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Ralph Steinman used his findings to help design treatments that may have prolonged his life.

IMMUNOTHERAPY

A fight for life that united a field

Nobel-prizewinner Ralph Steinman tried to beat his cancer with vaccines based on the dendritic cells he discovered.

BY LAUREN GRAVITZ

After a young Ralph Steinman co-discovered a new type of immune cell in 1973, he spent years battling to prove its importance in defending the body against pathogens, and to show how it could be used to fight disease. Thirty-four years later, he would look to that same cell to try to save his life.

Dendritic cells — named for their tree-like branches — direct and regulate the body's immune system by programming other cells to recognize and destroy intruders. Steinman, a physician–scientist at The Rockefeller University in New York, set his sights on using the cells in vaccines to prevent chronic infections, such as HIV and tuberculosis, and in cancer therapies. So when he was diagnosed with advanced pancreatic cancer in March 2007, it was only natural that he would pin his hopes on the cells that had been his life's work. Together with collaborators around the world, he designed therapies that made use of his own dendritic cells.

"He was running an experiment on himself and was willing to help out with every kind of study. He wanted to help himself, but he also viewed it as an incredible opportunity to learn something," says Ira Mellman, who worked with Steinman to develop his treatments and is vice-president of oncology research at the biotechnology firm Genentech in South San Francisco, California.

On 3 October, Steinman shared the Nobel Prize in Physiology or Medicine for his work, but he never heard the news. At the age of 68, after a four-and-a-half year battle with cancer, he died three days before the award was announced (see *Nature* **478,** 13–14; 2011).

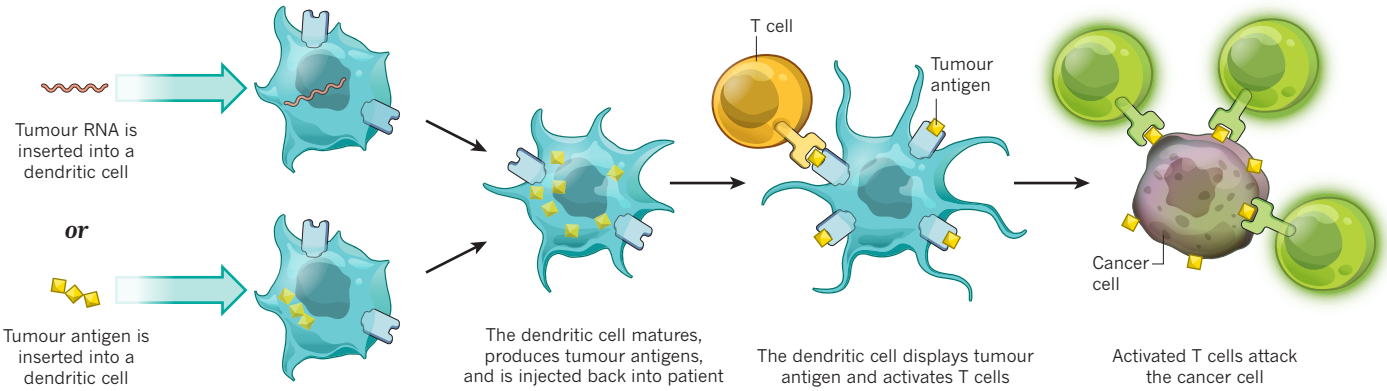
I first met Steinman during my two-year tenure as a science writer in the Rockefeller communications department. I was new to the immunology beat, and he kindly and patiently talked me through the intricacies of dendritic cells and their vast potential. When word of his cancer diagnosis emerged, his students and postdocs talked about it in hushed tones, telling me that immunologists at Rockefeller and beyond were using Steinman's dendritic cells in a personalized immunotherapy. I vaguely pictured his colleagues injecting him with homegrown cells right there in his lab. I could not have been more wrong.

"Everybody around the world who had something to share came forward, and he analysed and chose what looked most promising," says Sarah Schlesinger, a physician–researcher at Rockefeller who worked closely with Steinman and oversaw many of his experimental treatments. "We worked with dozens of colleagues, who helped in designing his therapy, evaluating the tumour and evaluating his immune response, and many worked with us to create single-patient protocols to treat him with experimental immunotherapy that went through the FDA [US Food and Drug Administration]."

Researchers across the field were eager to help the man who had always been generous with his time and knowledge. "Ralph was a collaborator, a competitor, but before everything he was a friend," says Jacques Banchereau, who began working with Steinman in the early 1990s and is now head of inflammation and virology at Roche in Nutley, New Jersey. ▶

HOW THE CANCER VACCINES WORK

In the immune system, dendritic cells can be used to trigger a response against cancer cells in various ways. In these two examples, antigens are introduced directly into the dendritic cells or generated *in situ* using tumour RNA. The cells then produce tumour antigens and direct T cells to seek out and destroy the cancer cells.



Shortly after Steinman was diagnosed he met with two former members of his lab, both of whom now run successful immunotherapy research programmes of their own. Michel Nussenzweig, at Rockefeller, and Genentech's Mellman sat down with him to discuss his case. "It was the weirdest experience, like we were having a lab meeting from the old days: talking about what experiments to do, what needed to be found out, how interesting it was, what you can and can't do," Mellman says. "It was a totally natural scientific discussion, except we were talking about his tumour."

ATTACKING THE CANCER

The scientists hatched a plan: Nussenzweig would take some of the tumour that would be removed during surgery and grow it in mice so that they would have enough material to test. Mellman would start a cell line that could be used to test the tumour's susceptibility to various drugs. A colleague in Toronto would sequence the tumour's DNA in the hope of finding a mutation that could inform drug choices, and a collaborator in Germany would extract peptides from the tumour's surface so that they could later be synthesized for use in a vaccine. And for treatment, Steinman would undergo conventional chemotherapy in combination with as many experimental therapies as made sense for his disease.

Steinman tried eight experimental treatments in all, one at a time, and for each one a single-patient, compassionate-use protocol was submitted to and approved by the FDA. One of the reasons that cancer is so lethal is that it uses a variety of tactics to prevent immune cells from recognizing and attacking it. So Steinman's line-up included three vaccines, all of which were based on dendritic-cell science. The first was GVAX, which has been tested against prostate and other cancers and is being developed at BioSante Pharmaceuticals in Lincolnshire, Illinois. It used irradiated cells from Steinman's tumour that had been engineered to produce a potent stimulator that attracts and activates dendritic and other immune cells. The second, developed by Argos Therapeutics of Durham, North Carolina, loaded Steinman's dendritic cells with RNA that had been extracted from the tumour (see 'How the cancer vaccines work'). The resulting dendritic cells, now decorated with tumour-specific antigens on their surfaces, were injected back into Steinman to teach other immune cells what to seek and destroy. The third vaccine, which was in clinical trials for melanoma at the Baylor Institute for Immunology Research in Dallas, Texas, attempted to boost the immune response by loading up Steinman's dendritic cells with peptide antigens from the surface of the tumour. Once injected back into the body, the cells would be prepared to recognize the cancer and coordinate an attack.

"It was the ultimate experience in personalized medicine," says Jedd Wolchok, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York, and one of Steinman's collaborators. It was never quite as tailored as Steinman would have liked, however. He believed, and others in the field agree, that the vaccines would probably work better if combined with a checkpoint-blockade inhibitor, which allows cancer-suppressed immune responses to ramp back up to full strength. Together, Steinman believed, the therapies would act as a one–two punch. He tried one such inhibitor, ipilimumab, on its own, but never in combination. Investigators, manufacturers and the FDA must all agree to protocols that involve experimental combinations, and Steinman and his team never got the permission they needed. Ipilimumab received FDA approval for melanoma treatment in March, and trials testing it in combination with dendritic-cell vaccines are only just beginning, in melanoma and renal-cell carcinoma.

> ***"It was the ultimate experience in personalized medicine."***

Which, if any, of the therapies extended Steinman's life is impossible to know. He lived years longer than his initial prognosis — survival time for patients with that degree of pancreatic cancer is usually measured in weeks to months. "Ralph was committed to the idea that his dendritic cells extended his life," Schlesinger says. "Certainly something did, but I don't think we'll ever know for sure what."

Those who monitored his treatment say that he was particularly responsive to a conventional chemotherapy, gemcitabine, which most people with pancreatic cancer become resistant to after just one or two treatment cycles. They also know that he had a measurable immune response: 8% of his cytotoxic, or killer, T cells were targeted to his pancreatic tumour. It was unclear, however, whether that was because of the dendritic-cell vaccines he received or because he had a natural immunity. Nor did anyone know whether the immune response helped to make the cancer susceptible to gemcitabine. "We knew at the outset that we wouldn't be able to tell which therapy made the difference," Schlesinger says. "We only had one patient, so there's no statistical significance."

A controlled experiment it was not, but Steinman's one-man trial moved the field forward. It answered a major question by showing that conventional chemotherapy could be given in conjunction with dendritic-cell vaccines. It bolstered Steinman's contention that experimental therapies should be tested in humans as quickly as possible, owing to the limitations of animal models. And it united the best minds in the field, all fighting for a common cause.

Anna Karolina Palucka, one of the investigators who oversaw the development of Steinman's dendritic-cell vaccine at Baylor, says that she and her colleagues are developing a full programme of immunotherapy against pancreatic cancer using the data gathered from Steinman's solo trial. And, in honour of him, the university will be opening a Ralph Steinman Center for Cancer Vaccines. "He started a completely new field," Palucka says. ■