

The one problem he can't solve

When he was diagnosed with a potentially fatal disease, **Steve Kirsch**—the Thomas Edison of Silicon Valley, who had conquered search, the mouse, web speed, and spam—believed his geek genius and startup fervor would help produce a cure. Other ailing tech titans have had the same conviction. Why doesn't it work that way?

BY DIANA KAPP

PHOTOGRAPHS BY JIM HUGHES

ATTACKING INTRACTABLE PROBLEMS IS MORE THAN A habit for Steve Kirsch—it's the only way he knows how to live. When the 54-year-old Los Altos Hills tech entrepreneur heard George W. Bush touting his education record in the 2000 election, he went straight to the Texas achievement database and ran the numbers himself. When they didn't add up, he placed ads in half a dozen major newspapers saying so. When Bush won anyway, Kirsch became the largest funder of the legal challenge of the election results. Another time, he single-handedly did away with half of the planet's junk faxes by filing a \$2.2 trillion lawsuit that forced the largest perpetrator to shut down. And once, when he read that the local United Way faced a \$15 million shortfall that was sure to affect more than 100 organizations, he emailed 65 business acquaintances with a plea for help—after pledging \$1 million of his own to get the ball rolling.

In technology, Kirsch has engineered a series of major successes: a better computer mouse (Mouse Systems); a more powerful document processor (Frame Technology, acquired by Adobe for \$500 million); a more accurate search engine (Infoseek, sold to Disney for about \$2 billion in stock); and a faster web connection (Propel). And he just spent five years writing an algorithm that's 99.99 percent effective, he claims, in outwitting spam. His company, Abaca, recently won a big contract from Yahoo to use the new software, and Kirsch is confident that it's just the beginning of a broadscale adoption.

So it's no surprise that when faced with a massive personal challenge, Kirsch had total faith that he could prevail against, or at least delay, the inevitable. In July 2007, Kirsch sat facing the Stanford hematologist he was

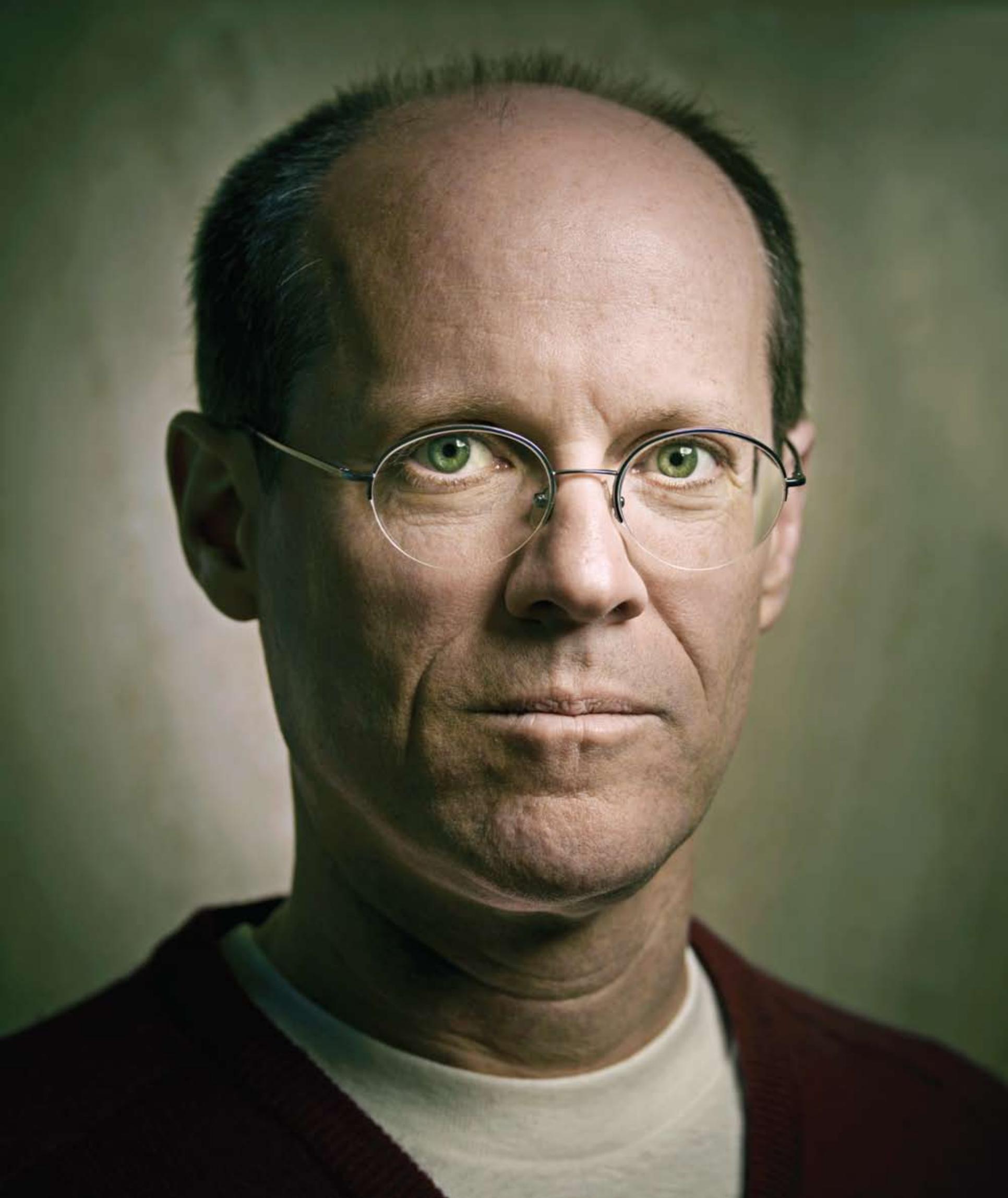
referred to after a routine blood test revealed that he was anemic. Dr. Steven Coutre ordered a second test, which showed a 10-times-higher-than-normal level of a particular class of antibodies. Coutre suspected that Kirsch had developed a rare blood cancer, Waldenström's macroglobulinemia (WM), and referred him for a bone marrow biopsy that afternoon to confirm the diagnosis.

Several weeks later, Kirsch posted the results on his personal website, not mincing words: "The biopsy confirmed Coutre's diagnosis with a 10 to 15 percent involvement of lymphoplasmacytic lymphoma [another name for WM]. In other words, it's quite possible that I'm going to die soon."

The pale-skinned technophile, whose green eyes never seem to stop darting around behind his wire-rimmed glasses, was not being melodramatic. He had already spent enough time poring through the scientific literature to know a great deal about his disease, starting with the fact that it's exceedingly rare—just two and a half cases per million people are diagnosed each year—and thus barely acknowledged with research funds. He was also aware that half of Waldenström's patients die within 5 years, and 80 percent within 10, and that the symptoms, including vision and hearing loss, can be devastating. The primary Waldenström's patient organization estimates that 20 percent of its members are too disabled to work. When Kirsch trolled through the group's donor list and noticed how many gifts were given "in memory of," he wept.

But the wallowing lasted a nanosecond, and then he decided to do what numerous Bay Area masters of the

OPPOSITE: **Steve Kirsch has been devising bold fixes all his life, so he figured conquering his rare blood cancer was just the next frontier.**



universe in his position have done: throw his money and his problem-solving abilities behind the search for a cure. The hubris behind these endeavors is easy to imagine. What's a rogue cell got on people who have figured out how to dominate cyberspace or how to fit a billion transistors on a chip about the size of a thumbnail? Many tech titans share a belief in the specific power of their expertise and entrepreneurship to transform the field of medicine, which is notoriously complicated, slow to change, and riddled with conflicting priorities. Researchers tend to compete rather than collaborate with each other, and pharmaceutical companies, facing billion-dollar drug-development costs, have grown risk averse, investing in proven approaches and me-too products in lieu of potentially game-changing ones. It's no surprise that our four-decade, billion-dollar War on Cancer has cut the death rate a paltry 7 percent in women and 12 percent in men—nor is it a shock that tech leaders are appalled at a record that would run any Silicon Valley startup right into the ground.

"Why doesn't technology give us medical treatments that are better, faster, cheaper?" asked Intel cofounder Andy Grove in a 2009 *New York Times* article. After being diagnosed with prostate cancer in 1995, Grove was the primary donor of a \$12 million gift to UCSF to launch what was then an unprecedented research initiative that

When Kirsch trolled through a Waldenström's organization's donor list and noticed how many gifts were given "in memory of," he wept.

would integrate basic science with practical clinical applications, a mission Grove has repeatedly described as no less than "a cultural revolution" in the medical industry. Grove was explicit about his belief in the technology model when he said he was dreaming of a system "that works, heaven forbid, like the chip world."

Other similarly driven tech folks have joined the go-for-broke club since then. In 2007, Netscape cofounder Marc Andreessen and well-known tech investor Ron Conway mounted "Fight for Mike" to help their good friend Mike Homer, an Apple and later a Netscape executive, beat Creutzfeldt-Jakob disease. Accelerate Brain Cancer Cure (ABC2) was started by AOL cofounder Steve Case and his investment banker brother, Dan—along with their wives—after Dan was diagnosed with the disease. (Homer and Case have both passed away.) San Francisco biotech VC Luke Evin is fighting his own disease, scleroderma, with big funds; engineer and CEO Hugh Martin of Pacific Biosciences is getting ready to throw millions at multiple myeloma, which he was diagnosed with in 2009; and Grove, now battling Parkinson's, has funneled \$75 million more into vanquishing that disease too. Tech entrepreneur Scott Johnson, who has multiple sclerosis, has made his Myelin Repair Foundation a full-time endeavor. The latest and splashiest such enterprise, almost a caricature of the trend, is

MASTERS OF THE (MEDICAL) UNIVERSE?

When threatened with death, the typical superstar Silicon Valley entrepreneur doesn't shy away. Here are seven others who hoped their drive, brains, and money would produce a cure. Instead, they've had to settle for slow, incremental advances. —D.K.



Steve Case

WHO: AOL cofounder
DISEASE: Brain cancer (his brother Dan's)
ROLE: Cofounded Accelerate Brain Cancer Cure (ABC2)
\$\$ COMMITTED: Helped raise \$14 million, primarily for high-risk proposals that wouldn't otherwise get funded
PROGRESS: Developed a vaccine that knocks out a compound that allows tumors to grow, extending median survival from 15 to 26 months; funded work that led to a clinical trial in which stem cells were used to deliver existing drugs directly to tumors

Scott Johnson

WHO: SV tech entrepreneur
DISEASE: Multiple sclerosis
ROLE: Founder and head of Myelin Repair Foundation
\$\$ COMMITTED: Helped raise \$16 million for core research at Stanford, Case Western Reserve, Northwestern, and the University of Chicago
PROGRESS: Uncovered 150 new possible myelin-repair drug targets; 90 drugs in development, with first Phase I trial predicted for 2014

Luke Evin

WHO: Life sciences VC
DISEASE: Scleroderma
ROLE: Chairman and leading contributor, Scleroderma Research Foundation
\$\$ COMMITTED: Leading donor in a \$30 million-to-date effort
PROGRESS: Provided seed funding for a preeminent center for care of and research on the disease at Johns Hopkins and is now doing the same at Stanford; established the largest blood and tissue bank now available to scleroderma researchers



Andy Grove

WHO: Intel cofounder
DISEASES: First prostate cancer, and now Parkinson's disease
ROLE: Initiated unprecedented UCSF "Manhattan Project" against prostate cancer and donates heavily to Parkinson's research from his family foundation
\$\$ COMMITTED: \$75 million to Parkinson's research; majority funder of the \$12 million UCSF initiative
PROGRESS: An antibody therapy for prostate cancer in clinical trials

Hugh Martin

WHO: CEO of Pacific Biosciences, a DNA sequencing company
DISEASE: Multiple myeloma
ROLE: Funder and adviser, Multiple Myeloma Research Foundation, started by Kathy Giusti, who also has the disease
\$\$ COMMITTED: Plans to start donating significantly in fall 2011
PROGRESS: 50 multiple myeloma tumors have been sequenced, producing 15 new disease pathways to investigate; MMRF has helped move multiple compounds into clinical trials, six of them now in Phase III

Sergey Brin

WHO: Cofounder of Google
DISEASE: Carries a gene mutation that puts him at between 20 and 80 percent risk for developing Parkinson's disease
ROLE: Heads groundbreaking attempt to collect 10,000 patient DNA samples and discover new gene-disease associations by using Google's math-centric approach
\$\$ COMMITTED: \$50 million
PROGRESS: 4,000 Parkinson's patients have donated DNA and personal data



Larry Ellison

WHO: Oracle founder and CEO
DISEASE: Age-related deterioration
ROLE: Founded Ellison Medical Foundation to fund basic research into biology of aging
\$\$ COMMITTED: \$340 million to date
PROGRESS: Allocated 780 research grants, ranging from \$100,000 to \$1 million

Sergey Brin's \$50 million-to-date battle against Parkinson's, a disease that Brin does not have but that a DNA spit test (done at his wife's personal genomics company) indicated he has a 20 to 80 percent risk of developing.

These folks are certainly admirable. We applaud their guts and their lofty missions, but it's striking how little we've heard about their achievements. There have been numerous incremental advances—compounds moved into trials and new research targets identified—but few breakthrough successes, and certainly no cures. When Kirsch asked Grove who had impressed him, his answer was, "Nobody." He was including himself, even admitting to the *New York Times* when already deep into his Parkinson's jihad that "the most important thing we have figured out is the various things we didn't know and should have known. That is what we have to show for seven years. It's very unsatisfactory." Adds Marc Shuman, the coleader of the Prostate Cancer Program at UCSF, who headed Grove's crusade for that illness: "Ask any one of these groups whether they have extended the life of someone by even one day." Some claim that they have, but the point is, these efforts are unlikely to change the course of medicine in any monumental way.

Kirsch would eventually come to similar conclusions, but his path offers fascinating insight into the two-part dynamic behind these quests: the belief that technological genius can move mountains in medicine, and the heartbreaking realization that it can't.

THOUGH I SPENT MANY HOURS OVER THE PAST THREE years talking alone with Kirsch about his Waldenström's journey, I can't say I got to know him well. He talked very little about his three daughters—Julia, 8, Alexandra, 14, and Katherine, 16—or his wife, Michele, or what it felt like to be facing decline and probably early death. In fact, most of what I have come to understand about Kirsch I gleaned from his sprawling website entries. The Internet seems to be where he lives and breathes. His site is *Alice in Wonderland*-esque: Each click in his link-filled pages reveals a seemingly endless hall of new doorways, all stuffed with diatribes on everything from why humans could be extinct by 2100 to the critical nature of the Integral Fast Reactor project.

He takes a similarly manic approach to his disease,



Kirsch in the living room of his Los Altos Hills home. He is juggling his need to fund the search for a cure with his desire to ensure his family's financial future without him.

recording the dates and times of every infusion and blood count, the names of all his nurses, and his own comparative data analysis, complete with graphs. He even posted a photo of the rash he developed during one of his treatments. He views this cataloguing as a combination of public service and open-source living, but I came to see the tunneling amalgam of facts, theories, and digressions also as a map of Kirsch's brain.

I found myself wondering whether Kirsch might have Asperger's syndrome, a condition on the high-functioning end of the autism spectrum sometimes referred to as "geek syndrome," because it seems to be disproportionately prevalent among wonks and explains their odd mix of exceptional intellectual ability and social awkwardness. Kirsch's serial pursuit of exceedingly esoteric topics is classic Asperger's behavior, as is the way he shifted his eyes away from mine whenever we spoke, and the stilted quality of his speech—short bursts followed by unpredictable silences. The rhythm of our back-and-forth always felt off. I later learned that he gave MIT a gift to create a program to improve the interpersonal skills of engineering students.

What Kirsch lacks in social acumen, however, he makes up for in personal fortitude and drive. With his life at stake, he went into a typical all-cylinders campaign that felt a lot like one for a new startup, only this time the "product" was a cure for Waldenström's. While giving himself a crash course on the workings of blood and the immune system, Kirsch reached out to every

other big effort mounted by a well-known figure against his or her own disease, including the directors of both Michael J. Fox's renowned foundation for Parkinson's research and Michael Milken's Prostate Cancer Foundation, as well as the much lauded Multiple Myeloma Research Foundation founded by Harvard MBA and former pharmaceutical executive Kathy Giusti, which has raked in \$150 million and a glowing profile in the *New Yorker*. Kirsch condensed his findings into a nine-point how-to-cure-it list, which included setting up a foundation, hiring good people, and developing a strategic plan that balances short- and long-term goals.

The first step, as in any tech venture, was to find the most brilliant person in the room and bet on him or her, the way VC money has bet on Facebook's Mark Zuckerberg or Twitter's Jack Dorsey. That part was easy: Kirsch found his genius in Irene Ghobrial, a 37-year-old researcher at Boston's Dana-Farber Cancer Institute who had received one of the only grants the National Institutes of Health (NIH) ever awarded for Waldenström's research. Within months of his diagnosis, Kirsch was on a plane to meet her. Soon after, Ghobrial's lab became the Steve and Michele Kirsch Laboratory, in honor of the \$1 million he would donate over the course of five years. His funds would pay for about 60 percent of Ghobrial's work on Waldenström's, allowing her to add two researchers to her team and freeing her from the constant burden of grant writing.

The money also allowed her to stretch the conservative medical model the NIH expected of her. She was getting impressive results from a one-two-punch drug combo against multiple myeloma, another cancer involving white blood cells. The first drug smoked the bad cells out of the bone marrow, and the second bombed them out of existence. But Kirsch's money and restless intellect allowed her to test other drugs specifically against Waldenström's. "Steve doesn't take any answer for granted," Ghobrial says. "I really respect that. It makes us start thinking outside the box. The NIH doesn't generally give you money to start high-risk research."

To fulfill his pledge to Ghobrial, and hopefully do more, Kirsch asked the board of his own philanthropic foundation to focus almost entirely on Waldenström's. This was a major turnabout for the Kirsch Foundation, which had made enough donations to largely civic, educational, and environmental groups to land Steve and his wife in the no. 5 slot on *Worth Magazine's* "25 Most Generous Young Americans" list in 2002.

Keenly focused on efficiency—getting optimal bang for his research buck—Kirsch asked Ghobrial and her team to determine what it would take to bring knowledge about Waldenström's even with what was known about other, much better understood cancers. Her conclusion: \$50 million. Kirsch ponied up an additional \$1 million and gave another \$300,000 to the Leukemia and Lymphoma Society to create viable cell lines, but stipulated that the balance of those funds needed to be raised elsewhere—and told Ghobrial whom to call for help: former Stanford board chair Peter Bing, a big-league

"Thursday we start breaking the rules," Kirsch wrote me excitedly in May 2008, when he decided to try an unconventional drug regimen—the kind of paradigm-shattering effort he thought medicine needed.

philanthropist and a WM patient himself. Kirsch also devised a system to incite those doing research to compete with one another for additional funding. "It's like *Survivor*," he joked. "Someone gets voted off."

Quickly, Kirsch's own treatment began to reflect a tech entrepreneur's approach to medicine. Six months after his diagnosis, his vision started to blur, so he checked in at Stanford Medical Center to get his first infusion of a drug called Rituxan. He had a bad reaction to it and was incensed to learn that the dose (at about \$16,000 a cycle) doesn't change regardless of how the patient responds, a result of medicine's strict credo of administering drugs only precisely as they have been clinically tested. "It shows you how crude the treatments are," he told me, the corners of his mouth twitching as he talked. "It doesn't matter that a different dose might be much more effective."

Kirsch had just finished reading *The Patient from Hell*, about a Stanford climatologist who uses his climate-analysis approach to create his own cancer treatment. Inspired, Kirsch decided to develop an individualized Rituxan regimen, based on a paper he'd read about a new low-dose protocol. To him, this was the kind of paradigm-shattering effort medicine needed—the kind that led cell phones to give way to smartphones and Skype—but his Stanford oncologist refused to go along. So Kirsch quit the doc and her world-class medical institution and found Dr. Shane Dormady, at the less prestigious El Camino Hospital in Mountain View. "I met with him today. Thursday we start breaking the rules," he wrote me excitedly in May 2008. He also touted his plan on his blog: "I'll be making history. I'll be the only person on the planet that I'm aware of to try a lower dose of Rituxan."

Uncharacteristically, Kirsch then let himself be lulled by the one fairy-tale ending that exists in this realm—not coincidentally, the one that sounded most like the kind of dramatic breakthrough he had come to expect in tech. He learned that in 1993, an oncologist working on chronic myelogenous leukemia (CML) had tested several compounds, and in short order, one of them—eventually renamed Gleevec—became the wonder drug for CML. Suddenly, what had been a sure death sentence was a survivable disease, as 98 percent of patients went into full remission. The Gleevec story became the pot of gold at the end of Kirsch's rainbow: "So it's been done before," he blogged. "We just need to put the necessary money and talent to work."

In the meantime, Kirsch was stuck with experimenting. He decided to switch from his low-dose Rituxan regimen to a drug that was getting promising results in one of Ghobrial's clinical trials, and over the next few years he would try one other treatment. But none of these seemed like a potential Gleevec.

THERE DIDN'T SEEM TO BE ANY "AHA" MOMENT THAT made Kirsch decide to lay down the "I-can-cure-Waldenström's" torch—or at least he never characterized it that way to me. Oddly enough, his

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work on spam, which he has continued throughout his medical odyssey, was what gradually convinced him that beating back a technological menace (like junk emails) was entirely different from beating back malignant cells.

He couldn't help but compare the two problems. Spam, he knew, is a well-defined scourge. Like coding software or designing a search engine, or any of the other tech feats that are accomplished weekly in Silicon Valley, fighting spam involves predictable markers and rock-solid underlying principles. It's tricky, of course, and has confounded hundreds of computer geeks, in part because spammers morph their algorithms to outsmart new filters in much the same way that our cells adapt to resist new drugs. But in the end, spam could be wrestled to the ground by someone with tenacity and the right technological prowess.

But Waldenström's—or any other major disease, for that matter—is unlikely to yield to this kind of “Manhattan Project.” Drug tests on humans take anywhere from 6 to 12 years, and huge numbers of subjects must agree to participate, at a cost of up to \$20,000 per volunteer. Patients with the same disease don't necessarily respond to the same drugs; responders often turn into nonresponders, as Kirsch can attest; and asking three experts can yield three different answers—another frustration Kirsch experienced. In fact, a few months back, the FDA pulled Avastin, a drug used against metastatic breast cancer, off the market on the very same day that the EU's regulatory agency voted to keep it on. The truth is that cures for most major diseases still elude us, and effective new drugs to control them are few and far between. No more than one in 10,000 compounds that start down the development path make it onto pharmacy shelves.

All of this explains why the typical process of searching for cures looks nothing like what Kirsch went through to conquer spam. For that, he and a small team spent five years generating ideas, writing software to test his theories, and then retesting

and tweaking based on error rates that showed up instantly on the computer. When he finally hit on his winning idea—to use the amount of spam the *recipient* receives rather than the amount the sender produces to determine the “spamminess” of a particular message—his spam filter was ready for business within six months.

Compare this with Grove’s assault on Parkinson’s, which Grove began with a big bet on stem cell therapy—thought to be the long-awaited silver bullet for stricken nerve cells. At the first stage of research, which was who knows how many years and steps away from an actual cure, the therapy was successful in the lab but failed when tested on mice. Next, Grove tested some proteins that had been shown to enhance nerve cell performance. Again, the experiment was successful in the lab, but when the proteins were introduced into the human system, they failed to pass into the brain, where they needed to be. “After ten years in the Parkinson’s field, we may finally have three drugs in Phase I [where the drug’s safety and efficacy are tested on small groups of people] and Phase II [tested on larger groups of people],” Grove said in a *Wired* article, by Thomas Goetz, about Brin and his Parkinson’s crusade. “That’s more than ever before. But let’s get real. We’ll get the results in 2012, then they’ll argue about it for a year, then Phase III results [where the drug is compared with standard treatments, in even larger groups] in 2015, then argue about that for a year—if I’m around when they’re

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done...” He didn’t finish his thought, but I felt as if Kirsch were doing it for him when he told me, shaking his head, “You can put in all the funding and all the king’s men, and it’s still a crapshoot.”

For Kirsch, there was another major stumbling block: money. He had invested \$30 million in his foundation, but a year into his crusade came the crash, and the value of the investment went down 30 percent. On top of that, compared to funding sources for diseases like prostate and breast cancer, which touch an enormous number of people, there’s a minuscule well to tap for Waldenström’s (not to mention a much smaller number of potential research subjects—Giusti has 13 times the patient pool to access in her fight against multiple myeloma). Asking friends for money felt like asking for a “handout,” Kirsch says.

Even if he could find more funding, it would still be a drop in the bucket compared to the kind of money being thrown at conventional medical research. It costs several hundred million dollars to develop a single drug, which explains pharmaceutical giant Amgen’s \$3 billion annual R&D budget—and that figure pales beside the budget of the NIH, which is 10 times as big. Major private groups like the American Cancer Society direct \$130 million to research in one year, making star fundraiser Giusti’s \$150 million in 13 years look like chump change.

Kirsch had also been blinded by his belief in the value of his technical smarts. Gifted as he was in his own

realm, no number of rave reviews in *Network Computing* (which confirmed the 99.99 percent effectiveness of his spam filter) would ever turn him into a molecular biologist capable of the creative twists that lead to big breakthroughs. Grove said basically the same thing when I asked him what about his efforts had been harder than he had expected. “Applying judgment in fields where your basic knowledge is flimsy,” he said.

“How many diseases have been cured by someone who has that disease?” Kirsch said one afternoon in his Abaca office. He seemed to be asking himself as much as me. “Name one.”

Kirsch’s big revelation, though, was that becoming the public face of the Waldenström’s fight was never going to satisfy what matters to him most of all: having the broadest possible impact. Ridding the world of spam, he believes, would be a true social good. “With spam, I can change the life of everybody on the planet—or, at least, of hundreds of millions of people,” he told me. A Waldenström’s cure, even assuming he could really help advance one, would only help 1,500 people a year—a calculus that some people might think is odd, given that lives would be saved, but that Kirsch genuinely believes in. Perhaps that’s why, in the end, he couldn’t continue mustering the same passion for his Waldenström’s work as he could for spam busting. Plus, he concluded that the skills needed to promote a cause and raise tons of money weren’t among his true talents.

Kirsch realized that no number of rave reviews in *Network Computing* would ever turn him into a molecular biologist capable of the creative twists that lead to big breakthroughs.

BY LAST FALL, KIRSCH WAS OFF THE DRUG HE HAD abandoned his low-dose Rituxan protocol to try, and on to yet another. He was feeling “cautiously optimistic” about his prognosis, mainly because even though his condition worsened soon after his diagnosis, it has remained stable throughout his treatment. “It’s likely I have at least five years, probably more,” he wrote on his website.

Meanwhile, Ghobrial won a second federal grant, which she credited to Kirsch’s funding of the preliminary work that distinguished her proposal, and is excited about a new compound she’s testing. She and Kirsch are still in regular contact.

Overall, despite his personal decision to back off, Kirsch believes his efforts have been worthwhile. He has a top cancer researcher completely invested in his case, and he’s hopeful about her various projects. Just last week he told me he still had “many more tricks in the bag. It’s all about buying time.” ■

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