The Treatment

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Why is it so difficult to develop drugs for cancer?

1.

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 phasing 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 Is- rael 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 im- possible 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 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 discus- sions." 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.'

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. They go on and on and on. 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."

2.

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 ""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 6MP could kill a lot of cancers, 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 land- scape."

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 devel-oped 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 ' 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.

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.

3.

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.

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 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?

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."

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."

4.

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?

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.

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.

5.

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. According to proto- col, when the results began to come in, the data-monitoring committee would call Jacobson, and Jacob- son would call Bahcall.

On February 25th 2009, 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.

6.

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

Synta Pharmaceuticals Corp. (NASDAQ: SNTA), a biopharmaceutical company focused on discover- ing, 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 Meet- ing of the American Society of Hematology (ASH) in New Orleans. . . .”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 expo- sure 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.”