Bert Vogelstein

LUDWIG WORKING FROM HOME

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The cancer detector

IN EARLY 2020, BERT VOGELSTEIN watched with growing dread as the novel coronavirus infection (COVID-19) that emerged from China swept across the globe and infiltrated all 50 states of the U.S. By early April, COVID-19 had surpassed heart disease and cancer as the country's leading cause of death per day and brought the nation's economy to a standstill. But Vogelstein's distress turned to resolve when he realized that he and his team were in a unique position to help. A drug they had previously found might quell a dangerous over-reaction of the immune response known as a "cytokine storm" could potentially prevent the same condition in people with severe COVID-19.

"We thought," says Vogelstein, "'This is a way our lab can contribute right now. That's what we should be focusing on.'"

Though infectious disease is not quite Vogelstein's bailiwick, the proposed intervention bore some similarity to his team's primary focus these days: secondary cancer prevention—the application of cancer genomics to catching cancers early, before they spread and turn deadly. To that end, the team he leads as Co-director of Ludwig Johns Hopkins has in recent years designed and evaluated minimally invasive tests (or "liquid biopsies") to screen patients for multiple undiagnosed malignancies. In 2019, they reported the advantages of using one such test to screen colorectal cancer patients for disease recurrence; In April this year, they published the results of the first clinical evaluation in the general population of a blood-based screening test for multiple cancers. Now Vogelstein hopes to similarly nip in the bud a potentially lethal complication of COVID-19. "What we're trying

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Preempting a storm

Cytokines are small signaling proteins produced by immune and other cells to put the body on high defensive alert, usually in response to infections. In some instances, the immune system fails to switch off this protective response even after the infection has been brought under control, and instead pumps out more and more cytokines. Their unbridled release causes intense, systemic inflammation and other corrosive physiological responses that can devastate internal organs and cause often lethal pneumonia. The complication is associated with a variety of conditions, including transplant rejection, certain cancer immunotherapies, bacterial infections and viral diseases such as influenza, SARS—and now COVID-19.

"It's not the virus destroying the lungs, but the body's reaction through these cytokines that is too much," explains Vogelstein. "It's too vigorous a response, and that ends up causing more problems than the infection itself."

A study Vogelstein led with Ludwig Johns Hopkins researchers Vernea Staedtke and Shibin Zhou and published in *Nature* in 2018 described a series of cascading events mediated by immune cells that precipitated such storms. That study showed that drugs known as alpha-1AR antagonists, including the cheap and widely available drug prazosin, could squelch cytokine storms in mice. To assess the applicability of those findings to humans, Vogelstein's team and their colleagues did a retrospective analysis of patients hospitalized for acute respiratory distress (ARD), which is often caused by cytokine storms in COVID-19 and other diseases. It revealed that men diagnosed with ARD who had been taking prazosin had a 36% lower risk of requiring a ventilator or dying than those who had not. In May, Vogelstein and his colleagues began a clinical trial to test whether the drug might also be effective in preventing cytokine storms when given preemptively to COVID-19 patients.

Know thy enemy

None of this is to say Vogelstein has lost sight of his main quarry, which for the past four decades has been cancer. When he was a young medical student in the late 1970s, the causes of malignancies were largely a mystery. "Cancer was basically a black box," he says. "It was like an alien that came from outer space and invaded people's bodies."

During a pediatrics internship in 1974, Vogelstein encountered a family whose four-year-old daughter had leukemia. Vogelstein had no answer when the father asked him, "Why did this happen to my beautiful little girl?" The question haunted Vogelstein and factored into his decision to switch from

Vogelstein with Ludwig Johns Hopkins Co-director Ken Kinzler.

Photo by Flynn Larsen

pediatrics to full-time research. Thanks in good measure to his own efforts, Vogelstein now has some answers.

In fact, we now know more about the root causes of cancer than we do about many other diseases. "That's been a giant first step," Vogelstein says. "Yet, we're still unable to prevent cancer or cure it to the degree that we'd like. Eventually, it'll come — the translation to patient benefit. But in the intervening years, it's frustrating that you understand so much about the disease but can't really do much about it for most patients."

Cancer is primarily caused by the sequential accumulation of mutations in cells. "Obviously, there are a bunch of other factors involved, but, in essence, cancer is a genetic disease," Vogelstein says. "If you don't have mutations, you're not going to have a cancer."

Much of our modern understanding of cancer can be traced back to discoveries made in Vogelstein's lab, beginning with his methodical description of how mutations accumulate to drive the progression of colorectal cancers (CRCs). In 1989, his group showed that a gene called p53 was mutated in CRCs, and many other tumors besides. This study and their other work on the biochemistry of p53 led to the surprising discovery that it is not a tumor promotor, or oncogene, but rather a tumor *suppressor* gene whose protective function is disabled by mutations.

Over the next several years, Vogelstein's lab implicated many other genes and mutations

in not only colon cancer, but other cancers as well, including those of the breast and pancreas. Step by step, he and Kenneth W. Kinzler, who co-directs the Ludwig Center at Johns Hopkins, were slowly prying open the black box and laying the foundations for a new and deeper understanding of the origins of cancer and its progression.

In 2006, Vogelstein and Kinzler published the first comprehensive profile of all the expressed genes, or exome, in breast and colorectal cancers. It was a bold undertaking that some had considered impossible. This study, published in *Science*, and others revealed several new cancer genes, including PIK3CA, which, like P53, is one of the most commonly mutated genes across cancers. His team would go on to sequence the genomes of scores of other cancers, a feat that was significantly bolstered by Ludwig support following the establishment of the Hopkins Center in 2006.

Vogelstein said his lab didn't start out with such an audacious plan in mind—it was just that as their experience grew, so too did their ambition and confidence. "We started with one gene at a time, sequencing it in a group of cancers," Vogelstein says. "Then we continued that with sequencing small groups of genes. We followed that with sequencing classes of genes. Then we said, 'Well, now that we know how to do this, let's go the extra mile. Why not look at all 20,000 genes?' Remarkably, several trainees in our lab concurred that this was not crazy. In retrospect, it was totally crazy."

A yen for translation

When it comes to cancer, Vogelstein has never been satisfied with just knowing something about why it develops and how it spreads. He's had another goal in mind from the start. "One way to look at it is we were not driven by intellectual curiosity. A lot of scientists are. We were not," he says. "We were interested in trying to do something to reduce morbidity and mortality from cancer. The basic research that we did was generally geared towards understanding enough so that we could formulate reasonable hypotheses and reasonable strategies to attack the disease. This line of thought and this view was integral right from the beginning."

He attributes his way of thinking in part to his time as a pediatrician, when he first became aware that the most dramatic improvements in child health came not from treatments but from vaccinations and other public-health measures. "So, even though treating cancers is extremely important and worthwhile, in the end analysis I thought the best way to reduce cancer deaths would be through primary or secondary prevention," Vogelstein says.

In the early 1990s, he and Kinzler began focusing in earnest on transforming the genetic alterations they had discovered into tools for detecting cancers early. "Before that time, the cancer biomarkers that were used to follow patients with cancer were all relatively nonspecific. They were associated with cancer, but they weren't causative," Vogelstein explains. "We thought that the mutations themselves—these mutations that are the proximate cause of cancer—could actually be used as biomarkers to detect cancer early because they're exquisitely specific."

Their first major success in this area came in 1991 and 1992, when Vogelstein and his colleagues published papers showing that mutations in bladder cancers can be detected in the urine of patients with the disease and that colon cancer mutations are similarly detectable in the stool. This line of inquiry culminated in the first FDA-approved genetic test for the early detection of cancer, called Cologuard. "That was approved about five years ago and it's estimated that 40 million Americans will take that test over the next decade," Vogelstein says.

As a first step toward improving secondary

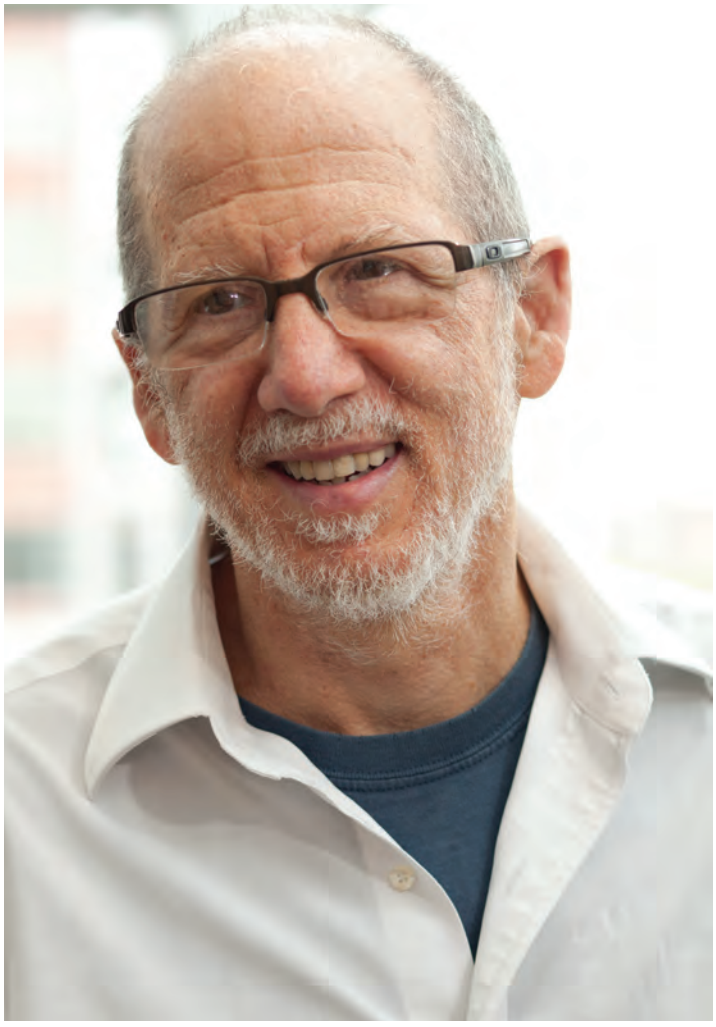

Photo by Flynn Larsen

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prevention, he and his colleagues focused on detecting cancer *recurrences* in patients. "Technically, that's actually much less challenging than trying to detect cancers in completely asymptomatic people not known to have cancer," Vogelstein says. Joining a five-year, $10 million cancer prevention initiative launched by Ludwig and the Conrad N. Hilton Foundation, the Ludwig Johns Hopkins team examined the use of liquid biopsies to monitor CRC patients for such recurrences, working in partnership with Ludwig-supported researchers in Australia.

In two studies published in 2019 in *JAMA Oncology*, a collaboration between the labs of Vogelstein, Kinzler, and Peter Gibbs, a Ludwig alumnus in Melbourne, showed that circulating tumor DNA (ctDNA) in the blood of cancer patients could be used to not only detect colorectal cancer recurrence earlier but also as a real-time monitor of the effectiveness of chemotherapy given after surgery for cancer. "Peter told us that in colon cancer, if you treat people with micro-metastatic disease too small to be seen on X-rays, you can actually cure nearly 50 percent of them even though their tumors have already metastasized," Vogelstein says.

Taking the leap

In the late 1990s, Vogelstein and Kinzler developed a new cancer mutation screening technology called digital PCR for the

detection of DNA shed by colon tumors. "Since then, we've been looking to extend that technique so we could look at more molecules," says Vogelstein. "Back then, we could only look at a few hundred at a time, but by the early 2000s, our lab had developed a way to look at millions at a time with a technique called BEAMing."

Building on that technology, the team published two papers in *Science Translational Medicine* in 2013 and 2014 demonstrating that they could detect the presence of most uterine tumors and a third of ovarian tumors in Pap smears, as well as many other tumors in ctDNA. They subsequently launched PapGene, a Baltimore-based biotech company established to develop liquid biopsies. In 2019, PapGene was acquired by Third Rock Ventures and incorporated into a new company named Thrive Earlier Detection, which raised $110 million in Series A financing. Thrive's first priority is to further develop the most ambitious iteration of the Ludwig Johns Hopkins team's liquid biopsy technologies, CancerSEEK. Initially reported in *Science* in 2018, CancerSEEK evaluated the levels of eight proteins and a variety of mutations in DNA shed into the blood by tumors to detect malignancies that account for more than 60% of cancer deaths in the U.S.

"Support from Ludwig has been instrumental to our lab's success for more than a decade," says Vogelstein. "It has permitted us the freedom to pursue our ideas in an unfettered way. Many of these ideas are off the beaten path, some might even have seemed crazy at the time they were formulated. But occasionally, one pans out and has the potential to mitigate suffering and deaths from cancer in a new way. The freedom to pursue those ideas through focused research is precious—perhaps the greatest gift a foundation can provide to its scientific staff."

In April 2020, the Ludwig Johns Hopkins team, working with the Geisinger Health System and their colleagues at Thrive, published the results of the first major test of their cancer-screening technology, a clinical trial involving nearly 10,000 women between the ages of 65 and 75. "It was the first prospective interventional trial of a multi-cancer blood test in individuals who were not known to have cancer," says Vogelstein.

Published in *Science*, the study found that the liquid biopsy more than doubled the number of cancers detected when added to traditional screening, safely detecting 26 previously undetected malignancies. Most of the cancers were localized by diagnostic PET-CT, and 12 could be surgically removed with the intent to cure. Combining the blood test with standard of care screening such as mammography and colonoscopy improved the sensitivity of detecting breast, colon and lung tumors from 47% to 71%. The blood test was also able to detect seven cancers for which screening tests do not exist, such as thyroid, kidney, and ovarian cancers. More than half of the cancers that occurred during the study were detected by either blood testing or traditional screening.

Vogelstein says the launch of Thrive Earlier Detection is a "giant leap forward" toward his dream of making cancer screening a routine part of annual medical exams—but there's more work to be done. "The dream will only be realized when the tests can be made available to the public outside of a research study, which will need regulatory approval. It will require people actually getting the test and the demonstration that it actually helps them—something we and our colleagues at Thrive are diligently working on. Until then, it's research," Vogelstein says. "The vision that Ken and I had no longer seems like science fiction, but we haven't landed on the moon yet."

Photo by Flynn Larsen