

# THE NEW YORKER

MEDICAL DISPATCH

## BUYING A CURE

*What business know-how can do for disease.*

by Jerome Groopman

JANUARY 28, 2008



Medical philanthropies are encouraging researchers to share data and meet deadlines

Last May, Kathy Giusti was in midtown Manhattan pitching her current venture to an audience of potential investors. Giusti, a forty-eight-year-old Harvard Business School graduate and former pharmaceutical executive, believes that medical breakthroughs shouldn't be left to chance. In 1998, she created the Multiple Myeloma Research Foundation, a charitable organization dedicated to the lethal blood cancer, which afflicts more than fifty thousand Americans and has no known cure. Most medical charities focus on increasing public awareness and on raising money to distribute to researchers, in the hope that some of the work will lead to a new drug or a cure; Giusti runs hers as if it were a for-profit business, expecting high returns on the money she raises from "investors"—her term for philanthropists. Her staff includes four scientists, who track myeloma research at academic institutions around the world, advising her on which projects are most likely to lead to new therapies for patients, and are thus the best candidates for funding. (Drug companies have typically not been interested in developing drugs for myeloma, preferring to focus on diseases that affect large numbers of people, for which treatments are most profitable.) Researchers who receive money from Giusti's foundation are required to meet strict deadlines for demonstrating progress. "We try to get academics to work like businesspeople," she told her audience in Manhattan. "Money gives you power to drive people's behavior."

Giusti's organization maintains a tissue bank of more than fourteen hundred bone-marrow samples and nearly twelve hundred blood samples from patients with myeloma, which researchers use to test novel compounds, and it helps finance clinical trials of experimental myeloma drugs. Since 2001, twenty-one drugs derived in part from research funded by the foundation have entered clinical trials, and eight are currently in Phase II—a track record that pharmaceutical companies would envy.

Since Giusti established her foundation, medical philanthropies that apply business principles to their work have

become increasingly common. In 2002, Scott Johnson, a former C.E.O. of several Silicon Valley startups who suffers from multiple sclerosis, created the Myelin Repair Foundation, with the goal of facilitating academic research into treatments for the damaged nerves characteristic of patients with the disease. Johnson identified five leading M.S. researchers and persuaded them to collaborate on a research program funded by his foundation. “The academic system is broken,” Johnson told me. “Researchers focus on publishing to get tenure. It’s all about credit for discoveries.” (Johnson hopes to have a drug ready for lab testing in 2009.) Two years ago, Susan G. Komen for the Cure, the oldest and largest philanthropic organization dedicated to breast cancer, hired a new C.E.O., Hala Modellmog, the former president of Church’s Chicken, the fast-food franchise. (The organization’s departing C.E.O. was a former health-care executive.) “We have followed a traditional paradigm,” Modellmog told me. “But we believe there is a smarter way to do things.” This year, Komen is considering allocating thirty-five million dollars of its hundred-million-dollar research budget to support a new initiative called Promise Grants, which would require recipients to share data with one another and to observe strict guidelines. “We need flexibility and speed to discover new treatments and deliver them to patients,” Modellmog said.

Giusti told me that she has been contacted by several other new medical charities, including the Lance Armstrong Foundation, which is devoted to cancer; the Kirsch Foundation, which supports research into Waldenström’s macroglobulinemia, a rare blood cancer; and ABC2, which was created in 2001 by Steve Case, the co-founder of AOL, and his brother Dan Case to combat brain cancer. (Dan Case died of the disease in 2002.) But Giusti’s aggressive approach to myeloma research has been controversial among some academic scientists, who argue that it’s unrealistic—even counterproductive—for patients and their advocates to think that with enough money and the right business model they can buy a cure.

Giusti’s move from the pharmaceutical industry to the nonprofit world began in December, 1995, when she was thirty-seven years old and living in Lake Forest, Illinois. “I was on the fast track at Searle”—the pharmaceutical company—“for a leadership position,” Giusti, who has short blond hair, intense blue eyes, and an energetic voice, told me. For four years, she had overseen the marketing of Searle’s popular arthritis drugs, including Daypro, and she was in charge of developing the strategy for selling a new one, Celebrex. She travelled frequently, and as Christmas approached she was exhausted and losing weight. She had an eighteen-month-old daughter, and she and her husband, a real-estate developer, had been trying to conceive again. In late December, Giusti visited her doctor, who ordered some blood tests and referred her to a fertility specialist. “Two days after Christmas, the doctor called and said he wanted me to come back and get the tests done again,” she recalled. She repeated the blood tests, and in early January she received a phone message from the physician, asking to meet with her and her husband.

“I was driving back to Lake Forest from a regional sales meeting and finally reached him,” Giusti said. “I was on my car phone, and I was driving, and I said, ‘Look, I know something is horribly wrong. My father was a doctor, and you wouldn’t ask me to come in with my husband unless something was really bad.’ And he said, ‘Well, just come in and I will talk you then.’ And I said, ‘No. You need to tell me now.’ I’m driving down the Kennedy Expressway in Chicago, and this guy was telling me that I likely have myeloma. I got home that night, and I just looked at my husband and said, ‘I think that I have cancer, and we’ve got to go in tomorrow morning.’” The next day, on their way to the doctor’s office, Giusti and her husband stopped at a bookstore, where Giusti consulted a copy of “Harrison’s Principles of Internal Medicine,” a textbook widely used in medical schools. “My husband and I were sprawled out in Borders reading this medical book, and, the more I read, I just had this huge knot in my stomach,” Giusti recalled.

Myeloma is a cancer of plasma cells, which are normally found in bone marrow and produce antibodies that help the body fight infections. Under a microscope, plasma cells are easy to identify: they are robin’s-egg blue and have a pale area behind the nucleus. When such cells become cancerous, they produce excessive amounts of a single kind of antibody, called a monoclonal protein, and release it into the blood. The malignant plasma cells can cause bone lesions, dangerously high levels of calcium in the blood, kidney failure, and nerve damage. Since 2003, several new drugs have been approved by the F.D.A. for treating the disease, including thalidomide, which was linked to severe birth defects after it was prescribed as a sedative to pregnant mothers in the nineteen-fifties and sixties, and Velcade, the first approved drug from a class of compounds that disable a structure in plasma cells called a proteasome, and by doing so kill the cell. Many myeloma patients are also given bone-marrow transplants, which are thought to extend the length of remissions. Even so, the cancer cells invariably return, evolving in such a way that they no longer respond to treatment.

Giusti had a bone-marrow transplant in 2006, and her cancer is in remission. But in public presentations she

describes her case as “incurable.” Kenneth Anderson, a professor at Harvard Medical School and a myeloma expert at the Dana-Farber Cancer Institute, in Boston, recently summed up the cancer’s grim prognosis in the journal *Nature Reviews Cancer*. “In spite of conventional and high-dose chemotherapies,” he wrote, “it remains uniformly fatal owing to intrinsic or acquired drug resistance.”

The causes of myeloma are unknown, but risk factors include exposure to radiation and pesticides, and, possibly, having close relatives with the disease. Giusti’s maternal grandfather had myeloma, and she told me that after she received her diagnosis she realized that she could “market” herself to researchers as an “interesting case,” because she has a healthy, identical-twin sister, Karen Andrews; she discovered that doctors were eager to compare the sisters’ plasma cells. “I did searches at the Searle library to see who was the best in myeloma in the country,” Giusti said. “I needed to meet with people at Northwestern, the University of Chicago, the University of Arkansas, the Mayo Clinic, the Fred Hutchinson center, and Dana-Farber. I called all the doctors, and they all called me back, because I was smart enough to say in the message that I have an identical twin. I knew they were thinking, She is young, she is otherwise healthy, she has an identical twin, and she could be a fascinating research specimen.”

Giusti met with seven myeloma specialists and received contradictory advice. “Some people thought I should get a transplant immediately, while others thought that, because I was so healthy, I could potentially watch and wait,” she said. Ultimately, she chose the more conservative approach, in part because she knew that she would not be able to conceive safely while taking the toxic drugs that are given to patients before a bone-marrow transplant. (Nevertheless, she and her sister provided plasma cells to several researchers.) “I put a plan together, and I went through the whole I.V.F. program to get pregnant,” Giusti said. “After two tries, nothing was working, and I was really down in the dumps. I was, like, ‘O.K., I’m dying, and I can’t get the second child.’ That was when my whole life was crashing, and I finally decided to try I.V.F. one more time, and my whole life changed when I found out I was pregnant. At that point, I realized that nothing was more important to me than finishing the pregnancy. We decided to move East, because now, with two little ones and the potential of my dying—back then I was supposed to live, at best, three years—I wanted to be where my twin sister could help my husband raise the kids.” In July, 1997, four months after quitting her job at Searle, and after giving birth to a healthy boy, Giusti moved with her family to southern Connecticut, where Andrews—who had two children of her own—and Giusti’s in-laws lived.

The previous summer, Giusti had attended a patient seminar in Florida sponsored by the International Myeloma Foundation, a philanthropic organization founded in 1990 that helps educate patients and doctors about the disease, and sponsors frequent meetings of myeloma specialists. The group also provides funding for research, according to the traditional model, in which individual investigators apply to the foundation for grants. “They asked me to be on the board,” Giusti said of the foundation’s directors. “So I started working for them, taking on the job of writing a business plan, because it turned out they didn’t have a business plan. But the more I was challenging them about where they are heading and what they are doing with research and funding research, the more the I.M.F. was getting annoyed with me. So they booted me off the board.” (Susie Novis, the president of the I.M.F., disputed Giusti’s account. “She never challenged us about our research funding,” Novis told me. “One day, at dinner, she mentioned to me that she was setting up her own foundation. That was a clear conflict of interest and she was asked to resign at the next board meeting.” Novis added, “We don’t agree with the business model.” Still, she said, “We share the same goal: to end myeloma.”)

In October, 1997, Giusti and her sister held a dinner at the Hyatt Regency hotel in Old Greenwich, Connecticut, to raise money for myeloma research. They invited their friends in the New York area, including employees at Time, Inc., where Karen Andrews was an in-house counsel; they raised four hundred and fifty thousand dollars. Giusti was unsure how to distribute the money. “I looped entrepreneurial management at business school intentionally,” she said, using Harvard slang for taking a course pass/fail, “because I thought I’d never be an entrepreneur. But, if you were able to raise that kind of money on your first event, you were meant to do bigger and better things. And so I did. I incorporated as a 501(c)(3)—the I.R.S. designation for a non-profit organization. She distributed most of the money she had raised to researchers and used the remainder to set up her foundation. Andrews’s colleagues helped Giusti create a logo and a letterhead, and she began to contact potential donors. “I really had to ask for significant dollars to make the foundation happen, and at a time when there was no proof that I could do it,” she said. In 1999, Bill McKiernan, a Harvard Business School classmate and the C.E.O. of an Internet company in California, gave her a million dollars. (He has since raised two hundred thousand more.) At the same time, Giusti was being treated by Kenneth Anderson, at Dana-

Farber, who prescribed bisphosphonates, medications that help protect bones from deterioration.

Giusti realized that in order to accelerate the development of new myeloma drugs, she needed to foster greater collaboration between researchers at different academic institutions. In 2002, she decided to assemble a consortium of scientists who would be required to submit their research proposals to a steering committee for approval, and to publish their results jointly. In exchange, the scientists would receive access to a tissue bank of myeloma blood cells and bone marrow, as well as administrative and organizational support for lab tests and clinical trials. She approached eight institutions. Four—the Dana-Farber Cancer Institute; the Mayo Clinic Cancer Center; the H. Lee Moffitt Cancer Center, in Tampa; and the Princess Margaret Hospital, in Toronto—accepted her offer. The consortium now has thirteen members, and at least two more institutions are expected to join this year.

Giusti figured that she needed a budget of at least three and a half million dollars to launch the consortium, and five million dollars to sustain it. A portion of the money would be used to pay clinical-research coordinators and data collectors, who would oversee trials of myeloma therapies at each academic center. In 2003, Giusti approached the writer Michael Crichton, who she knew had a family member with myeloma. Crichton gave Giusti's consortium half a million dollars to support the creation of the tissue bank. He told me that he admired Giusti's efforts to encourage academic researchers to cooperate with each other and to be accountable to donors and patients. "She had gone and talked to all these people, and she was very clear about how she intended to make them all work together," Crichton said. Giusti told him that she was having some difficulty getting philanthropists to understand what a tissue bank was and why it was important, he recalled. "And I understood it, so I said I would help with that, just out of the strong desire to see if anybody could pull it off—not simply to make the tissue bank but to actually get these fiefdoms to work together." Crichton went on, "I think there are a lot of people, in a lot of ways, who are coming to be very dissatisfied with medical research in terms of how it's organized. I'm guessing that the people in all these institutions must have intuited somehow that she was in some way the wave of the future."

Since 1998, Giusti's foundation has raised \$92.4 million. The consortium's steering committee, composed of three myeloma researchers from member institutions, advises Giusti on which experimental drugs to test in clinical trials, and her team of scientists, recruited from pharmaceutical companies, evaluates the committee's decisions. In the fall of 2006, the foundation funded lab studies of a compound called perifosine, which attacks a protein in myeloma cells, in combination with two other drugs frequently given to patients who have the disease. Within four months, the foundation had launched a clinical trial of all three drugs, in collaboration with Keryx Biopharmaceuticals, which makes perifosine. The trial is being held at four of the consortium's centers; the foundation helped recruit patients, assisted each center in obtaining approval from its affiliated hospital to conduct the trial, and paid for coordinators to supervise the process. In December, preliminary results were presented by a researcher at the University of Michigan (a consortium member), at a conference of the American Society of Hematology. As Peter Sportelli, the director of oncology at Keryx, put it, "It's extremely unusual for experimental drugs to move from the lab to clinical testing so quickly, and Giusti's foundation deserves a lot of credit for spurring the process along."

In September, I visited Kenneth Anderson's laboratory at the Dana-Farber Cancer Institute, which, during the past decade, has been awarded nearly eight million dollars from Giusti's foundation. The laboratory occupies a series of rooms along a narrow corridor, each crowded with incubators containing myeloma cells, centrifuges, and tissue-culture hoods. Postdoctoral researchers stood elbow to elbow, decanting chemical solutions into beakers and extracting DNA and RNA from cells. One took a plastic flask from an incubator and placed it under a microscope. Cells adhered to a matrix of human bone marrow; others floated in the culture medium. In the nineteen-nineties, Anderson and William Dalton, a myeloma researcher at the Moffitt Cancer Center, discovered that the behavior of myeloma cells depends on whether they stick to the matrix—which helps explain why it has been so difficult to treat the disease. Traditionally, experimental drugs were considered promising if they killed the floating myeloma cells, but, as Anderson and Dalton realized, the cells' behavior changes when they are attached to bone marrow—as they are in our bodies—and they frequently become resistant to the drugs. Now experimental compounds are tested against both freely floating and attached myeloma cells.

The day I visited the lab, researchers were screening several compounds that interfered with the myeloma cells' proteasomes. Because Velcade, the proteasome inhibitor recently approved by the F.D.A. for the treatment of myeloma, can have serious side effects, including nerve damage, and often becomes ineffective against the cancer, new proteasome inhibitors have been developed by several biotech startup companies, and Giusti's foundation has given

Anderson's lab money to study a promising one. The lab is also testing compounds that attack other parts of myeloma cells, including enzymes called kinases, and proteins that regulate cell survival and DNA replication.

Scientists at Giusti's foundation keep track of experimental drugs invented by pharmaceutical and biotech companies—usually for the purpose of treating diseases other than myeloma—by studying abstracts of articles in scientific journals, and by examining patent applications, which are publicly available. If the scientists identify a compound that they believe could be useful in treating myeloma, the consortium approaches the drug company that makes it, offering to cover the expense of having it tested at the consortium's centers, and, possibly, to cover some of the overhead costs of clinical trials. (The consortium allows the company to retain the right to any profit from sales of the drug if it is eventually approved by the F.D.A.)

In April, 2006, Steven Young, the executive director of the consortium, telephoned Joe Garlich, the chief scientific officer of Semafore, a biotech company in Indianapolis that is developing drugs to treat solid tumors, such as those of the prostate, kidney, and breast. "It was just sort of a courtesy call, to let us know they exist, and we really didn't think too much about it," Garlich told me. "There's not a lot of money floating into companies like ours, so we focussed single-mindedly on solid tumors, which we think will be our sweet spot." Two years earlier, Semafore had filed an application for a patent on a novel compound that blocks an enzyme called PI3 kinase, which plays a central role in cell survival. Scientists at Giusti's foundation speculated that the compound might be effective against myeloma, and in June, 2006, Giusti met with Garlich, who agreed to provide the compound, called SF1126, to the foundation. Tests at one of the consortium's laboratories showed that the compound was very active against the cancer.

That December, Giusti's foundation awarded Semafore a million dollars, to cover the costs of producing SF1126 and to help subsidize a clinical trial. (The trial is now under way.) "They bear the brunt of the cost, and it doesn't dilute our focus, because we still maintain all our people on solid tumors," Garlich said. "These guys aren't dummies; they look for things that are promising, and we get to tap into all their resources—the tissue bank, the experts, the clinical experience."

Not all the foundation's partnerships have worked so smoothly. Giusti said that consortium members have occasionally made "end runs" around the foundation: after accepting its funding and taking advantage of its experimental trials to test a compound in myeloma patients, they have negotiated a deal with a drug company to test the compound in, say, a set of patients whose disease is more advanced. "When researchers come to the consortium, all of the money is raised for them," Giusti said. "If they need it, and they give us a good case for the work, they will get the funding. And if it's a really great trial, and the company needs support, we will find funding for the company, too. But there are companies that still go directly to the centers. And here is where it gets ugly. Last spring, I said to the thirteen centers, 'Here are the five trials that are most important for us this year. Does everybody agree that we should be conducting these five trials this year? If you do not speak now, forever hold your peace.' " All thirteen centers said that they agreed with Giusti's choices. "Then I found out that one of the centers is going to do a trial with a drug company, of one of the five drugs—one of the most interesting ones—and they never told me," she said. "I was furious."

One leading myeloma expert who declined to join the consortium is Bart Barlogie, the director of the Myeloma Institute for Research and Therapy, at the University of Arkansas for Medical Sciences, in Little Rock. Among the largest such centers in the world, Barlogie's institute, which he established in 1989, has twenty faculty members, including seven who conduct basic research, and receives between six hundred and seven hundred new patients every year. "I report directly to our chancellor and have quite a number of degrees of freedom, so the usual bureaucratic bullshit I do not have to contend with," Barlogie, a native of Germany who worked at the M. D. Anderson Cancer Center for fifteen years, told me. He said that researchers at the institute have analyzed fifty thousand chromosome samples from myeloma patients, enabling them to identify abnormalities that may help to predict the severity of the cancer.

"We give patients our program, which we call Total Therapy, and we throw the kitchen sink at these patients," Barlogie went on. The patients receive chemotherapy, followed by two blood-stem-cell transplants, more chemotherapy, and other medications—treatment that takes between three and four years to complete. In 2003, Barlogie added Velcade and thalidomide to the patients' regimen. Of two hundred and thirty-one patients treated at the institute between 1989 and 1994, fifty-four—about twenty-five per cent—have survived for more than ten years, and half of these have never experienced a recurrence. (According to the National Cancer Institute, of the myeloma patients diagnosed between 1996 and 2003, only a third were alive five years later.) "So when people come to me and say,

‘Well, is myeloma curable?’ I pause and show them the consent form where we state, ‘The objective is to cure.’ ”

Barlogie, who is a member of the scientific advisory board of Giusti’s foundation, has argued that, by seeking to develop new drugs, her consortium risks overlooking opportunities to make existing treatments more effective. “The thirteen centers in the consortium do a little bit of this and a little bit of that,” he told me in August. “There are these many new drugs, and there is the issue of whether they should all be given initially, or only after patients enter remission. I want to continue to refine and improve on the Total Therapy approach.” He continued, “I am sort of the generalissimo here. I don’t believe in democratic rule when it comes to making medical choices and decisions.” (Despite his differences with the foundation, Barlogie is in discussions with it to develop a protocol for treating myeloma patients with an especially poor prognosis.)

Several researchers in the consortium also criticized the foundation’s methods, complaining that it frequently issued press releases, even when there was no new science to promote, and arguing that Giusti’s desire to control all aspects of the drug-development process could hinder progress on the disease. “Research is not just connecting the dots,” a prominent scientist who receives funding from the foundation told me. “You need creative latitude.” Several researchers said that negotiations between their academic institutions and the foundation had been difficult, and that Giusti often took credit for discoveries that would not have been possible without financial support from other sources as well, such as the National Institutes of Health.

“We’re still learning as we try to change the system,” Giusti told me. “To understand how to cure patients, we are going to have to break down a very broken system. And that’s not going to make us loved by everybody.” She went on, “Maybe we’ve been too tough. I actually thought we were not doing enough P.R. Academic centers and the biotech industry often go out too early, contacting media every time they do something in a mouse.” Last year, for the first time, Giusti issued report cards to each institution in the consortium, assessing it on such criteria as how quickly it implemented projects and completed the lab studies necessary before a compound could be tested in patients. (Five institutions earned top grades.)

In 2005, the foundation invested six million dollars in a project to study the myeloma genome—a complete record of the cancer cells’ DNA—which can help doctors determine how virulent a patient’s disease is likely to be, and which treatments might be most effective. The researchers on the project—a collaboration between the Broad Institute, in Cambridge, which is affiliated with M.I.T. and Harvard, and the Translational Genomics Research Institute (TGen), a non-profit organization in Arizona—post the genetic data as soon as they are analyzed, on a Web site that is accessible to the public. (Several academic centers, including Barlogie’s, are also studying the myeloma genome.) Under the terms of the agreement with the foundation, the Broad Institute and TGen may not file patents on the DNA sequences they discover, as some biotech companies have done.

Todd Golub, an oncologist, who is overseeing the myeloma-genome project at the Broad Institute, said that he admired Giusti’s pugnacity. “The notion of accountability is not omnipresent in academic research,” he said. “It’s important to have transparency, integrity, follow-through, and collaboration, regardless of where the money comes from.” However, he added, researchers should balance highly directed work of the kind Giusti’s foundation supports with more exploratory projects. “You need to find the sweet spot between just lobbing money over the fence versus believing we know everything that needs to be done,” he said.

With its focus on deadlines and drug development, Giusti’s approach is best suited to a disease such as myeloma, whose basic biology is at least partly understood. (For maladies that are still largely mysterious to doctors, such as A.L.S.—also known as Lou Gehrig’s disease—a more creative, open-ended research model may be needed.) Kenneth Anderson, whose lab receives funding from the N.I.H. and participates in drug studies financed by pharmaceutical companies, said, “Myeloma now is a paradigm for new drug development, because of partnerships that occur between academics, large pharmaceutical companies, small biotech, the F.D.A., the National Cancer Institute, and foundations. And, frankly, Giusti’s foundation has been a catalyst that created the urgency and awareness to make this progress possible.”

Even so, he went on, “No one company or foundation has all the answers. Those of us who are still in academia are in a unique and privileged position, because we can study the biology. We can understand the importance of putting good drugs together to increase the killing of the myeloma cells and avoid the development of drug resistance. Hopefully, we can create the urgency to work together.” ♦

ILLUSTRATION: JOOST SWARTE

---