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THE CANCER LETTER

Inside information on cancer
research and drug development

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THE SUMMER ISSUE OF THE CANCER LETTER

You are looking at The Cancer Letter's summer issue, a collection of stories we have compiled for you as we (and, we hope, you) go off on a brief summer recess.

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2019 AACI/CCAF Annual Meeting

OCTOBER 20-22 • WASHINGTON, DC



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Douglas R. Lowy, MD
Acting Director
National Cancer Institute



2019 AACI CHAMPION FOR CURES AWARD

The Jon M. and Karen Huntsman family



KEYNOTE SPEAKER

Devon Still
Childhood cancer awareness advocate and former NFL player

The annual meeting of the Association of American Cancer Institutes (AACI) and the Cancer Center Administrators Forum (CCAF) provides an opportunity to network with and learn from peers in the cancer research community. The meeting will cover topics of both scientific and operational value, equipping attendees with practical solutions.

This year's program includes sessions addressing:

- Artificial intelligence and Big Data
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- The biology of metastases
- NCI Cancer Center Support Grant
- CAR T-cell therapy
- Community outreach and engagement

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Registration rates increase September 20.

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Association of American Cancer Institutes

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The Cancer Letter is taking a publication break.
We will return on Sept. 6.

LETTER FROM THE EDITOR



The Summer Issue of The Cancer Letter

You are looking at The Cancer Letter's summer issue, a collection of stories we have compiled for you as we (and, we hope, you) go off on a brief summer recess.

The summer issue is about big themes, as opposed to immediate events, an invitation to visit our coverage that provides deep examination of the Chernobyl nuclear disaster, the founding and near dissolution of the Cancer Prevention and Research Institute of Texas, the reality of “moonshot” programs, and the hidden hazards of new surgical techniques for the treatment or prevention of cancer.

The Cancer Letter is the place to go for news—but also for perspective. Now in the middle of its 45th year, The Cancer Letter isn't a whole lot younger than the National Cancer Act of 1971, and as the 50th anniversary of the War on Cancer approaches, we are thinking history, pageantry even.

For this issue, we relaxed our standard definition of immediacy and invited Cy Stein, an oncologist at City of Hope and a former NCI fellow, to write the story of a spectacular failure in drug development: [page 5](#).

Failures are as interesting as triumphs, and suramin was a loud, gut-rupturing, systemic belly-flop.

The majority of oncologists practicing today haven't heard of suramin, which is just as well, because it was toxic and not efficacious in cancer. It caused Guillain-Barre syndrome, an autoimmune disease that brought on paralysis that put the NIH Clinical Center's ventilators to good use.

While the drug itself is now irrelevant, the scientific and political forces in play in Stein's story are still with us. There is all manner of hype, inability to recognize flawed science, the propensity to fall in line and do as you are told.

It's also a literary story—Cy and writer cousin Harry Stein co-wrote a novel titled [“The Magic Bullet,”](#) which is set at a place called the American Cancer Institute. Jacket copy describes the book as a “disturbing look at the ivory tower world of medicine, where hubris, not commitment and compassion, is the rule.”

I read “The Magic Bullet” in real time, as did most of my friends at NCI, who made it a parlor game to guess the identities of the NCI oncocrats who served as unwitting models for the sociopaths of ACI.

In this week's story in The Cancer Letter, Stein explains his decision to forego an authorship credit on “The Magic Bullet.”

“Because I was a young junior faculty member at the time, with a strong sense that publishing novels would be frowned upon by my then current institution,” he writes here.

As it happens, Stein's piece disputes another account of the suramin saga, in [“How We Do Harm,”](#) a non-fiction book by Otis Brawley and yours truly. Brawley stands by his version of events, and I say that much of the Brawley-Stein disagreement is a difference of opinion, and the two memoirists are just far enough apart to make for interesting reading.

The summer reading series appears on [page 11](#), [page 13](#), [page 17](#), and [page 21](#).



GUEST EDITORIAL

Learning from suramin: A case study of NCI's much-hyped cancer drug that crashed and burned—35 years ago



By **Cy Stein, MD, PHD**
City of Hope National Medical Center

Almost 35 years ago, while the nation suffered in the vicious grip of the HIV epidemic, a young man from South Carolina with AIDS named Boyd Helton found his way to the NIH Clinical Center in Bethesda. While there, he was recruited into a clinical research protocol designed to lower the expression of viral proteins in his blood, and, ideally, to increase the numbers of his circulating CD4+ T-cells.

The drug treatment examined in the clinical research protocol, an inhibitor of multiple viral and mammalian DNA and RNA polymerases, had been chosen because of work performed in the lab of Eric DeClerq, a noted Belgian scientist. The principal investigator on the treatment protocol was Sam Broder, in the

years before he successfully investigated AZT in patients with HIV, and later became NCI director.

The name of the drug was suramin.

Helton was Patient Zero in what I call the suramin saga, which culminated in the drug eventually entering clinical trials as an anticancer drug. After some initial apparent success in prostate cancer, suramin—for a radiant instant—became the cynosure of all eyes in solid tumor oncology.

It's a story that has made its way into books and—nearly—into the movies. I collaborated with my cousin Harry Stein, a professional writer, to produce "[The Magic Bullet](#)," a heavily fic-

tionalized take on the development of suramin.

So why isn't my name listed as an author?

Because I was a young junior faculty member at the time, with a strong sense that publishing novels would be frowned upon by my then-current institution.

The "Magic Bullet" was published in 1995 by Delacorte Press. The work briefly became a USA Today best-seller and was optioned to New Regency Pictures. The late Penny Marshall signed on as director, and a screenplay was commissioned from Paul Schrader, whose screen credits include "Raging Bull," "Bringing Out the Dead," and "First Reformed." Sad-

ly, the movie was never made. Penny soon backed out to do “The Preacher’s Wife,” rejecting the suramin saga in favor of Denzel Washington and Whitney Houston. Who could imagine? The studio brought in a second director and screenwriter, but after investing two million bucks, canned the entire project.

The brief hullabaloo surrounding suramin was a false dawn, the fool’s gold of cancer drug discovery: suramin could also produce mighty serious toxicity.

The approach to the pharmacologic challenge presented by this drug has also been mocked and derided over the past several decades. To add insult to injury, both the drug and the PI on all the clinical suramin trials were bashed in a 2012 book by Otis Brawley and Paul Goldberg titled “How We Do Harm,” published by St. Martin’s Press.

“If it didn’t work, double the dose”

I contend that the story surrounding the development of this drug is far more nuanced than most are aware of. I know, because I was responsible for much of it.

Now, almost 35 years later, with the benefit of the objectivity of time and distance, I believe it’s worthwhile to undertake take a dispassionate reappraisal of the suramin saga, both to set the story straight and to see what lessons can be learned.

In 1985, when the tale begins, the world of cancer treatment looked very different. In that world, chemo was king. The clinical wisdom about chemo treatment, expressed by the highest authority at the NCI was, “if it didn’t work, double the dose.”

We were also ominously informed that “you can’t make omelets without breaking eggs.” Perhaps the NCI doctor who so instructed me, a decent chap otherwise, was unaware this was Lenin’s

justification for the beastly treatment he meted out to anyone who disagreed with his inhuman policies during the Bolshevik Revolution of 1917.

In 1985, there were no cell phones and no Internet. Fax machines were still in development. There were no monoclonal antibody-based treatments for cancer, no tyrosine kinase inhibitors, and no immuno-oncology agents (except for perhaps BCG). 5-HT₃ receptor antagonists, such as Zofran or Kytril for emesis, were unknown. Oral hormonal agents for prostate cancer remained well beyond the far horizon, the successful marketing of taxanes was still years in the future, and the term “personalized medicine” was a non sequitur.



And if doubts you dared to have, it was best to leave them at the door or keep them to yourself. When consorting with the lords of cancer (the “oncocrats”, so named by Eli Glatstein, chief of radiation oncology at the NCI), be mindful you were a serf.



Though attitudes were changing, in 1985 the physician still retained much of his or her god-like aura. Patients heard, believed in, and accepted experimental treatments that could produce toxicities that today would be unacceptable. Cancer was a tough disease that required tough doctors!

The attending physicians who were our mentors, we were told, were the best of the best, the cream of the crop. Each was doing God’s work. As first-year fellows at the Medicine Branch of the NCI in 1985, this was the ambiance, the culture we young, eager physicians were expected to absorb without question or

doubt. And if doubts you dared to have, it was best to leave them at the door or keep them to yourself. When consorting with the lords of cancer (the “oncocrats”, so named by Eli Glatstein, chief of radiation oncology at the NCI), be mindful you were a serf.

Sometime in the second half of 1985, when I was a first-year fellow, Boyd Helton became my patient. I was responsible for ensuring his adherence to the suramin for HIV protocol, making certain he had his blood drawn and his treatments on time. Some doctoring was involved, but steering patients through clinical protocols at the NCI was mostly a clerical job for the highly educated.

Sam Broder was the fellowship director. He was cheerful, helpful, encouraging and usually respectful of the folks in the trenches who were doing their best to manage some very sick patients. I remember Sam as having a quick wit and a razor-sharp sense of humor. He wielded both like a stiletto in a knife fight, eviscerating an incautious or unbalanced opponent. Anyone, including cancer lords, who tried to match wits with Sam would come off second best. But for all his bonhomie, Broder set a high bar for the NCI fellows. He expected only the best from us; nothing less was acceptable.

One day, Boyd called me and said that no matter how much water he was drinking, he was still dehydrated and needed to drink more. He also complained of dizziness on standing. I brought him into the NIH Clinical Center for a blood draw and an exam. My first thought was that he had developed adult-onset diabetes. But that turned out not to be the case as his sugar was normal. Perplexed, I sent him home.

Three days later, Boyd called again, complaining of the same problem. Another trip to the Clinical Center and an in-depth investigation revealed that Boyd suffered from adrenocortical insufficiency, or Addison's Disease. His adrenal cortexes were not producing sufficient steroid hormones to allow him to retain sufficient salt and water for him to support his blood pressure. This adrenal gland dysfunction was a side-effect of his suramin treatment (C. Stein, et al., *Ann. Intern. Med.*, 1986 104:286-287). The problem was corrected and Boyd soon recovered.

From African trypanosomiasis to adrenal cancer

Several days later, I dispatched my medical student, Wayne Saville, to the library to gather published material on suramin. He returned with a treasure trove of information. Most significant were the observations that suramin could bind to and inhibit the functioning of various heparin-binding growth factors (e.g., platelet derived growth factor; information about basic fibroblast growth factor came a little later) that had been implicated in tumor growth.

Little or no information was found about any other toxicities of the drug, which had been used for many years in the treatment of African trypanosomiasis, as well as other tropical diseases. I learned that suramin had first been synthesized in 1916 by students

of Paul Ehrlich, and was referred to as Bayer 205 by Paul de Kruif in "Microbe Hunters," a book I'd read over and over as a youngster.

The drug intrigued me—perhaps it was an anti-HIV drug, and perhaps even more. For by this time, I learned, Alexandra Levine (who coincidentally more than 25 years later was to become my supervisor at the City of Hope) and her group at USC had seen a tumor response in a suramin-treated lymphoma patient with HIV (A. Levine et al., *Ann. Intern. Med.*, 1986 105:32-37).

If suramin could ablate the steroid-producing function of the adrenal cortex by causing the destruction of the zona fasciculata, could it perhaps also destroy malignant adrenocortical cells? This thought paralleled the history of mitotane, a DDT relative which also destroyed the normal adrenal cortex. In 1985, mitotane was the only active agent for the treatment of adrenocortical cancer.

Suramin needed to prove itself in the clinic as an anti-cancer drug. A trial in metastatic adrenocortical cancer required strong backing from one of the attending physicians. So, I brought my ideas to Charles E. "Snuffy" Myers, Jr., head of the Pharmacology Branch of the NCI. (The moniker "Snuffy" was his father's, who was thought to resemble an old cartoon character named Snuffy Smith).

Sam Broder was also very encouraging and remained so almost throughout.

Compared to the titanic egos found in the Medicine Branch of 1985, Snuffy seemed mild-mannered, affable and relatively non-judgmental. He was also open to new ideas. With the reputation of super-strength in clinical cancer pharmacology, Snuffy had recently won an award for his work in intraperitoneal chemotherapy from the Milken Family Foundation. On the other hand, with respect to the practice of clinical

medicine and oncology, he was perhaps less strong.

In "How We Do Harm," Brawley refers to Snuffy Myer's "beliefs" about suramin. He claims that science has demonstrated they were "without exception, wrong." But Brawley's Snuffy is not the Snuffy with whom I worked closely in the late 1980s.

He adhered to the same rules of evidence we all did. For example, the drug was not taken directly from Boyd Helton directly into patients with cancer. We first determined that the drug also wiped out the adrenal cortex in monkeys (P. Feullian, et al. *J. Clin. Endocrinol. Metab.*, 1987 65:153-158). Had Snuffy gone rogue, I would have ceased working with him. And I'm no reflexive defender of Dr. Myers. I've spoken to him perhaps once or twice in the past thirty years. But I never knew him to be a "nuke it, napalm it and damn the consequences" buccaneer as Brawley pictures him. He was far more thoughtful than that, except perhaps for a tendency to fly by the seat of his pants. Like everyone else, Myers was ambitious and accepted the prevailing orthodoxy, which had produced active treatments and even cures for some tumors. At the time, there simply was no other orthodoxy to believe in.

The other person I convinced to join the suramin team was Renato LaRocca. Renato and I had a long history together. We were interns and residents at the same medical center in New York City, and were now first-year fellows at the NCI. In our second year, we even joined the same molecular biology research laboratory. Renato was bright and articulate, and, in everyone's opinion, a superb physician. I thought him an excellent addition to the team, and one sorely needed.

That was the way Snuffy first became interested in the use of suramin as an anticancer agent. Other assertions by Brawley in his book were written many

years after the fact. In other areas, he also appeared to have relied on incorrect or second-hand information. For example, Brawley stated that he and the other first year fellows in 1988-9 saw “half of all adrenal cancers diagnosed in the United States.” This is an exaggeration. In the late 1980s, there were about 3-400 cases of adrenocortical cancer diagnosed yearly in the U.S. Our publication ([RV La Rocca, et al., J. Clin. Endo. Metab., 1990 71:497-504](#)) reported on only 17 of them, who were seen over a period of several years. Anyone can do the math.

After I wrote the treatment protocol, LaRocca and I shepherded it through the NCI IRB. In mid-1986 or thereabouts, we began accruing patients with metastatic adrenocortical cancer. These were patients with an aggressive disease that carried a grim prognosis. Most patients were willing to try just about anything. Within a short time, to our amazement, we saw our first objective disease responses. (Unfortunately, there were only 2PRs in 16 evaluable patients, and two other mixed responses in this trial. Five patients had stable disease for up to 10 months).

In the early going, it was all very exhilarating, until we also began to observe some of the novel toxicities of the drug. Suramin is a potent inhibitor of several lysosomal enzymes that are responsible for the digestion of glycosaminoglycans. These heparin-like molecules tend to accumulate in tissues, particularly the cornea, causing suramin keratopathy. This resulted in eye irritation that could require artificial tears, patching, and might require cessation of suramin dosing.

Glycosaminoglycans, particularly heparan and dermatan sulfates, can also circulate, functioning as inhibitors of thrombin (Horne, et al., *Am J. Hematol.*, 1988 71:273-279) to produce anticoagulation. Thus, it's difficult to understand Brawley's comments about Silvio Conte, a former member of the U.S. House

of Representatives who had prostate cancer and was treated with suramin. I never knew the man, because as of June, 1989 I was no longer a member of the suramin team. (Yep, the craziness finally caught up with me. You can get a sense of how crazy it really was from the pages of “The Magic Bullet.”)

Brawley states that Conte had a blood clot in his brain and linked it to his suramin treatment. At same time, Brawley correctly stated suramin is an anti-coagulant, which prevents clotting. It seems more likely to me that the well-known pro-coagulant effects of uncontrolled prostate cancer led to the thrombosis in Mr. Conte's brain.

Guillain-Barre syndrome

Ultimately, three patients with adrenocortical cancer and one other patient with a lymphoma also developed a “reversible” polyneuropathy that was reminiscent of Guillain-Barre syndrome ([R. LaRocca, et al., Neurology, 1990 40:954-960](#)). However, by no means were all these recoveries complete, and rehab could be difficult and time-consuming.

Should the trial have been stopped after the first two patients with adrenocortical cancer developed the Guillain-Barre-like syndrome? Some thought so at the time, because one day an FDA inspector wearing a bright, shiny silver badge came to have a chat with us.

Somehow, Snuffy contrived not to be present, so two edgy fellows, LaRocca and myself, defended the suramin trials before one badass FDA inspector. As I recall, we managed to convince him that with Myers's new dosing regimen, which required continuous infusion of drug as opposed to bolus dosing, peak plasma suramin levels would remain below 300 µg/mL. This seemed to be the plasma level above which most suramin toxicity developed. The suramin trials were allowed to continue.

I was badly affected by the suramin-induced polyneuropathy, and still remember the patients afflicted by it. But Myers, one of the best of the best, was the protocol PI, and neither he nor Sam Broder supported ending the trials. LaRocca and I trusted their judgment. Besides, it was only a question of breaking a few eggs, right? So, despite the polyneuropathy, not only were the trials continued, but treatment with suramin was opened-up to a general phase II trial.

Early on, we found a response in a patient with prostate cancer, and began a new trial in that disease, in which Mr. Conte participated. This is when the NCI made what was, in my opinion, a serious error. Myers, LaRocca and I were well-aware of the flaws in the prostate cancer trial. We knew we'd need some time to make sense of the data we had and to fix the problems we'd run into. For instance, the assay required to determine serum suramin levels was cumbersome and beyond the resources of many centers.

No one had cared about our work in adrenocortical cancer. But once those first few PSA and objective responses were seen in metastatic castrate resistant prostate cancer (mCRPC), all hell broke loose. We were told to provide information about the trial to anyone who asked. And so, investigators, like Steve Cvitkovic, would barge into my office with a set of demands that had to be filled immediately. The inevitable result would be disappointment, which often happens when drugs are pushed ahead too rapidly in trials.

Who made the choice to disseminate the trial? I'm not certain, though I doubt whoever did so had much of a choice. In those days, we had few good treatments for mCRPC. Rich and powerful men were dying from it in pain, in misery, and in droves. I think the oncocrats wanted the answer quickly and didn't want to wait around for years until we figured it out.

Magic bullet for prostate cancer?

In our original prostate cancer trial, a total of 38 patients were accrued. Six of 17 had eventual objective disease PRs, and 21/38 (55%) experienced a decrease of greater than or equal to 50% of their PSA. Ten patients had a decrease of greater than or equal to 75%. This translated into dramatically increased overall survival. These numbers, if validated, compare favorably with contemporary prostate cancer treatments.

Unfortunately, Brawley misstates the reasons for suramin's apparent early clinical success. The observed responses were not due to the simultaneous withdrawal of non-steroidal anti-androgens (e.g., flutamide). These drugs can indeed produce both PSA declines and objective responses in patients with mCRPC. The withdrawal phenomenon was first brought to my attention by Jayne Gurtler, of Metairie, LA, who noted a six-month response in one of her patients after withdrawal of bicalutamide. We were thus aware of this possibility before the trial in prostate cancer began.

Also, despite Brawley's claims, we were also aware of the extremely long plasma half-life of suramin, and the correlation between toxicity and peak plasma suramin levels. This is what Myers's dosing scheme (see below) tried to modulate. Regardless, just what were these men with advanced prostate cancer trying to accomplish in a clinical trial at the NCI, if their cancer was still sensitive to standard flutamide treatment?

I passed the information from Gurtler on to Myers, who I was told sent it along to Howard Scher at Memorial Sloan Kettering. Scher and his group performed a large trial that validated Gurtler's eagle-eyed finding. However, it is possible that the hydrocortisone that men received because of the damage suramin caused to the normal adrenal cortex produced some of the responses.

71% of those with prostate cancer who had pain (21 patients) experienced sufficient pain relief to stop or reduce their use of opiate analgesics by one-half (C. Myers, et al., *J Clin. Oncol.*, 1992, 10:881-889). Pain relief was the indication that Warner-Lambert sought FDA approval for in 1998.

However, two patients (5%) died of drug-related toxicity, one of DIC, the other of sepsis. Under Myers's dosing scheme, peak suramin plasma levels did not exceed 300 µg/mL, and neurologic toxicity was limited to grade 1 or 2 peripheral sensory neuropathy. Nevertheless, many cancer pharmacologists found this dosing scheme peculiar, as Brawley points out; I know at least one who said it made no sense at all. Perhaps in an academic sense it didn't. But the results speak for themselves.

As Brawley notes, the FDA turned Warner-Lambert down. They were correct to do so—the drug was too toxic. After that, suramin pretty much disappeared. Long before, the members of suramin



Looking backwards three decades, I wonder if the light suramin cast was worth the candle. In my opinion, probably not.



team had gone their own ways. It was an ugly divorce caused by the usual typical human emotions—greed, envy and fear.

“The Magic Bullet” is dated now, though you can still purchase it used on Amazon. But it's still kind of funny for such a dismal subject as cancer, if you read it as a character study.

As a final swipe at Myers, Brawley contended that “the change in PSA—which Snuffy believed to be an indicator of clinical improvement—isn't worth

much. It's a measurement made in a lab. It doesn't necessarily mean anything to an actual patient. Your PSA could go down, and you may not know the difference.”

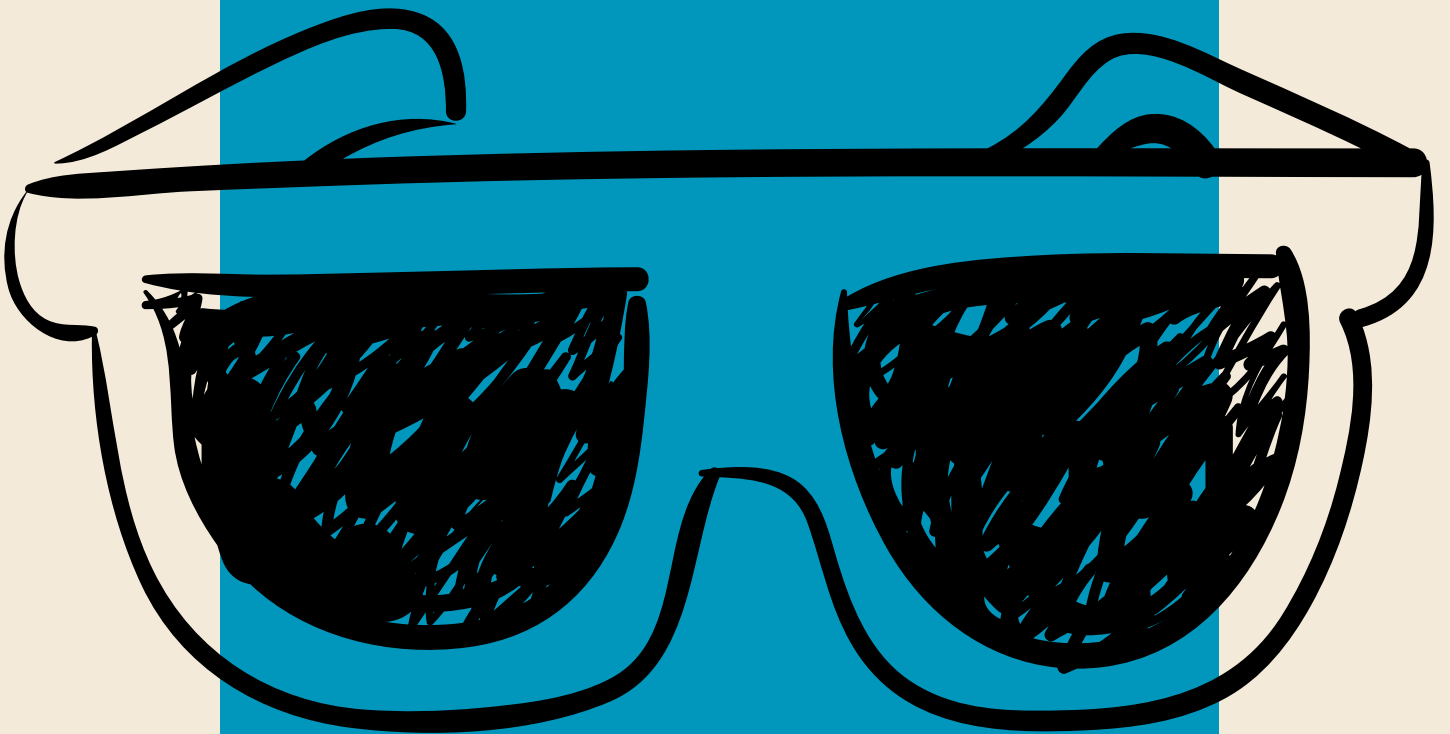
True, the FDA does not accept PSA as an endpoint for the evaluation of treatment efficacy in prostate cancer. Nevertheless, we now know that in mCRPC, PSA declines produced by drug treatments are predictive for prolonged overall survival. Patients whose PSAs decline >50% after treatment will survive significantly longer than those who do not reach that threshold; patients whose PSAs decline >75% will survive longer yet. And those patients whose PSAs decline >90% do the best of all. These patients may survive many years. As any medical genitourinary oncologist can attest, in clinical practice, PSA matters a hell of a lot.

Looking backwards three decades, I wonder if the light suramin cast was worth the candle. In my opinion, probably not. But then, I remember the

patient I was introduced to at the FDA ODAC hearing in 1998. He was treated with suramin at Johns Hopkins in 1990 with no toxicity and no evidence of disease since, a span of what was then eight years. When my role in the development of this drug was related to him, he couldn't have been more gracious and appreciative.

I was delighted to see that at least someone had benefitted from our hard work and stress, and of the willing sacrifices made by so many others.

**HERE ARE SOME OF OUR SERIES AND
LONG-RUNNING STORIES THAT ARE
SUITABLE FOR BEACH READING:**



Robert Peter Gale's series of stories on the HBO drama Chernobyl



Gale was there, in Moscow's Hospital Number 6, famously taking care of people injured in the nuclear plant disaster. He is also the author of two books that address Chernobyl, other nuclear accidents and radiation in general: "[Final Warning](#)" and "[Radiation: What It Is, What You Need to Know](#)."

How much of the HBO miniseries was true? How much was just truthy?

"Knowing the limited resources available to my Soviet colleagues to deal effectively with an event of this magnitude, I contacted Mr. Gorbachev through Armand Hammer, offering my help and that of my colleagues at the International Bone Marrow Transplant Registry (now the Centre for International Blood and Marrow Research)," Gale writes. "Anatoly Dobrynin, Soviet ambassador to the U.S., called me the

next day, asking me to come immediately to Moscow. Two weeks later, I recruited two UCLA colleagues (Paul Teraski and Richard Champlin) and one colleague from the Weizmann Institute in Israel (Yair Reisner) to help.

"I spent the following two years mostly in the Soviet Union, working with my colleagues at the Institute for Biophysics and Clinical Hospital 6, dealing with a bit more than 200 persons with acute radiation exposures. In the subsequent 30-plus years, I have been involved in several studies of the long-term medical consequences of the accident—ini-

tially in the ex-Soviet Union, and later in the Russian Federation, Ukraine and Belorussia; more details as the series progresses."

Gale's central question: Does historical fiction give writers the license to wander away from historicity?

Trying to put the Chernobyl disaster in historical perspective, Gale writes: "I knew each of the firefighters intimately, including the 29 who died. I never heard one of them express regret over what they had done to contain the Chernobyl disaster. These men are the real heroes.

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“In the miniseries, the liquidators are portrayed as being coerced into their mission. I interviewed many of them at the time of the accident, not 30 years later. Almost everyone I spoke with volunteered. Anyone with knowledge of Russians will recognize how these people respond to adversity. Recall Napoleon’s 1812 excursion into Russia, or the Nazi invasion of the Soviet Union in WWII. These people are tough; 20 million Soviets died fighting the Nazis. The notion that most liquidators were conscripted against their will shock people who know Russians respond to adversity: they thrive on it.”

Gale’s series of [four essays](#) is among The Cancer Letter’s most read stories so far this year, and it has been quoted worldwide. We have just given the Russian news publication Kommersant Nauka permission to excerpt and translate Gale’s essays.

To drill deeper into the Chernobyl story, you might want to look at Gale’s detailed account of becoming one of the first two humans to be injected with GM-CSF. The drug, which is used extensively in cancer and is now approved for boosting survival in people acutely exposed to myelosuppressive doses of radiation, was first used to treat Chernobyl patients at Hospital Number 6 (The Cancer Letter, [May 29, 2015](#)).

The full series is posted [here](#).

Chernobyl, the HBO miniseries: Fact and fiction

Two weeks ago, HBO began screening a five-part series on Monday nights on the Chernobyl nuclear power facility (NPF) accident, which occurred more than 30 years ago on April 26, 1986.

[Read more](#)

Chernobyl, the HBO miniseries: Fact and fiction (Part II)

Last week, I discussed events resulting in the Chernobyl NPF accident, including unique aspects of the reactor-design which contributed to the accident, and which resulted in release of radiation to the environment. I also discussed the initial Soviet response. Next, I focus on the immediate medical consequences and the response of Soviet government to medical interventions.

[Read more](#)

Chernobyl, the HBO miniseries: Fact and fiction (Part III)

With episode four of the series, we moved even further from reality than in prior episodes.

[Read more](#)

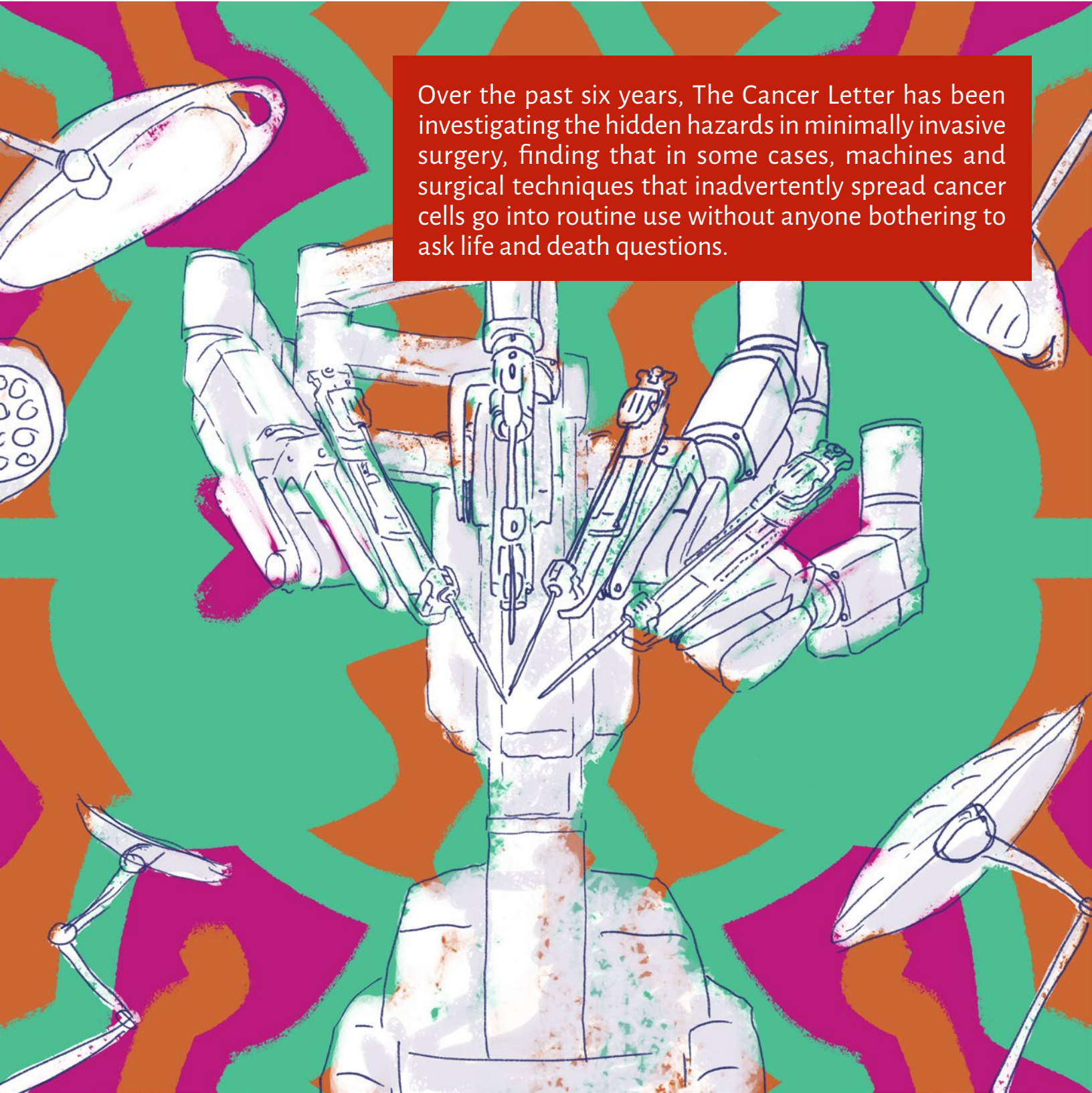
Chernobyl, the HBO miniseries: Fact and fiction (Part IV)

Readers will be pleased to learn this is the final installment of my reviews of the HBO Chernobyl miniseries, which just ended its TV run June 3. The series, which has received extraordinary critical acclaim, had a vast global audience.

[Read more](#)

When Surgical Innovation Kills

Over the past six years, The Cancer Letter has been investigating the hidden hazards in minimally invasive surgery, finding that in some cases, machines and surgical techniques that inadvertently spread cancer cells go into routine use without anyone bothering to ask life and death questions.



Reporter Matthew Ong's coverage has saved lives, resulted in action by several federal agencies, and contributed to changes in FDA regulation. His investigative work has altered the way in which surgical devices—including power morcellators and robotically-assisted surgical devices—are used, and potentially, approved.

The Cancer Letter's investigation first focused on power morcellation, a surgical procedure routinely used to break up uterine tissue into fragments. This procedure was adopted before gynecologists appreciated a risk that might have been obvious: that devices that work along the same principles as food processors would spew out tissues that are, in fact, undiagnosed cancers, letting malignant cells fly through the patients' bodies. This procedure was popular, yes, but it has also been proven to be deadly.

While power morcellators have largely been abandoned in part as a result of our coverage, minimally invasive surgeons are now turning to other ways to mince up tissues that should be taken out intact. The basic principles of cancer surgery taught in medical schools hold, in part, that tumors and other at-risk masses should be presumed malignant.

In some cases, gynecologists have been reported to use manual methods for pushing tissue closer to the body surface and cutting uteri into strips, thus breaking up undiagnosed cancers and unwittingly causing stage IV disease.

Gynecologic oncologists—physicians who specialize in treating uterine cancers—are learning that their routine minimally invasive surgical techniques for treating cervical cancers are shortening the lives of many women, causing great suffering.

Now, other surgical specialists are adopting minimally invasive devices—notably, the da Vinci Surgical System,

a robot with multiple arms—and using them to operate on breast cancer, without data on whether the procedure or technique would be safe for cancer patients and patients who are at high risk of having an undetected cancer.

In medicine, the standard approach to innovation is to ensure that novel treatments and procedures are at least as good as conventional approaches—before offering them to patients. Building on years of investigative work, Ong demonstrates in 2018 and 2019 that minimally invasive surgeons are prone to doing the exact opposite: entire specialties have been adopting new, potentially harmful procedures as the standard of care before ascertaining safety and noninferiority in prospective clinical trials.

As it appears, many minimally invasive surgeons practice in a culture that prioritizes innovation over safety of patients even in a setting where a cancer has been diagnosed—bolstered by a multibillion-dollar industry that produces surgical devices that aren't rigorously tested and regulated.

On Feb. 28, 2019, FDA issued a [safety advisory](#) aimed at tightening regulation of robotic devices in minimally invasive surgery. Now, device manufacturers looking to market surgical tools for use in the prevention or treatment of cancer may be required to study long-term oncologic endpoints in prospective surgical trials—to establish noninferiority of robotic procedures and demonstrate cancer-related safety and effectiveness.

In 2018 and 2019, Ong showed how five years of unpleasant surprises—and painstaking reporting in The Cancer Letter—changed how gynecologists, oncologists, and surgeons think about the role of cancer in minimally invasive surgery, proving that cancer-related outcomes should no longer be treated as an afterthought.

Ong's series, which have won 10 awards from seven organizations, are posted here:

- **How Medical Devices Do Harm** (2014-2017) <https://cancerletter.com/morcellation/>
- **When Surgical Innovation Kills** (2018-2019) <https://cancerletter.com/articles/surgery/>

Notable stories:

Harvard physician, whose cancer was spread through morcellation, seeks to revamp FDA regulation of medical devices

On Oct. 17, 2013, a surgical instrument called a power morcellator tore into the uterus of Amy Reed, an anesthesiologist at Beth Israel Deaconess Medical Center, pulverizing what were believed to be benign fibroids.

Reed's "minimally invasive" hysterectomy, a routine procedure, was performed at the Brigham and Women's Hospital, a teaching hospital of Harvard Medical School.

Alas, Reed's uterus contained an occult sarcoma, which the morcellator proceeded to spread through her abdominal pelvic cavity. Over ensuing months, as Reed battled to stay alive, her husband, Hooman Noorchashm, a cardiothoracic surgeon and, at the time, a lecturer at Harvard, waged a national campaign to put an end to the practice of power morcellation.

[Read more](#)

Urgent FDA action turns power morcellators into rarely used gynecological procedure

The power morcellator should no longer be used for hysterectomies or fibroid removal in the vast majority of women getting these procedures, FDA declared in a highly anticipated guidance document Nov. 24.

Using a new authority that bypasses public comment, the agency stopped short of imposing an outright ban on the device, but severely restricted its use.

[Read more](#)

How Medical Devices Do Harm

Friends call him The Hoomanator, a darkly comical conflation of his first name, Hooman, and morcellator, the medical device he has aggressively campaigned against.

Enemies—who are great in number—call him much worse.

Over the past two years, Hooman Noorchashm, a cardiac surgeon at Thomas Jefferson University Hospital, has been accused of launching a “campaign of distortions,” threatened with legal action, subjected to security searches and publicly chastised.

Over a two-year investigation, The Cancer Letter tracked Noorchashm and his

wife, Amy Reed, as they challenged FDA, Congress, hospitals, the gynecology profession and manufacturers of medical devices. Their struggle began with a routine hysterectomy, during which a device called a power morcellator disseminated Reed’s undetected sarcoma. Today, as Amy’s aggressive disease spreads, the couple continues to draw public attention to the blind spots in the U.S. medical device regulatory system.

[Read more](#)

FDA finds lapses in reporting of patient harm, deaths resulting from medical devices in hospitals nationwide

After a broad survey of reporting standards at hospitals across the U.S., an FDA investigation recently concluded that the vast majority of the 17 institutions inspected did not file timely reports of injuries and deaths caused by medical devices.

The inspections earlier this year were triggered by public scrutiny of power morcellation, a surgical procedure known to spread undetected uterine cancer via the device’s spinning blades, as well as by reports of infections associated with contaminated duodenoscopes, flexible, lighted tubes that are threaded through the mouth, throat, and stomach into the top of the small intestine.

[Read more](#)

GAO: Power morcellation is a unique case study in patient harm

Hundreds died over two decades as reporting requirements were ignored.

FDA’s passive reliance on self-reporting by hospitals and device manufacturers allowed harm caused by power morcellators to go unnoticed for over two decades—likely contributing to injury and deaths of hundreds of women, according to the U.S. Government Accountability Office.

[Read more](#)

Amy Reed, physician and patient who ‘moved mountains’ to end widespread use of power morcellation, dies at 44

When Amy Reed enrolled at the University of Pennsylvania medical school in 2001, she could not have possibly imagined that she would save more lives as a patient than as a physician.

The final phase of her medical education began on Oct. 17, 2013, when Reed, then 41, checked in at Brigham & Women’s Hospital—her husband’s workplace at that time—to undergo a common gynecological procedure that would fundamentally redefine her career, and, ultimately, consume her life.

[Read more](#)

Gynecology's deadly surprise: Cancers are frequently missed prior to routine procedures

As they reach for surgical tools, gynecologists vastly underestimate the probability that their patients have undiagnosed uterine cancers, a study by Yale University researchers found.

[Read more](#)

Minimally invasive surgery lowers survival in cervical cancer, new studies show

Women who were subjected to minimally invasive surgery for early-stage cervical cancer were four times more likely to die from that disease within three years, three times more likely to have a recurrence within three years, and had shorter overall survival, compared to women who underwent open surgery, according to two groundbreaking studies published in The New England Journal of Medicine Oct. 31.

[Read more](#)

Using a robot to perform mastectomies, a New Jersey surgeon sets off a firestorm over surgical outcomes

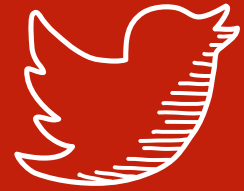
How much rigor should be required when surgeons innovate? FDA's advisory asks for long-term cancer-related data.

Last August, Stephen A. Chagares, a breast surgeon, made an announcement that startled some of his colleagues at New Jersey's Monmouth Medical Center.

At internal meetings and in a press release, Chagares declared that he would perform a robotic mastectomy—a new and relatively untested minimally invasive surgical procedure. According to the press release, his first patient, Yvonne Zucco, 56, was being treated for stage IIa breast cancer.

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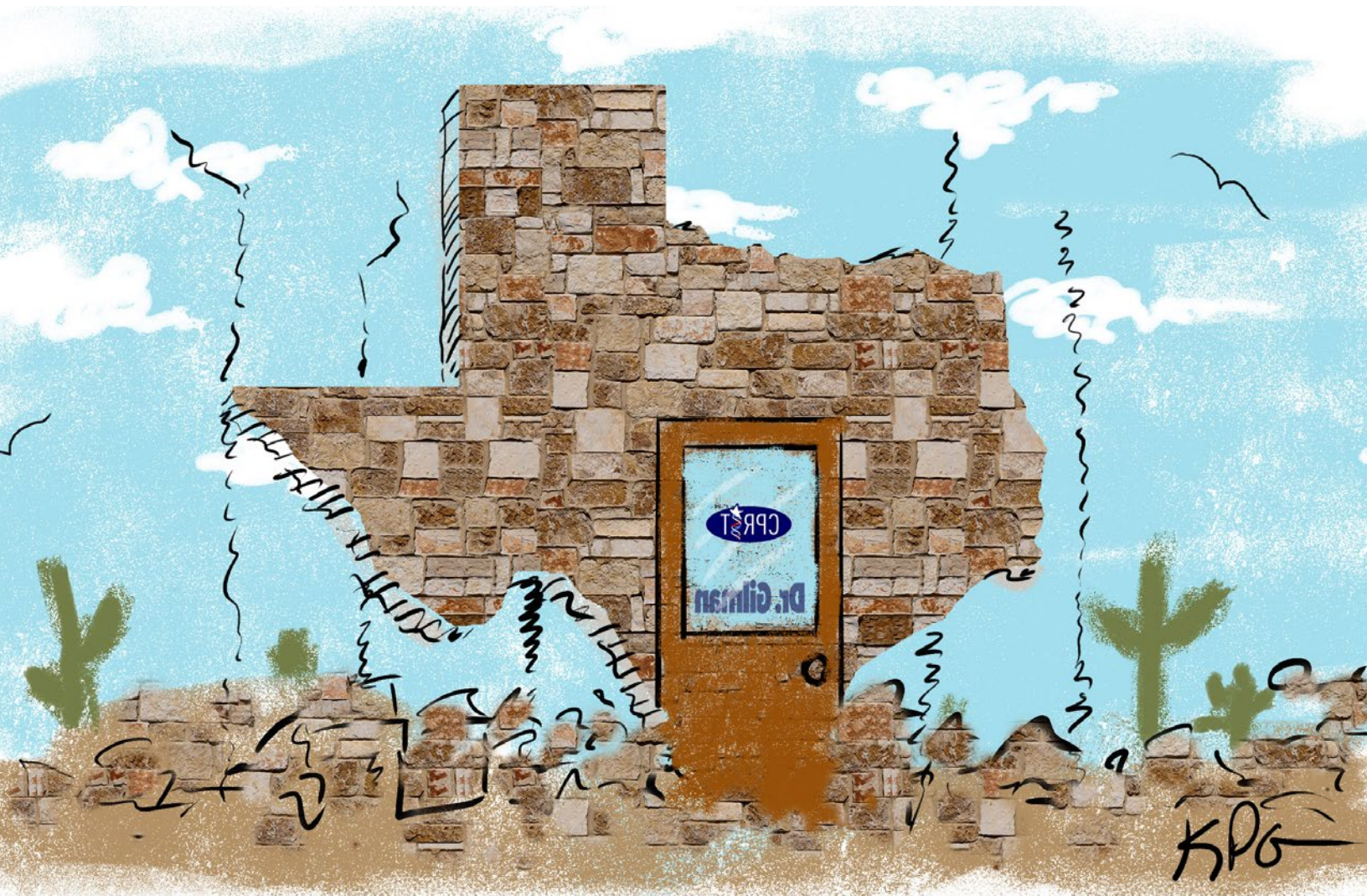


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Slamming the Door

HOW AL GILMAN TAUGHT TEXAS A LESSON IN SCIENCE

On Nov. 5, Texas voters will decide on Proposition 6, which would authorize a second installment of \$3 billion in General Obligation Bonds for Cancer Prevention and Research Institute of Texas. CPRIT is a unique state-funded initiative that is distributing \$300 million a year to cancer research and other cancer causes in Texas.



As they cast their votes, Texans should remember Alfred Gilman, a Nobel laureate, a scientist of extraordinary courage and one hell of a good guy. Gilman designed CPRIT's highly-respected peer review system, served as its first scientific director, defended its integrity from attacks by politicians, and inspired America's top cancer scientists to stand up for good science. He died in December 2015.

The Cancer Letter covered the concurrent controversies at the Cancer Prevention and Research Institute of Texas and MD Anderson Cancer Center in real time, and after the battles concluded, we returned for a re-examination that was made possible in part because of insight provided by Gilman. Call it a 14-part series, or call it a book.

The full series is posted [here](#).

Part I: The hazard of promising

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.

[Read more](#)

Part II: Cancer's Butt

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.

[Read more](#)

Part III: 18,000 bosses

Between the fall of 2011 and the spring of 2012, I watched MD Anderson from afar, and I didn't think about CPRIT at all.

Friends who attended early meetings with Ronald DePinho soon after he became MD Anderson's president said that he was literally grading presentations made to him by faculty members and administrators.

"This was a C-," he would say.

It was difficult to get a B.

[Read more](#)

Part IV: Nobel laureate in crosshairs

In early 2012, Gilman was under the impression that CPRIT was functioning smoothly.

Then, to his surprise, the first of a series of controversies surfaced.

CPRIT's peer reviewers had evaluated 40 applications for Multi-Investigator Research Applications, the largest CPRIT grants designed to fund team science, recommending that seven of these project receive funding. This was no small undertaking. The applications described multiple projects and core facilities.

Proposals for these projects—abbreviated as MIRAs—take a long time to write and a long time to review. The CPRIT committees worked hard to complete the review, but committee members were enthusiastic. There was a lot of good science on the table. In fact, one of the grants received the best score ever for an application of that type.

[Read more](#)

Part V: Gilman's resignation

Gilman's letter of resignation, dated May 8, 2012, concludes with a hard slam:

"The purpose of this letter is to indicate my intention to resign from CPRIT, effective (with your permission) on October 12, 2012. At that time I will have worked for CPRIT for over three years—I believe longer than originally anticipated.

"During that time we have launched strong programs because funding decisions have been based on high-level competitions, where the judges have been some of the best cancer researchers and physicians in the country—free of conflicts of interest and all coming from outside of Texas.

[Read more](#)

Part VI: The provost's choice

After my conversation with Gilman, I called MD Anderson and asked to talk with somebody about the \$18 million grant for a biotech incubator.

First, folks at the press shop told me that they view the controversy arising from the application as CPRIT's problem.

Let's see: the wife of president of MD Anderson gets a grant seemingly out of turn, causing a political disaster, and this is not an MD Anderson problem?

DePinho was initially silent on the controversy, but after the Houston Chronicle published a hard-hitting editorial that laid out a series of questions about the grant, he responded with a letter that portrayed the central question in the controversy as a "difference of opinions."

[Read more](#)

Part VII – DePinho's stock tip revisited

On May 25, 2012, I received an email from Len Zwelling:

Paul: It can't get worse than having our President pushing his own stock on TV. Len

I clicked on the provided link to CNBC. What I saw was indeed difficult to process: a video of Ron DePinho, extolling the virtues of the stock of AVEO Pharmaceuticals Inc., a company he co-founded.

On the CNBC program "Closing Bell with Maria Bartiromo" May 18, DePinho brought up AVEO in the context of the upcoming meeting of the American Society of Clinical Oncology.

[Read more](#)

Part VIII – A conversation with DePinho

The \$18 million never made it from Austin to Houston.

MD Anderson's initial stance was to deflect all CPRIT-related questions to CPRIT, but this didn't make the controversy go away. So, the cancer center suggested that the grant undergo scientific review, as well as commercial.

Recently, I asked Dan Fontaine, MD Anderson's executive chief of staff why the money never changed hands.

[Read more](#)

Part IX – "Furnituregate"

I first heard something about a red sofa that cost an impressive amount of money soon after I started to cover the controversy at the Cancer Prevention and Research Institute of Texas.

The sofa, I was told, was to be purchased with MD Anderson funds for the office of Lynda Chin. I wanted to look into it, but I want to look into many things, and some take precedence over others. This seemed to be fun, but it was undeniably trivial.

The sofa in question was intended for the same entity CPRIT was being asked to fund. Had I been able to get it through my thick skull that the furniture was a part of the same story that was causing the ungluing of CPRIT, I would have filed my freedom of information requests sooner.

When it finally appeared, my friends referred to this story as "furnituregate."

[Read more](#)

Part X – Silencing faculty voice

In the fall of 2012, just before Al Gilman's departure, MD Anderson officials cracked down on internal critics.

On Sept. 26, 2012, Raphael Pollock, head of MD Anderson's Division of Surgery, was summoned to the office of Thomas Burke, then the executive vice president and physician-in-chief, and was relieved of his duties.

Pollock, who is Jewish, was fired on Yom Kippur, the Day of Atonement.

[Read more](#)

Part XI: Gilman's teachable moment

During our first conversation in the spring of 2012, Gilman said that he would go public unless he received assurances that CPRIT would retain its integrity after his departure.

He wanted guarantees that the structure he built would not be turned into a political pigsty. With guarantees being hard to come by, it was obvious that he would end up slamming the door hard. Publicly.

[Read more](#)

Part XII: Scientists vote with their feet

In their op-ed piece, Gilman and Sharp stated what it would take to fix CPRIT's problems. That was the polite version of the Gilman Plan.

The spoken version was more blunt: get rid of the "assholes" on the oversight board, jettison the administrators, then—maybe—CPRIT's credibility would be restored.

Maybe the place will become functional someday, but only the oversight committee is sent packing and after the Gogolesque characters are kicked out of CPRIT's offices in Austin. Until that

occurred, an effort to rebuild would require CPRIT to turn to the scientific establishment on some other planet.

[Read more](#)

Chair of CPRIT oversight committee: “Better to get them all out of the way now”

What were Texas politicians and CPRIT officials thinking as they were pounded by blistering letters of resignation?

Condemnation seemed to be rolling off their backs as they marched toward what they thought was their great triumph.

Jimmy Mansour, chairman of CPRIT’s oversight committee, mistakenly hit Reply All, sending an especially contemp-

tuous email to a scientist who was announcing his resignation from CPRIT. In the email that came into public view because of his sloppiness, Mansour, a telecommunications entrepreneur, belittles scientists and the peer review process.

The email is also remarkable because it illustrates the reluctance on the part of CPRIT officials to recognize that the institute that distributes \$300 million a year in state funds is, in fact, in the midst of a crisis.

[Read more](#)

Part XIV: How Al got it right

Gilman’s resignation enabled him to retain the most precious of all privileges: the ability to look at himself in the mirror.

By slamming the door loudly and publicly—and by triggering an impossible-to-ignore resignations of scientists who conducted peer review at the Cancer Prevention and Research Institute of Texas—he made it clear that the institute’s scientific review was in danger of being subverted, and that its funds were at risk of being raided by politicians.

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

“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.’”

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To the Moon

For the past three years, The Cancer Letter has been covering the U.S. government's Cancer Moonshot initiative.

We found it captivating for two reasons:

1. The moonshot focused squarely on the challenges of bringing about interoperability of data systems in patient care and elimination of silos in cancer research, and
2. Unlike the doubling of the NIH budget, the moonshot represents an effort to direct money to cancer, as opposed to the entire biomedical research.

The 2016 White House effort has been hailed as a historic milestone in modern oncology and compared to Richard Nixon's National Cancer Act.

President Barack Obama began his final year in office with two goals for cancer research: to achieve 10 years of progress within five years, and to “cure cancer as we know it.”

The reins were handed to Vice President Joe Biden in honor of his son, Beau Biden, who died from brain cancer in May 2015. The vice president pushed for systemic change, but the devil was in the details.

Focusing on breaking down what he called “siloes” in oncology, Biden wanted to rethink all the aspects of cancer research and cancer care: making electronic health records interoperable, increasing research funding, boosting participation in clinical trials, as well as streamlining data and regulatory processes.

Biden proved to be an effective power broker. Cancer groups rallied to his cause, seeking endorsements, committing to progress, and forming collaborations.

Systemic change cannot be covered piecemeal. Politics, policy, and science are inseparable in the moonshot: this is why The Cancer Letter decided to

create a comprehensive record of this effort, laying out each story with granular detail.

At 66 stories in 2016—51 written by reporter Matthew Ong—The Cancer Letter's coverage of the moonshot served as a rallying point for key players in oncology, highlighting red-button issues, and influencing national discourse on the moonshot.

In December 2016, Congress passed the 21st Century Cures Act, endorsed the “Beau Biden Cancer Moonshot” and authorized \$1.8 billion for cancer research—setting the tone for the research agenda at NCI for the next seven years, as well as the intellectual framework for informatics and data sharing in oncology.

The full series is posted here: <https://cancerletter.com/moonshot/>

Notable stories:

Obama announces Moonshot to cure cancer

President Barack Obama announced a moonshot aimed at curing cancer, a project to be led by Vice President Joe Biden.

The United States can do “so much more,” Obama said in his seventh and final State of the Union address Jan. 12. “Last year, Vice President Biden said that with a new moonshot, America can cure cancer. Last month, he worked with this Congress to give scientists at the National Institutes of Health the strongest resources they've had over a decade.

“Tonight, I'm announcing a new national effort to get it done. And because he's gone to the mat for all of us, on so many issues over the past 40 years, I'm putting

Joe in charge of mission control. For the loved ones we've all lost, for the family we can still save—let's make America the country that cures cancer once and for all.”

[Read more](#)

NCI's new genomic platform seeks to enable data sharing for Biden's moonshot

NCI is preparing to open the Genomic Data Commons, a \$20 million big data endeavor aimed at making raw genomic data publicly available.

The GDC, NCI's largest bioinformatics effort since the ill-fated caBIG, will go live June 1. The database will be interoperable and publicly available to qualified researchers. Anyone will be able to submit data for consideration.

While work on the GDC began over two years ago, the initiative is being launched at a time when leading oncology groups are positioning themselves to play a central role in the White House's moonshot initiative.

[Read more](#)

Virtual is not enough: FDA's critics call for full integration of oncology center under Biden's moonshot

The White House moonshot to accelerate progress in cancer research directs FDA to consolidate its oncology portfolio.

However, oncology insiders say the manner in which the presidential initiative will be implemented could make the difference between political balderdash and genuine improvement in FDA regulation of cancer therapies.

The entire controversy boils down to the interpretation of one word: Virtual.

[Read more](#)

CONVERSATION WITH THE CANCER LETTER

Pazdur named acting director of FDA's new cancer center

Richard Pazdur, currently the director of the FDA Office of Hematology and Oncology Products, will serve as acting director of the newly formed FDA Oncology Center of Excellence.

The exact structure, budget and staffing for the program will be determined in an ongoing process, Pazdur said to The Cancer Letter.

“Because I will be working to develop the structure of the OCE with input across all centers, it would be premature to speculate about what the ultimate structure of the OCE will be,” Pazdur said. “The framework of the OCE will evolve over time, so as not to disrupt the ongoing work in each center.”

[Read more](#)

NCI's moonshot advisory panel identifies 10 opportunities in cancer research

The Blue Ribbon Panel—a group of experts selected to identify scientific opportunities for the National Cancer Moonshot Initiative—has submitted 10 recommendations to the National Cancer Advisory Board.

The panel proposes creating tumor atlases and national networks for patient engagement, immunotherapy clinical trials, and data sharing. Recommendations also include supporting research on drug resistance, fusion oncoproteins,

symptom management, and development of cancer technologies.

“The Blue Ribbon Panel recommendations outline a set of opportunities that, if implemented, will transform our understanding of cancer and result in new opportunities to more effectively prevent and treat the disease,” the authors write.

[Read more](#)

Obama signs cures act, funding Biden's moonshot and boosting NIH, NCI, FDA budgets over 10 years

President Barack Obama Dec. 13 signed the 21st Century Cures Act, a bill that changes regulatory standards at FDA, slates additional research funds for NIH, and authorizes \$1.8 billion over seven years for Vice President Joe Biden's National Cancer Moonshot Initiative.

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Loehrer spoke with
Matthew Ong, a reporter with
The Cancer Letter.

A



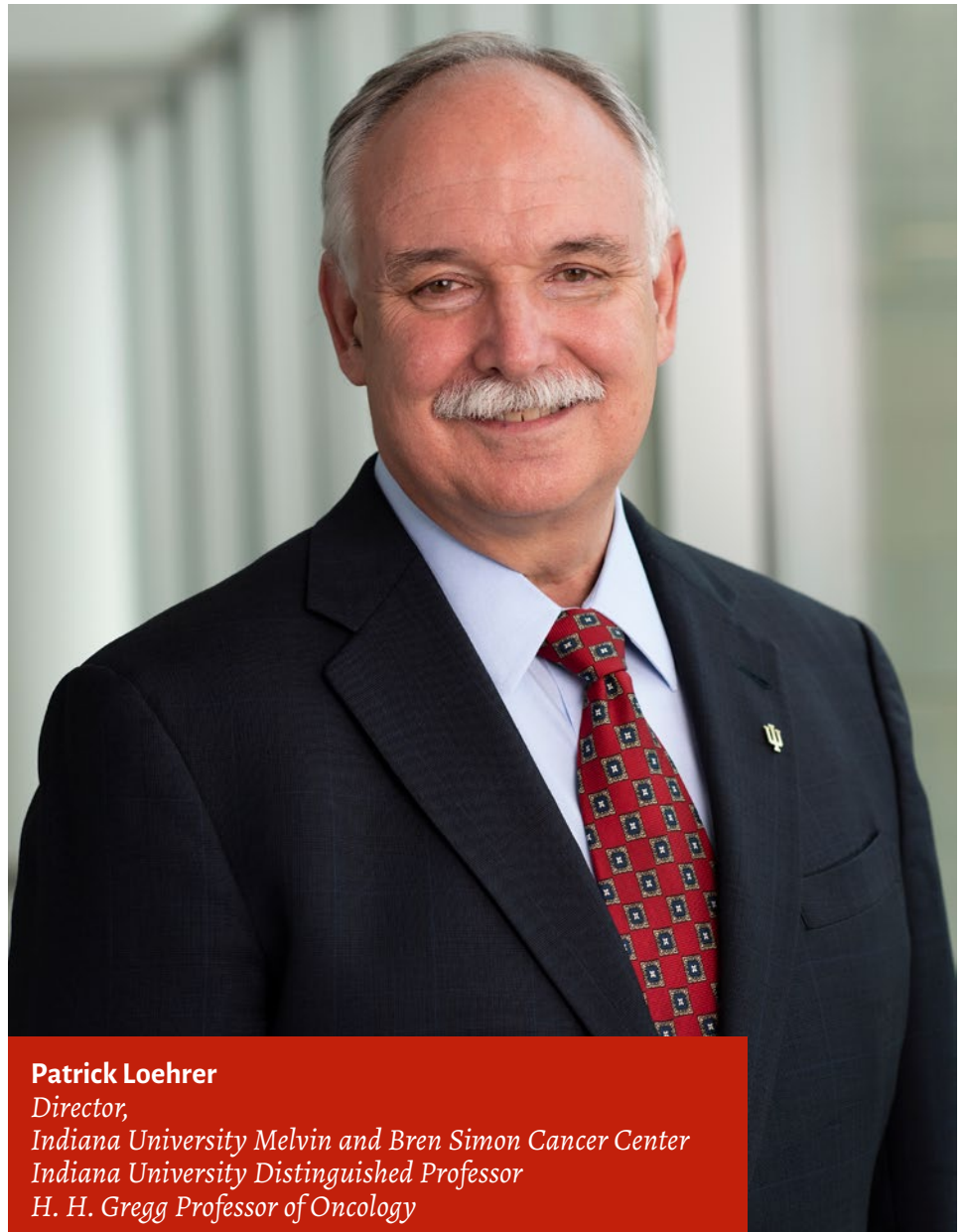
CONVERSATION WITH
THE CANCER LETTER

Indiana University Simon Cancer Center becomes 51st NCI-designated comprehensive cancer center

“

It is my hope that this designation will leverage additional support to help advance our activities to further impact the burden of cancer for all patients in Indiana and beyond.

”



Patrick Loehr

Director,

Indiana University Melvin and Bren Simon Cancer Center

Indiana University Distinguished Professor

H. H. Gregg Professor of Oncology

The Indiana University Melvin and Bren Simon Cancer Center has achieved comprehensive status—becoming the only NCI-designated comprehensive cancer center in Indiana.

“We are very proud,” said Patrick Loehrer, director of IUSCC, Indiana University Distinguished Professor, associate dean for cancer research, H. H. Gregg Professor of Oncology, and professor of medicine at IU School of Medicine. “The last time a Midwest institution received comprehensive status was 11 years ago for the University of Chicago.”

The cancer center received an “outstanding” rating by NCI reviewers and was awarded a five-year, \$13.8 million grant that supports the center’s research programs and shared facilities. That marks an increase of 43 percent from the previous five-year funding period.

NCI Acting Director Douglas Lowy announced the designation Aug. 6 at Indiana University.

“Designated cancer centers are recognized for their state-of-the-art research programs and strong commitment to delivering cutting-edge cancer treatment for patients,” Lowy said in a statement. “They are at the core of the nation’s cancer research effort.”

The comprehensive designation comes with IUSCC’s second Cancer Center Support Grant renewal, after Loehrer and his team recruited 32 faculty over the past five years and invested in the cancer center’s population science programs.

“This has been our goal since I became director. In our first venture five years ago, we thought we were close,” Loehrer said to The Cancer Letter. “Over the last several years, we have made a conscientious effort to make a stronger case for comprehensiveness.

“In terms of our total commitment to the cancer center, it has been millions

of dollars that have been involved. Our development office has brought our current total endowment close to \$100 million through philanthropic support. A large proportion lie in endowed chairs used for mid- to senior-level recruits. Institutionally, we secure about \$3 million to \$4 million a year through philanthropic efforts.”

IUSCC now has nearly 250 researchers, who altogether hold 459 grants that total more than \$60 million in external funding.

“We’re very involved with really promulgating clinical research, so we’ve had a twofold increase in our number of investigator-initiated grants,” Loehrer said. “We’ve had over a threefold increase in our multi-PI grants—a 47% increase in our NCI funding, and a 40% increase in funding per our members. Also, 17% of our publications have an impact factor greater than 10.

“I believe all of these factors contributed to convincing the site visitors that we were an outstanding institution. Our score went from 30 to 22—an eight-point improvement—of which we’re very proud. It further underscores the depth and breadth of our research.”

In addition to recognizing the center’s laboratory and clinical research, NCI reviewers said IUSCC has “very well-designed community outreach efforts to serve the needs” of the state of Indiana. This includes initiatives to increase HPV vaccination rates, as well as developing, testing and disseminating interventions to increase screenings for breast, cervical and colorectal cancer in racially diverse and rural populations in Indiana.

Also, reviewers commended the cancer center’s work in western Kenya—in partnership with Moi University, IUSCC helped fund and establish the Chandaria Cancer and Chronic Diseases Center.

“Our work in Kenya, I think, is very important,” Loehrer said. “It’s come along

extraordinarily well. When I first visited Eldoret 15 years ago, there were just maybe a couple of hundred patients seen and they had basically no standardized treatment.

“Today, we’re seeing about 800 patients a month in our cancer clinics now. We are screening about 1,000 women a month for cervical and breast cancer screening. We’ve opened a \$5.5 million cancer and chronic care building.”

Will IUSCC henceforth be known as the IU Simon Comprehensive Cancer Center?

“I love that. That’s part of the discussion—what are we going to call ourselves?” Loehrer said. “We are basically going to have an all-cancer-center retreat in the next couple of months, and we have our strategic plan in place. But we want to go over this with all of the membership and redefine our direction of where we’re headed.”

Loehrer spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: Congratulations! This makes you the only cancer center to have a comprehensive designation in Indiana, right?

Patrick Loehrer: Correct.

How long have you been working on it?

PL: This is a 20-year journey. We’ve been an NCI designated center since 1999, and I’ve been director of the cancer center for nine years. I succeeded Steve Williams, the founding director, who

unfortunately succumbed to melanoma a decade ago.

How long did it take to get the comprehensive designation?

PL: A lifetime.

I guess I'll wait another 30 years for The Comprehensive Cancer Letter...

PL: Well actually, this has been our goal since I became director. This was my second CCSG renewal. In our first venture five years ago, we thought we were close. Over the last several years, we have made a conscientious effort to make a stronger case for comprehensiveness.

What goes into making the case for the reviewers at NCI that IUSCC deserves comprehensive designation?

PL: As you know, the guidelines for comprehensiveness is to show excellence in basic, clinical and population research, and to also demonstrate inter-programmatic collaborations. And so, we focused on those areas.

Additionally, the reviewers pay particular attention to the impact of outreach and engagement especially in population science. We have, I believe, done an extraordinary job in that area. I'm very proud of our leaders of our Cancer Prevention and Control Program, Drs. Susan Rawl and Todd Skaar, and of Dr. Victoria Champion, who is the associate

director of population science and community engagement. The CPC program got an outstanding rating and we were very, very pleased.

How will the comprehensive designation empower your work and mission in Indiana?

PL: This is a continuum. So, our researchers who have been working incredibly hard will continue to do so. This designation bolsters them with a sense of confidence and much deserved respect, if you will. It acknowledges their hard work. With this designation, we now sit at the roundtable of other elite cancer centers in the country.

It is my hope that this designation will leverage additional support to help advance our activities to further impact the burden of cancer for all patients in Indiana and beyond.

How much did you have to spend to develop IUSCC into a comprehensive-level institution?

PL: That's a good question. I'm going to guess that we probably spent north of \$100,000 on this, just for the grant preparation itself. In terms of our total commitment to the cancer center, it has been millions of dollars that have been involved.

Our development office has brought our current total endowment close to \$100 million through philanthropic support. A large proportion lie in endowed chairs used for mid- to senior-level recruits. Institutionally, we secure about \$3 million to \$4 million a year through philanthropic efforts.

Did you have to engage in intensive recruitment over the past five years or more?

PL: Yes, indeed. The job of the cancer director primarily is for fundraising and for recruitment. And then at home, our job is to make the lives of our researchers better, by trying to improve their shared resources and helping with pilot projects. We recruited 32 new cancer center members over the past five years.

In that recruitment process, which disciplines did you focus on growing?

PL: We put a particular emphasis on population science, because that was one of the areas we believed would help us secure comprehensive status. About five years ago, we recruited Dr. Jiali Han to be the founding director of the Department of Epidemiology at the IU Fairbanks School of Public Health. He's a cancer epidemiologist who came from Harvard, and he brought gravitas to that position.

We also recruited Dr. Lois Travis, who has done work with survivorship, particularly in the testis population, which builds upon the work of Larry Einhorn here, who is the world's preeminent clinical researcher for testis cancer.

We have worked on developing the pharmacogenomics program. We worked with the university to create a university-wide Precision Health Initiative (PHI), which is a \$120 million investment towards precision medicine encompassing cancer, neurodegenerative disease and regenerative medicine. PHI is the first recipient of the IU Grand Challenges program.

Within the PHI, we have prospective cohorts for triple negative breast cancer, which is one of the most common cancers in Indiana, for multiple myeloma, in which we have a very strong myeloma program, and for pediatric sarcomas. The PHI has several pillars, which includes Chemical Biology and Biotherapeutics; Genomic Medicine; Data and Informatics; and Cell, Gene and Immune Therapy.

The key elements of the Precision Health Initiative are led by researchers from the cancer center, which is now actually integrated into the fabric of the university's precision medicine program. Obviously, these themes have great ties with cancer, but precision medicine fits across other diseases like Alzheimer's, diabetes, and other non-communicable chronic diseases—our efforts have helped shape the direction for the university.

What sets IU Simon Cancer Center apart from other cancer centers in the region?

PL: There are a number of areas that I think the IU Simon Cancer Center is known for. Obviously, our clinical work has been incredibly strong. Dr. Larry Einhorn and his apostles over the last several decades have basically transformed the most common cause of death in young men—testicular cancer.

In the 1970s, it was about a 5% cure rate, and now it's 95%, and it's because of a plethora of trials that he has led or influenced. This provided for a strong platform for clinical research. In many ways, we are the cradle of cooperative groups. In the early 1980s, we created a research organization called the Hoosier Oncology Group, now known as the Hoosier Cancer Research Network (HCRN), which has more than 200 sites around the globe. This initially was set

up with an academic community partnership that has now mostly consisted of linkages with academic centers.

Together with Steve Rosen [then director of the cancer center at Northwestern], we established the Big Ten Cancer Research Consortium, which uses the HCRN as its administrative source. We have 13 of the 14 Big Ten institutions as members. The Big Ten has the largest number of NCI-designated cancer centers of any athletic conference in the country, and it focuses on largely the Midwest—cancer centers working together to do clinical and translational research.

We've also created the AMPATH Oncology Program, which links numerous North American institutions with Moi University and Moi Teaching Referral Hospital in western Kenya. And this is considered by many a model for global oncology. So, from a clinical research perspective, I think we're incredibly strong.

We've had a number of areas of innovation—Dr. Wade Clapp and his colleagues have the first and only pathway driven in pediatrics in the country focused on NF1 and RAS signaling. We have the only normal tissue bank for breast tissue in the world, the Komen Tissue Bank, which has well over 5,000 specimens.

Hal Broxmeyer, one of our researchers, is, as far as I know, the first and only PhD to be president of ASH. He was a pioneer in umbilical cord transplant and has spent a career researching stem cells, in particularly hematopoiesis. He most recently has underscored the importance of hypoxia in the collection and analysis of in-vivo studies. Everything that we have studied with pathways—in terms of what we study in the laboratory—may be turned upside down, because we have not been previously studying them in the physiologic conditions of hypoxia, and he's leading that effort.

One final point is our work in symptom science and how we have integrated precision medicine. Not only do we have a precision medicine tumor board that serves the university, but we have several outreach sites now in the rural parts of the state in which they call in on a weekly basis and we discuss this, but we've also used pharmacogenomics to help us understand the selective toxicity of patients with these drugs.

Dr. Bryan Schneider is leading the first trial looking at pharmacogenomic markers that help predict the neurotoxicity of African American women using taxanes and breast cancer. This is a trial that's just opened up in the ECOG-ACRIN Cancer Research Group. It's the first trial of its kind, focusing in on understanding why African Americans may have greater toxicity with paclitaxel, but also seeing whether an alternative taxane (i.e. taxotere) can actually have improved outcomes in these patients because of better tolerability and compliance.

We've chatted about this previously—the NCI reviewers, obviously, commended IUSCC for its work in Kenya. What did the reviewers say?

PL: They very much praised our work, because of the vision of our cancer center to decrease the burden of cancer in Indiana, but also beyond. Our work in Kenya, I think, is very important.

I personally would love to see global oncology become much more woven into the fabric of comprehensive cancer centers. The vast majority of cancer centers in the country are involved in global research, to some degree.

To the best of my knowledge, there is not currently a cancer center in the country now that has a scientific program focused on global oncology in the

NCI Core Grant. But all of us are doing work in those areas, so my hope is that it will help serve as a stimulus to make this work much more common and cohesive with the cancer centers around the country.

What's the latest from AM-PATH at Eldoret in Kenya? How is the program coming along?

PL: It's come along extraordinarily well. When I first visited Eldoret 15 years ago, there were just maybe a couple of hundred patients seen and they had basically no standardized treatment. Today, we're seeing about 800 patients a month in our cancer clinics now. We are screening about 1,000 women a month for cervical and breast cancer screening. We've opened a \$5.5 million cancer and chronic care building.

And I'm delighted to say that we now finally have approval from the government of Kenya and the International Atomic Energy Agency, so we're expecting radiation therapy equipment to be delivered this fall with the first patient treated either the end of this year or the beginning of next year.

That's been something I've been looking forward to for the past 15 years. And this will be the first radiation unit serving the public sector in western Kenya, which has a catchment area of around 20 million people, so we're very excited about that.

What are your plans and next steps for IUSCC? Or, should I say, IUSCCC?

PL: I love that. That's part of the discussion—what are we going to call

ourselves? There are formal announcements of this to the public today, on Aug. 6. Dr. Douglas Lowy, who's the acting director of the NCI, is here to make the announcement. We're very excited about that.

We are basically going to have an all-cancer-center retreat in the next couple of months, and we have our strategic plan in place. But we want to go over this with all of the membership and redefine our direction of where we're headed.

I think, again, we're very keen to focus on a number of different areas, including building on prevention, early detection, and population health, and focusing on biology to bedside research—again, our theme of precision medicine and not only with the understanding of the biology of tumors, but also through pharmacogenomics. And finally, a big pillar for us is health care disparities and survivorship and symptom science.

Were there any specific improvements—in NCI grant funding, perhaps—that led to an increase in your score?

PL: I'm glad you asked that question. We're very involved with really promulgating clinical research, so we've had a twofold increase in our number of investigator-initiated grants. We've had over a threefold increase in our multi-PI grants—a 47% increase in our NCI funding, and a 40% increase in funding per our members. Also, 17% of our publications have an impact factor greater than 10.

I believe all of these factors contributed to convincing the site visitors that we were an outstanding institution. Our score went from 30 to 22—an eight-point improvement—of which we're

very proud. It further underscores the depth and breadth of our research.

Right, which makes you the 51st NCI-designated comprehensive cancer center.

PL: Yes. We are very proud. The last time a Midwest institution received comprehensive status was 11 years ago for the University of Chicago.

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THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

Measures to improve clinical trial enrollment: Marshfield Clinic Cancer Care and research approach

Part II of a two-part series



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It is estimated that, each year, as few as 2–3% of cancer patients enter clinical trials. In [part I](#) of this series, we discussed four key barriers to participation: physician barriers, protocol barriers, research team barriers, and insurance barriers. In part II, we will look at solutions to these barriers and how to implement them in the clinical setting.

Physician engagement

The biggest physician barriers to research participation are lack of training and inadequate time and compensation^{1,2}. Since most health care systems measure physician productivity by number of patient appointments, medical procedures, and relative value units (RVUs), the additional time needs for research training and participation are inherently discouraged^{3,4}. There is no additional compensation offered for the increased workload required of physicians who want to enroll patients in clinical trials.

There are multiple engagement strategies that have been implemented by Marshfield Clinic in an effort to improve physician participation and subject enrollment. A citizenship and engagement matrix has been developed at Marshfield Clinic that defines physician expectations in research. The matrix includes research meeting attendance, enrollment of participants in clinical trials, and taking on the role of principal investigator as new trials are opened. Defining these expectations helps oncologists to manage their time and encourages improved communication with clinical research staff⁵.

Other strategies include hosting a robust biweekly study selection feasibility meeting, sharing the feasibility meeting facilitator role and working with non-oncology service line leadership to ensure ongoing support for clinical trials. At Marshfield Clinic, oncologists take turns presenting potential studies

to their colleagues. This rotation promotes engagement and often sparks insightful discussion. The selection process is further enhanced when varying experiences and perspectives are combined in the decision-making process.

In the same spirit, the oncologists are reaching out to the service line leaders to facilitate better working relationships among ancillary departments. This early-stage collaboration is essential when opening trials that require involvement of various specialties.

The majority of practicing physicians have expressed their desire to utilize clinical trials as treatment options^{3,4}. Additionally, these physicians are basing their treatment decisions on evidence gained through clinical trials. Making clinical trial participation accessible in the clinic setting has great potential to improve patient outcomes.

One method of accomplishing this goal is physically relocating research staff in the clinical area of the health system. More frequent face-to-face interaction between oncologists, nurses, and research staff results in increased awareness of available clinical trials and increased patient contact with research staff.

Protocol solutions

There is a discrepancy between the needs of the writers and administrators of research protocols and those of the physicians who are relied upon to enroll patients to the protocols^{6,7}. Maintaining the integrity of the data results in strict eligibility criteria for many treatment trials makes it difficult, at times, to enroll realistic patient populations. Study chairs must consider the possibility of allowing physicians some discretion when enrolling patients. The data is not truly pragmatic if it is gathered entirely from patients who do not fit the usual profile of the disease being treated.

The selection process utilized by a clinic when deciding which clinical trials to open requires thoughtful consideration and realistic feasibility analysis. Ensuring the clinic has an appropriate patient population that may meet the eligibility criteria is often challenging, yet paramount to the success of the trial.

In addition, sites should consider conducting a formal cost analysis that considers all resources that may be needed and the staff workload to successfully execute the study. It is paramount to not only consider the patient care costs, but to include the administrative costs. It is also important to note that highly complex protocols or protocols that focus on rarer cancers may not enroll many patients, but are often opened for orphan diseases or specific patient population.

To minimize the administrative barriers, health care systems should consider the use of Central Institutional Review Boards (CIRB) whenever possible. The National Cancer Institute's CIRB is an example of a well-run CIRB and allows for the streamlined review of NCORP studies.

In addition, research sites should have well-documented processes for opening studies. As in many cases in health care, a one-size fits all approach will not work since administrative processes must be scalable to fit the needs of the study. Without proper planning, small obstacles can completely stall the opening of a study.

During all phases of the study opening process, study teams need to be on the vigilant lookout for software and websites that may require I.S. Security Review, unique study training requirements, or special drug or specimen storage requirements. It is important for the oncology research team to have a strong working relationship with IT/IS, Legal, Compliance/Privacy, Lab and Pharmacy.

The importance of regular communication of new protocols cannot be

overemphasized and communication methods must go beyond email. Principal Investigators should provide study updates at department and/or service line meetings. Study enrollment progress and goals should be reported along with enrollment challenges.

In addition, health care systems should consider the use of technology to increase clinical trial enrollment. It is common for NCORPs, and other large oncology research centers, to have hundreds of active protocols. Tools must be developed or purchased to streamline the identification of potentially eligible study participants and, likewise, identify protocols that match a patient's disease.

Research team solutions

Building the right team model for your health care system is critical to the long-term success of an oncology clinical trials program. In the past, many oncology research groups have chosen to develop disease-specific teams to implement clinical trials. While this method is suitable to large clinics where physicians treat only one type of cancer, it is not cost effective in smaller health systems and most community practices, where provider disease specialization is not possible. Smaller systems frequently require study teams to be based on geographical location. This means that research team members must receive education and training in all types of cancer.

Many oncology clinics have utilized a disease-based model in research, which has resulted in multiple "silos" of staff rather than a cohesive group. Shifting to a team-based model has resulted in increased clinical trial enrollments at Marshfield Clinic. Oncologists are partnered with a research nurse and coordinator who implement and manage any trials that are pertinent to that oncologist's patients, regardless of diagnosis.

In addition, new research support positions have been created, which allows more time for nurses and coordinators to screen and meet with patients. A key position is a dedicated project manager for clinical trials. This role facilitates the opening of new clinical trials in a timely manner, ensuring that patients have a variety of studies available to them.



Since most health care systems measure physician productivity by number of patient appointments, medical procedures, and relative value units (RVUs), the additional time needs for research training and participation are inherently discouraged.



Traditionally, education and training of research teams have taken the form of attending conferences hosted by research organizations⁸. While there is some benefit to attending industry conferences, it may not be the best way to provide education. There may be more benefit to research staff to attend small classes or clinics that focus on a related group of topics. This method allows for greater detail in the information disseminated and encourages peer discussions.

At Marshfield Clinic, research staff are encouraged to attend NCORP research base meetings and to serve on the committees associated with those research bases. These activities expose team members to researchers from many regions of the country and, at times, globally. The insights gained in these relationships assist Marshfield Clinic staff and management in their efforts to develop best practices in the clinical trial program.

Finally, never underestimate the power of positivity. Research staff at Marshfield Clinic were asked to send a group email to the research team and oncologists each time a new patient is enrolled to a clinical trial. All members of the team then have the opportunity to reply with positive reinforcement and encouragement.

This practice has resulted in a change in the culture of the research department to one in which staff is engaged and supportive of one another, as well as invoked a friendly competition among teams.

Insurance barriers

One of the most frustrating aspects of cancer treatment is the constant battle with insurance companies over treatment reimbursement and clinical trial participation in general. Most federally funded reimbursement programs allow patients to participate in clinical trials, however, there are differences among states in the interpretation of these clauses^{1,9}. Federally funded programs should be consistent throughout the country.

Private insurance companies have long denied patients participation in clinical trials based on the potential for adverse

events with investigational products¹⁰. During treatment trials, investigational drugs or devices are typically provided by the research organization. Therefore, the insurance companies are only being asked to pay for standard of care treatment.

Since there is no way to accurately predict which patients will have adverse reactions to any medication, it is unreasonable to assume that adverse events increase in investigational drugs by the time clinical trials reach phase II and III. Perhaps legislation to close this loophole is necessary in order to provide patients with more treatment options.

Marshfield Clinic is constantly reviewing and revising their prior authorization process. After an initial investigation into the desired components and wording of prior authorization submissions, staff were trained on how to submit prior authorizations and follow up, as needed, based on the response from the insurance company.

Providing accurate information and appropriate details concerning the clinical trial, patient condition, and rationale for treatment decisions is key to the approval of the prior authorization. However, even with a well-documented process, the oncology team is relying on the Prior Authorization Team to ensure the request receives the appropriate approvals.

In many cases, insurance companies will broadly deny all requests for participation without looking at the study. The only way to resolve this is through appealing the decision, which unfortunately is costly in staff time and delays the patients' treatment. It is imperative that health care systems fight for the inclusion of clinical trials in plans they manage or own.

While there are many barriers to enrolling patients in clinical research trials, there are solutions out there. It is im-

perative that traditional practices at the administrative, physician, and research staff levels be evaluated for their continued effectiveness. It is necessary that insurance practices be standardized so that greater coverage is available to all oncology patients.

As medical advancements continue at a rapid pace, physicians, health systems, and insurance companies must be willing to adapt practices to accommodate patients' treatment needs.

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