

The New York Times

December 21, 2012

Is the Cure for Cancer Inside You?

By DANIEL ENGBER

Claudia Steinman saw her husband's BlackBerry blinking in the dark. It had gone untouched for several days, in a bowl beside his keys, the last thing on anybody's mind. But about an hour before sunrise, she got up to get a glass of water and, while padding toward the kitchen, found an e-mail time-stamped early that morning — "Sent: Monday, Oct. 3, 2011, 5:23 a.m. Subject: Nobel Prize. Message: Dear Dr. Steinman, I have good news for you. The Nobel Assembly has today decided to award you the Nobel Prize in Physiology or Medicine for 2011." Before she finished reading, Claudia was hollering at her daughter to wake up. "Dad got the Nobel!" she cried. Alexis, still half-asleep, told her she was crazy. Her father had been dead for three days.

The Nobel Foundation doesn't allow posthumous awards, so when news of Ralph Steinman's death reached Stockholm a few hours later, a minor intrigue ensued over whether the committee would have to rescind the prize. It would not, in fact; but while newspapers stressed the medal mishap ("[Nobel jury left red-faced by death of laureate](#)"), they spent less time on the strange story behind the gaffe. That Steinman's eligibility was even in question, that he'd been dead for just three days instead of, say, three years, was itself a minor miracle.

In the spring of 2007, Steinman, a 64-year-old senior physician and research immunologist at Rockefeller University in New York, had come home from a ski trip with a bad case of diarrhea, and a few days later he showed up for work with yellow eyes and yellow skin — symptoms of a cancerous mass the size of a kiwi that was growing on the head of his pancreas. Soon he learned that the disease had made its way into nearby lymph nodes. Among patients with his condition, 80 percent are dead within the first year; another 90 percent die the year after that. When he told his children about the tumor over Skype, he said, "Don't Google it."

But for a man who had spent his life in the laboratory, who brought copies of *The New England Journal of Medicine* on hiking trips to Vermont and always made sure that family vacations overlapped with scientific symposia, there was only one way to react to such an awful diagnosis — as a scientist. The outlook for pancreatic cancer is so poor, and the established treatments so useless, that any patient who has the disease might as well shoot the moon with new, untested therapies. For Steinman, the prognosis offered the opportunity to run one last experiment.

In the long struggle that was to come, Steinman would try anything and everything that might extend his life, but he placed his greatest hope in a field he helped create, one based on discoveries for which he would earn his Nobel Prize. He hoped to reprogram his immune cells to defeat his cancer — to concoct a set of treatments from his body's own ingredients, which could take over

from his chemotherapy and form a customized, dynamic treatment for his disease. These would be as far from off-the-shelf as medicines can get: vaccines designed for the tumor in his gut, made from the products of his plasma, that could only ever work for him.

Steinman would be the only patient in this makeshift trial, but the personalized approach for which he would serve as both visionary and guinea pig has implications for the rest of us. It is known as cancer immunotherapy, and its offshoots have just now begun to make their way into the clinic, and treatments have been approved for tumors of the skin and of the prostate. For his last experiment, conducted with no control group, Steinman would try to make his life into a useful anecdote — a test of how the treatments he assembled might be put to work. “Once he got diagnosed with cancer, he really started talking about changing the paradigm of cancer treatment,” his daughter Alexis says. “That’s all he knew how to do. He knew how to be a scientist.”

First, Steinman needed to see his tumor. Not an M.R.I. or CT scan, but the material itself. The trouble was that most people with his cancer never have surgery. If there’s cause to think the tumor has spread — and there usually is — it may not be worth the risk of having it removed, along with the bile duct, the gallbladder, large portions of the stomach and the duodenum. Luckily for Steinman, early scans showed that his tumor was a candidate for resection. On the morning of April 3, 2007, less than two weeks after his diagnosis, he went in for the four-hour procedure at Memorial Sloan-Kettering Cancer Center, just across the avenue from his office at Rockefeller University.

After two hours on the operating table, his surgeon, Dan Coit, lifted the tumor from his abdomen. It was about two and a half inches long. Coit stitched a short thread across its top and a longer one on the side — an embroidered code to help the pathologists get oriented — and sent the specimen upstairs, wrapped in a towel and nestled in a tray of ice.

Claudia and Alexis were waiting in the lobby, along with Sarah Schlesinger, a longtime friend and member of Steinman’s lab, who is also a board-certified pathologist. It would be her job to manage the disbursement of the tumor to Steinman’s colleagues around the world, so its every nuance could be tested and its fragments incorporated into the drugs that would compose his treatment. When she arrived at the lab upstairs and held the tumor, it was still so warm that she could feel the heat through her latex gloves.

She chopped and sliced the tumor into samples, based on a list that Steinman helped draw up beforehand. A few grams would be placed in screw-top vials filled with a preservative for their RNA. Steinman’s administrative assistant would take another piece to Boston on an afternoon train, and some would go to a former student, Kang Liu, so she could sew confetti-sized squares of the tumor into [living mice](#). If there was any left, they would send it to a researcher in Baltimore named Elizabeth Jaffee, who had mastered the art of culturing pancreatic cancer in a dish.

The mass was big enough that Schlesinger could get through all the items on the list. In the days, weeks and months that followed, Steinman's cancer was sent to labs in Boston and Baltimore, Toronto and Tübingen, Germany, Dallas and Durham, N.C. With help from friends and former students, he would squeeze every bit of data from his cancer that he could.

Steinman's last experiment would be, in many ways, the culmination of a new trend in cancer research: designing custom treatments for each patient. When he got sick, Steinman knew that the five-year survival rate for his kind of tumor was, at most, 1 in 10, even at Sloan-Kettering, one of the best oncology centers in the world. Typically, patients live six months. But he also knew that his chances might not be as bad as they looked. The means and medians of his disease were drawn from populations and so did not reflect the fact that every tumor is unique. Even tumors that look the same — cancers starting from a common organ, or a common kind of cell — may behave in different ways: some shrink and some expand; some succumb to chemotherapy. Now doctors can scan each tumor for clues about its DNA and use those clues to determine its strengths and weaknesses. Steinman could have his case described right down to the letters of its genome, in hopes of figuring out which therapies might work best for him.

This “personalized” approach to treating cancer, which subdivides the classic types according to distortions in their genes, has been growing at a rapid pace. In the past few years, laboratories financed by the government have set out to build a [comprehensive atlas of the cancer genome](#) — to collect 500 tumors from each of 25 kinds of the disease and then to analyze their DNA and RNA at a cost of more than \$100 million a year. The advent of inexpensive genome sequencing has produced a gold rush in the commercial sector, too, with the promise that anyone's tumor can be sliced and processed and analyzed, until its genetic fingerprint is decoded.

“It was thought a while ago that cancer would be too complex for us to really get our hands around it,” says Raju Kucherlapati, one of the principal investigators on the Cancer Genome Atlas and a professor of genetics at Harvard Medical School. But current research showed that “the total number of major biochemical pathways that are altered is not limitless.” If that's true, then doctors might use these genomic data to improve their patients' odds. Instead of applying a one-size-fits-all approach to treatment, they could select a mix of therapies from a standard arsenal, choosing only those that matched the features of a patient's tumor. “I would venture to say that within the next 10 years, we could see a very significant revolution in the way that we think about and treat cancer,” Kucherlapati says.

The genomic approach that Kucherlapati and others have advanced sees every person's cancer as a snowflake — a crystal made from several dozen basic shapes. But this idea has lately run across a deeper layer of complexity and one that is only now being outlined in the lab. For a [paper published in the spring of 2012](#), a group of scientists based in London looked at tiny pebbles of disease from four kidney-cancer patients. Instead of limiting their analysis to a single piece of each tumor — one piece of tissue, excised after surgery or drawn out through a needle — the

researchers took malignant cells from all over the patients' bodies. They sliced specimens from more than half a dozen spots on the primary tumor, and then more from places where the cancer had spread: in the lungs, the chest wall and the fat surrounding the kidneys. When they compared the genomes at each location, they found a whole suite of tumor types with only a distant family resemblance, as if each spot and organ had become the home for its own phylum of disease. The growths were related — they had all descended from a common ancestor — but the cancer had mutated in new directions, sprouting a canopy of branches and twigs on its evolutionary tree. Samples drawn right from a kidney — as close as possible to where the tumor started — shared only a third of their mutations with the other offshoots.

A number of [recent studies](#) came to similar conclusions. Taken together, they reiterate what has long been known but not quite grasped in such detail: that even a single cancer patient carries a private ecosystem of pathology within her body, a tropical rain forest of disease. If the old chemotherapies and radioactive treatments worked like napalm to blast away the canopy, the new breed of personalized therapies target only specific plants. For some cancers, the more homogeneous ones, they do the job just fine. For others, though, the approach comes up against the relentless rules of Darwinian selection. Wipe out one subtype of a cancer — the clone that seems most aggressive, say, or the one that's most prevalent in a biopsy — and you may have slowed the disease or thinned it out. But the cells left behind might represent a fitter strain and fill the niche.

Faced with this troubling complexity, doctors have fallen back on treating cancer like a game of Whac-A-Mole: find the harshest clone and knock it down, then repeat the process when the tumor reappears. Or else doctors will attack the tree right at its trunk, by finding those ancestral genes that every species in the body shares. But there's another way to counter cancer's biodiversity. Our bodies come equipped with a system custom-built to handle pathogens in all their many forms. If the immune organs could be activated against a cancer, we might find a pathway through the jungle and, maybe, to a cure.

"The work that the immune system does to sculpt itself around a cancer — that's really the ultimate type of personalized medicine," says Jedd Wolchok, a cancer immunotherapy expert at Memorial Sloan-Kettering who consulted on Steinman's treatment. "The immune system's job is to recognize the signs of danger and then with very exquisite precision to mobilize antibodies" and T-cells "that very, very precisely bind to individual targets." Once that system locks on to its target, it can make adjustments, too, shaping the response to match the contortions and mutations of a tumor in real time. "It's a therapy that lives," Wolchok says, "rather than a medicine that passes in and out of the system."

That's the approach Steinman believed in most; it's the one he was pursuing in his lab for many years before he got sick. But for a cancer vaccine to work, for any vaccine to work, the body has to learn the difference between its healthy cells and the ones that have been transformed into disease.

It has to recognize its evil twin. And the part of the immune system that makes that possible, the mechanism by which our cells learn to kill one thing and leave another alone, was the focus of Steinman's whole career.

The cell Steinman hoped would save his life looks something like a sea anemone or a ruffled shrimp dumpling. But when it's viewed flat under the microscope, those squiggly sheets of membrane extend in cross section, like long, sinewy arms. That's how they looked one day at Rockefeller in the early 1970s, when Steinman first spotted them in a dish of cells cultured from a crushed-up mouse spleen. When he announced his finding at a meeting in Leiden, the Netherlands, in 1973, he said those appendages reminded him of his tall and graceful wife. He thought about calling them claudiacytes.

Instead, with the assent of his supervisor at Rockefeller, the cell biologist Zanvil Cohn, Steinman declared his cells "dendritic," from the Greek *dendron* for tree. This was, he intuited, a kind of cell that had never before been characterized and that served as the missing link in the body's adaptive response to pathogens. Over the next few decades, Steinman would devote all of his work to the [expansion of this idea](#): he would show his immune cell was not, as many suspected, just an oddball form of the macrophages, but something else entirely — a sentinel that guards our bodies from infection by teaching the soldiers of the immune system to distinguish their enemies from their friends.

The dendritic cell can lurk in the outer layers of the skin, in the throat, in the lining of the intestines and on any other surface where a bacterium or virus might try to edge its way into our flesh. When the cell grabs hold of something strange, it absorbs that foreign matter, digests it and drapes the macerated bits along its membrane. Then the cell inches its way along lymphatic ducts to the places in the body where immune cells gather and communicate and presents these bits as signs of an invasion.

Few took this work seriously in the early years. Lab mates dismissed Steinman's spindly plasms; in the late 1970s, he lost his government grants. But the work went on, with Steinman evangelizing for his discovery until he inspired a network of immunologists to join his field. "He loved to see himself as a dendritic cell," Schlesinger says. In a talk he gave in 2007, after winning the Lasker Award for Basic Medical Research, he [waved his arms around in demonstration](#), like the conductor of a symphony with a dendrite baton.

By the 1990s, his discovery had given life to an old idea: that a more perfect knowledge of our immune system would lead to vaccines for otherwise intractable diseases. If the dendritic cell could be hijacked and put to use, if those markers on its membranes could be manipulated, then doctors might be able to inoculate their patients against H.I.V., tuberculosis or even cancer. Early experiments based on this premise came to little in clinical trials, though; Steinman and his colleagues learned it wouldn't be enough to load the dendritic cells with antigen, to give the body's

bloodhounds sweaty socks. The cells would need another signal too — something to inspire them to share their message with the rest of the immune system. In the absence of that “go” signal, a dendritic cell might do the opposite of what was intended: it might parade its antigens around the lymph nodes as an example of what should be ignored, not what should be killed. Depending on the context, a dendritic cell could induce action or inaction, immunity or tolerance.

But Steinman never lost faith in his discovery as a vehicle for medicine. When he learned that he was sick, he signed up to have his tumor engineered into three existing, experimental vaccines. Each of these had been in testing for patients with other types of cancer, but Steinman had them customized with samples from his own disease. First he tried one, called GVAX, made from his irradiated cancer cells and fitted with a gene that, upon injection, sounds a warning call that recruits dendritic cells. Then he tried a pair of treatments using dendritic cells that were filtered from his blood, loaded with his cancer’s RNA (in one) or peptides (in the other) and put back into his body. In each case, fragments of his tumor would serve as both the quarry and the bait.

“It was just like the old days,” says Ira Mellman, a former trainee in Steinman’s lab and, by the time Steinman got sick, vice president of research oncology at Genentech in San Francisco. “We were all sitting around discussing what next week’s experiments should look like, except this time the experiments were him.” As the treatment plan took shape, Schlesinger managed reams of paperwork. For access to each experimental drug, Steinman would need to enroll himself in a single-patient, compassionate-use protocol with approval from the Food and Drug Administration. (The government receives around 1,000 applications for these one-person treatments every year and grants almost all of them, as long as the patient has cooperation from doctors and the relevant drug companies.)

Schlesinger also served as Steinman’s physician for the vaccine treatments, administering the shots, taking blood and checking up to see how he was doing. The team kept track of his response to each immune-based treatment as it played out in his T-cells. But the real benchmark, and the better index of his disease, was a carbohydrate protein called CA19-9 — a tumor byproduct that was also measured in his blood. When his levels were going down, it meant the cancer was in retreat. After each phase of his experiment, Steinman plotted out his readings and pasted them into slides on PowerPoint.

The same vaccines that Steinman received have shown promise in other patients. The irradiated-cell approach may increase survival for some patients with metastatic prostate cancer. A team based at Baylor University in Dallas has found encouraging results for reinfused dendritic cells in Stage 4 melanoma. But for the man who would later win the Nobel Prize for discovering dendritic cells, would these treatments work at all?

Steinman stayed in good health for the first few years — he still went for runs in Central Park or along the Charles in Boston — though the numbers from his blood tests were at times

disheartening. His T-cells showed some signs of activation: they could recognize the markers from his cancer, but there was no way to tell if they were getting inside his tumor. “He wanted to see a much better response,” says Rafick-Pierre Sekaly, an immunologist at the Vaccine and Gene Therapy Institute of Florida who helped to analyze the data. In between the experimental treatments, Steinman was taking a drug called gemcitabine, a chemotherapy traditionally used in the treatment of pancreatic cancer to which he had a very good response. When he took gemcitabine, his CA19-9 would founder; the cancer would start to disappear. When he switched onto the vaccines, the tumor readings inched back up. “That was so upsetting to him, that he always needed the chemotherapy,” Sekaly says.

When he wasn’t on vaccines or chemotherapy, Steinman tried whatever else he could find. He had his tumor’s genome sequenced, to check for special vulnerabilities. At Genentech, Mellman tested a sample of Steinman’s tumor in a dish against the company’s whole library of pharmaceuticals. “We threw at his cells every drug that we had in development at the time,” he says, including many that hadn’t yet entered clinical trials. Meanwhile, the mice that received pieces of Steinman’s tumor served as minifactories for the production of his cancer and also as his patient-avatars in the lab. When one of Mellman’s drugs showed promise in a dish — a signaling inhibitor called vismodegib — he sent it for a trial in the cancer-ridden mice. When they responded, too, Steinman took it himself. It did not appear to work.

Still, years went by and Steinman’s disease never spread far enough to kill him. Was it just the chemotherapy that kept his tumor growth in check? Or had his custom-made vaccines acted in more subtle ways? It’s now well known that immunotherapies can linger in the body [even as a tumor grows](#), and then start to shrink the tumor later on. It’s also possible that the vaccines and chemo worked in concert. But with no other patients for comparison and so little time between treatments to let the data run their course, the details remained a mystery. Mellman expressed skepticism about the treatment’s efficacy. Schlesinger was more positive, as was Coit, his surgeon. “I mean, look at his course,” Coit said. “The average survival even after a complete resection is measured in months, maybe a year and a half, and yet he kept going and going and going. You can’t help wondering if some of it had to do with this very innovative, novel approach.” As for Steinman himself, he wouldn’t make a claim one way or the other. “He totally, definitely felt that it was helping him,” says his daughter Alexis, but feeling is different from knowing. Though he kept careful notes about his treatment and joked with Schlesinger of writing up his one-man trial for The New England Journal of Medicine — in a case study titled “My Tumor and How I Solved It” — in the end there wasn’t any proof.

“Ralph was this remarkable mixture of optimism and skepticism,” Mellman says. “He always knew how this was going to end, and that he was living on borrowed time.”

At her mother’s suggestion, Alexis Steinman flew to New York, on Sept. 11, 2011, and found her father in a sickly state. For the first time since he had the disease, Steinman had begun to

deteriorate. He was coughing so violently, her mother had told her, that she thought he might have broken a rib.

Alone with Alexis, Steinman said: “I have cancer in my bones.” Until then, he lived with his disease in much the way he lived before: working long days in the lab and long nights at his computer; traveling to conferences around the world; treating the lab to Entenmann’s cake. Now, for the first time since his diagnosis, he started losing hope in his treatment plan. He became depressed.

The cancer had stopped responding to gemcitabine, and his CA19-9 readings were out of control. On Sept. 18, he tried one more drug — a targeted therapy that had shown some very modest benefits and seemed well suited to his case, at least according to the data from his cancer genome. But it was too late; the disease had already spread throughout his body.

Steinman started planning for the end. “You know how they have those events in the Caspary” — the auditorium at Rockefeller University — “where somebody comes and plays classical music and they talk about you?” he asked Claudia. “I don’t want any of that.” He also told her that there should be no sitting shiva on his behalf. (“I don’t want people coming to the house for seven days,” he said.) Then he met with his closest friend at Rockefeller, a former grad student named Michel Nussenzweig. They discussed what would happen to Steinman’s students and his postdocs. Some he called himself, apologizing for leaving them before their work was done.

On the night of Sept. 24, Steinman ate dinner with his family in a faculty apartment on the Upper East Side of Manhattan. Claudia was there, and their three children and three grandchildren, too. The next morning, sitting on his bed, Alexis saw that he was finding it very hard to breathe. “I think I need to go to the hospital,” he announced. When they arrived at Sloan-Kettering to see his oncologist, he said, “I don’t think I’m getting out of here.”

He died five days later.

On a sunny day last August, almost one year after Steinman won the Nobel Prize, I saw his tumor for myself. Its cells were plastered to the bottom of a plastic case, 20 million tiny cancers crowded into a space the size of a large matchbox. A few days before my visit, the cancer was taken out of the freezer and left to thaw. As I peered at the last living remnants of Steinman’s body through a low-power scope, Sara Solt, a lab technician at Johns Hopkins, gave me her assessment: “Those handlike substances,” she said, referring to some spears of cytoplasm, “they almost look mean.”

For someone who has never seen a pancreatic cancer cell, though, Steinman’s disease didn’t look so mean at all — not black or jagged, just a bunch of soft-edged pentagons and distorted squares, with a few translucent tendrils jutting from their membranes.

The lab at Hopkins is run by Elizabeth Jaffee, the expert on vaccines for pancreatic cancer who received a part of the tumor for analysis. The vaccine she is testing in the clinic matches one of

those Steinman received: it mixes bits of tumor — targets for the patient's immune response — with a signal that recruits dendritic cells. As we sat together in her office, Jaffee reviewed what remains unknown about the method. It's not yet clear [how best to pick those targets](#). Steinman could have used a more standardized approach, with certain proteins preselected to maximize response; instead, he went with samples of his own disease, hoping these would give his dendritic cells something more to go on. But his tumor might have yielded a thousand targets for his T-cells, a protein soup swimming with red herrings. We still don't know which strategy works best, Jaffee told me.

There's another challenge, too, that Steinman had little chance to work around. Any cancer that has grown big enough to harm your health is one that has already figured out a way to hinder any T-cells that come after it. It has evolved a path around the body's natural defenses. So it stands to reason that if you want to make an immune-based treatment work, you have to add in some other tumor-fighting drug, one that counteracts the tumor's schemes for keeping immunity in check. "Vaccines alone are not going to be enough," Jaffee said. "When in cancer, especially metastatic cancer, has one agent ever cured anybody? It doesn't do it."

Scientists have only just begun to understand how a tumor can shield itself from T-cells and to make a set of drugs that work against those mechanisms. When Steinman began his treatment, he and others in the field knew of one drug, called ipilimumab, that could do just this. Taken on its own, the drug appeared to extend the lives of patients with metastatic melanoma by months or even years. Yet the company that makes it, Bristol-Myers Squibb, was trying hard to get approval for single-agent use and wouldn't allow Steinman to pair the drug with his vaccines. Researchers may have worried that the untested combination could have side effects that would delay its approval. (Citing company policy against discussing individual cases, Bristol-Myers declined to comment on Steinman's treatment.) So Steinman tried the drug on its own in 2010. Instead of charging up his immune cells to fight off the pancreatic cancer, it knocked his T-cells into overdrive. They attacked his intestines and his pituitary gland, leading to dehydration and diarrhea. He ended up in the hospital.

"One of the problems we have in our field is that it's very hard to combine two agents," Jaffee said, referring to the bureaucratic hurdles she has faced in using ipilimumab. When she put the drug together with one of the vaccines that Steinman received, both treatments were enhanced. More than a fourth of those enrolled in her preliminary trial for pancreatic cancer — patients who expected to live for two or three months on average — have now survived for at least a year. Even so, Jaffee had trouble getting enough doses from Bristol-Myers Squibb to start a second, bigger test. The company eventually agreed, after ipilimumab was approved by the F.D.A., but the whole process set her research back by a couple of years. "This is my biggest frustration," she said.

The same was true for Steinman. As the years went by, he was confronted time and again with the limits of what was understood and what was possible. He hoped to integrate his vaccines with

chemotherapy and take the treatments simultaneously rather than in sequence. Jaffee's lab has shown that this approach can enhance the immune response in a different way than ipilimumab does, by killing off a kind of T-cell that's friendly to a tumor. Or else he might have combined the immunotherapies with drugs selected on the basis of his tumor's DNA. But no one really knows how best to put these things together, just as no one really knows which antigens a vaccine should target nor how best to mobilize dendritic cells. Scientists now realize that dendritic cells come in dozens of different forms, some of which may be more effective in vaccines than others.

The disconnect between the extraordinary promise of cancer immunotherapies and the vagaries of their application, between the possible and the merely doable, always bothered Steinman. He used to tell his family that his work on dendritic cells might not be relevant until long after he was dead — that it would take years to determine whether vaccines based on his discovery could truly be effective in the treatment of disease. "All of this stuff was literally developing in real time as Ralph's disease was developing," Mellman says, "and the disease was ahead, unfortunately." If Steinman's personalized treatments worked at all, it was in spite of everything that was still unknown. "It was a laboratory experiment that worked for a while, we think, but we can't go back and repeat it, so we'll never know for sure," Mellman says.

More experiments are on the horizon. Jaffee is building on Steinman's work by combining the latest round of immune boosters with a dendritic-cell vaccine. There is progress in immunotherapy for other cancers, too: ipilimumab is being used for treating melanoma, and related drugs are in the pipeline that make a tumor more vulnerable to attack. In 2011, The New England Journal of Medicine published the results of a method known as "[adoptive T-cell transfer](#)," in which T-cells are extracted from the body and reprogrammed to go after cancer cells. This has proved a potent treatment for some patients with advanced leukemia, but it poses greater health risks than the vaccines that rely on dendritic cells. "We're going to learn a lot over the next 10 years," Jaffee said, as we walked through the lab. "We're just at the beginning. This is going to be the start of a whole new field."

Steinman knew he wouldn't live to see that field reach its full potential. It has been almost 40 years since he discovered the dendritic cell, and doctors have only now begun to make immunotherapies that work. By all accounts, that sluggish pace was deeply frustrating to Steinman, even before he got sick. "His mind went so fast, and he always wanted everything done yesterday," Schlesinger says. Years ago, the two of them were on their way to their lab, and Steinman was in a foul mood because a trial they hoped to run was taking longer than expected. After some back and forth about the details, he stopped to consider what he had accomplished in his long career. "He said to me, 'You know, all this time has gone by, and we haven't cured cancer or found a vaccine for H.I.V.' " And then he paused, and told her, "We've got to get to work."

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