Bill Schuette was in the best shape of his life. After retiring at 51 from his job as a high school principal, he’d set out to “get healthy and stay healthy,” says the Versailles, Ohio, father of three.

After intensive training, he’d walked the 2,175-mile Appalachian Trail, from Springer Mountain, Georgia, to Mount Katahdin, Maine. He led weeks-long bicycle tours around Ireland and the Greek Islands. He ran triathlons. He competed in the Senior Olympics. But 6 years into his health makeover, in 2006, his chest began to hurt when he was breathing hard.

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**EXPOSING CANCER’S SOFT SPOT**

*Fusion genes that drive solid tumors are a new target for precision therapies.*

by Dan Ferber // illustration by Julien Roure
April 2007, Schuette, then 58, gathered his wife, Connie, his two adult sons, and daughter for a meeting with his oncologist. The doctor explained that Schuette had a form of lung cancer called adenocarcinoma. Thousands of tiny tumors peppered each lung. Surgery was impossible. Radiation couldn’t reach them all. And at best chemotherapy could contain them—for a while.

Over the next two years, Schuette took seven chemotherapy drugs. None stopped the cancer, and the side effects were hard to take. Schuette could no longer hike, bike, or swim. He couldn’t keep food down. “There were times I could hardly get out of bed,” he says. Early in 2009, his doctor told him he wouldn’t see another Christmas.

Then, on June 2, 2009, he saw a television news report. A woman in her 50s, a nonsmoker with adenocarcinoma like Schuette, said chemotherapy hadn’t worked for her, so she’d taken an experimental drug called crizotinib that targeted a rare mutation in her tumor. “My cancer is melting away,” she told the reporter.

“You’ve got to be kidding me,” Schuette said, looking at his wife. Within weeks he was in a phase I clinical trial taking the drug himself, seeking a new lease on life.

The hope is that crizotinib is the first of a new class of drugs that will do for solid tumors what Gleevec did for the blood cancer, chronic myeloid leukemia (CML).

Crizotinib opens the door for a class of diagnostics, prognostics, and therapies that target cancer-driving mutated genes in common solid tumors. They specifically block a fusion protein—produced by an abnormal fusing of two genes in cancer cells. The new diagnostic and prognostic tests would assess a patient’s cancer by looking at these fusion genes. And new drugs, like crizotinib, would target the resulting fusion proteins.

The first fusion gene-targeted drug, called imatinib or Gleevec, was developed in the 1990s to arrest CML. “It changed a disease that was a death sentence within three to five years to a disease that’s now a manageable condition” with a five-year survival rate of 90 percent, says medical oncologist and HHMI investigator Brian Druker of Oregon Health & Science University, who helped develop the drug.

Researchers have since found several fusion genes in other blood cancers but for years had less luck in common solid tumors of the breast, prostate, colon, lung, and pancreas, which account for 80 percent of U.S. cancer deaths.

Their luck is beginning to change. Arul Chinnaiyan, an HHMI investigator at the University of Michigan Medical School, and other scientists have uncovered a variety of gene fusions in prostate, breast, thyroid, kidney, brain, and salivary gland cancers.

These discoveries, along with Gleevec’s success and promising results with crizotinib, have fueled “a gold rush” among cancer researchers to find new gene fusions in solid tumors, says oncologist and HHMI investigator Charles Sawyers of Memorial Sloan-Kettering Cancer Center. “How many exist? And, let’s find out as fast as possible because the implications are just enormous.”

A REAL PUZZLE

The groundwork for the current gold rush was laid more than a decade ago when Druker and Sawyers helped develop Gleevec.

Through a series of discoveries in the 1960s and 1970s, scientists learned that in patients with CML, chromosomes 9 and 22 invariably swapped segments—what has come to be called a genetic “translocation.” By the 1980s, researchers had sequenced DNA at the break point in the CML translocation and discovered a hybrid between two genes. The gene fusion produced a protein called BCR-ABL that drove white blood cells to divide incessantly.

Druker worked with colleagues at the pharmaceutical company Ciba-Geigy (now Novartis) to find a compound—imatinib—that specifically blocked BCR-ABL in leukemia cells. Druker then joined forces with Sawyers to direct the clinical trials that demonstrated the compound’s remarkable ability to stop leukemia. Marketed under the name Gleevec, the cancer therapeutic was approved by the Food and Drug Administration in 2001.
Since then researchers have learned that Gleevec and drugs like it are no panacea, as the aberrant target gene in many patients’ cancer eventually mutates again to confer resistance. Sawyers and colleagues at Bristol-Myers Squibb have developed a drug called dasatinib that targets Gleevec-resistant BCR-ABL, and researchers are developing similar backup therapeutics for other Gleevec-like drugs.

The success of Gleevec and related drugs has inspired researchers to step up their hunt for the molecular defects underlying other cancers. By the mid-2000s, fusion genes akin to BCR-ABL had been found in various types of leukemia and lymphoma as well as in rare bone and soft-tissue cancers. But none had turned up in common solid tumors.

“It was a real puzzle why people weren’t finding these things,” says cancer biologist Jonathan Pollack of Stanford University School of Medicine. Some researchers argued that cancer-driving fusion genes were difficult to detect among the many abnormal chromosomes in solid tumors. Others argued that they simply didn’t exist. Researchers hunted instead for cancer-causing genes that were mutated, copied excessively (amplified), or deleted.

In 2005, Chinnaiyan was busy hunting for such defective genes in prostate cancer when his graduate students showed him a surprising DNA sequence. His team had sifted through 20,000 candidate human genes and focused on two that were overexpressed in prostate tumors. Mutated versions of each were known to alter cell growth in other cancers. The DNA sequence revealed that the front end of each gene was replaced by part of a third gene, called TMPRSS2, which is activated by the male hormone testosterone.

Chinnaiyan’s team had discovered what myriad cancer researchers had missed: the first recurrent gene fusions in a common solid tumor. The two mutated genes, called ERG and ETV1, were overexpressed in 50 percent and 10 percent, respectively, of prostate tumors examined. Their ubiquity suggested that they might drive prostate cancer, the researchers reported in Science in 2005.

The work kicked off a whirlwind of new research on prostate cancer, raising hopes of better prognostics and targeted therapies. In a 2007 Nature paper, Chinnaiyan’s team reported four previously unknown types of gene fusions in prostate tumors. This diversity suggested for the first time that gene fusions played a major role in driving common solid tumors.

Chinnaiyan has since found recurring gene fusions in breast and stomach cancer and in melanoma. And because the driving genetic lesions of many cancers are unknown, the hunt is now on for gene fusions in other solid tumors. Chinnaiyan’s results “energized and reinvigorated a whole new field of study,” Pollack says.

LUNG CANCER PILL

Exciting news came in August 2007, just a few months after Bill Schuette received his diagnosis. Hiroyuki Mano’s team at the Japan Science and Technology Agency in Saitama, Japan, reported in Nature that they’d discovered a gene fusion that drives tumor formation in about 5 percent of patients with non-small-cell lung cancer.

The fused lung cancer gene, known as EML4-ALK, encodes a cellular signaling enzyme called a tyrosine kinase. Both Gleevec and crizotinib block tyrosine kinases. Pfizer had produced crizotinib to treat cancers that had genetic alterations in ALK or another tyrosine kinase gene, including lymphoma, brain, and rare stomach and esophageal cancers. In 2006, oncologists at Massachusetts General Hospital in Boston and elsewhere had begun testing crizotinib’s safety as part of a clinical trial. The Nature paper was big news, says thoracic oncologist Alice Shaw,
who treats lung cancer patients and develops new therapies at Massachusetts General. “We got very excited because it suggested a new therapeutic target,” Shaw recalls.

Within months, molecular pathologists at the hospital had developed a way to identify the EML4-ALK gene fusion in tissue biopsies from lung cancer patients. The Massachusetts General team treated its first EML4-ALK-positive lung cancer patient with crizotinib in December 2007. “He could barely breathe and was wheelchair bound,” Shaw recalls. “Within a week or two he completely turned around.”

Inspired, Shaw and her colleagues began screening more lung cancer patients for the EML4-ALK gene fusion and treating those patients having the fusion with crizotinib as part of the phase I clinical trial. At the June 2009 American Society of Clinical Oncology (ASCO) meeting in Florida, Eunice Kwak of the Massachusetts General team reported that crizotinib stabilized the disease in 15 of 19 of these patients and significantly reduced the total mass of tumor tissue in 10 of them. ABC World News picked up on that report, and on Shaw’s experience treating her first patients, and beamed it into Bill Schuette’s living room in Ohio.

Schuette, at that point, was very sick. “I was totally out of energy. I had lost weight and was in tremendous pain. Anytime I would cough it would bring me to my knees.”

The news sent him to the computer. Schuette e-mailed Shaw, who returned the call quickly. She asked a few medical questions and requested a sample of biopsied lung tissue, which revealed that his tumors had the EML4-ALK fusion. Two weeks later, on August 12, 2009, Schuette sat in a hospital room at Massachusetts General, where he took his first dose of crizotinib.

A TRAIL OF BREADCRUMBS
When a fusion gene is seen repeatedly in a particular type of tumor, it suggests, but doesn’t prove, that the resulting fusion protein alone can drive tumor growth. It’s good news if it does, though, because Gleevec-like drugs that block the activity of a driving fusion gene, such as tyrosine kinase, often stop the tumor.

But each fusion gene must be tested to see whether it drives cancer on its own or whether it needs backup. For example, cells engineered to express BCR-ABL or EML4-ALK become cancerous, and mice engineered to express the two fusion genes develop leukemia or lung cancer, respectively. But mice engineered to produce the most common prostate cancer fusion gene, TMPRSS2-ERG, do not develop prostate cancer, Sawyers says.

To discover what else might be needed to drive prostate cancer, Sawyers obtained 218 prostate tumors, about half of which harbored the TMPRSS2-ERG fusion gene and sequenced 157 genes from each that have been linked to prostate cancer. One short stretch of chromosome 3 was deleted in almost all the tumors with the TMPRSS2-ERG fusion. Three of the eight genes in that deleted segment have hallmarks of genes that suppress tumor formation, and the three may turn out to collaborate with ERG to cause prostate cancer. “It’s a trail of breadcrumbs, so we’ll see,” he says.

To stop gene fusions from causing cancer, it’s also important to understand how these hybrid genes form in the first place, says molecular immunologist Fred Alt, an HHMI investigator at Children’s Hospital Boston. First, DNA must break cleanly at two chromosome locations inside a single cell. Second, the ends of the broken DNA must be brought together and attached to create a chromosomal translocation. Third, cells with this translocation must outgrow normal cells. In 2007, Alt’s team reported in Nature that they’d found a cellular pathway that can perform the second step, attaching broken ends of unrelated genes on different chromosomes. In 2009, they reported, again in Nature, that this pathway generates recurrent translocations that correlate with lymphoma. The pathway may also promote cancer-causing translocations in other tissues, he says.

Two HHMI investigators, Chinnaiyan and Michael G. Rosenfeld, of the University of California, San Diego School of Medicine, have recently shown that testosterone signaling actually spurs translocations in the prostate. This hormone binds to a gene-activating protein called the androgen receptor, and the resulting complex helps regulate thousands of prostate genes, including TMPRSS2. Chinnaiyan suspected that, when it binds testosterone, the receptor brings the TMPRSS2 and ERG into proximity within the cell’s nucleus, creating an opportunity for them to trade segments.

Chinnaiyan’s team confirmed this hypothesis by adding testosterone to cultured prostate cells, then fragmenting their DNA with ionizing radiation. The TMPRSS2-ERG fusion was created only if testosterone was present, the researchers reported in Science in November 2009. The results could explain why the TMPRSS2-ERG fusions occur only in the prostate, the sole organ where testosterone plays a dominant role in coordinating cellular physiology, Chinnaiyan says. Rosenfeld’s team reported similar results in Cell in December 2009. They also detailed how
By studying gene fusions—in blood cancers and solid tumors—Brian Druker, Charles Sawyers, and Arul Chinnaiyan have revealed vulnerabilities in tumors that can be targeted and successfully treated.

the androgen receptor recruits two enzymes that help to cut and rejoin the DNA. By studying how translocations occur, “we want to understand and screen for drugs or approaches to mitigate and abrogate the events,” Rosenfeld explains.

TOWARD PERSONALIZED MEDICINE

As researchers elucidate how fusions form, Chinnaiyan and others are pushing to use what’s already known to help cancer patients. By 2010, Chinnaiyan had found 23 different types of recurring gene fusions in patients with prostate tumors, and he’s seeking new prognostics that use the presence of a specific fusion gene as a genetic fingerprint. By correlating patients’ genetic fingerprints with their clinical outcome, he hopes to develop a knowledge base to help doctors distinguish fast-growing and invasive prostate tumors that require aggressive treatment from slow-growing tumors that do not.

Knowing that a patient has a cancer-driving fusion gene is not enough, however; scientists must find a way to block it. In July 2010, Chinnaiyan reported in *Nature Medicine* that 2 percent of prostate cancer patients—and a similar fraction of patients with gastric cancer and melanoma—have a gene fusion that encodes a tyrosine kinase. Chinnaiyan suspects that patients will be treatable with a kinase inhibitor. Although they’re a small fraction of all prostate cancer patients, they still represent several thousand cases a year in the United States alone.

Other gene fusions will be tougher to target. Most of the gene fusions found so far in prostate cancer encode gene-activating proteins, called transcription factors, rather than kinases. Drug companies have struggled for years to produce compounds that block specific transcription factors. Chinnaiyan, however, has recently identified a workaround. By blocking an enzyme required by the transcription factors, his team was able to block their activity, he reported in September 2010 at the annual scientific retreat of the Prostate Cancer Foundation. Even better, drug companies have already developed compounds that block that enzyme, he says.

Down the road, Chinnaiyan and others envision personalized cancer treatment. With such treatment, physicians would classify every cancer by its driving mutation or mutations; characterize it by its aggressiveness; and treat it with one of an armamentarium of Gleevec-like drugs that target each tumor’s Achilles heel.

In the meantime, doctors are helping whomever they can. In June 2010, Shaw and her colleagues returned to the annual ASCO conference to report the results of their expanded phase I trial on crizotinib. The drug stopped cancer from advancing in 87 percent of the 82 EML4-ALK-positive, late-stage lung cancer patients treated and shrank tumors in 57 percent of them. Results were so encouraging that investigators launched an international randomized phase III trial of EML4-ALK-positive non-small-cell lung cancer patients whose cancer withstood one earlier chemotherapy regimen. “It’s a great story,” says Sawyers.

One of the patients in the phase I trial is Schuette. From the first day he was treated, his pain disappeared and his energy returned, he says. A CT scan two months later showed that most of his tumors were gone. Since then Schuette and his wife have visited their far-flung children and grandchildren in Virginia, New York, and California. He’s back to swimming—up to a mile at a time. “I cherish the opportunity to be able to get back into the pool and do that,” he says.

Bill Schuette knows that his tumors, like leukemias treated with Gleevec, will eventually develop resistance to crizotinib. He may benefit from one of the backup therapies that Shaw says are under development. But for now, Schuette says, “I’ll take every day.”