

# *The New Yorker*

## **DR. FAIR'S TUMOR**

**A specialist believes that the future of cancer therapy lies in tailoring treatments to individual tumors**

**BY JEROME GROOPMAN**

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“My colon cancer is considered incurable, so I set out on my own,” Dr. William R. Fair told me when I met him not long ago in his office, on the Upper East Side. He had just finished seeing patients, had taken off his white coat, and was sitting in a high-backed leather swivel chair. His polished oak desk was cluttered with papers; the bookshelves on the walls were crammed with medical journals. Even so, he had the slightly willed serenity of a C.E.O. who has taken up gardening in retirement. He’s sixty-three and, with light-blond hair, a ruddy complexion, and clear blue eyes, looked good for his age. He smiled a lot when he talked about his illness, as if to put his visitor at ease. But from the measured, polite comments of his colleagues, you can infer the type of person he used to be: hard-charging, tightly wound, masterful, impatient. In short, he’d had all the personality traits of the topflight surgeon he was: someone who would rather do something, anything, than nothing at all.

These days, he’s trying to save his own life by pushing past the usual methods of cancer treatment. Most cancer therapies are arrived at through a one-size-fits-all approach: candidate drugs are first screened in the test tube against prototype tumors, and then given to groups of incurable patients in hit-or-miss clinical trials. Dr. Fair, having joined the ranks of the “incurable,” has become convinced that his best chance for an effective treatment is to study his own cancer cells in his own laboratory, and develop therapies that are specific to his own cancer—made-to-measure medicine. And so far the results have been altogether encouraging.

For thirteen years, from 1984 until 1997, William Fair was the chairman of urology at the Memorial Sloan-Kettering Cancer Center, one of the premier cancer hospitals in the world. He was an eminent surgeon, who specialized in tumors of the prostate, bladder, testis, and kidney. He would perform as many as five operations a day, direct research projects on surgical oncology, and attend to all the administrative hassles—making personnel decisions, adjudicating turf wars, negotiating salaries—that arose in his department.

“I had the typical surgeon’s Superman complex, and ignored the initial symptoms,” he says, recounting the history of his illness. For the greater part of 1994, he suffered from fatigue, heart palpitations, light-headedness. Despite his exhaustion, he kept up his intense schedule of surgery, research, and administration. “He’s one of those go-go guys who work twenty-four hours a day, seven days a week,” says Dr. Skip Heston, who has

collaborated with Fair for twenty-five years as the principal laboratory scientist in the urology department. “That year, I didn’t like the way Bill looked.”

Neither did Fair’s wife, a former Army nurse, and, without consulting him, she made an appointment for him to see an internist. When he found out, he cancelled: he just didn’t have the time. Finally, she and Heston prevailed on him to get a checkup. He turned out to have severe anemia—the result of a tumor in his colon which was leaking blood.

“When you come down with cancer,” Dr. Fair says, “there are two ways to go—either clam up or be totally open.” He informed the staff at Memorial Sloan-Kettering of his condition, and they immediately rallied to his aid. He would receive the best of care at his own hospital. Even so, the surgeon’s authority is not easily relinquished. In January, 1995, he was being wheeled toward the operating room when he recognized a patient on another gurney as the man he had previously been scheduled to operate on that morning. Propping himself up on an elbow, Fair assured the patient that he had taken care of everything—that he had arranged for an excellent replacement and had everything under control.

His own operation, conducted by the chief of colorectal surgery there, had two objectives: to remove the tumor and surgically explore the affected area. If the cancer proved to be limited to the bowel, and not to have spread into adjacent lymph nodes or other areas of the abdomen, the operation would probably be curative. Unfortunately, two lymph nodes adjacent to the tumor turned out to have metastatic deposits of cancer.

William Fair was shaken by the news. The chance that he would be alive in five years was about forty per cent. When cancer is found in a lymph node, he knew, there are usually other deposits of cancer around, too small for even the best surgeon to identify and remove. Dr. Fair was also aware that colon cancer is particularly resistant to both radiation and chemotherapy. At this point, Dr. David Kelsen, an oncologist at the hospital who specialized in bowel cancers, recommended something called adjuvant chemotherapy. In this treatment, the toxic drugs are given with the idea that they are more effective when the tumor mass has been removed and the remaining cancer is present in small, residual amounts. But adjuvant chemotherapy would at best raise Dr. Fair’s chances of survival to fifty-fifty.

For three months, drugs were instilled directly into William Fair’s abdomen; he then received another twelve months of intravenous treatment. Even during the treatment, Dr. Fair continued to practice. “I’d do a three- or four-hour surgery, finish, run up and get chemotherapy, and then return for another operation,” he says. His son, William III, who runs a health-care company, recalls a sixtieth-birthday trip to the Galápagos that Dr. Fair insisted on taking two weeks after completing chemotherapy in 1996: “He was weak and took along I.V. fluids and medications to bolster himself. But even there he moved ahead of the guide, jumped into a sea kayak, and off he went, solo.”

Dr. Fair told himself that his life would return to the pattern it had followed for some three decades. And for a year after his treatment this appeared to be true, almost as if he had willed it to be. Then, in January of 1997, a routine follow-up CAT scan showed the cancer growing as a mass in a lymph node near his liver.

Dr. Fair recalls being “emotionally shattered.” The chances that he would be alive in five years had plummeted to about one in ten. And none of the treatment possibilities were especially promising. Since chemotherapy and radiation were toxic and not very effective, and there were no convincing data that such treatment would extend his life, he chose palliative surgery. The tumor mass would be snipped out, in the hope not of eradicating it but of slowing its progression.

It wasn't Dr. Fair's style to hang back. His family members well remember the time when, on safari in Tanzania, they were in a car crash. Despite several broken ribs and a broken wrist, he attended to a serious leg wound that his wife had incurred, stanching the bleeding and sewing up the wound using a Swiss Army knife and some suture material he'd brought along. But in the consulting rooms at Memorial Sloan-Kettering, Dr. Fair was being told that the standard arsenal of medical intervention had been exhausted. There was, the best medical wisdom had it, little to do but wait.

That's when Dr. Skip Heston decided to get a piece of Fair's tumor for his lab. “The idea was to create an entirely new treatment,” says Heston, a tall, husky, brown-haired man. “And everyone's tumor is individual. So we needed to get our hands on Bill's.” Heston waited outside the operating room and secured a piece of the cancer as it was being excised from near the base of the liver. Then came the difficult part.

First, the mass of cancer was meticulously transported in a closed, sterile container to the fourth floor of the adjoining Rockefeller Research Building. If the specimen should be contaminated by any free-floating bacteria, the cancer cells could die. Cancers that seem invincible in the body are delicate, hothouse flowers in the laboratory: they must be carefully nourished, protected, cosseted. So the researchers worked within a special sterile chamber called a laminar-flow hood. The mass was dispersed, and the cells were placed in petri dishes containing a plasma-like fluid that had the nutrients and hormones necessary for cell growth. Then the petri dishes were moved into an incubator, where they could be kept at body temperature and exposed to a humidified mixture of oxygen, nitrogen, and carbon dioxide identical to that within the human bloodstream. And soon the cancer cells began to grow. The first major hurdle had been overcome. There was now a ready supply of cells to characterize and investigate. Heston and his colleagues were about to embark on a private war against Dr. Fair's tumor.

Cancer does not exist. Cancers do. That is, the word “cancer” doesn't name one disease, or one type of cell, but hundreds of them. Even within categories of cancer, such as cancer of the breast or the lung or the colon, each person's tumor is unique. Every tumor has a particular repertoire of deranged genes acting in the particular milieu of that individual. And it is this repertoire of aberrant genes which dictates the behavior of the cancer: whether it grows slowly, as a solitary mass, or spreads explosively; whether it dies back when exposed to radiation and chemotherapy or proves stubbornly resistant to them.

But though cancers are various and individual, the available anticancer therapies tend to be standardized and seldom address the unique characteristics of a patient's particular tumor. For the most part, these therapies work like carpet bombing: the target is

sometimes hit, but often it is not, because cancer cells tend to be well armored against attack, and, in any case, the therapies do considerable collateral damage to normal tissue. What Dr. Fair needed was a sort of therapeutic smart bomb, and that required, first of all, learning more about the nature of the target. Heston, in his fourth-floor lab, harvested a portion of Dr. Fair's cancer cells from the incubator cultures and analyzed the cells for altered genes. A specific derangement of a gene called p53 was found. The p53 gene normally restrains cell division; when it's mutated, cells can grow wildly, which is to say cancerously.

For the same reason that the behavior of wildlife in captivity may tell you more about captivity than about wildlife, it's hard to test anticancer drugs in a petri dish. To get a better sense of a cancer's real vulnerabilities, you need to have the cells grow as a tumor in an animal. So Heston injected some of the cancer cells into the flanks of special, immune-deficient mice, which allow foreign, human-cancer cells to grow within them. (Normal, immune-competent mice reject human cells.) By last summer, a second milestone had been passed. Now that Heston and his colleagues had a population of lab animals afflicted with Dr. Fair's tumor, they could test new kinds of treatment on them.

William Fair had finally made the decision to resign as chairman of his department in the spring of 1997. He continued to practice at Memorial Sloan-Kettering, but he began to devote more of his time and attention to the pursuit of an effective treatment. While Heston tested the mice, Fair decided he was open to any approach to healing, including the New Agey stuff that he used to dismiss. (His son recalls his former references to "touchy-feely West Coast nonsense.") "Many of my colleagues think I'm bizarre," he says imperturbably, and describes his regular program of yoga, meditation, prayer, vitamins, and a high-soy, low-fat diet, which he has followed for the past year and a half. Relaxation has never come easily to him, and it still doesn't. "I went to California to a stress-reduction course," he told me, "and then I caught the red-eye back so I wouldn't miss any work." And, unlike many enthusiasts of alternative medicine, Dr. Fair has not abandoned his rational assessment of these techniques, and his expectations are modest. "I don't kid myself," he says. "What I know is that they are expanding my life, not necessarily extending it." His experience has even affected the way he talks to his own patients—he is now more likely to address their emotional concerns as well as their strictly physical ones. "As a doctor, he always went the extra mile, but he saw everything as either winning or losing," his son told me. "Now I think he realizes he can heal without curing."

In early August of 1997, Dr. Fair received further devastating news. A CAT scan revealed that a new mass of cancer had appeared in the lymph node near the liver; a recurrence had been expected, but not so soon. To find a mass only eight months after the palliative surgery suggested that the tumor was particularly aggressive. In an effort to slow the cancer's progress, Fair's colleagues recommended a toxic chemotherapy drug called CPT-11. Dr. Fair struggled with the advice. The drug had been developed generically, like all other chemotherapeutic agents—screened against prototype cancer-cell lines and then given to end-stage cancer patients. It had a very small chance of causing significant shrinkage of his tumor and no real likelihood of eliminating it. "If you have only a hammer, everything looks like a nail," he concluded. There had to be

something else at hand. He had his experimental animals all set up. Now he just needed something to test on them.

He came up with two agents, reaching into the past for one and into the future for the other. The first was a Chinese herb, packaged and available under the name “SPES.” The second was a tumor vaccine. Both preparations were selected rationally, using the tumor cells that Dr. Heston was growing in the incubator and in his mice. Both represent powerful trends that promise to have a notable impact on contemporary medicine.

It’s easy to imagine how the old Dr. Fair would have regarded talk of treating cancer with herbs: narrowed eyes, flared nostrils, and all. Alternative medicine has customarily been long on promises and short on research—an area where charlatans prey upon people who are at their most susceptible. At the same time, it’s hard to ignore three thousand years of Asian empiricism. Besides, important drugs in cancer therapy have been derived from botanical sources: Taxol, for breast and ovarian tumors, from the needles of the Pacific yew tree; vincristine, for lymphoma and leukemia, from the periwinkle plant. In a similar way, folk experience with purple foxglove for dropsy led to the identification and use of digitalis for heart failure, and the indigenous use of cinchona bark for malaria led to quinine and chloroquine pills for the malady.

These days, the major pharmaceutical companies have been searching actively for new therapies derived from exotic-seeming natural sources. For example, Dr. Roger Perlmutter, the senior vice-president for basic research at Merck, oversees projects that collect samples from giraffe dung in Namibia, geysers in Iceland, plants on Tonga, and sea worms in Guam. These natural products are processed through high-intensity enzyme screens in an effort to identify new antimicrobial, anti-inflammatory, and anticancer compounds.

Dr. Sophie Chen, a biophysicist, conducted similar research at Merck. She’s now a professor at New York Medical College, but William Fair first encountered her, in September of 1997, at a meeting at Lake Tahoe sponsored by CaP CURE, the charity that Michael Milken had set up to help fight prostate cancer. Dr. Fair, in his professional capacity, described his program’s interest in developing new treatments for prostate cancer, and Dr. Chen told him about some work she was doing in conjunction with Professor Xu-Hui Wang, the director of traditional Chinese medicine at Shanghai Medical University.

Dr. Wang’s great-grandfather had been a court physician to the last Emperor, and had inherited a body of knowledge and practice which survived China’s political and cultural changes. Dr. Wang and Dr. Chen were studying an herbal preparation for prostate cancer called PC-SPES. She had found that it restrained certain mutant genes in prostate-tumor cells and so hastened the death of these otherwise long-lived cells. The preparation contained substances that mimicked certain human hormones, but it also had high levels of compounds resembling genistein—a chemical that appears to inhibit several cancer-promoting enzymes. Dr. Fair then told her about his own situation, asking if she was aware of any active herbal therapies that might be assessed against his colon cancer. She put him in contact with Dr. Wang.

“Dr. Wang asked me if my cancer had a p53 mutation,” Dr. Fair recounts. Then Wang provided him with the parent preparation, SPES, which he believed was worth screening against tumors that had this signature aberration. Fair says he was skeptical: “When you look at some of the claims of these herbal potions, they are said to do everything for everyone.” But he knew he had nothing to lose, and he was impressed by Dr. Chen’s scientific rigor, so he decided to test it out.

Dr. Heston added a water extract of SPES to the regular diet of the immune-deficient mice carrying Dr. Fair’s colon cancer. Other tumor-bearing mice were fed the regular diet as controls. Within a few weeks, the tumors in the SPES-fed mice had shrunk by fifty per cent, while the tumors in the control mice had continued to grow. When Dr. Fair learned of the results, in September of last year, he started taking large quantities of the herb. The only side effect he experienced was diarrhea, and he adjusted his dose until it was tolerable. Twelve months later, he is still taking SPES every day.

The idea of a vaccine against cancer may not have the ancient lineage of the Chinese apothecary, but, however futuristic it sounds, it has been sought for more than a century. In fact, when John D. Rockefeller, Jr., began supporting what is now Memorial Sloan-Kettering about a century ago, it was in part to pursue such a vaccine. In the simplest terms, a vaccine primes your immune system to detect a particular foreign protein and thereby target the microbial intruder with which that protein is associated. But cancers, too, are marked by foreign proteins—proteins produced by the cancer’s mutant genes. The puzzling thing is that the body doesn’t dependably recognize those cells as aberrant and destroy them with killer T cells. Somehow, successful cancers manage to sidestep or short-circuit that response, so that immunity never develops. An effective tumor vaccine would train the body’s killer T cells to recognize the cancer and purge it in the routine way that they purge germs.

One scientist who has had some success in creating a first-generation tumor vaccine is Dr. Ronald Levy, of Stanford. He has long pursued the idea of customized cancer therapy, and understands the scientific and social complexities of the quest. A specialist in lymphoma—a cancer of a class of white cells found within the lymph nodes and the spleen—Dr. Levy recognized that the tumor of every lymphoma patient had a unique signature protein, called an idiotypic immunoglobulin. If a person’s immune system could be trained to scent out this protein, his body’s own armamentarium could be directed against the disease.

“He had one foot in the grave,” Dr. Levy recalls of the first patient he treated in his program, some seventeen years ago. The lymphoma had grown into palpable masses, not only within internal organs but as nodules on the skin as well. Dr. Levy extracted the signature lymphoma protein from the cancerous tissue and injected it into mice; these mice produced antibodies against the protein. Now Levy determined which antibody was the most potent, produced it in quantity, and infused the substance into the dying patient.

A near-miraculous regression of the lymphoma occurred. Within several months of treatment with the customized antibody, there was no evidence of any tumor.

This astounding result launched a major initiative in Dr. Levy's laboratory, which was conducted in partnership with a California biotechnology company, IDEC Pharmaceuticals, in 1986. Of fifty patients who received the customized treatment—typically, over a six-week period—about seventy-five per cent saw significant shrinkage of their tumors which lasted for nearly a year: six patients in the group with advanced lymphoma have remained in complete clinical remission, with no tumor detectable by CAT scans or physical examination, for up to ten years. Using newly available diagnostic techniques, Dr. Levy has found evidence of minute numbers of circulating lymphoma cells among those patients in long-term remission; what appears to keep their cancers at bay is the immune response triggered by the initial antibody therapy. Unfortunately, the cost of producing the customized therapy was too great for the approach to be commercially viable. "It was good medicine, but not good business," Dr. William Rastetter, IDEC's C.E.O., explained to me recently.

But even though Dr. Levy's anti-body approach was not practicable, a proof of principle had been achieved. He had evidence that the immune system could be directed to recognize a protein unique to a tumor and cause the regression of an otherwise incurable disease. So in the early nineties the Stanford team turned to tumor vaccines, attempting to get the cancer patients to produce antibodies of the sort the mice had produced. It's a simpler technique, but one that Levy has shown to be clinically effective.

Levy's current approach is to take a lymphoma patient's idiotypic immunoglobulin, the cancer's signature protein, and create a vaccine from it. One of his procedures is to mix it with a sample of the patient's own white blood cells, which modify the tumor protein to a form that sparks an especially potent immune response. As of July of this year, ten patients with widespread cancer have been vaccinated by this procedure, and the tumors of four of them have shrunk significantly; in fact, three have seen their disease disappear completely. No significant side effects have arisen from the treatment.

William Fair, like other cancer specialists, is keenly interested in Levy's successes, but he knows that different kinds of tumors appear more or less susceptible to containment by the immune system. Lymphoma may be particularly sensitive to the attack of antibodies and killer T cells. Yet the challenge has made researchers all the more intent on trying to mobilize the immune system against currently intractable cancers, like colon cancer. So when Dr. Fair turned to a longtime friend and former Sloan-Kettering researcher, Dr. Eli Gilboa, for help in creating a customized tumor vaccine, Gilboa responded with alacrity, for scientific as well as for personal reasons.

Dr. Gilboa, who by that time was at Duke, is an internationally acclaimed biologist, who bridges the worlds of cancer genetics and clinical therapy. His laboratory at Duke was already testing a generic form of a tumor vaccine for different types of incurable bowel cancer. Uncertain which signature protein on Dr. Fair's colon cancer might spark the most effective immune response, Dr. Gilboa spent the early part of this year working with the incubated cell lines that Skip Heston had prepared, and he created a vaccine that presented the full range of mutated proteins in William Fair's tumor. His laboratory assessed that vaccine by simulating its effects on Dr. Fair's immune system in a test-tube setting. It triggered large numbers of killer T cells from Dr. Fair's blood, which, when mixed with his colon-cancer cells, destroyed them.

This individualized vaccine could be administered only with F.D.A. approval. Dr. Kim Lyerly, the clinician working with Dr. Gilboa at Duke, submitted a protocol for the single patient, Dr. William Fair. The F.D.A. often permits a single course of therapy for a single patient under so-called compassionate protocols, and it did so in this case. In a laboratory refrigerator at Duke, there is a vaccine with Dr. Fair's name on it, waiting for him.

Dr. Fair knows that as a patient he has been extraordinarily privileged, because of his knowledge and his contacts. The pursuit of unconventional therapies customized to a particular tumor is not an option for most cancer patients. But he hopes that one day it will be. He ticks off the obstacles that must be surmounted: the preservation of viable tumor cells and their perpetuation in the laboratory; labor-intensive assays both in test tubes and in small animals, in order to screen compounds for activity against the growing tumor; and the considerable financial resources and intellectual commitment of research groups, like those at Sloan-Kettering and at Duke, in order to characterize the genes of the cancer and develop an individual approach.

None of these obstacles will give way easily. Some fifteen years ago, a company named Biotherapeutics was established to screen tumors against a battery of known drugs and immune therapies and try to select treatment accordingly. It failed, not for any lack of paying customers but because its results were disappointing. At that time, the knowledge and technology were wanting, and the arsenal of available therapies was meagre: much less was known about genetic mutations that promote cancer, and the assays of therapies against tumor cells growing in a test tube were poor predictors of their clinical effect in the patient. Significant advances have been made since then, and even greater advances should be made in the decades ahead. There will be improvements in laboratory assessment of treatments, yielding ever swifter and more accurate results. Using automated techniques, microchips should provide a readout of genetic sequences and mutations within minutes. And "rational design" of new drugs and vaccines against tumor proteins will be sped along by models of the three-dimensional structure of these proteins, which can be generated by high-performance computers. But though foreseeable developments in technology will accelerate the process, it will remain intensive and costly. "People pay to have their sperm banked," Dr. Fair observes. "The affluent may someday pay to have their tumors banked and analyzed at the time of diagnosis."

That scenario will become likely if there are clinical successes from the use of harvested tumor tissue as the template for novel drugs or vaccines. And even now, preceding any such success, very wealthy cancer patients might well decide to fund such enterprises. But could such attempts, if they proved effective, remain a prerogative solely of the rich? It's hard to imagine it: the public outcry would be too intense. Yet how would the F.D.A. regulate the widespread use of lab-bench remedies? And how would insurers adapt, particularly in a country that already carries inordinately high health-care costs?

Dr. Fair is content to let others wrestle with such questions. A CAT scan done at the end of July, of this year, some eleven months after William Fair began taking SPES, showed that the cancer had shrunk and there were no new deposits anywhere. He is pleased about the news, of course, but is far from complacent. He knows that until the components of

SPES are identified and tested against other colon cancers with p53 mutations he cannot conclude cause and effect in his case. It is still no more than an anecdote. But it's an impressive anecdote, all the same: the expected course of his disease is relentless growth, and, given the rapidity with which his cancer had recurred previously, his results are distinctly unusual. Dr. Fair says that he has decided to "get as much mileage out of the herbal and alternative therapies as possible" and that he is prepared to pursue his second customized therapy, a tumor vaccine, if the cancer begins to grow. He recalls the darkest days of his treatment, when the mass beneath his liver was discovered and he first learned that the odds of his survival had dropped precipitately. "The thought of analyzing my own cancer crossed my mind, but, frankly, I was more concerned about life and death," Dr. Fair says, sounding a little baffled by his slowness. Then he brightens. "When it was suggested to me, of course, I realized it was a fantastic idea."

*(This is the second of two reports from the cancer wars.)*