontario Institute for Cancer Research. The American Association for Cancer Research International – Canada is SU2C Canada's scientific partner.

The leader of the SU2C Canada Cancer Stem Cell Dream Team: Targeting Brain Tumor Stem Cell Epigenetic and Molecular Networks, is **Peter Dirks**, neurosurgeon and senior scientist at The Hospital for Sick Children in Toronto, who was the first to identify cancer stem cells in brain tumors in 2003.

The co-leader is **Samuel Weiss**, director of the Hotchkiss Brain Institute and professor in the Cumming School of Medicine at the University of Calgary, who was awarded the Canada Gairdner International Award in 2008 in part for his discovery of adult neural stem cells in the brains of adult mammals.

The team will take a three-pronged approach to understanding and targeting brain cancer stem cells that resist treatment and fuel tumor regrowth. Their first approach is to perform detailed analysis of BTSCs taken from 70 different glioblastomas or ependymomas and grown in the laboratory.

The team's second approach will be to screen a collection of chemicals on the same BTSCs for potential new drugs and drug combinations that are effective against these cells. Finally, the team will test five new potential drugs that they have already identified as very promising by tests performed in laboratory mice to find out which drugs or drug combinations might kill glioblastomas or ependymomas.

The Dream Team hopes to bring new drugs for brain cancer into clinical trials in the third and fourth years of their research funding.

The team's other principal investigators are: **Cheryl Arrowsmith**, senior scientist at the University Health Network in Toronto; **Gary Bader**, associate professor at the University of Toronto; **Amy Caudy**, assistant professor in the Department of Medical Genetics and Microbiology at the University of Toronto; **Nada Jabado**, senior scientist/professor at the Research Institute of the McGill University Health Centre; **Mathieu Lupien**, scientist at UHN; **Marco Marra**, director of the BC Cancer Agency Genome Sciences Centre; **Trevor Pugh**, scientist at UHN; **Michael Salter**, director of The Hospital for Sick Children Research Institute; **Michael Taylor**, neurosurgeon and senior scientist at The Hospital for Sick Children; and **Michael Tyers**, professor at the University of Montreal.

Serving as advocate on the team is **Wendy Durigon**, founder of Jessica's Footprint Foundation, named in honor of her daughter Jessica, who died of brain cancer in 2003.

KEITH HANSON MCGREGOR was named CEO of the **European Society for Medical Oncology.**

McGregor is currently ESMO's chief operating officer. He joined ESMO in 2009 as senior director of the Business Division.

In addition to managing the commercial aspects of the business, he helped develop services including:

OncologyPRO, ESMO's online professional resources portal; the ESMO Preceptorship program; ESMO Press, an editorial project producing over 10 educational books on a yearly basis; and the expansion of services to the oncology community in Asia, mainly with the ESMO Asia Congress.

ESMO President Fortunato Ciardiello, said: "Dr. McGregor has a track record of successful relationships with all the society's stakeholders as well as vast experience in developing valuable products and services for professional medical societies. The implementation of his ideas have contributed to make ESMO a society well recognized and appreciated in the global oncology community. This is proof that he is the right person to work with the society's leadership to drive ESMO towards an even brighter future."

M. BEATRIZ CURRIER joined the executive leadership of **Miami Cancer Institute** at Baptist Health South Florida as director of Cancer Patient Support Services.

Currier will lead a multi-specialty cancer support services team comprised of physicians who specialize in psychiatry, integrative medicine, cancer rehabilitation and pain management, as well as a team of clinicians who will address the psychosocial and physical well-being of cancer patients.

Prior to joining Miami Cancer Institute, Currier was medical director of Sylvester Oncology Support Services, medical director of the Courtelis Center for Psychosocial Oncology and chief of Clinical Psychiatry Services at Sylvester Comprehensive Cancer Center. She also served as division chief of Psychosomatic Medicine in the Department of Psychiatry at University

of Miami Miller School of Medicine.

A diplomat of the American Board of Psychiatry and Neurology with a subspecialty certification in psychosomatic medicine, Currier is also a reviewer for several journals and has served as a principal investigator on several pharmaceutical studies.

H. BENJAMIN HARVEY, of Massachusetts General Hospital, and **COURTNEY MORENO**, of Emory University, received the 2016 Bruce J. Hillman Fellowship in Scholarly Publishing from the **American College of Radiology**.

"Both awardees are highly successful junior faculty members who have shown by their accomplishments an interest in pursuing scholarly journalism as an integral part of their future careers," said Bruce Hillman, founding editor-in-chief of the Journal of the American College of Radiology.

"This publishing fellowship—which provides a concentrated medical editing, journalism and publishing experience—encourages careers in radiology journalism through hands-on experience and ultimately advances the field."

Harvey, who is on the faculty in the radiology department at Massachusetts General Hospital, has led a group of research efforts focused on improving the practice of radiology, point-of-care clinical decision support and liability issues. Moreno, who is an assistant professor of radiology and director of the ultrasound division at Emory, has research interests in health policy and medical journalism and medical publishing.

Both will spend two weeks with Hillman; Ruth Carlos, JACR deputy editor; journal staff members; and representatives of Elsevier, JACR's publisher. After the on-site component of the fellowship, the fellows will work on a project to enhance the appeal of the journal. Fellows may be invited to work with JACR as members of its editorial board.

THE VAN ANDEL RESEARCH INSTITUTE-Stand Up To Cancer Epigenetics Dream Team's first clinical trial moved forward, targeting metastatic colorectal cancer.

The trial is led by VARI-SU2C Epigenetics Dream Team members Nilofer Azad and Nita Ahuja, at Johns Hopkins University's Sidney Kimmel Comprehensive Cancer Center, with scientific oversight and support provided by the Dream Team. The phase II trial will further test a combination therapy that includes guadecitabine (SGI-110), which corrects errors in methylation.

Phase I has been underway since 2013; by conducting the next phase of the trial through the Dream Team, investigators will be able to add 40 more patients to phase II and perform additional specimen collection and analysis. These enhancements will provide a more thorough look into the efficacy of a potential new treatment for metastatic colorectal cancer.

"We're thrilled to support this promising trial as part of the VARI-SU2C Epigenetics Dream Team," said Peter Jones, Dream Team co-leader and VARI's research director. "Through this collaboration, we have an exceptional opportunity to further develop the next generation of epigenetic cancer therapies. The initial results from phase I were very encouraging, and we look forward to the results of phase II."

Phase II began enrolling patients in January. Although the trial is based at Johns Hopkins, clinical work will also occur at University of Southern California, Memorial Sloan Kettering Cancer Center and VU University Medical Center in the Netherlands. Guadecitabine is supplied by Astex Pharmaceuticals Inc.

The VARI-SU2C Epigenetics Dream Team was established in October 2014 and brings together scientists and clinicians from across the U.S. and abroad to move promising epigenetic therapies into clinical trials.

Drugs and Targets

Venetoclax Receives Third FDA Breakthrough Designation

Venetoclax received its third Breakthrough Therapy Designation from the FDA, for a combination treatment with hypomethylating agents for patients with untreated acute myeloid leukemia who are ineligible to receive standard induction therapy.

Venetoclax is an inhibitor of the B-cell lymphoma-2 protein, being developed by AbbVie in partnership with Genentech and Roche.

In April 2015, the FDA granted Breakthrough Therapy Designation to single agent venetoclax for the treatment of CLL in previously treated (relapsed/refractory) patients with the 17p deletion genetic mutation. In January 2016, AbbVie announced that the FDA granted priority review for the single agent NDA application, and granted a second Breakthrough Therapy Designation for venetoclax supported by the investigational study in combination with rituximab for the treatment of patients with relapsed/refractory chronic lymphocytic leukemia.

The BCL-2 protein prevents apoptosis of some cells, including lymphocytes, and can be over expressed in some cancer types. Venetoclax is designed to selectively inhibit the function of the BCL-2 protein. Venetoclax is currently being evaluated in phase III clinical trials for the treatment of relapsed/refractory CLL, along with studies in several other cancers. Venetoclax is an investigational compound and its safety and efficacy have not been evaluated by the FDA or any other health authority.

FDA issued a complete response letter to a Biologics License Application submitted by Telesta Therapeutics Inc. for MCNA. FDA said that additional phase III clinical trial for MCNA would be necessary to adequately establish MCNA's efficacy and safety.

The FDA also encouraged Telesta to meet with them to discuss further clinical development of MCNA.

Michael Berendt, Telesta's CEO and chief scientist, said: "We are very disappointed with the FDA's decision. Since we began our dialogue with the FDA in February 2014, we have clearly communicated that we believe that MCNA is a safe and efficacious agent for the treatment of high risk non-muscle invasive bladder cancer patients who have failed front line BCG therapy. The FDA decision, at this point, to require an additional clinical trial, is a setback for under-served bladder cancer patients, our dedicated staff, and our investors who have funded our efforts to obtain MCNA approval in the U.S. MCNA would have been the first new bladder cancer therapeutic to reach the market since 1998."

"We will, over the next few months, work closely with the FDA, our advisors and our development partners to analyze the clinical and regulatory path forward in the United States and Europe, as well as the current competitive landscape and the costs and timelines to conduct a second phase III trial for MCNA."

MCNA is a biologic therapy is being developed as an alternative to surgery for high-risk, non-muscle invasive bladder cancer patients who are refractory to or relapsing from first line therapy with bacillus Calmette-Guérin. MCNA is derived from the cell wall fractionation of a non-pathogenic bacteria.

Dana-Farber Cancer Institute announced an immuno-oncology collaboration with Array BioPharma.

The research team at Dana-Farber's Robert and Renée Belfer Center for Applied Cancer Science will work with Array scientists on novel immune-oncology targets. Financial terms of the agreement are not being disclosed.

"We are very enthusiastic about working with Array to develop novel immune-oncology drugs because their team has a strong track record of drug discovery success yielding innovative cancer therapies. Together we have the potential to deliver novel molecules that target unique mechanisms to harness the immune system and result in durable efficacy," said Kwok-Kin Wong, scientific co-director of the Belfer Center, and professor of medicine at Harvard Medical School.

The Mayo Clinic in Jacksonville, Fla. will collaborate with Morphotek Inc., a subsidiary of Eisai Inc., in a clinical study in patients with folate receptor alpha positive, triple-negative breast cancer.

The study is supported by a $13.3 million grant from the Department of Defense and provides funding for a 280-patient phase II clinical trial testing an anti-FRA vaccine in patients with TNBC. Correlative studies within the grant will utilize Morphotek's proprietary FRA diagnostic assays to quantify FRA expression in patients' tumors and blood with the intent of developing companion assays.

"We are excited about this clinical study with Mayo Clinic in the field of anti-FRA therapy," said Daniel O'Shannessy, head of translational medicine and diagnostics at Morphotek. "The FRA pathway and development of potential FRA-positive cancer treatments are a key focus of Morphotek. The use of FRA diagnostics in TNBC complements our current development strategy with our investigational agent, farletuzumab, which is being tested in cancers known to express FRA."

Farletuzumab is currently being tested in a clinical study in first-relapsed, platinum-sensitive ovarian cancer patients with low CA125 levels.