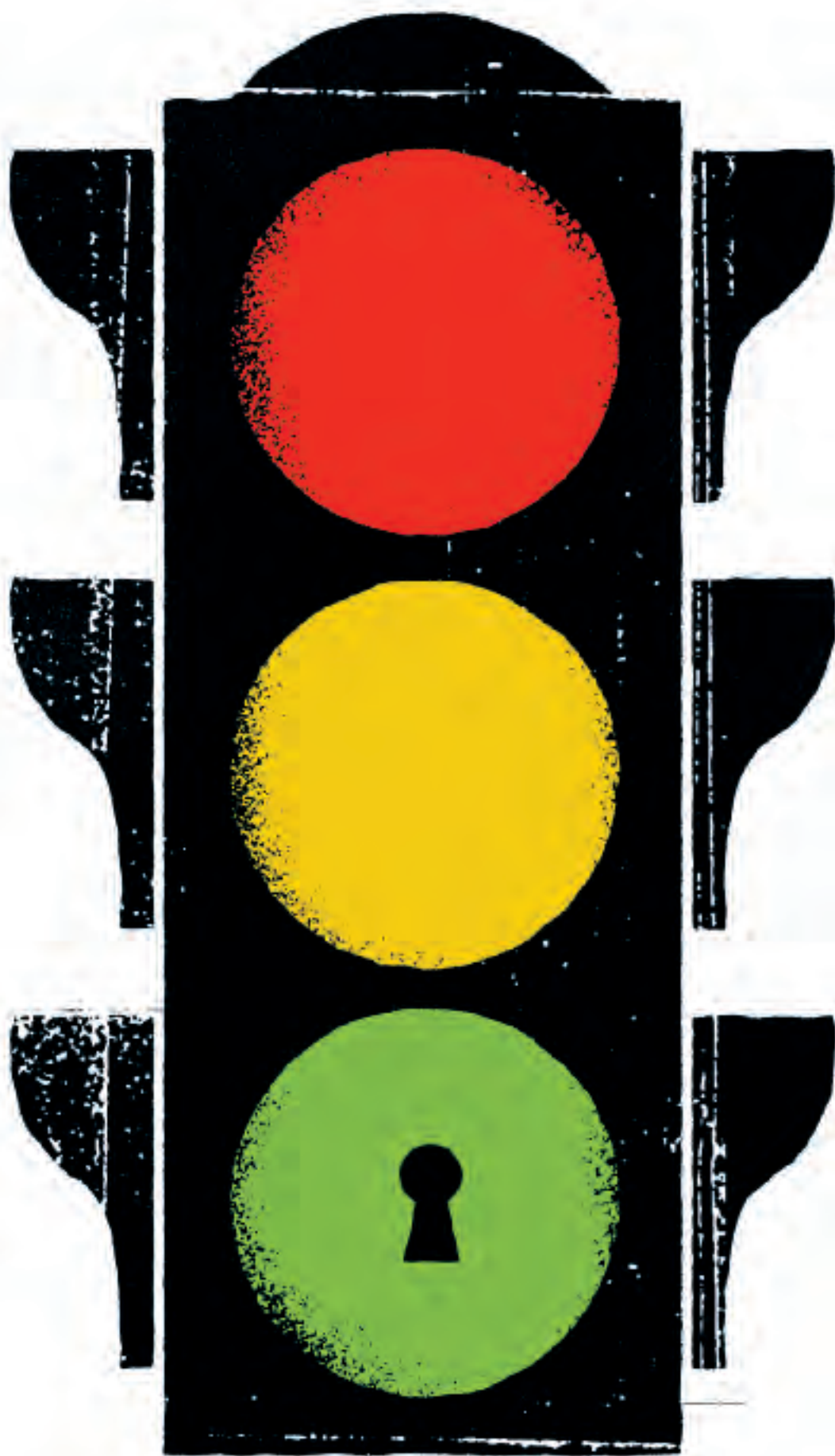


PROCEED WITH CAUTION

FOR EACH MAN WITH
PROSTATE CANCER,
WHICH TREATMENT GETS
THE GREEN LIGHT?
BY SARAH C.P. WILLIAMS
ILLUSTRATION BY
THE HEADS OF STATE



ON VALENTINE'S DAY

2001, Jim Foley learned he had prostate cancer. Suddenly, the 56-year-old engineer from a New York City suburb faced a daunting dilemma: What next? Though he can explain the ins and outs of compressors and steam turbines effortlessly, Foley was clueless about prostate cancer. He knew no one with the disease, he says, and was unprepared for the lack of clarity his diagnosis—and prognosis—offered.

Of the roughly 190,000 men diagnosed with prostate cancer in the United States every year, many have slow-growing tumors that are unlikely to spread. Without treatment, men with nonaggressive tumors will likely live for decades and eventually die of something unrelated. But others will have cancers that spread to lymph nodes and bones. Predicting, on initial diagnosis, which tumors are deadly is a matter of guesswork for physicians.

The blood test used to screen men for prostate cancer—called PSA because it measures the level of prostate-specific

antigen—is little help in predicting how a tumor will progress. PSA levels can be just as high in men with slow-growing cancers, or no cancer at all, as in men with aggressive tumors. Because doctors tend to err on the side of caution, patients with nonaggressive tumors are often treated the same as those with more high-risk cancers. As a result, the value of the PSA test has long been debated.

“It’s a major clinical challenge,” says HHMI investigator Arul Chinnaiyan, at the University of Michigan Medical School. “We end up overtreating because physicians can’t tell the difference between these aggressive tumors and not-so-aggressive ones.”

With Chinnaiyan’s recent discovery of a gene that drives more than half of prostate cancers, however, and work by other HHMI investigators, physicians may soon have new tools to predict the course of prostate cancer and identify the most aggressive tumors.

They’re developing new treatments, too, and Foley can attest to their success: In 2008, during a recurrence of his cancer, he was one of the first patients to enroll in a clinical trial for a novel prostate cancer drug developed in part by HHMI investigator Charles Sawyers at Memorial Sloan-Kettering Cancer Center (MSKCC). Today, Foley’s cancer is in remission. When he thinks “What next?” he’s planning his retirement or his next trip to Virginia or Iowa to visit his daugh-

ters and grandkids, not deciding how to treat his cancer.

LOTS OF OPINIONS

Foley’s diagnosis came after an annual PSA test, which men are encouraged to undergo beginning at age 50. A PSA of up to 4 (measured in nanograms per milliliter) is generally considered normal. Higher levels can be okay too, though—it varies from person to person. The rate at which PSA changes is often more indicative than its level. The red flag for Foley came when his PSA rose from 4 one year to 10 the next.

In December 2008, the *New England Journal of Medicine* presented the case of a 63-year-old man with rising PSA scores and polled more than 3,000 doctors on how they would treat him. They were split three ways: about 39 percent said they would remove the patient’s prostate; about 33 percent would treat the tumor with radiation; and about 29 percent would wait and monitor the patient’s PSA levels.

With this lack of consensus, the decision often comes down to a gut reaction by an informed patient. Foley and his doctors—including oncologist Michael Morris at MSKCC, who became his primary prostate cancer doctor—weighed the options after considering his PSA levels, his age, general health, and MRI scans.

For Foley, an MRI technique considered experimental at the time revealed that his cancer had already spread to his

seminal vesicles, so a course of radiation and hormone therapy seemed the best option. In his case, PSA was a valid warning sign that caught his cancer before it spread even further. PSA and scans leave others in the dark as to whether their cancer is growing and how aggressive treatment should be. There is a lack of useful diagnostic tests to classify a prostate cancer. In the near future, though, genetic analysis of tumors may fill this void.

Chinnaiyan's team studies genes that, when rearranged incorrectly, cause prostate cancer. His research relies on a large bank of prostate cancer tissue samples at the University of Michigan. Using microarrays—a technology that can quickly analyze the activity of massive numbers of

genes in a sample—Chinnaiyan has looked at the molecular signatures of hundreds of prostate cancers. Traditionally, researchers sort through such data by looking for genes expressed in all the

cancers. But Chinnaiyan didn't think that was the best approach. Instead, he looked for genes that were expressed at high levels in some, but not necessarily all, of the cancers. He calls these genes "outliers" and reasons that typical averaging techniques would cause scientists to miss them.

His analysis paid off—it found parts of two normal genes that had been combined into one single cancer-causing "fusion gene" in about half the tumors he analyzed. One of the normal genes was in a family of transcription factors; the proteins produced by these genes bind directly to DNA and can activate cancer-causing genes that are turned off in a healthy prostate. This "ETS transcription factor" was fused with the on-off switch from an unrelated prostate gene—one regulated by male hormones. So whenever this fusion gene came into contact with testosterone, a constant presence in the prostate, the ETS transcription factor was switched on and went into action turning on other cancer-causing genes.

Chinnaiyan's work was published in 2005; his fusion gene was the first to be linked to prostate cancer, and the discovery drew wide acclaim from the prostate cancer community. Chinnaiyan believes the fusion gene could lead to treatments and, even sooner, to new ways



JIM FOLEY (LEFT) HAS BATTLED PROSTATE CANCER SEVERAL TIMES WITH THE HELP OF ONCOLOGIST MICHAEL MORRIS (RIGHT) AND A CLINICAL TRIAL THAT'S HAD HIM IN REMISSION MORE THAN A YEAR.

PROSTATE PIRATES

Like the liver and just a few other organs, the prostate gland has the ability to regenerate itself. In castrated mice, the prostate shrinks to a tenth of its original size. But giving the mice testosterone restores the prostate. HHMI investigator Owen Witte, at the University of California, Los Angeles, thinks some prostate cancers may be co-opting the gland's regenerative properties. ¶ *"The majority of cells in the gland require testosterone for their maintenance but there is a group of cells that can survive in the absence of testosterone and re-grow the whole organ,"* explains Witte. He has created numerous prostate cancer cell lines and mouse models that can report what genes and proteins are activated when prostate cancers grow. With the help of these tools, he is studying what role stem cell-related proteins in the prostate might play in cancers. He has found one protein—dubbed prostate stem cell antigen—in higher levels in prostate cancers, a hint that cancers could be pirating the prostate regeneration system. By understanding how different molecules interact at different points during prostate cancer growth, Witte hopes his research will lead to treatments to stop the tumors at their earliest stages. —S.W.



THERE'S GOT TO BE SOMETHING BETTER THAN PSA, AND HHMI INVESTIGATORS (LEFT TO RIGHT) DANIEL A. HABER, ARUL M. CHINNAIYAN, TODD R. GOLUB, CHARLES L. SAWYERS, HAVE SET THEIR SIGHTS ON FINDING IT.

to detect and track prostate cancer if the gene can be monitored in blood or urine.

He has already found a related indicator in urine, a metabolite called sarcosine that's elevated when prostate cancer exists. According to Chinnaiyan, one ETS fusion gene boosts sarcosine production. Screening men's urine for sarcosine levels, he says, could be one way to monitor disease, alongside or instead of blood tests for PSA.

Screening men's blood for genetic markers of prostate cancer—which could potentially differentiate cancer types, unlike PSA—is also on the horizon. HHMI investigator Daniel Haber, of Massachusetts General Hospital, thinks blood holds clues not only for prostate cancer but also for most other cancers. Haber wanted to study genetic mutations in various cancers and, because repeated biopsies of tumors are often invasive and costly, he turned to an emerging technology to detect rare cancer cells—called circulating tumor cells, or CTCs—that break off tumors and enter the bloodstream.

“The initial literature [on CTCs] goes back to the 1800s, when a woman with advanced breast cancer was found to have tumor cells in her blood,” Haber says. “Really, we've always known that cancer spreads through the bloodstream, but we haven't been able to see the CTCs.”

Unsatisfied with the sensitivity of commercial CTC detection kits, Haber collaborated with Mehmet Toner, a biomedical engineer at Massachusetts General Hospital, to develop and test a new kind of detection device. While the commercial technology can detect only one or a few cells per teaspoon of blood, Haber and Toner's technology can force that same teaspoon of blood through a centimeter-wide silicon chamber that has 80,000 microscopic pillars in it, each coated with antibodies that can bind to cells. The pillars can sort through billions of blood cells per teaspoon of blood: the antibodies grab the rare cells that originate from tumors while blood cells flow right on by.

Once he's gathered these circulating cells, Haber can analyze them to identify which, if any, possess particular pieces of genetic information. For example, he can track whether circulating prostate cancer cells have Chinnaiyan's fusion gene.

“This could really add to PSA in terms of being able to identify which cases of cancer may be more likely to spread,” says Haber. The technology is still in early days, though Haber says it's raising as many questions as it's answering. Do only certain types of cancer cells enter the bloodstream? When during early cancer development are these cells first detectable? What makes

circulating cells more likely to lodge in a new place and cause a metastatic cancer?

OVERCOMING RESISTANCE

In 2001, Foley went through the first course of treatment for his prostate cancer: radiation, which kills cancerous cells wherever it's directed, and two common anti-hormone drugs—Lupron and Casodex. Both aim to block testosterone in the prostate. Physicians had known since the late 19th century that thwarting male hormones from acting on cells was one way to treat prostate cancer. The ETS fusion gene discovered by Chinnaiyan now explains why this works (in the cancers that it causes)—testosterone turns on the cancer-causing fusion gene; blocking testosterone turns off the rogue fusion gene.

Lupron directly decreases the amount of circulating testosterone, while Casodex works by binding to testosterone receptors, so that the hormone itself cannot. Used in conjunction, the drugs lowered Foley's PSA to less than 1.

The problem with Lupron and Casodex is that enterprising cancer cells eventually evolve resistance to them. In 2006, almost five years to the day after Foley finished radiation treatment and hormone therapy, his PSA started rising. By July 2006, it was 13, higher than when

he'd first been diagnosed. His doctor put him back on the anti-hormone drugs, but the PSA dropped only slightly and then started rising again.

"Essentially 100 percent of men who go on these drugs eventually develop resistance to them," says Sawyers, who turned his attention from drug-resistant leukemias to drug-resistant prostate cancers after developing a drug that overcame resistance to the successful drug Gleevec in leukemia patients. What happens in prostate cancers, Sawyers found in mouse models, is that cancer cells start overproducing testosterone receptors. There are still trace amounts of testosterone in the prostate, even when patients are being treated with Lupron. If the number of receptors begins to increase, those tiny amounts of testosterone eventually find free receptors and once again turn on cancer-causing genes.

Sawyers' drug-hunting mind went to work. "What we needed was a new drug that's not perturbed by higher levels of the receptor." So Sawyers' lab made a cell line overexpressing the receptor and screened it for compounds that would still block the

receptor. One compound emerged: MDV3100, a drug that blocks testosterone receptors, like Casodex, but blocks them earlier in their activity cycle—before they transition from being free in the watery interior of a cell to being inside a cell's nucleus and able to bind DNA.

By February 2008, Foley's PSA had risen drastically—hitting 22—and his cancer spread to half a dozen lymph nodes. He had just returned from a conference in California, where more than 700 prostate cancer patients met to share stories, learn about how to live with their disease, and hear about new treatment options. "It was so encouraging to hear that the fact that I had slipped into advanced prostate cancer wasn't a death sentence," says Foley. "There were still treatments that would allow me to keep going."

When Foley returned to New York, Morris presented him with an alternative to chemotherapy: Sawyers' MDV3100 was in clinical trials, and Foley qualified to be one of the first patients to try it. He joined the trial—a dose escalation trial in which patients are put on increasing doses of the drug and checked for side effects.

Between February 8 and 15, 2008, thanks to MDV3100, Foley's PSA dropped from 22 to 12. In the next month it dropped to 2 and then a month later to less than 1. It's been undetectable since, and his lymph node tumors have all but disappeared. He'll continue on the drug until it stops working, Foley says, which he hopes is many years away.

"When you first get those high numbers, you never think you'll see low numbers again," says Foley. "But it just dropped like a rock. I was blown away."

MAKING PREDICTIONS

Not all prostate cancers are the same. In the clinical trial that Foley attributes with giving him a second life, some patients didn't see such dramatic improvements. Sawyers is collaborating with Haber to determine whether there are different markers in the CTCs of patients helped by the drug versus those who saw less improvement. They want to develop a rapid screening test to show who the drug might benefit.

To complicate matters, there may be variety within a single patient's cancer. "One individual might have multiple distinct cancers within the prostate gland that are independently arising," says Todd Golub, an HHMI investigator at the Dana-Farber Cancer Institute. Instead of one tumor that spreads, he hypothesizes, a cancer-ridden prostate could often have separate tumors, each genetically distinct.

"So if you sample one of these tumors," Golub says, "it's not necessarily going to be predictive of how the other ones are going to behave. The tumor you die of may not be the tumor that was biopsied and genetically analyzed."

It's a vexing problem—to analyze all these potentially different tumors in the prostate, the whole gland would need to be removed, and then there would be no measure of which tumors grew. This situation is, in part, leading to dead ends in prostate cancer research, Golub believes. He's collaborating with a group of
(continued on page 56)

**NOW RESEARCHERS MUST
TURN [CHINNAIYAN'S
DISCOVERY OF THE FUSION
GENE] INTO DETECTION
METHODS, WAYS TO MONITOR
THE DISEASE, AND
NEW TREATMENTS FOR
PROSTATE CANCER.**

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(PROCEED WITH CAUTION)

researchers in Sweden, where the wait-and-see approach is used much more often than in the United States. Golub's Swedish collaborators have followed a large cohort of prostate cancer patients from early diagnosis to see whether their tumors worsen—this approach is more difficult in U.S. cohorts as the prostate is more often removed. To identify differences between prostate cancers, Golub is using DNA chips to quantify the genetics of bits of biopsied tumors.

He's also working—as many researchers are—to create drugs to target the fusion gene identified by Chinnaiyan.

As for Foley, he's become an outspoken advocate for prostate cancer patients learning about their disease and staying informed of the latest drugs and clinical trials. "Do the research, read the data, talk to doctors. If my cancer rears its head again, I'll look to other trials." In January, on inauguration day, he and one of his prostate cancer groups sent a petition to President Obama requesting more federal funding for prostate cancer research. He's also started a

prostate cancer support group in his hometown and is active in online message boards, touting his success with MDV3100.

Though Chinnaiyan's discovery of the fusion gene is heralded as the greatest leap in understanding prostate cancer in the past decade, it's only half the battle toward changing the way prostate cancer is dealt with clinically. Now researchers must turn that discovery into detection methods, ways to monitor the disease, and new treatments for prostate cancer, so that the disease can be managed in a more personalized way. PSA needs a helping hand. ■

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