Driven
Bert Vogelstein is on a mission to change the outlook for people with cancer.

BY SARAH GOFORTH
On Friday afternoons, unarmed visitors to Bert Vogelstein’s laboratory enter at their own risk. Vogelstein and four other faculty members at Johns Hopkins Medical School in Baltimore gather with two dozen trainees in the lab’s central space. Presentations begin with a mandatory joke and end, if they dare go long, with rapid-fire assault by Nerf gun. No one is safe from friendly fire.

Vogelstein, a lean 64-year-old, is equally merciless when the time comes for Q&A—probing trainees when a premise lacks sufficient evidence or a proposal falls short of actionable. For while the mood in the lab is light, the subject matter at hand is serious. The real battle here is against cancer, the arsenal a broad range of disciplines and experimental approaches.

Having spent three decades uncovering the molecular pathways that allow tumor cells to multiply and spread, Vogelstein is now focused on using that knowledge to save lives. To that end, he and his faculty colleagues—with whom he jointly manages the lab—are very deliberate when it comes to selecting new lab members and creating an environment that brings out their best work.

“People have to care more about the final goal than individual credit,” says Vogelstein of the team, which includes medical students, interns, and research trainees in disciplines from chemistry to pathology to computational biology. “This is the rule in industry, which long ago recognized that you need people with diverse talents working on projects together, but it’s uncommon in academia. We try to be our own harshest critics. We also try to have fun.”

In addition to lab meeting antics and friendly billiards battles, the lab shares a Delaware beach house that members reserve in weekly slots. For years the lab even had its own band, called Wild Type, with Vogelstein at the keyboard, laboratory codirector Ken Kinzler on drums, and vocals delivered by a rotating lineup of musical postdocs.

The work-hard, play-hard model clearly works for this team. Studies from Vogelstein’s lab on the genetic roots of cancer are among the most widely cited in all of science. Through painstaking genomic analyses of human tumors, he and his team demonstrated that cancers usually result from the slow accumulation of key mutations over years. Their work formed a paradigm upon which much of modern cancer research is based.

The group was also the first to decipher the molecular mechanisms underpinning a common human cancer. Working with colorectal tumors, they helped prove the existence of tumor suppressor genes, which prevent the growth of tumors by keeping cell division in check. Mutations in the genes have been implicated in many different types of cancer malignancies.

**Biology for Mankind**

A Hopkins-trained MD and HHMI investigator since 1995, Vogelstein, typically dressed in jeans and a crisp white button-down, is director of the Ludwig Center for Cancer Genetics and Therapeutics at Hopkins. His work has earned him multiple prestigious awards, and he was one of 11 to win the inaugural Breakthrough Prize in Life Sciences established in 2013 by Facebook founder Mark Zuckerberg and others. You wouldn’t know it, looking at Vogelstein’s orderly office, where the walls are mostly bare except for family photos and a postcard depicting a famous Jack Russell terrier, with whom Vogelstein shares a nickname (to his three grandchildren, he is “Uggie”).

“He hasn’t sought out any of that attention,” says Vogelstein’s colleague Ken Kinzler. Kinzler, who first joined the lab in 1983 as a graduate student and is now among the group that manages it, was trained in toxicology and pharmacology, and he shares Vogelstein’s sense of purpose. “We’re not here because we love biology,” he says. “We’re here because we love biology as it serves mankind.”

That ethos has taken the lab in a practical new direction in recent years. Despite great gains in understanding the biological basis of cancer, long-term survival rates for most cancers are little different than they were in the 1970s, when Vogelstein entered the field. There are exceptions for a handful of cancer types where new treatments have been particularly successful or early diagnostic tests have allowed clinicians to find and treat tumors before they spread. But by and large, says Vogelstein, the outlook for cancer patients remains unnecessarily grim.

“The situation has dramatically changed in our understanding of cancer. It wouldn’t be accurate to say, however, that the situation has dramatically changed in terms of what we can do for a patient with cancer,” says Vogelstein, who began his career as a pediatrician with a special interest in oncology and transitioned to full-time research out of frustration that he could do so little for his patients. “We clearly don’t understand the entire disease, but at what point do you understand enough to spend your time trying to exploit that knowledge? Over the last decade we decided that time has come.”

Roughly two-thirds of the lab’s energy, he estimates, is now devoted to developing early diagnostic tools. A quarter goes to creating new treatments; the rest is spent on questions in basic biology the group deems most relevant to saving lives.

**A Matter of Time**

The eldest of five children in a close-knit Jewish family, Bert Vogelstein’s capacity for academic success was not always obvious. As a child, he was so often absent from school that he was nearly expelled—twice—for underperformance.

“Sometime in middle school, I decided I wasn’t learning as much as I wanted,” he says. Most days his father, an attorney, would drop his son off at school on his way to work. Instead of heading to class, Vogelstein
would walk to the Enoch Pratt Public Library, a downtown Baltimore landmark. He would spend all day reading—science fiction, histories, biographies, whatever captured his interest. “I didn’t know I was doing some delinquent thing. I was just learning in my own way,” he says.

Today, Vogelstein prefers reading the scientific literature over attending conferences. Unlike most senior scientists, he rarely travels for work, preferring to generate ideas within his lab and a small circle of frequent collaborators. Part of that is simple time management. Vogelstein’s higher priorities include meeting with his trainees at least weekly, designing experiments, and working at the bench—sometimes to an uncommon degree. (Soon after joining the lab, postdoctoral researcher Margaret Hoang was surprised to learn that when the lab ran out of a glycerol buffer used to dye DNA in many experiments, Vogelstein mixed the new batches himself. “I asked the technicians where I could get more buffer, and they were like, ‘Oh, Bert always makes it.’ Imagine my nerves, asking my new boss to make my buffer,” she remembers with a laugh.)

By the time he entered the University of Pennsylvania as an undergraduate, Vogelstein was serious about his studies. He majored in mathematics and excelled at it, briefly pursuing a master’s degree before he was lured into medicine for the opportunity to improve people’s lives. As an intern and resident in pediatric oncology, however, he grew increasingly frustrated with how little he knew about his young patients’ disease. “In the 1970s, cancer was a black box,” he says. “It just seemed to come from outer space and hit people without any rhyme or reason. It was bleak.”

Wanting to use his time for maximum impact, he redirected his attention to research. At the time there were several prevailing hypotheses explaining the origins of cancer: Scientists knew cancer cells were variants of normal cells that had gone rogue, but some thought the cause was a defect in the immune system or an infectious agent. Swayed by evidence suggesting that exposure to environmental contaminants or radiation correlated with cancer incidence, Vogelstein was among a minority of scientists who suspected the roots were in genetic alterations. But he could only prove that by finding the affected genes and showing that, in cancer cells, they were mutated. In 1978, Vogelstein applied for a junior position in a new cancer research program at Hopkins, under the supervision of Donald Coffey, a scientist known for questioning dogma and encouraging his trainees to do the same.

“From the very beginning, it was important to me to study human tumors.”
—BERT VOGELSTEIN

“From the very beginning it was important to me to study human tumors,” Vogelstein says. Many senior scientists discouraged him from taking that approach, arguing that it was impossible to conduct effective experiments without relying on animal models. “I thought that, even though your ability to do some types of experiments is limited, if you choose what to examine carefully and get the right kinds of tissue samples, you could get at things that you couldn’t learn any other way,” says Vogelstein. He joined a group of young scientists at Hopkins who had gained access to colon tumor samples in various stages of progression and began looking for disease-causing genes.

Laying a Foundation
In 1989, Vogelstein and a handful of trainees showed that a gene called $p53$ was mutated in colorectal cancers and a large number of other tumors. Though several groups had identified the $p53$ protein 10 years earlier, its gene was not known to be important in human cancer. Moreover, Vogelstein’s team found that $p53$ was not an oncogene, or tumor promoter, as had been thought. Rather, it is a tumor suppressor whose protective function goes haywire in the mutated form. That

The Long Path from Normal Tissue to Colon Cancer’s Spread

- **Risk Assessment**
  - APC/β-catenin
  - KRAS/BRAF
  - SMAD4/TGF-βRII
  - PIK3CA/PTEN
  - TP53/BAX

- **Early Detection**
  - Normal → Small Adenoma → Large Adenoma

- **Prognosis & Treatment**
  - Cancer → Metastasis

Genetic Instability
Bert Vogelstein hopes his work will lead to simple blood or urine tests to detect early genetic changes in cancer.

discovery, and his group’s subsequent elucidation of the biochemical mechanisms behind how p53 works, led to a surge of research that continues today.

Over the next several years, he and Kinzler discovered a string of other colon cancer genes, developing a new model for cancer progression by examining human tumors for mutations. In the following years, the group uncovered dozens of genes and mutations that play a role in other cancers, including breast and pancreatic. Their lab, and its influence, grew quickly.

By the turn of the millennium, their ambitions had grown too. In 2005, Vogelstein and Kinzler set out to sequence the first “cancer genome” in 22 breast and colorectal tumor samples. To find the most important genes, they limited their search to the areas of the genome thought to harbor most disease-causing mutations. These are the protein-coding regions, or exomes, of each tumor’s DNA. But even this focused approach would still require hundreds of thousands of experiments to extract and amplify these 13,000 genes. Most of their peers thought the goal was far too difficult for a single lab to undertake, says Charles Sawyers, an HHMI investigator at the Memorial Sloan-Kettering Cancer Center. This being before the era of high-throughput sequencing, Vogelstein’s team would need to accomplish the work by brute force and find millions of dollars to fund it.

“Everyone knew we needed to know the sequence of all the genes in cancer cells,” says Sawyers. But even the most successful labs were targeting 100 genes or fewer at a time, for practical and financial reasons. “That was a huge compromise because you didn’t know which genes were most important to sequence, so you had to hedge your bets. Bert wasn’t willing to do that,” says Sawyers. “It was the most audacious thing to take on as an individual lab, but he wasn’t going to let anyone stop him from doing the right experiment.” To supplement his funding from HHMI, Vogelstein raised money from other philanthropic sources and formed a partnership with a sequencing company to industrialize the process.

In 2006, his group published the first genome-wide study of breast and colorectal cancers in a landmark paper in the journal Science. The analysis revealed several new cancer genes and many that were already
Their work, published in June 2013, in the journal *eLife*, showed that targeted therapies are often only effective when used in combination with others. The medical community faces many barriers—mostly financial or imposed by the pharmaceutical industry—to taking that approach, says Sawyers, a senior editor at the journal. “Bert isn’t so much someone who wants to march on Washington, but the *eLife* paper provides unbelievable ammunition for those of us who are convinced of the value of combination therapies,” he says.

“That’s the challenge, to take this incredible intellectual triumph of understanding this group of diseases and actually do something about them in people,” says Vogelstein. “And that is starting to happen. But it will take time and it will take a lot of effort.”

Increasingly, his time is devoted to creating diagnostic tools that detect cancer mutations in the blood before symptoms appear. In a collaboration with Sawyers, who helped develop the targeted therapeutic Gleevec that changed the outlook for patients with chronic myeloid leukemia, Vogelstein is designing screens for prostate cancer that detect cancer-causing mutations in DNA from blood plasma. He is developing similar assays to detect pancreatic and colorectal cancers.

The dream, he says, would be for cancer screening to be a routine part of annual medical exams. A doctor would order standard cancer biomarker analysis along with DNA sequence screening for genetic alterations in blood or urine samples. The trick is to design tests that are inexpensive and easy to administer.

“There are many reasons I’m excited about early detection,” says Vogelstein. “It’s not just reducing deaths by early detection or prevention, although that is of course important. It’s the suffering and the misery that you can preclude when you detect somebody’s cancer early enough that they can be cured by surgery alone.”

If transforming his lab from a basic research powerhouse to a more clinically focused enterprise was an unconventional move, it didn’t surprise anyone who knew him well. “Many rules exist just because that’s the way it’s always been. My dad was never a fan of that,” says R. Jacob Vogelstein, the eldest of Bert Vogelstein’s three children and a neuroscientist at the Johns Hopkins Applied Physics Laboratory. “We were encouraged to ask, ‘Why is it like this?’ If there was no good reason, we didn’t follow the rule.” For instance, on late-night trips to the grocery store, Vogelstein would let his kids ride around the store in motorized carts intended for the disabled. “All a kid wants to do is ride that cart,” says Jacob, “and the answer is, you can’t because it’s against the rules. But when there are six carts and absolutely no one in the store, my dad had no qualms. Why shouldn’t I have my own motorized cart?”

Had Vogelstein been born with a stronger tie to tradition, he might have become a rabbi—the 14th generation of such on his mother’s side of the family.

“I broke the trend, but it’s still in my genes,” he says with a wry smile. “There’s an old expression: If you have two rabbis you have three opinions. They can argue against themselves if they have to. And one of the things that is critical in science, I think, is to not accept the status quo. We try to teach that to our trainees, to think Talmudically; to try to prove themselves wrong.”