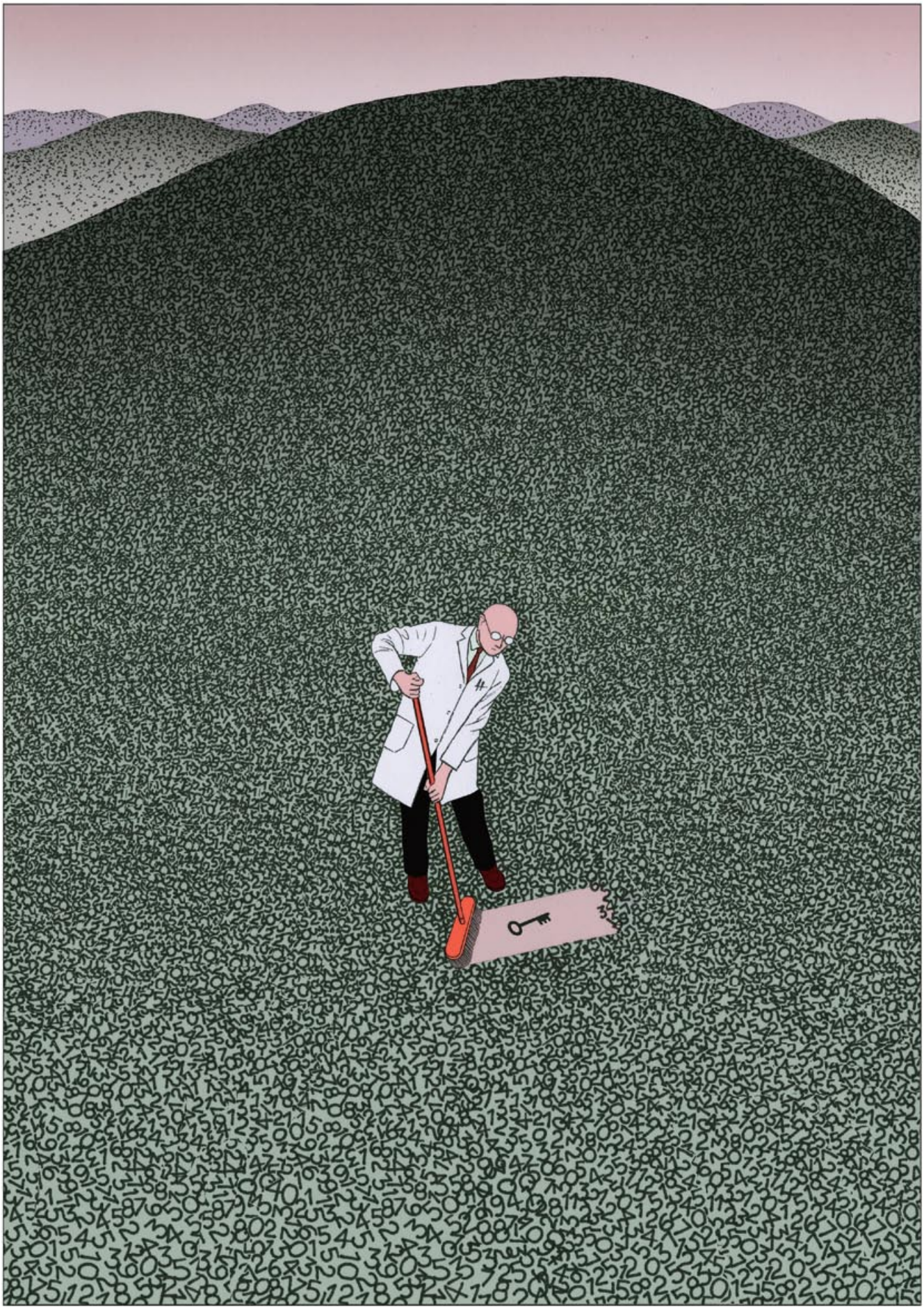

GUY BILLOUT

THE TREATMENT

Why is it so difficult to develop drugs for cancer?

BY MALCOLM GLADWELL

In the world of cancer research, there is something called a Kaplan-Meier curve, which tracks the health of patients in the trial of an experimental drug. In its simplest version, it consists of two lines. The first follows the patients in the "control arm," the second the patients in the "treatment arm." In most cases, those two lines are virtually identical. That is the sad fact of cancer research: nine times out of ten, there is no difference in survival between those who were given the new drug and those who were not. But every now and again—after millions of dollars have been spent, and tens of thousands of pages of data collected, and patients followed, and toxicological issues examined, and safety issues resolved, and manufacturing processes fine-tuned—the patients in the treatment arm will live longer than the patients in the control arm, and the two lines on the Kaplan-Meier will start to diverge.

Seven years ago, for example, a team from Genentech presented the results of a colorectal-cancer drug trial at the annual meeting of the American Society of Clinical Oncology—a conference attended by virtually every major cancer researcher in the world. The lead Genentech researcher took the audience through one slide after another—*click, click, click*—laying out the design and scope of the study, until he came to the crucial moment: the Kaplan-Meier. At that point, what he said became irrelevant. The members of the audience saw daylight between the two lines, for a patient population in which that almost never happened, and they leaped to their feet and gave him an ovation. Every drug researcher in the world dreams of standing in front of thousands of people at ASCO and clicking on a Kaplan-Meier like that. "It is why we are in this business," Safi Bahcall says. Once he thought that this dream would come true for him. It was in the late summer of 2006, and is among the greatest moments of his life.

Bahcall is the C.E.O. of Synta Pharmaceuticals, a small biotechnology company. It occupies a one-story brick nineteen-seventies building outside Boston, just off Route 128, where many of the region's high-tech companies have congregated, and that summer Synta had two compounds in development. One was a cancer drug called elesclomol. The other was an immune modulator called apilimod. Experimental drugs must pass through three phases of testing before they can be considered for government approval. Phase 1 is a small trial to determine at what dose the drug can be taken safely. Phase 2 is a larger trial to figure out if it has therapeutic potential, and Phase 3 is a definitive trial to see if it actually works, usually in comparison with standard treatments. Elesclomol had progressed to Phase 2 for soft-tissue sarcomas and for lung cancer, and had come up short in both cases. A Phase 2 trial for metastatic melanoma—a deadly form of skin cancer—was also under way. But that was a long shot: nothing ever worked well for melanoma. In the previous thirty-five years, there had been something like seventy large-scale Phase 2 trials for metastatic-melanoma drugs, and if you plotted all the results on a single Kaplan-Meier there wouldn't be much more than a razor's edge of difference between any two of the lines.

That left apilimod. In animal studies and early clinical trials for autoimmune disorders, it seemed promising. But when Synta went to Phase 2 with a trial for psoriasis, the results were underwhelming. "It was ugly," Bahcall says. "We had lung cancer fail, sarcoma next, and then psoriasis. We had one more trial left, which was for Crohn's disease. I remember my biostats guy coming into my office, saying, 'I've got some good news and some bad news. The good news is that apilimod is safe. We have the data. No toxicity. The bad news is that it's not effective.' It was heartbreaking."

Bahcall is a boyish man in his early forties, with a round face and dark, curly hair. He was sitting at the dining-room table in his sparsely furnished apartment in Manhattan, overlooking the Hudson River. Behind him, a bicycle was leaning against a bare wall, giving the room a post-college feel. Both his parents were astrophysicists, and he, too, was trained as a physicist, before leaving academia for the business world. He grew up in the realm of the abstract and the theoretical—with theorems and calculations and precise measurements. But drug development was different, and when he spoke about the failure of apilimod there was a slight catch in his voice.

Bahcall started to talk about one of the first patients ever treated with elesclomol: a twenty-four-year-old African-American man. He'd had Kaposi's sarcoma; tumors covered his lower torso. He'd been at Beth Israel Deaconess Medical Center, in Boston, and Bahcall had flown up to see him. On a Monday in January of 2003, Bahcall sat by his bed and they talked. The patient was just out of college. He had an I.V. in his arm. You went to the hospital and you sat next to some kid whose only wish was not to die, and it was impossible not to get emotionally involved. In physics, failure was disappointing. In drug development, failure was *heartbreaking*. Elesclomol wasn't much help against Kaposi's sarcoma. And now apilimod didn't work for Crohn's. "I mean, we'd

Mass screening isn't as elegant as rational drug design, but it provides the chance of a completely unexpected discovery.

done charity work for the Crohn's & Colitis Foundation," Bahcall went on. "I have relatives and friends with Crohn's disease, personal experience with Crohn's disease. We had Crohn's patients come in and talk in meetings and tell their stories. We'd raised money for five years from investors. I felt terrible. Here we were with our lead drug and it had failed. It was the end of the line."

That summer of 2006, in one painful meeting after another, Synta began to downsize. "It was a Wednesday," Bahcall said. "We were around a table, and we were talking about pruning the budget and how we're going to contain costs, one in a series of tough discussions, and I noticed my chief medical officer, Eric Jacobson, at the end of the table, kind of looking a little unusually perky for one of those kinds of discussions." After the meeting, Bahcall pulled Jacobson over: "Is something up?" Jacobson nodded. Half an hour before the meeting, he'd received some news. It was about the melanoma trial for elesclomol, the study everyone had given up on. "The consultant said she had never seen data this good," Jacobson told him.

Bahcall called back the management team for a special meeting. He gave the floor to Jacobson. "Eric was, like, 'Well, you know we've got this melanoma trial,' " Bahcall began, "and it took a moment to jog people's memories, because we'd all been so focussed on Crohn's disease and the psoriasis trials. And Eric said, 'Well, we got the results. The drug worked! It was a positive trial!' " One person slammed the table, stood up, and hollered. Others peppered Eric with questions. "Eric said, 'Well, the group analyzing the data is trying to disprove it, and they can't disprove it.' And he said, 'The consultant handed me the data on Wednesday morning, and she said it was boinking good.' And everyone said, '*What*?' Because Eric is the sweetest guy, who never swears. A bad word cannot cross his lips. Everyone started yelling, 'What? What? What did she say, Eric? Eric! Eric! Say it! Say it!' "

Bahcall contacted Synta's board of directors. Two days later, he sent out a company-wide e-mail saying that there would be a meeting that afternoon. At four o'clock, all hundred and thirty employees trooped into the building's lobby. Jacobson stood up. "So the lights go down," Bahcall continued. "Clinical guys, when they present data, tend to do it in a very bottoms-up way: this is the disease population, this is the treatment, and this is the drug, and this is what was randomized, and this is the demographic, and this is the patient pool, and this is who had toenail fungus, and this is who was Jewish. They go on and on and on, and all anyone wants is, Show us the fucking Kaplan-Meier! Finally he said, 'All right, now we can get to the efficacy.' It gets really silent in the room. He clicks the slide. The two lines separate out beautifully—and a gasp goes out, across a hundred and thirty people. Eric starts to continue, and one person goes like this"—Bahcall started clapping slowly—"and then a couple of people joined in, and then soon the whole room is just going like this—clap, clap, clap. There were tears. We all realized that our lives had changed, the lives of patients had changed, the way of treating the disease had changed. In that moment, everyone realized that this little company of a hundred and thirty people had a chance to win. We had a drug that worked, in a disease where nothing worked. That was the single most moving five minutes of all my years at Synta."

In the winter of 1955, a young doctor named Emil Freireich arrived at the National Cancer Institute, in Bethesda, Maryland. He had been drafted into the Army, and had been sent to fulfill his military obligation in the public-health service. He went to see Gordon Zubrod, then the clinical director for the N.C.I. and later one of the major figures in cancer research. "I said, 'I'm a hematologist,' " Freireich recalls. "He said, 'I've got a good idea for you. Cure leukemia.' It was a military assignment." From that assignment came the first great breakthrough in the war against cancer.

Freireich's focus was on the commonest form of childhood leukemia—acute lymphoblastic leukemia (ALL). The diagnosis was a death sentence. "The children would come in bleeding," Freireich says. "They'd have infections. They would be in pain. Median survival was about eight weeks, and everyone was dead within the year." At the time, three drugs were known to be useful against ALL. One was methotrexate, which, the pediatric pathologist Sidney Farber had shown seven years earlier, could push the disease into remission. Corticosteroids and 6-mercaptopurine (6-MP) had since proved useful. But even though methotrexate and 6-MP could kill a lot of cancer cells, they couldn't kill them all, and those which survived would regroup and adjust and multiply and return with a vengeance. "These remissions were all temporary—two or three months," Freireich, who now directs the adult-leukemia research program at the M. D. Anderson Cancer Center, in Houston, says. "The authorities in hematology didn't even want to use them in children. They felt it just prolonged the agony, made them suffer, and gave them side effects. That was the landscape."

In those years, the medical world had made great strides against tuberculosis, and treating t.b. ran into the same problem as treating cancer: if doctors went after it with one drug, the bacteria eventually developed resistance. Their solution was to use multiple drugs simultaneously that worked in very different ways. Freireich wondered about applying that model to leukemia. Methotrexate worked by disrupting folic-acid uptake, which was crucial in the division of cells; 6-MP shut down the synthesis of purine, which was also critical in cell division. Putting the two together would be like hitting the cancer with a left hook and a right hook. Working with a group that eventually included Tom Frei, of the N.C.I., and James Holland, of the Roswell Park Cancer Institute, in Buffalo, Freireich started treating ALL patients with methotrexate and 6-MP in combination, each at two-thirds its regular dose to keep side effects in check. The remissions grew more frequent. Freireich then added the steroid prednisone, which worked by a mechanism different from that of either 6-MP or methotrexate; he could give it at full dose and not worry about the side effects getting out of control. Now he had a left hook, a right hook, and an uppercut.

"So things are looking good," Freireich went on. "But still everyone dies. The remissions are short. And then out of the blue came the gift from Heaven"—another drug, derived from periwinkle,

that had been discovered by Irving Johnson, a researcher at Eli Lilly. "In order to get two milligrams of drug, it took something like two train-car loads of periwinkle," Freireich said. "It was expensive. But Johnson was persistent." Lilly offered the new drug to Freireich. "Johnson had done work in mice, and he showed me the results. I said, 'Gee whiz, I've got ten kids on the ward dying. I'll give it to them tomorrow.' So I went to Zubrod. He said, 'I don't think it's a good idea.' But I said, 'These kids are dying. What's the difference?' He said, 'O.K., I'll let you do a few children.' The response rate was fifty-five per cent. The kids jumped out of bed." The drug was called vincristine, and, by itself, it was no wonder drug. Like the others, it worked only for a while. But the good news was that it had a unique mechanism of action—it interfered with cell division by binding to what is called the spindle protein—and its side effects were different from those of the other drugs. "So I sat down at my desk one day and I thought, Gee, if I can give 6-MP and meth at two-thirds dose and prednisone at full dose and vincristine has different limiting toxicities, I bet I can give a full dose of that, too. So I devised a trial where we would give all four in combination." The trial was called VAMP. It was a left hook, a right hook, an uppercut, and a jab, and the hope was that if you hit leukemia with that barrage it would never get up off the canvas.

The first patient treated under the experimental regimen was a young girl. Freireich started her off with a dose that turned out to be too high, and she almost died. She was put on antibiotics and a respirator. Freireich saw her eight times a day, sitting at her bedside. She pulled through the chemo-induced crisis, only to die later of an infection. But Freireich was learning. He tinkered with his protocol and started again, with patient No. 2. Her name was Janice. She was fifteen, and her recovery was nothing short of miraculous. So was the recovery of the next patient and the next and the next, until nearly every child was in remission, without need of antibiotics or transfusions. In 1965, Frei and Freireich published one of the most famous articles in the history of oncology, "Progress and Perspective in the Chemotherapy of Acute Leukemia," in *Advances in Chemotherapy*. Almost three decades later, a perfectly healthy Janice graced the cover of the journal *Cancer Research*.

"I see so much love reflected back in his adorable little face."

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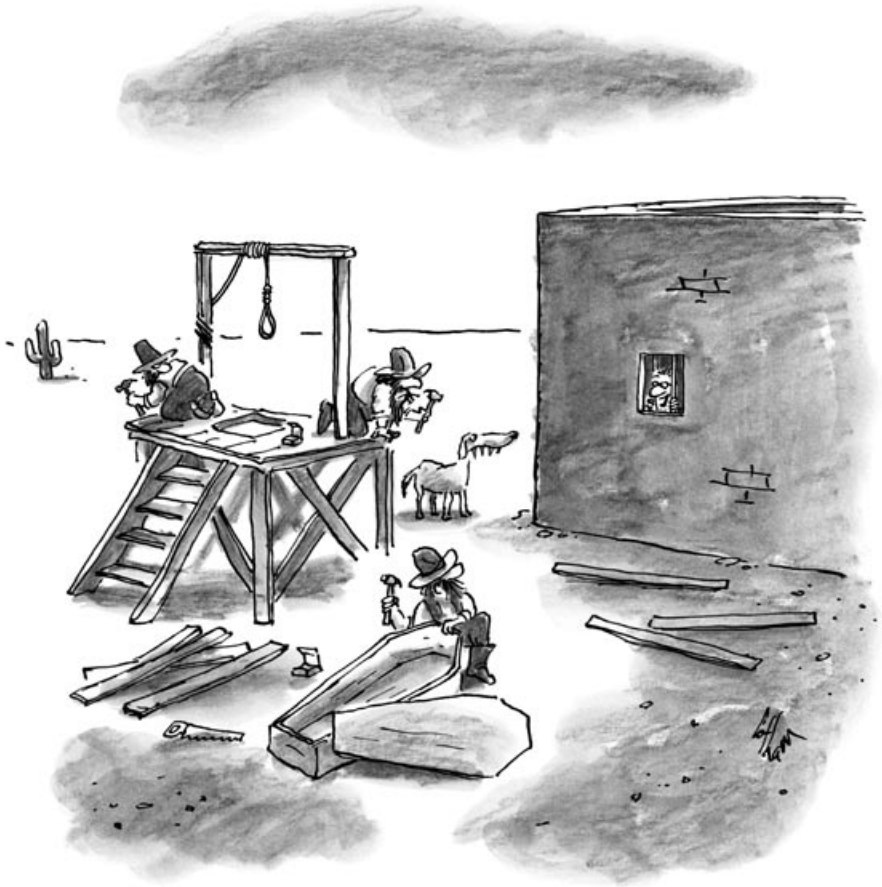
What happened with ALL was a formative experience for an entire generation of cancer fighters. VAMP proved that medicine didn't need a magic bullet—a superdrug that could stop all cancer in its tracks. A drug that worked a little bit could be combined with another that worked a little bit and another that worked a little bit, and, as long as all three worked in different ways and had different side effects, the combination could turn out to be spectacular. To be valuable, a cancer drug didn't have to be especially effective on its own; it just had to be novel in the way it acted. And, from the beginning, this was what caused so much excitement about elesclomol.

Safi Bahcall's partner in the founding of Synta was a cell biologist at Harvard Medical School named Lan Bo Chen. Chen, who is in his mid-sixties, was born in Taiwan. He is a mischievous man, with short-cropped straight black hair and various quirks—including a willingness to say whatever is on his mind, a skepticism about all things Japanese (the Japanese occupied Taiwan during the war, after all), and a keen interest in the marital prospects of his unattached co-workers. Bahcall, who is Jewish, describes him affectionately as "the best and worst parts of a Jewish father and the best and worst parts of a Jewish mother rolled into one." (Sample e-mail from Chen: "Safi is in Israel. Hope he finds wife.")

Drug hunters like Chen fall into one of two broad schools. The first school, that of "rational design," believes in starting with the disease and working backward—designing a customized solution based on the characteristics of the problem. Herceptin, one of the most important of the new generation of breast-cancer drugs, is a good example. It was based on genetic detective work showing that about a quarter of all breast cancers were caused by the overproduction of a protein called HER2. HER2 kept causing cells to divide and divide, and



"I can help you guys form a union."

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scientists set about designing a drug to turn HER2 off. The result is a drug that improved survival in twenty-five per cent of patients with advanced breast cancer. (When Herceptin's Kaplan-Meier was shown at ASCO, there was stunned silence.) But working backward to a solution requires a precise understanding of the problem, and cancer remains so mysterious and complex that in most cases scientists don't have that precise understanding. Or they think they do, and then, after they turn off one mechanism, they discover that the tumor has other deadly tricks in reserve.

The other approach is to start with a drug candidate and then hunt for diseases that it might attack. This strategy, known as "mass screening," doesn't involve a theory. Instead, it involves a random search for matches between treatments and diseases. This was the school to which Chen belonged. In fact, he felt that the main problem with mass screening was that it wasn't mass enough. There were countless companies outside the drug business—from industrial research labs to photography giants like Kodak and Fujifilm—that had millions of chemicals sitting in their vaults. Yet most of these chemicals had never been tested to see if they had potential as drugs. Chen couldn't understand why. If the goal of drug discovery was novelty, shouldn't the hunt for new drugs go as far and wide as possible?

"In the early eighties, I looked into how Merck and Pfizer went about drug discovery," Chen recalls. "How many compounds are they using? Are they doing the best they can? And I come up with an incredible number. It turns out that mankind had, at this point, made tens of millions of compounds. But Pfizer was screening only six hundred thousand compounds, and Merck even fewer, about five hundred thousand. How could they screen for drugs and use only five hundred thousand, when mankind has already made so many more?"

An early financial backer of Chen's was Michael Milken, the junk-bond king of the nineteen-eighties who, after being treated for prostate cancer, became a major cancer philanthropist. "I told Milken my story," Chen said, "and very quickly he said, 'I'm going to give you four million dollars. Do whatever you want.' Right away, Milken thought of Russia. Someone had told him that the Russians had had, for a long time, thousands of chemists in one city making compounds, and none of those compounds had been disclosed." Chen's first purchase was a batch of twenty-two thousand chemicals, gathered from all over Russia and Ukraine. They cost about ten dollars each, and came in tiny glass vials. With his money from Milken, Chen then bought a six-hundred-thousand-dollar state-of-the-art drug-screening machine. It was a big, automated Rube Goldberg contraption that could test ninety-six compounds at a time and do a hundred batches a day. A robotic arm would deposit a few drops of each chemical onto a plate, followed by a clump of cancer cells and a touch of blue dye. The mixture was left to sit for a week, and then reëxamined. If the cells were still alive, they would show as blue. If the chemical killed the cancer cells, the fluid would be clear.

Chen's laboratory began by testing his compounds against prostate-cancer cells, since that was the disease Milken had. Later, he screened dozens of other cancer cells as well. In the first go-around, his batch of chemicals killed everything in sight. But plenty of compounds, including pesticides and other sorts of industrial poisons, will kill cancer cells. The trouble is that they'll kill healthy cells as well. Chen was looking for something that was selective—that was more likely to kill malignant cells than normal cells. He was also interested in sensitivity—in a chemical's ability to kill at low concentrations. Chen reduced the amount of each chemical on the plate a thousandfold, and tried again. Now just one chemical worked. He tried the same chemical on healthy cells. It left them alone. Chen lowered the dose another thousandfold. It still worked. The compound came from the National Taras Shevchenko University

of Kiev. It was an odd little chemical, the laboratory equivalent of a jazz musician's riff. "It was pure chemist's joy," Chen said. "Homemade, random, and clearly made for no particular purpose. It was the only one that worked on everything we tried."

Mass screening wasn't as elegant or as efficient as rational drug design. But it provided a chance of stumbling across something by accident—something so novel and unexpected that no scientist would have dreamed it up. It provided for serendipity, and the history of drug discovery is full of stories of serendipity. Alexander Fleming was looking for something to fight bacteria, but didn't think the answer would be provided by the mold that grew on a petri dish he accidentally left out on his bench. That's where penicillin came from. Pfizer was looking for a new heart treatment and realized that a drug candidate's unexpected side effect was more useful than its main effect. That's where Viagra came from. "The end of surprise would be the end of science," the historian Robert Friedel wrote in the 2001 essay "Serendipity Is No Accident." "To this extent, the scientist must constantly seek and hope for surprises." When Chen gathered chemical compounds from the farthest corners of the earth and tested them against one cancer-cell line after another, he was engineering surprise.

What he found was exactly what he'd hoped for when he started his hunt: something he could never have imagined on his own. When cancer cells came into contact with the chemical, they seemed to go into crisis mode: they acted as if they had been attacked with a blowtorch. The Ukrainian chemical, elesclomol, worked by gathering up copper from the bloodstream and bringing it into cells' mitochondria, sparking an electrochemical reaction. His focus was on the toxic, oxygen-based compounds in the cell called ROS, reactive oxygen species. Normal cells keep ROS in check. Many kinds of cancer cells, though, generate so much ROS that the cell's ability to keep functioning is stretched to the breaking point, and elesclomol cranked ROS up even further, to the point that the cancer cells went up in flames. Researchers had long known that heating up a cancer cell was a good way of killing it, and there had been plenty of interest over the years in achieving that effect with ROS. But the idea of using copper to set off an electrochemical reaction was so weird—and so unlike the way cancer drugs normally worked—that it's not an approach anyone would have tried by design. That was the serendipity. It took a bit of "chemist's joy," constructed for no particular reason by some bench scientists in Kiev, to show the way. Elesclomol was wondrously novel. "I fell in love," Chen said. "I can't explain it. I just did."

When Freireich went to Zubrod with his idea for VAMP, Zubrod could easily have said no. Drug protocols are typically tested in advance for safety in animal models. This one wasn't. Freireich freely admits that the whole idea of putting together poisonous drugs in such dosages was "insane," and, of course, the first patient in the trial had nearly been killed by the toxic regimen. If she had died from it, the whole trial could have been derailed.

The ALL success story provided a hopeful road map for a generation of cancer fighters. But it also came with a warning: those who pursued the unexpected had to live with unexpected consequences. This was not the elegance of rational drug design, where scientists perfect their strategy in the laboratory before moving into the clinic. Working from the treatment to the disease was an exercise in uncertainty and trial and error.

If you're trying to put together a combination of three or four drugs out of an available pool of dozens, how do you choose which to start with? The number of permutations is vast. And, once you've settled on a combination, how do you administer it? A child gets sick. You treat her. She goes into remission, and then she relapses. VAMP established that the best way to induce remission was to treat the child aggressively when she first showed up with leukemia. But do you treat during the remission as well, or only when the child relapses? And, if you treat during remission, do you treat as aggressively as you did during remission induction, or at a lower level? Do you use the same drugs in induction as you do in remission and as you do in relapse? How do you give the drugs, sequentially or in combination? At what dose? And how frequently—every day, or do you want to give the child's body a few days to recover between bouts of chemo?

Oncologists compared daily 6-MP plus daily methotrexate with daily 6-MP plus methotrexate every four days. They compared methotrexate followed by 6-MP, 6-MP followed by methotrexate, and both together. They compared prednisone followed by full doses of

"Strange—more people are buying the sex bot than the I-told-you-so bot."

6-MP, methotrexate, and a new drug, cyclophosphamide (CTX), with prednisone followed by half doses of 6-MP, methotrexate, and CTX. It was endless: vincristine plus prednisone and then methotrexate every four days or vincristine plus prednisone and then methotrexate daily? They tried new drugs, and different combinations. They tweaked and refined, and gradually pushed the cure rate from forty per cent to eighty-five per cent. At St. Jude Children's Research Hospital, in Memphis—which became a major center of ALL research—no fewer than sixteen clinical trials, enrolling 3,011 children, have been conducted in the past forty-eight years.

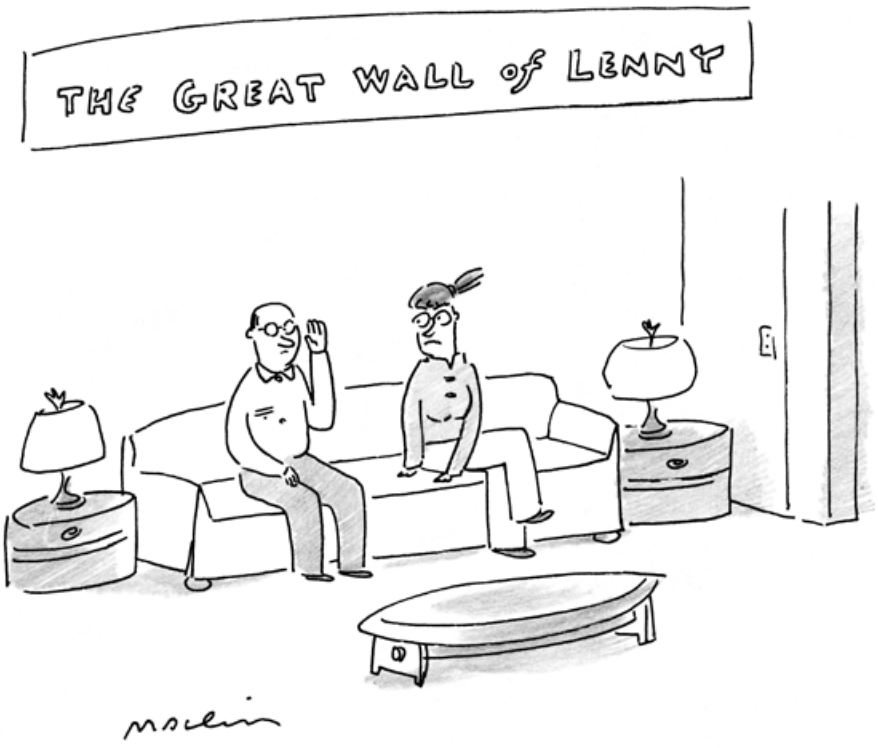
And this was just childhood leukemia. Beginning in the nineteen-seventies, Lawrence Einhorn, at Indiana University, pushed cure rates for testicular cancer above eighty per cent with a regimen called BEP: three to four rounds of bleomycin, etoposide, and cisplatin. In the nineteen-seventies, Vincent T. DeVita, at the N.C.I., came up with MOPP for advanced Hodgkin's disease: mustargen, oncovin, procarbazine, and prednisone. DeVita went on to develop a combination therapy for breast cancer called CMF—cyclophosphamide, methotrexate, and 5-fluorouracil. Each combination was a variation on the combination that came before it, tailored to its target through a series of iterations. The often asked question "When will we find a cure for cancer?" implies that there is some kind of master code behind the disease waiting to be cracked. But perhaps there isn't a master code. Perhaps there is only what can be uncovered, one step at a time, through trial and error.

When elesclomol emerged from the laboratory, then, all that was known about it was that it did something novel to cancer cells in the laboratory. Nobody had any idea what its best target was. So Synta gave elesclomol to an oncologist at Beth Israel in Boston, who began randomly testing it out on his patients in combination with paclitaxel, a standard chemotherapy drug. The addition of elesclomol seemed to shrink the tumor of someone with melanoma. A patient whose advanced ovarian cancer had failed multiple rounds of previous treatment had some response. There was dramatic activity against Kaposi's sarcoma. They could have gone on with Phase 1s indefinitely, of course. Chen wanted to combine elesclomol with radiation therapy, and another group at Synta would later lobby hard to study elesclomol's effects on acute myeloid leukemia (AML), the commonest form of adult leukemia. But they had to draw the line somewhere. Phase 2 would be lung cancer, soft-tissue sarcomas, and melanoma.

Now Synta had its targets. But with this round of testing came an even more difficult question. What's the best way to conduct a test of a drug you barely understand? To complicate matters further, melanoma, the disease that seemed to be the best of the three options, is among the most complicated of all cancers. Sometimes it confines itself to the surface of the skin. Sometimes it invades every organ in the body. Some kinds of melanoma have a mutation involving a gene called BRAF; others don't. Some late-stage melanoma tumors pump out high levels of an enzyme called LDH. Sometimes they pump out only low levels of LDH, and patients with low-LDH tumors lived so much longer that it was as if they had a different disease. Two patients could appear to have identical diagnoses, and then one would be dead in six months and the other would be fine. Tumors sometimes mysteriously disappeared. How did you conduct a drug trial with a disease like this?

It was entirely possible that elesclomol would work in low-LDH patients and not in high-LDH patients, or in high-LDH patients and not in low-LDH ones. It might work well against the melanoma that confined itself to the skin and not against the kind that invaded the liver and other secondary organs; it might work in the early stages of metastasis and not in the later stages. Then, there was the prior-treatment question. Because of how quickly tumors become resistant to drugs, new treatments sometimes work better on "naïve" patients—those who haven't been treated with other forms of chemotherapy. So elesclomol might work on chemo-naïve patients and not on prior-chemo patients. And, in any of these situations, elesclomol might work better or worse depending on which other drug or drugs it was combined with. There was no end to the possible combinations of patient populations and drugs that Synta could have explored.

At the same time, Synta had to make sure that whatever trial it ran was as big as possible. With a disease as variable as melanoma, there was always the risk in



a small study that what you thought was a positive result was really a matter of spontaneous remissions, and that a negative result was just the bad luck of having patients with an unusually recalcitrant form of the disease. John Kirkwood, a melanoma specialist at the University of Pittsburgh, had done the math: in order to guard against some lucky or unlucky artifact, the treatment arm of a Phase 2 trial should have at least seventy patients.

Synta was faced with a dilemma. Given melanoma's variability, the company would ideally have done half a dozen or more versions of its Phase 2 trial: low-LDH, high-LDH, early-stage, late-stage, prior-chemo, chemo-naïve, multi-drug, single-drug. There was no way, though, that they could afford to do that many trials with seventy patients in each treatment arm. The American biotech industry is made up of lots of companies like Synta, because small start-ups are believed to be more innovative and adventurous than big pharmaceutical houses. But not even big firms can do multiple Phase 2 trials on a single disease—not when trials cost more than a hundred thousand dollars per patient and not when, in the pursuit of serendipity, they are simultaneously testing that same experimental drug on two or three other kinds of cancer. So Synta compromised. The company settled on one melanoma trial: fifty-three patients were given elesclomol plus paclitaxel, and twenty-eight, in the control group, were given paclitaxel alone, representing every sort of LDH level, stage of disease, and prior-treatment status. That's a long way from half a dozen trials of seventy each.

Synta then went to Phase 3: six hundred and fifty-one chemo-naïve patients, drawn from a hundred and fifty hospitals, in fifteen countries. The trial was dubbed SYMMETRY. It was funded by the pharmaceutical giant Glaxo Smith Kline. Glaxo agreed to underwrite the cost of the next round of clinical trials and—should the drug be approved by the Food and Drug Administration—to split the revenues with Synta.

But was this the perfect trial? Not really. In the Phase 2 trial, elesclomol had been mixed with an organic solvent called Cremophore and then spun around in a sonicator, which is like a mini washing machine. Elesclomol, which is rock-hard in its crystalline form, needed to be completely dissolved if it was going to work as a drug. For SYMMETRY, though, sonicators couldn't be used. "Many countries said that it would be difficult, and some hospitals even said, 'We don't allow sonication in the preparation room,' " Chen explained. "We got all kinds of unbelievable feedback. In the end, we came up with something that, after mixing, you use your hand to shake it." Would hand shaking be a problem? No one knew.

Then a Synta chemist, Mitsunori Ono, figured out how to make a water-soluble version of elesclomol. When the head of Synta's chemistry team presented the results, he "sang a Japanese drinking song," Chen said, permitting himself a small smile at the eccentricities of the Japanese. "He was very happy." It was a great accomplishment. The water-soluble version could be given in higher doses. Should they stop SYMMETRY and start again with elesclomol 2.0? They couldn't. A new trial would cost many millions of dollars more, and set the whole effort back two or three years. So they went ahead with a drug that didn't dissolve easily, against a difficult target, with an assortment of patients who may or may not have been ideal—and crossed their fingers.

SYMMETRY began in late 2007. It was a double-blind, randomized trial. No one had any idea who was getting elesclomol and who wasn't, and no one would have any idea how well the patients on elesclomol were doing until the trial data were unblinded. Day-to-day management of the study was shared with a third-party contractor. The trial itself was supervised by an outside group, known as a data-monitoring committee. "We send them all the data in some database format, and they plug that into their software package and then they type in the code and press 'Enter,' " Bahcall said. "And then this line"—he pointed at the Kaplan-Meier in front of him—"will, hopefully, separate into two lines. They will find out in thirty seconds. It's, literally, those guys press a button and for the next five years, ten years, the life of the drug, that's really the only bit of evidence that matters." It was January, 2009, and the last of the six hundred and fifty-one patients were scheduled to be enrolled in the trial in the next few weeks. According to protocol, when the results began to come in, the data-monitoring

"It advanced the technology, but it's not a game changer."

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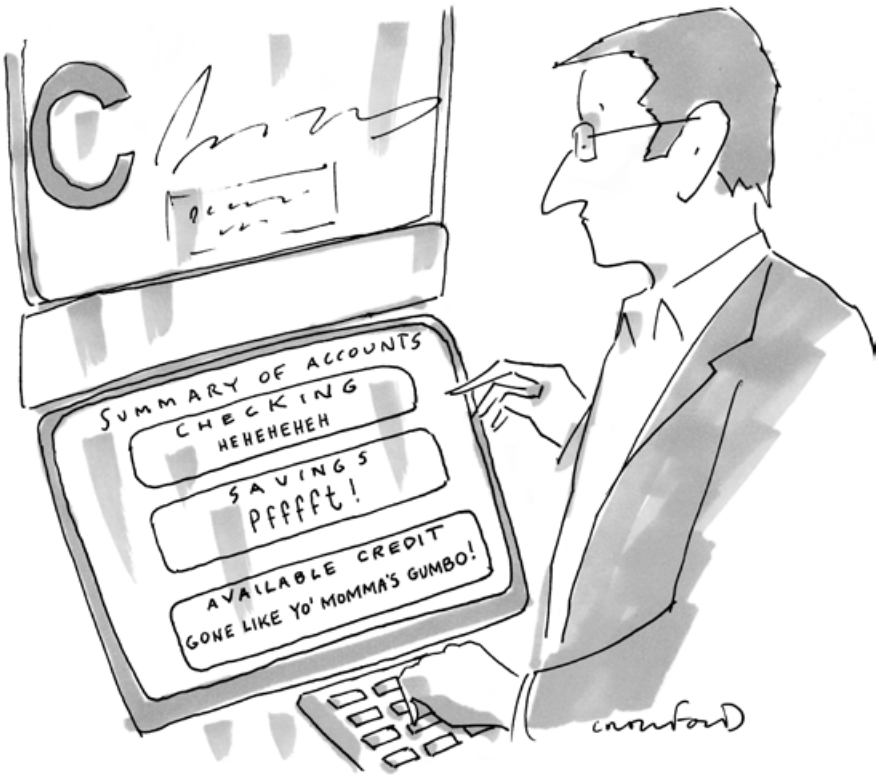


committee would call Jacobson, and Jacobson would call Bahcall. "ASCO starts May 29th," Bahcall said. "If we get our data by early May, we could present at ASCO this year."

In the course of the SYMMETRY trial, Bahcall's dining-room-table talks grew more reflective. He drew Kaplan-Meiers on the back of napkins. He talked about the twists and turns that other biotech companies had encountered on the road to the marketplace. He told wry stories about Lan Bo Chen, the Jewish mother and Jewish father rolled into one—and, over and over, he brought up the name of Judah Folkman. Folkman died in 2008, and he was a legend. He was the father of angiogenesis—a wholly new way of attacking cancer tumors. Avastin, the drug that everyone cheered at ASCO seven years ago, was the result of Folkman's work.

Folkman's great breakthrough had come while he was working with mouse melanoma cells at the National Naval Medical Center: when the tumors couldn't set up a network of blood vessels to feed themselves, they would stop growing. Folkman realized that the body must have its own system for promoting and halting blood-vessel formation, and that if he could find a substance that prevented vessels from being formed he would have a potentially powerful cancer drug. One of the researchers in Folkman's laboratory, Michael O'Reilly, found what seemed to be a potent inhibitor: angiostatin. O'Reilly then assembled a group of mice with an aggressive lung cancer, and treated half with a saline solution and half with angiostatin. In the book "Dr. Folkman's War" (2001), Robert Cooke describes the climactic moment when the results of the experiment came in:

> With a horde of excited researchers jampacked into a small laboratory room, Folkman euthanized all fifteen mice, then began handing them one by one to O'Reilly to dissect. O'Reilly took the first mouse, made an incision in its chest, and removed the lung. The organ was overwhelmed by cancer. Folkman checked a notebook to see which group the mouse had been in. It was one of those that had gotten only saline. O'Reilly cut into the next mouse and removed its lung. It was perfect. What treatment had it gotten? The notebook revealed it was angiostatin.

It wasn't Folkman's triumph that Bahcall kept coming back to, however. It was his struggle. Folkman's great insight at the Naval Medical Center occurred in 1960. O'Reilly's breakthrough experiment occurred in 1994. In the intervening years, Folkman's work was dismissed and attacked, and confronted with every obstacle.

At times, Bahcall tried to convince himself that elesclomol's path might be different. Synta had those exciting Phase 2 results, and the endorsement of the Glaxo deal. "For the results not to be real, you'd have to believe that it was just a statistical fluke that the patients who got drugs are getting better," Bahcall said, in one of those dining-room-table moments. "You'd have to believe that the fact that there were more responses in the treatment group was also a statistical fluke, along with the fact that we've seen these signs of activity in Phase 1, and the fact that the underlying biology strongly says that we have an extremely active anticancer agent."

But then he would remember Folkman. Angiostatin and a companion agent also identified by Folkman's laboratory, endostatin, were licensed by a biotech company called EntreMed. And EntreMed never made a dime off either drug. The two drugs failed to show any clinical effects in both Phase 1 and Phase 2. Avastin was a completely different anti-angiogenesis agent, discovered and developed by another team entirely, and brought to market a decade after O'Reilly's experiment. What's more, Avastin's colorectal-cancer trial—the one that received a standing ovation at ASCO—was the drug's second go-around. A previous Phase 3 trial, for breast cancer, had been a crushing failure. Even Folkman's beautifully elaborated theory about angiogenesis may not fully explain the way Avastin works. In addition to cutting off the flow of blood vessels to the tumor, Avastin seems also to work by repairing some of the blood vessels feeding the tumor, so that the drugs administered in combination with Avastin can get to the tumor more efficiently.

Bahcall followed the fortunes of other biotech companies the way a teen-age boy follows baseball statistics, and he knew that nothing ever went smoothly. He could list, one by one, all the breakthrough drugs that had failed their first Phase 3 or had failed multiple Phase 2s, or that turned out not to work the way

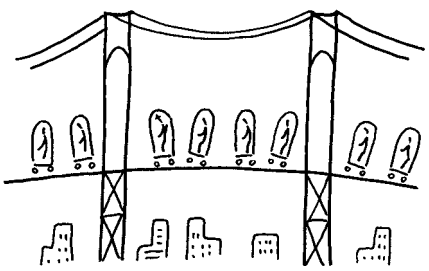
they were supposed to work. In the world of serendipity and of trial and error, failure was a condition of discovery, because, when something was new and worked in ways that no one quite understood, every bit of knowledge had to be learned, one experiment at a time. You ended up with VAMP, which worked, but only after you compared daily 6-MP and daily methotrexate with daily 6-MP and methotrexate every four days, and so on, through a great many iterations, none of which worked very well at all. You had results that looked "boinking good," but only after a trial with a hundred compromises.

Chen had the same combination of realism and idealism that Bahcall did. He was the in-house skeptic at Synta. He was the one who worried the most about the hand shaking of the drugs in the SYMMETRY trial. He had never been comfortable with the big push behind melanoma. "Everyone at Dana-Farber"—the cancer hospital at Harvard—"told me, 'Don't touch melanoma,' " Chen said. " 'It is so hard. Maybe you save it as the last, after you have already treated and tried everything else.' " The scientists at Synta were getting better and better at understanding just what it was that elesclomol did when it confronted a cancer cell. But he knew that there was always a gap between what could be learned in the laboratory and what happened in the clinic. "We just don't know what happens in vivo," he said. "That's why drug development is still so hard and so expensive, because the human body is such a black box. We are totally shooting in the dark." He shrugged. "You have to have good science, sure. But once you shoot the drug in humans you go home and pray."

Chen was sitting in the room at Synta where Eric Jacobson had revealed the "boinking good" news about elesclomol's Phase 2 melanoma study. Down the hall was a huge walk-in freezer, filled with thousands of chemicals from the Russian haul. In another room was the Rube Goldberg drug-screening machine, bought with Milken's money. Chen began to talk about elesclomol's earliest days, when he was still scavenging through the libraries of chemical companies for leads and Bahcall was still an ex-physicist looking to start a biotech company. "I could not convince anyone that elesclomol had potential," Chen went on. "Everyone around me tried to stop it, including my research partner, who is a Nobel laureate. He just hated it." At one point, Chen was working with Fujifilm. The people there hated elesclomol. He worked for a while for the Japanese chemical company Shionogi. The Japanese hated it. "But you know who I found who believed in it?" Chen's eyes lit up: "Safi!"

Last year, on February 25th, Bahcall and Chen were at a Synta board meeting in midtown Manhattan. It was five-thirty in the afternoon. As the meeting was breaking up, Bahcall got a call on his cell phone. "I have to take this," he said to Chen. He ducked into a nearby conference room, and Chen waited for him, with the company's chairman, Keith Gollust. Fifteen minutes passed, then twenty. "I tell Keith it must be the data-monitoring committee," Chen recalls. "He says, 'No way. Too soon. How could the D.M.C. have any news just yet?' I said, 'It has to be.' So he stays with me and we wait. Another twenty minutes. Finally Safi comes out, and I looked at him and I knew. He didn't have to say anything. It was the color of his face."

The call had been from Eric Jacobson. He had just come back from Florida, where he had met with the D.M.C. on the SYMMETRY trial. The results of the trial had been unblinded. Jacobson had spent the last several days going over the data, trying to answer every question and double-check every conclusion. "I have some really bad news," he told Bahcall. The trial would have to be halted: more people were dying in the treatment arm than in the control arm. "It took me about a half hour to come out of primary shock," Bahcall said. "I didn't go home. I just grabbed my bag, got into a cab, went straight to LaGuardia, took the next flight to Logan, drove straight to the office. The chief medical officer, the clinical guys, statistical guys, operational team were all there, and we essentially spent the rest of the night, until about one or two in the morning, reviewing the data." It looked as if patients with high-LDH tumors were the problem: elesclomol seemed to fail them completely. It was heartbreaking. Glaxo, Bahcall knew, was certain to pull out of the deal. There would have to be many layoffs.



The next day, Bahcall called a meeting of the management team. They met in the Synta conference room. "Eric has some news," Bahcall said. Jacobson stood up and began. But before he got very far he had to stop, because he was overcome with emotion, and soon everyone else in the room was, too.

On December 7, 2009, Synta released the following statement:

> Synta Pharmaceuticals Corp. (NASDAQ: SNTA), a biopharmaceutical company focused on discovering, developing, and commercializing small molecule drugs to treat severe medical conditions, today announced the results of a study evaluating the activity of elesclomol against acute myeloid leukemia (AML) cell lines and primary leukemic blast cells from AML patients, presented at the Annual Meeting of the American Society of Hematology (ASH) in New Orleans. . . .
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> "The experiments conducted at the University of Toronto showed elesclomol was highly active against AML cell lines and primary blast cells from AML patients at concentrations substantially lower than those already achieved in cancer patients in clinical trials," said Vojo Vukovic, M.D., Ph.D., Senior Vice President and Chief Medical Officer, Synta. "Of particular interest were the ex vivo studies of primary AML blast cells from patients recently treated at Toronto, where all 10 samples of leukemic cells responded to exposure to elesclomol. These results provide a strong rationale for further exploring the potential of elesclomol in AML, a disease with high medical need and limited options for patients."

"I will bet anything I have, with anybody, that this will be a drug one day," Chen said. It was January. The early AML results had just come in. Glaxo was a memory. "Now, maybe we are crazy, we are romantic. But this kind of characteristic you have to have if you want to be a drug hunter. You have to be optimistic, you have to have supreme confidence, because the odds are so incredibly against you. I am a scientist. I just hope that I would be so romantic that I become deluded enough to keep hoping." ♦