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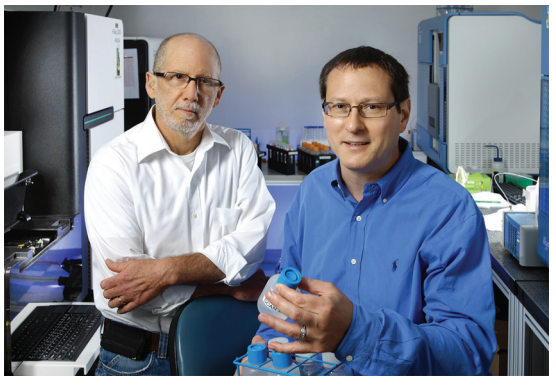
An Interview with Bert Vogelstein and Kenneth Kinzler

Bert Vogelstein was a young assistant professor in 1983 when Kenneth Kinzler came to interview for a position as a graduate student. Wearing a powder blue suit, and sporting a deep Philadelphian accent, Kinzler was hired on the spot. It was an exciting moment. Vogelstein had just embarked on what would become a career-defining approach to cancer—looking for genetic mutations in human tumors, specifically colorectal tumors. Over the next five years, working with Kinzler and other members of his lab at Johns Hopkins, Vogelstein would discover that colorectal cancers arise as the result of a stunningly specific sequence of genetic alterations. They published their results in 1988 in the *New England Journal of Medicine*. The following year, they showed that the crowning mutation in the sequence occurred in the then-obscure *p53* gene. Discovered ten years earlier, *p53* [*TP53* (tumor protein 53)[1]] was thought to be an oncogene, inspiring cancers when intact and overexpressed, not when mutated or missing. Vogelstein and his colleagues showed that in its healthy state, the p53 protein is a tumor suppressor—the first ever found. They would go on to show that *p53* mutants are found in a broad array of cancers. A rush of papers elucidating the role of *p53*, along with other tumor suppressors such as adenomatous polyposis coli (*APC*), flowed from the lab. Between 1990 and 1996, Vogelstein was the most cited biomedical scientist in the world, followed immediately by Kinzler. In the early 2000s, overcoming considerable technical and intellectual hurdles, they moved from pinpointing individual mutations to mapping the entire genome of cancer cells. They have been celebrated with accolades and awards—Vogelstein was among the first recipients of the Breakthrough Prize in the Life Sciences, which carries three million dollars—yet the two men appear almost oblivious to the attention. Vogelstein lives a circumscribed life, moving between his home in Baltimore and his lab, which is located two blocks from where he was born. He and Kinzler thrive on their creative partnership, which extends beyond science—in the 1990s they were members of a lab rock band, Wild Type, and also on their deep friendship. We spoke at the Ludwig Cancer Research Center at Johns Hopkins University, which they codirect and where they have turned their attention to developing new methods for detecting and treating cancer.



Bert Vogelstein and Kenneth Kinzler. ©Johns Hopkins Kimmel Cancer Center. Reproduced with permission.

One of your former post-docs described you as the Lennon and McCartney of science. I was wondering, who's John and who's Paul in this relationship?

Vogelstein (V): I'm not sure how well I know the Beatles but maybe he's closer to McCartney and I'm closer to Lennon in the following way. When we approach a problem my approach is to read—I read voraciously. It maybe takes me two weeks of reading to come up with some answer but he gets the same answer in two minutes, intuitively.

Kinzler (K): I was going to say the reverse because Paul, in some ways, is more multidimensional. And Bert's being modest. It's not just that he reads. He has an incredible amount of talents and almost an eidetic memory. He knows a lot and does a lot with it. I tend to know very little but get the most out of it. There's definitely a complementarity to how we work.

Barbara Walters, who recently retired, would often ask her subjects to come up with a list of adjectives to describe themselves. I was wondering if you could come up with a few words to describe each other.

V: Wow! This is my chance [laughs]. Well, one is intuitive. The second is logical. I think that's one of the things that binds us—we both have very logical minds. Another would be multitalented. He's the one that builds the microscopes and does the bioinformatics and many other things over the years that I couldn't do.

So, inventive?

V: Inventive is excellent. Another would be practical. I guess

[1] Human genes: *TP53*, tumor protein 53 (also known as *p53*); *APC*, adenomatous polyposis coli.

the contrast to that would be abstract, which sometimes I tend to be, for better or worse. He's wickedly smart—he'll never admit it but he's certainly one of the smartest, if not the smartest individual, I've ever met.

(To K) Your turn.
K: He mentioned that we were both logical. Bert has the keenest, most astute mind I've ever seen—he gets every detail and gets it right. He's also creative and abstract. Because he thinks more abstractly, he comes up with solutions that may first appear impractical to me, but they're actually the way to go. Driven, kind, and caring. He takes care of our post-docs and our trainees—current as well as past.
V: I commented on his professional skills. I should have mentioned some personal ones. He's incredibly generous to everyone. And unselfish. I've heard other people describe Ken as unassuming but that's kind of an understatement. I don't know what the opposite of arrogant is but whatever that is, that's him.

You met in 1983. Ken came as a graduate student into the lab and (to V) you said that afternoon, he was the smartest person you'd ever met. You saw something in him.
V: Immediately.

That meeting would be a turning point in both of your lives. But I want to go back even earlier—much earlier—to see how your lives came to intersect. Both of your families came to the US from Germany. (To V) It's well known that you come from a long line of rabbis.
V: The lineage is on my mother's side—her maiden name is Perlmutter. Her father was a rabbi, her brother was a rabbi, and her father's father was a rabbi. It went back many generations. My grandmother and grandfather on my mother's side came here in the early 1900s. There was a very strong academic component. My mother was a dominant figure in my own nuclear family so there was always a lot of stress on scholarly pursuits. That was ingrained upon us from a very early time in childhood.

Was she largely a homemaker?
V: She was totally a homemaker except she worked as a volunteer for charitable organizations. My father was an attorney. At first growing up, I wanted to be an attorney just because he was. My family is actually full of attorneys—two of my brothers are attorneys.

Was there ever a possibility of your becoming a rabbi?
V: No. To this day, I think my mother would have preferred if I had continued that lineage of rabbis. Her brother was a rabbi but that didn't appeal to any of us. My father was much more secularly oriented.

(To K) Can you give me a sense of your heritage?
K: Germany is correct. My grandparents, maybe my great-grandparents, were the generations that emigrated. It's easier to talk about the family I know best, which is my mother and father. Any kindness or empathy I have, I learned from my mother—also probably a bit of my precision and anality. My father was an engineer. He was very, very smart. He had to quit and work in the fields before he finished high school.

Where?
In New Jersey. He enlisted in World War II without a high school degree. He went and took an entrance exam at, I think, Fort Dix, New Jersey, and had been on the train all night getting there. He finished it in half the time and put his head down and went to sleep. The sergeant came over and said, "Check your answers." He said, "I don't have to." It turns out he scored the highest that had ever been scored. He went on, afterwards, and got his college degree at Drexel University in engineering. He continued to teach himself. He went back and, just for fun, got his equivalent of going to high school at 65. I learned a lot from him.

(To V) You were, at least through high school, significantly self-taught.
V: I never liked school. I was asked to leave after the second grade. Starting in about seventh or eighth grade, the stuff that I was learning became, let's say, insufficiently stimulating. So my father used to drop me off at school in the morning on his way to work. I didn't go to school. I went to the library that was located a couple of blocks away and I just started reading things, everything that I could.

What kinds of things?
V: I started out reading a lot of biographies because I wanted to learn about people. I was always interested in people. That came from my family. In my family, people were everything. They have this saying in Hebrew—*tikkun olam*, which means "fix the world." That's what everybody's duty is. They don't mean that literally but almost literarily: contribute in whatever way you can to make the world better. So I read a lot of biographies of people who had helped fix the world.

Any in particular that stood out for you?
V: I always liked Mark Twain because he was an iconoclast. He thought differently than just about everyone else. I liked Jules Verne because of his imagination.

Interesting that you're choosing figures from literature.
V: My favorite character in the Bible was always—still is—Abraham because he was the original iconoclast. I read a lot of science fiction. Then I started getting some interest in biology. After I was politely asked to leave public school in

the second grade, my mother put me into a private school, which was a very Orthodox [Jewish] one.

You grew up in Pikesville, which is a Jewish suburb outside of Baltimore.
V: Still is very Jewish. Because the school was so orthodox, it had very little biology. Evolution, that kind of thing.

Do you think that going to such an orthodox school contributed to your hating school?
V: Actually, I liked that school because, strange as it sounds, they didn't mind that I wasn't there. But in the tenth grade, I was politely asked to leave. They noticed eventually that I was not attending, so I went back to public school. One of my teachers when I was a senior was named Paul Bolenbaugh. I remember him in particular because he reinforced this idea that the main thing that you learn in school should be how to learn, not all these ridiculous facts and names.

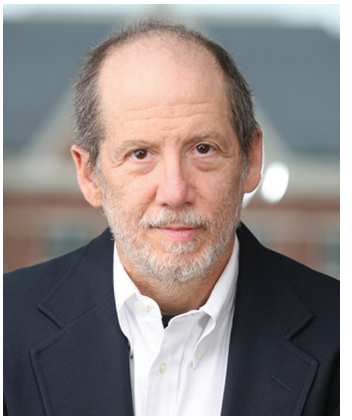
I've heard you describe yourself as bookish and serious.
Serious, no. Bookish, yes.

Not serious?
V: It depends on what you mean by serious. If you work on cancer, you've got to be serious in some ways, right?
K: I don't know if I would describe you as serious. He's astute and keen but he loves to tell jokes.

You've said that you were shy and not terribly popular at school, though you did have a few close friends. I was thinking how ironic that is because many years later, judging by the number of times your work has been cited, you would become the most popular scientist on the planet. I don't know that you've ever thought of it in that way.
V: No, I haven't. I think of popular in terms of people interacting with people. I'm still shy—I don't particularly like giving lectures or meeting other people. I'm always in the lab. My best friend is Ken. I have very few friends, other than the people that are in the lab. I don't socialize at all.

You don't do a lot of traveling—you've described your life as circumscribed to a two block radius from your office. (To K) You grew up in Philadelphia.
V: In a blue collar neighborhood—row houses.

How did you like school?
K: I wasn't a big fan of school early on and I was almost asked to leave—they wanted to put me in a special school for the slow. I didn't start reading until fourth grade. Then I started to read pretty heavily on my own. I read a lot of science fiction, like Bert, then I moved on to reading about things like submarines and dirigibles and lots of mechanical stuff. I actually started to do better as the years went on. I went to a high school that had about 800 in the graduating class. In junior and senior year, they had in physics and calculus what they called "directed and independent study," which meant you didn't go to lectures. You learned on your own. You did a few experiments, killed time, and every week you took a test.



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You went on to a fairly specialized school, The Philadelphia College of Pharmacy—
K: And Science. There were only a few toxicology programs at that time.

How did you become interested in toxicology?
V: I can't tell you why but I was very much interested in science. My heroes were Dr. Spock and stuff like that.

From Star Trek.
K: For some reason, I viewed cancer as a problem that I wanted to work on. It could be that my parents were older so maybe cancer was a bigger issue. My father was 50 when I was born, so I have older cousins. It's sort of a mystery, but that's probably why I chose toxicology.

Did you have any mentors?
K: The directed independent study program had some professors that were key. At college, I did have a mentor who was a physics professor. His name was Professor Bierly. He was a character, but he helped me take the next steps towards being a professional.

Also, maybe your dad?
K: My dad was a huge influence. He loved math—math puzzles by Martin Gardner, he would just do those all the

Kenneth Kinzler. ©Johns Hopkins Kimmel Cancer Center. Reproduced with permission.

time. He taught me trigonometry before I entered high school but he taught it to me from the point view of how you use it in the real world. He also taught me how to make a cabinet.

Watching you talk, I'm thinking that he taught you to think not just with your head but also your hands.
K: I owe that to him.

(To V) Despite all your absences, you got into the University of Pennsylvania and went there in 1966.
V: For the last two years [of high school] I did go to classes. I had good grades.

You were thinking about pre-med—possibly out of the tikkun olam feeling that you wanted to do something of benefit for humanity. But there was something about math that just really drew you.
V: It was two professors—Jerry Kazdan and Steve Shatz, both in the math department. I hadn't yet picked a major. It was the beginning of my sophomore year and they picked me. That had a huge impact on me because it was the first time that anyone who I admired or considered a senior person other than my parents picked me. They said, "Listen, you appear to be really good at this. We would really like you to be a part of our department."

Was it a fulfilling major?
V: It was immensely fulfilling because I love math. I love the logic of it, the tautological nature of it, and because I got this constant feedback from them. They didn't put any pressure on me to go into math professionally, although they would have obviously liked that. I always had this thing that I wanted to go to medical school—the *tikkun olam* business. I was talking to Jerry in my senior year about what to do, and his advice was, "Well, suppose you were a multimillionaire and you didn't have to make a living. What would you do?" I give that advice to other young people now.

You decided to go to medical school.
V: I envisioned it might be a more direct route to helping people. Also I wasn't completely confident in my mathematical abilities. I saw [Jerry and Steve] and other professors and I wasn't convinced I was as good as them.

You ended up coming back to Hopkins.
V: They had a pamphlet—I read it when I was 13. It was called *The Making of a Physician*. It made it seem like a very rewarding way to spend your life, as a research physician. I never really wanted to practice.

You said that you're not terribly social. You're perfectly happy to interact with just a handful of people—
V: Ken and my family and a couple of others, that's all I need.

As a physician, you'd be interacting with hundreds of patients, so research was perfect. You did your internship and residency in pediatrics but it sounds like you were still a bit indecisive. You weren't clear it would be cancer research. How did you choose that?
V: I hadn't done enough research at that point to make a decision that this is how I wanted to spend my life. I took care of my first patient while I was interning in pediatrics. She was this little girl who came in one night with leukemia. Her father was a mathematician at a local college. He was young, my age. I could see the incredible pain that he was going through and I particularly empathized with him because I identified with him. That was a startling sort of experience. What was especially devastating about it, in addition to the plight of the little girl, was there was just no hope. He would ask me, "Why did my little girl get this disease?" I had no idea, absolutely none. It was like a plague from outer space. I thought, "This can't stand, we've got to figure out what's going on." That's in part why I chose to work on cancer. I was able to continue doing research when I was an intern and resident. One night, during my second year, a technician couldn't work out an assay and I said, "Listen, let me try." I basically worked all night and I was in a sort of flow state. You know this concept of flow by this guy—I can't pronounce his name . . .

Mihalyi Czikszentmihalyi—I was going to bring him up because I read an interview in which you talked about how you may seem absentminded in your day-to-day life but that's because you're totally focused on

your work. From Csikszentmihalyi's perspective, the only way to stay creative is to protect your time.
V: Yes, I think that's true.

Going back, you did two years at the National Cancer Institute and then, in 1978, came to Hopkins to work with Donald Coffey. He got you to really question dogma.
V: I wasn't a trainee with him. He was responsible for recruiting me as an assistant professor and then I worked with him in a collaborative spirit. I always viewed him as my mentor. He's just full of wisdom.

I went back and looked at your publications from that time. The words that popped out were terms like nuclear matrix, supercoiled loops, hypermethylation.
V: When I arrived at Hopkins, the thing that I started working on with Don was basically his idea. He saw that the problem with cancer was that there was something wrong with nuclear structure. Over that first four- or five-year period, I gradually came to think that the answer to cancer was going to be found in the genes. The technologies required to test that hypothesis were coming online with gene cloning.
K: Bert was the first person who thought you could actually use these technologies to look at human tumors.

That was an unpopular idea.
V: Very unpopular. Senior people at the time said, "No, you have to look at experimental systems, model systems, culture. Because you can't really test things just by looking at human tumors." My belief, and that may have been partly influenced by having gone to medical school, was that if you're ever going to show that this is what really happens in people, you're going to have to look at humans. We began to develop techniques. Some of the things that are now used routinely, we developed in the early '80s, like using archival specimens of tumors. If you look in any academic hospital, like Hopkins, we have blocks of tumors that go back to the 1800s.

You would later use these methods to discover that cancer is the result of a specific sequence of mutational events. Did you have an inkling back in the early '80s that was going to be the case?
No.

There's a wonderful book by Siddhartha Mukherjee called The Emperor of All Maladies. He writes that you were inspired by observations made in the 1950s by George Papanicolaou, who was working on cervical cancer, and Oscar Auerbach working on lung. They had independently observed that cancers don't arise all at once but that they undergo a series of discreet transitional phases. Were they an influence on you?
V: Papanicolaou was, though for a slightly different reason—more in terms of early detection. But Doll and Armitage and others definitely had an influence. They showed, using a strictly mathematical analysis, that there was an exponential relationship between cancer incidence and age, suggesting that it was a multi-hit phenomenon. Now, in the early '80s, I can't honestly tell you that I'd already incorporated their thinking into mine. At that point, if you'd have asked me, "Well, a person gets a mutation, then they get cancer," I would have said, "That seems reasonable." No mutations had ever been identified. But once we started looking at mutations—and that work really started with Ken—that's when we discovered new genes, new mutations. Once we started doing that, I think we realized that it wasn't going to be as simple as a single mutation.

(To K) How did you come to work in Bert's lab?
K: I had this interest in cancer and toxicology but I had no intention of doing anything beyond my bachelor's degree and going to get a job. But the toxicology program had some internships—I spent nine months working at Dupont. From the toxicology faculty and my mentor at Dupont, Tim Pastoor, I learned that you could go to graduate school. I really didn't know what a PhD was—that was a revelation. I was working at Dupont until August of my junior year. I came back senior year. I had to all of a sudden take the Graduate Record Exams and apply to places. Basically, I applied to any schools I hadn't missed the deadline for. Fortunately, Hopkins had one of the later deadlines and they had an anticancer drug development program. I came here and was still largely clueless. I was in the office of the Director of Graduate Programs, Mette Strand, when Bert called and said he wanted me to come over there.

He literally called while you were in the office?
K: While I was in the office. So that's how the match was made.

That's fortuitous! You met soon after. Do you have any idea why Bert was so impressed by you?
K: I do not know. I came here in a powder blue suit because it was the only suit I had.

Maybe he figured you had to be smart to pull that off!
K: Bert and I hit it off extremely quickly. I very quickly understood that this was a great guy to work for—smart and exceptional. My first projects were related to matrix, but I did have an interest in genetics, maybe because the data showed radiation leading to cancer. Oncogenic viruses were a very big thing at the time but the idea that

genetics might be the basis of cancer was something Bert and I both shared.

Bert said earlier that it was not until you arrived that they uncovered the first mutation.
K: It was the first time that we started to do reverse genetics. Instead of taking a candidate and asking, "is it mutated?" the approach is, there's 20,000 genes in the genome. Are they mutated in cancer? Basically we started looking at amplicons, a type of mutation where you get many extra copies. In some cells, there are so many extra copies that it creates abnormal chromosomes that you can see.

Were you observing them through stains?
K: Through stains and stuff like that. But then the question is, what are the genes? So, we developed ways to isolate the genes that are amplified in a tumor and to figure out what they were. Then we identified GLI [glioma-associated oncogene]—that was the first example. That sort of story has been repeated over and over through the decades.

Were you in the lab when Bert decided to focus on human colon cancer?
K: It was made before I joined the lab and that was largely because of a funding opportunity—a benefactor.
V: The formal name of the foundation was the Clayton Fund but the person responsible was Ben Baker, who was a physician here. His wife, Julia, had colon cancer and he became very interested in having research done at Hopkins to understand her disease, maybe even do something about it. That was extremely helpful in the beginning because there was no way we could have gotten funding.

(To V) You've said that you "knew in your gut" that the human tumor approach was going to work. You are a great believer in hunches and have said that many major scientific discoveries originated as a hunch. How would you define a hunch?
V: A hunch is something you suspect to be true but the evidence isn't great enough to warrant that an unbiased person would think it's likely to be true. The best kind of hunch is one that others in the field do not think is going to be supported once the evidence comes in because then, if you are right, you have done something that's iconoclastic, that's novel, that could be game changing. That's the best kind of hunch to have.

Absolutely. Where do you think hunches come from?
V: They're just insights. That's something that my math professors taught me. One of them, Steve, trained as a theoretical physicist and switched to math. I asked him why and he said he didn't think his insights were good enough in physics but they were in math. I had no idea what he meant because I didn't know what an insight was. Many years later, I understood that you have these hunches or insights that are what distinguish the really successful scientists. He knew that there was something about how his brain worked that allowed him to have insights about mathematical problems—that would allow him to choose the *right* problems. Because that's the first thing required for success—you have to choose something that's worth working on and that is likely to bear fruit. That's one of the hardest things to do in research. It's not just in science. Some people have hunches about music or art or finance.

You've said that creativity lies in bringing together aspects of nature that have not been connected before.
V: Yes, I have said that, because as humans we really can't create anything. I can say, "Make this sheet of paper turn into a billion dollars." It won't. I think that explains part of the success that Ken and I have had. It's knowing two kind of things. For example, I think abstractly. Maybe it's from years of studying the Talmud and having these completely abstract arguments that have absolutely nothing to do with reality. It trains you to think in certain ways. But I had no practical experience. When I got out of high school, I couldn't fix a car. Ken could fix a car. He built an NMR (nuclear magnetic resonator) while he was in college. When I was in college, I didn't build anything. I solved math problems. I think welding together this abstract approach with a practically oriented approach is one of the reasons that we pull these things off together in ways that I don't think either one of us could do alone.

Going back to the colon cancer story, you were gathering clues. At some point, you had this hunch that it's not just one or two mutations, it's a whole sequence—and the sequence has to happen in a particular order. How did you get from suspecting genes were involved to this very clear, almost crystalline, vision?
V: We did it logically. We started using a genetic approach that I invented in the early '80s to see if tumors were clonal, because at that time, it wasn't clear. In fact, the only data in the literature said they were not. So we started in a completely unbiased way. And that has characterized a lot of the work that Ken and I have done together—we try not to assume anything.

You keep each other honest in that regard?
V: Yes.
K: We love to disagree [laughs].
V: So we looked in the same patient and traced the same tumor over time by microdissecting it. We found that they were clonal—the early tumors as well as the late. And they were the same clone. That was the point when I realized, "Yes, this is right. Let's now find the responsible genes." And then it became clear that you weren't

going to be able to explain the whole [tumor series] with the same gene or single group of genes. We could take a tumor and we could see that the late lesion had changes that the middle and early lesion didn't have. They were clues, not the actual genetic alterations, in the beginning, but the evidence was clear. That's when we published the paper in the *New England Journal* [*of Medicine*] that described what some people call the classic model for colorectal tumorigenesis. But that was not a publication that came out of the blue. That was the fifth or sixth or tenth publication in this series that allowed us to get there.

There was a flurry of papers starting in 1990, many focusing on the famous tumor suppressor gene p53 that, before your work, was thought to be an oncogene. The p53 story was a big one.

V: It was the first tumor suppressor gene—we discovered that. Again, that came about through what I would consider a logical series of events. We had this model and we knew there was a gene on chromosome 17 that we thought acted like a tumor suppressor. That was tenuous because at that point no one had ever identified the beast—any tumor suppressor gene. It was just a theoretical concept. Suzie Baker was a graduate student in the lab and her thesis project was to identify the tumor suppressor gene on chromosome 17, which was an audacious thesis project because we didn't know any tumor suppressor gene existed. But somehow she accepted it. Now, in reality we didn't expect that she would actually discover it.

Was she just tenacious?

V: No, no, let me tell you how she discovered it. We knew it was somewhere on chromosome 17p, the short arm. We tried to narrow it down by looking at lots of colon tumors and seeing if there was a common area that was always lost when a region was lost. So she did that and we kept getting to this tiny region. There weren't many genes known there. One that mapped in the region was *p53*. Now, *p53* had been discovered ten years earlier. Everyone in the world thought it was an oncogene. It was exactly the opposite of what we are looking for. But we couldn't get out of it.

You couldn't get out of it?

V: We couldn't escape the region. So, we said, "Okay let's formulate a test and get rid of this damn thing so that we can find the real gene." The test was based on Al Knudson's hypothesis—that it takes two hits of a gene to get a tumor suppressor gene revealed.

Two hits?

V: Both alleles have to be mutated. That's how we suspected there was a tumor suppressor gene on chromosome 17—one copy [of the short arm] was often lost in colon cancer. If the Knudson hypothesis were true, then the other allele had to be mutant. We figured, let's take one tumor that has a loss and sequence its [remaining] *p53* gene. Back then sequencing wasn't done like it is today, it was done by cloning. So Suzie cloned the *p53* gene. On a Friday afternoon in December of 1988 she came to me with an autoradiograph. She said, "Look, there's a mutation not present in the normal DNA from this person. And the change is a valine to alanine." My response was, "That's one of the most trivial changes you can imagine. That could not be the thing we're looking for, it must be some sort of artifact." But, saying that, there was obviously part of us that hoped it was right. So, she went back and did it again—she looked at two or three more tumors. If something is real and important, you don't have to study thousands of tumors, you just have to study a few. They all had mutations and they all had mutations at different spots. So the only sequence that had been published until then on *p53* was actually mutant.

Nobody realized that?

V: We looked back and it came from a cancer cell. It was just assumed to be the normal sequence of *p53*, in part because no one suspected *p53* to be mutated in human tumors.

How long was it before you realized its true identity?

V: As soon as we got the second one. So, six weeks later. We knew at least 70% of colon cancers have a loss of 17p at the chromosomal level so that meant it was likely involved in at least those 70%—likely more because there are other ways to inactivate it besides chromosomal loss. We suspected that it was involved in a lot of other cancers so Suzie joined forces with Janice [Nigro], another graduate student in the lab, and looked at a bunch of other tumor types—breast cancers and brain tumors, whatever we had in the lab. Several months later we were able to publish another paper showing that it's in lots of tumors.

What was the general reaction?

V: It was perfect in the sense that the initial reviewers didn't believe it, which is what you expect if you come up with something really good. It didn't take long, though, especially with the second paper, for people to realize the implications of it. If you look at the curve of p53 publications from 1979, when the protein was discovered by six different groups, it's pretty flat. And then in 1989—woosh!—because it's a common denominator of cancers. Then shortly after that other investigators, not us, realized that classic DNA tumor viruses—SV40 [simian vacuolating virus 40], papillomaviruses like HPV [human

papillomavirus]—the way they work is they encode proteins that inactivate p53 at the protein level.

You would discover that the inactivation of p53 is actually one of the very end steps in tumor formation and that another gene, APC [adenomatous polyposis coli], plays an initiating role.

V: We actually knew *p53* was late right from 1988. If we looked at sequential biopsies of the same tumor, we could see loss of the 17p chromosome in a late tumor but it wasn't in the early part of the tumor. Once we discovered the target of those losses, *p53*, Suzie went back to the same DNA samples but now looked for a mutation in the remaining allele. If we looked in the advanced tumor, it was there, and if we looked at the intermediate or earlier lesions it wasn't.

K: The story for *APC* is very similar to *p53* except that the loss was seen in the early lesions as well.

I'm interested in the evolution of your collaboration. (To K) I noticed that you were a co-author on a fair number of papers in the '80s and early '90s. But starting in 1996, your name is on all the papers coming out of the lab.

V: Ken was just too smart so there was no way I was going to let him let him out of my lab. We called it the KV lab for years until we became the Ludwig Center.

K: I think it was largely clear in our minds because I did something that was quite unusual. I did my thesis work with him and I then stayed on and did my postdoc with him—that's almost unheard of. The thought process was, we're inventing the science as we go along. The science would be better if we worked together as a team. I joined the faculty in 1990.

In addition to the publications pouring forth, you also had new technologies coming out of the lab. For example, SAGE [Serial Analysis of Gene Expression].

K: SAGE has been surpassed, but it did set a precedent. And it was based on a hunch that was true—that the digital counting approach to looking at transcription is the most precise and analytical way to go. There's another technology that we co-invented in the 1990s, called digital PCR. Again that was based on the premise that the most sensitive way to quantitate mutations is to look at molecules and count them individually. You can look at somatic mutations as biomarkers—you can look in the blood, in stool using these digital technologies.

This is the concept of a liquid biopsy?

K: Yes, exactly. That was enabled by the digital PCR technology.

You would use some of these techniques—and some new ones—to begin sequencing the entire genome of cancer cells. I'm wondering how that work came about.

V: We were urged on actually by one of our postdoctoral fellows, who is now in Italy.

K: It was Alberto Bardelli.

V: He now runs his own lab in Italy. In part due to his encouragement, we started thinking about going towards gene families instead of individual genes. The first gene family, which we published in *Science*, was the tyrosine kinases.

In which cancer?

V: This was all in colon cancer at that point. Over the next several years we gradually increased the number of genes we were sequencing at once. We eventually did all the kinases. We did the genes involved in chromosome instability. We did the lipid kinases. About 2004–2005, it was a logical extension to just do everything. That was really a quantum leap to look at all of the genes. It was a quantum leap technologically but it was part of a continuum that had gone back, really, 30 years. It was just getting larger and larger until the time that we thought it could actually be done.

What technology did you use?

K: We were using Sanger-based sequencing. The sequencing advances had been made by other people—the development of Sanger onto high-throughput automation platforms and then the advent of next generation sequencing. Our role has largely been in the application of that to cancer.

V: Ken is being a little modest. In order to do it with Sanger sequencing, we needed about 450 000 primers, because there were about 220 000 or so amplicons, or exons, that we needed to sequence. That was something Ken figured out how to do. The second part was figuring out a way to handle all the data—a huge number of bioinformatic challenges, which Ken was able to handle.

You had massive amounts of data containing a bewildering array of mutations. You discovered that these mutations belonged to a discrete set of pathways—and that the same core pathways were disrupted in a given tumor type. How did you come to perceive order in that bewildering array?

V: It wasn't only me—Ken and I function so well because we are always talking about these issues. Having been fortunate enough to be able to see all of the data laid out in front of us for all of these tumors, it forced us to think about how to organize them in a meaningful way. And it became clear that one way to do that was to think about it like yeast genetics. If you do a screen of yeast mutants, you find lots of mutants. They may all give you the same phenotype. But if a mutation in a gene has the same phenotypic effect as a mutation in another gene, they're

likely not randomly associated. Maybe the protein encoded by gene 1 that's mutated in yeast 1 is related either upstream or downstream to the protein product of gene 2 in yeast 2.

Your lab has been an incredibly active place. It sounds unique in other respects. I've heard stories about people having to wear Burger King crowns while giving presentations or having to make a joke at the beginning of a lab talk. I've heard about ping pong and billiard tables. Is this all true?

K: We do ask people to wear a crown but that's a trade secret—we don't want it to be printed. We don't want people that take themselves too seriously.

I have to tell you, it's already been printed.

V: [Laughs] That's fine—it's no longer off the record.

K: People do tell jokes. We have a joke box. If they don't have a joke, they can pick one out.

V: We work extremely hard to prepare PhDs, predoctoral and postdoctoral, for their future careers. One thing that's required of them is to be able to present. If you can tell a joke well, you can deliver a seminar well. We make people tell jokes just so they get in the habit of trying to entertain their audience.

What a good idea!

V: There's a method to the madness.

It sounds like there's a method in the way you choose who comes into your lab in the first place. You might get a couple of hundred people applying for only five positions. What do you look for?

K: We're looking for stars who are hardworking, creative, and motivated. We're also looking for personality—that gets back to the Burger King crown. We want someone who doesn't take themselves too seriously and who is able to have a good give and take, an exchange. Someone could be a superstar but if they don't work well with others, they won't work well within our group.

The two of you were in a music band with members of your lab. You stopped. Do you have any plans to pick it up again?

K: It's a lot of work. Bert's more talented than me but I don't think he will be offended by my saying that neither of us was as talented as the other members of the band. The other members were natural musicians. Bert and I preferred the sheet music kind of approach. Bert still plays the piano. I have not touched the drums in quite a few years. We might have a reunion at some time.

V: It gave the lab a kind of esprit de coeur but I don't think either of us expected to put in as much time as we did.

Drs. Vogelstein and Kinzler with their band, Wild Type. ©Johns Hopkins Kimmel Cancer Center. Reproduced with permission.

You've said that the people in your lab are not just scientists, they're kind of like artists.

K: There's more to doing science than reading a lot of articles and knowing a lot of things. There's an art to the execution, there's an art to its presentation, to its analysis. We try to find those artists when we recruit to the laboratory.

V: I've heard it said that the artists of the 21st century are actually scientists in the sense that what artists used to do was paint a picture of reality that was not obvious to others. In one sense, that's what scientists now do to a great extent. The pictures they paint are actually quite a bit more accurate than historical artistic ones but they still have the same qualities—that hidden beauty that you bring out, either through experimental methods or theoretical science. Or true artistry. The other aspect is, a lot of scientists, not just in our lab, are often good musicians or good artists. Some of the same pathways in the brain must be involved.

You just talked about beauty. I'm interested in your perspective on the role that aesthetics plays in what you do—that feeling of rightness or symmetry.

V: The word symmetry is critical in science. It started in physics—now they talk about supersymmetry. But there is an underlying beauty and symmetry that everyone can see. It's particularly appreciated by scientists. Ken and I often, in our conversations with each other and with others in the lab, use symmetry as the way to think about problems. You often hear a scientist say, "Wow, that's a gorgeous experiment."

Or elegant.

V: It doesn't really reflect the results of the experiment, it just reflects something about how the experiment was designed. It's very similar to how a picture is painted. There's just

something about it. When it's there, I don't know exactly how you know it's beautiful, but it is.

Science is often viewed as an objective enterprise but that's a mythical view because there's also a lot of human emotion in science. I was wondering, what about empathy in science—does that play a role?
V: Look at Ken and talk to him for a few minutes. Does he fit a stereotype of what a scientist is? Ken, why don't you answer that question?
K: To the extent that running a successful lab requires running a successful team, empathy is a very important process. Because you have to understand the people that you're training and the people around you.
V: That was a good answer! You can also see how smart I am because I give all the hard questions to him.

Here's one for you. I think you'd both say that you love what you do—a lot. What role does love play in science?
K: Well, to do what we do, you have to be passionate about it. I think there's nobody more dedicated than Bert. Bert will be pipetting from a hospital bed. He will never stop. He's off the chart in terms of dedication and truly passionate. I have other interests. I'm not quite as focused and dedicated as Bert.

What other interests?
K: I like to build things—I'm a tinkerer. I tinker inside the lab but I also tinker outside the lab.

Around the house?
K: I have hobbies. Bert's first hobby, first love, first passion is science—to the point where he has few other interests besides family and science.
V: I think that's true. Ken and I have had conversations about this before. I've had them with my son Joshua. We all feel that we're really lucky that we get paid to do this. It's a real job.
K: You do play racket ball but I think the only reason you play is so that you can do your science better.
V: It's my form of exercise, it's true. But [science] is not something I consider a burden. It's just what I like doing the best.

I just had an image of a Talmudic scholar. They spend hours studying—it's what they love to do.
K: That's pretty accurate.
V: That's a good image. There's something else about a Talmudic scholar. Sometimes they can spend time alone studying, but it's much more fun in terms of the emotion, the love, if they have someone to argue with.
K: [Laughs.]
V: I mean that's what Talmudic scholars do—they argue with each other. I've heard that law schools now will accept Talmudic scholars who have not gone to college.

Because they have that training.
V: Yes. I can stay home and read and think up experiments but that would not be nearly as much fun as talking to Ken—in a very real sense, arguing with Ken. Other people, when they hear us doing it, may not understand. But we actually feel that's an important part of what we do—obviously polite arguments but forceful ones. We're trying to arrive at the best possible way to do things, the best possible way to run our lab. And we don't always agree.

It sounds like a form of play. Bert, you have said that if you love playing with toys, you'll love science. And Ken you've mentioned the tinkering—taking things apart and putting them in a new configuration, whether that's a piece of equipment or a theory.
V: Ken is the tinkerer. But I do love new toys.

You mean equipment?
V: I love pieces of equipment, which are toys. Ken may build them, I'm more likely to buy them. Either way, we both enjoy them. We're not singular in that sense. That is part of the fun of doing science. You get all these new instruments with all these lights and dials. That's why many of us, if not most of us, feel it's not really a job. Part of it is unpleasant—writing grants, that kind of thing. But the actual doing it, it's just fun.
K: I think we made this point before about the arguing—if Bert and I agreed on everything, it wouldn't make much sense to work as a team. We always try to tell people two heads are better than one. It's trite, but it's true.

It has to be the right two heads!
K: The other quote we like is "great minds think alike, but so do weak ones."
V: We often have our contentious discussions with the trainees so they can observe. One of the things we try to inculcate in our trainees is that we often disagree, and that they should feel free to disagree with us. And second, that what they read in the scientific literature is not something that they should necessarily believe. Even though the experimental results may be true, the interpretation of those results is not necessarily correct. People often don't interpret their results right either because there isn't enough knowledge available at the time or because they're trying to emphasize the positive because they need to get grants.

To get a grant, you need to tell a good story. What do you think about the role of storytelling in science?
V: It's essential. One of the things we inculcate in trainees

is that each paper should be a story. They'll often write a first draft of the paper and then they'll give it to Ken or me. They'll be surprised that virtually all the words have been changed, even though the results are the same. The difference is that it tells a story—it has a beginning, middle, and end. There has to be some message which is conveyed in a way that holds the reader's attention if it's going to make an impact.

K: Bert is the master at doing that. But it's not just storytelling. I think it comes back to what I told you about Bert being able to distill essential observations out of complex data. I think his gift there serves him well in his writing and storytelling.

What's essential to a story—a story that grabs you—is conflict or a problem that needs to be solved. The story is all about how you fix it—how life goes out of balance and how it comes back into balance. Going back to the '80s, cancer was a black box. Somebody like you, with years of experience, can tell the dramatic story of why a seemingly straightforward set of experiments is so important.

V: That's an interesting perspective. Your comments bring a sense of drama which I hadn't appreciated but it's probably a critical part of telling a story. Even if it's a comedy, there's got be some drama.

Over the last eight to ten years you've moved away from the abstract and theoretical to a much more hands on, applied, translational focus. You're much more focused on finding early diagnostic tests—this idea of liquid biopsies. I was fascinated by the area you're pursuing—using anaerobic bacteria as a new therapy for eating away at tumors. Which do you find most promising?

V: First that whole change in direction was largely Ken's doing. So Ken why don't you answer?

K: I guess I love the word continuum. Some of the work, like the liquid biopsy and so forth, can trace its roots back for more than two decades now. I think why the emphasis seems to have changed more recently is that the technology has allowed us to get a pretty complete picture of what's there. We have an incomplete but reasonably expansive view of the cancer genome landscape. It's time to put even more effort into those translational goals. To answer your question, we think that the use of somatic mutations as biomarkers, one application being liquid biopsy, is very important. We're particularly interested in its potential in prevention settings to identify people with previously undiagnosed cancer because we think that prevention is the way to have the most immediate impact on cancer—detecting it early. We consider early detection a type of prevention. We also recognize that cancer will remain a disease no matter how effective our early detection strategies are. We're also excited about the therapeutic applications.

V: If you look at our backgrounds—Ken was a pharmacologist and I was a physician. We've always looked at this issue of cancer, not as something abstract to study, but as a real disease that affects people's lives. As time progressed, it became clear, like Ken said, that we know something about it. It's no longer a black box. It's time to jump over the wall, even though we don't know what's on the other side, and see if we can do what we actually started out to do, which is to get people out of the clinics and away from the morgues.

You've said that for cancer, long-term survival rates aren't much different than they were in the 1970s. Part of the reason cancer has been such an intractable foe is that in any given tumor, there are heterogeneous resistant cells lurking. You've been advocating combination therapies.

V: Combination therapies early. One of the points we've made is that the way pharmaceutical companies run trials is not optimal from a patient's point of view because it's essentially impossible for a single drug, a targeted agent, to cure. We've tried to encourage companies to get together earlier in the process—after phase 1 but before phase 3. And I think that encouragement has had a little effect—you're starting to see that now. The other thing, which Ken mentioned, is we're trying to develop new ways to target mutations. Hopefully in the next decade one of those attempts will bear fruit.

Are you generally optimistic about the future of cancer biology—that cures will be found within the foreseeable future?

V: Yes. I think the words you chose there nicely illustrate that point because that's the way everybody thinks about cancer—cures. I'm way more optimistic. I can't believe that in a hundred years, cancer will be the problem that it is now. It's going to be much less and the reason it's going to be much less is that it'll be prevented or detected early. Another part will be because it will be treated better. But to win the war against cancer, it's going to require more than just trying to develop therapies for patients with advanced disease. It's going to require a lot of thought about how you can detect cancers early or even prevent them, which is the best way to reduce deaths. One analogy that I use is to compare it to heart disease. With heart disease, the focus has always been on prevention not on treatment of patients who have had massive infarcts. In cancer, it's been the opposite. There's historical and economic reasons for that but I think we could learn a lot from our cardiovascular researcher friends.

I'm happy to hear your optimism. People are clearly optimistic about you. You were one of the first recip-

ients of the Breakthrough Prize in the Life Sciences, which comes with a three million dollar award. A lot of people must be asking, what will you do with it?
V: Not a lot of people—I don't talk to a lot of people [laughs]. I'm spending it on my grandchildren's education. Some of it will go to support various charitable causes—including my passion, which is research, and my wife's passion, which is early childhood education.

I've read that you've started taking vacations.
V: I don't know how that ugly rumor started.

Is there any truth to it?
V: Ken, do you remember me taking a vacation?
K: Uh, no.
V: I do go to visit my grandchildren.

How about you, Ken?
K: I take vacations. But I'm not one to relax on the beach. I like to be doing stuff. I tend to work in the mornings before everybody wakes up.
V: He also stays up late at night. Some people have said he gets more done when he's on vacation because he doesn't have all the interruptions—me bugging him.

I read a paper years ago by a biologist at Rensselaer Polytechnic Institute, named Jane Koretz, about how doing science puts her in touch with her true nature. It's similar to what you were saying earlier about a flow state. But you're also in touch with what's best in you—your skills and talents. She writes: "There is an indescribable satisfaction in developing and using one's unique combination of skills and talents to their utmost." I was thinking that in your case, there is a possibility that you have each elicited in the other those skills and talents—what's unique and best about each of you.
V: I've never felt that I was the best.
K: Let me get that. Bert's very good at bringing out the best in other people. And I do think science provides you the opportunity to do things you like. The process that excites me most is when we're doing something in a different way and we're figuring out how to do it. If you ask Bert, when he makes a new discovery or finds a new hunch, that's when I think he's most excited.
V: But I don't think either of us has the kind of personality that it would ever cross our mind that we're the best in the world.

There's your modesty. It's not about being the best in the world, it's being able to express what's best in yourself. It gets to what we were talking about earlier with regard to the links between art and science. Often people think of science as being supremely objective. But I think there's huge room for self expression. I say that and yet I'm aware that the whole concept of self for you is problematic. Do you know what I mean?
V: Yes, in that sense I think it's right on. Self-expression is great, it is. And you don't have to believe in special qualities about yourself to enjoy that self-expressive aspect.

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