

~~Hed: A Discovery Runs Full Cycle~~

~~Dek: [\[\[strap\]\] Immunotherapy](#)~~

~~[[hed]] A fight for life that united a field~~

~~[[stand]] Nobel-winner Ralph Steinman ~~won~~tried to beat his cancer with novel vaccines based on the Nobel Prize for his discovery of an immune cell that, decades later, dendritic cells he used in an attempt to save his life discovered.~~

~~By Lauren Gravitz~~

When a young Ralph Steinman discovered a new type of immune cell in 1973, he spent years fighting to prove ~~the basic science behind this new dendritic cell's~~ importance in defending the body against pathogens, and to show that it might be helpful in fighting disease. Forty-five years later, he would look to that same cell to try ~~and~~to save his life.

Dendritic cells — ~~___~~ named for the ~~dendrite-looking tentacle~~tree-like branches sticking out on all sides — ~~___~~ direct and regulate the body's adaptive immune system by programming other immune cells to recognize and destroy an intruder. ~~And although it took 20 years for the cells' existence to gain widespread acceptance, Steinman believed from the start that they could be harnessed to help cure disease.~~

Steinman, a physician scientist at The Rockefeller University in New York, set his sights on using ~~dendritic~~the cells in vaccines to prevent chronic infections, such as HIV and tuberculosis, and in therapies that ~~instructed~~would instruct the immune system to attack and eliminate cancer. So when he was diagnosed with stage IV pancreatic cancer in March, 2007, ~~he pinned~~it was only natural to pin his hopes on the dendritic cells ~~he~~that had ~~discovered so many years before~~been his life's work. Together with scientific collaborators around the world, he designed a personalized therapy using his own dendritic cells. ~~On October 3, Steinman won the Nobel Prize for his discoveries, but he never heard the news. After a 4.5-year battle with cancer, he died three days before the award was announced.~~body's 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, the vice president of oncology research at biotech company Genentech in South San Francisco, California, who worked with Steinman to develop his treatment.~~

~~On 3 October, Steinman won the Nobel Prize in Physiology or Medicine for his discoveries, but he never heard the news. 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 for therapeutic use. When word of his diagnosis first emerged, his students and post-docs talked about it in hushed tones, telling me that immunologists ~~there~~at the ~~university~~Rockefeller and beyond were using ~~his~~Steinman's own dendritic cells to

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create an immunotherapy specifically designed to attack his tumor. I vaguely pictured his colleagues injecting him with homegrown cells right there in ~~the labs of Rockefeller~~ his lab. I could not have been more wrong.

“Everybody around the world who had something to share came forward, and he analyzed and chose what looked most promising,” says Sarah Schlesinger, a clinical investigator at Rockefeller who worked closely with Steinman and oversaw many of his experimental treatments. “We worked with dozens of colleagues around the world who have helped—in designing his therapy, evaluating the tumor, 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.” [Food and Drug Administration].”

Shortly after Steinman received his diagnosis he met with two ~~prior lab~~ former members of his lab, both of whom now run successful immunotherapy research programs of their own. Michel Nussenzweig, of Rockefeller, and ~~Ira Mellman, the vice president of oncology research at Genentech in South San Francisco, 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 tumor.”

The scientists hatched a plan: Nussenzweig would take some of the tumor that was removed during surgery and grow it in mice in order to have enough material available to test. Mellman started a cell line ~~for~~ [[for what purpose?]]. A colleague in Toronto performed a full-genome sequence of the tumor’s DNA ~~for~~ [[for what purpose?]]. And for treatment, Steinman would undergo traditional chemotherapy in combination with as many experimental therapeutics as made sense for his specific disease. ~~He viewed his situation as a scientific problem to be solved. 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.~~ Mellman says.

Steinman tried eight different experimental therapies in all, one at a time, and for each one a single-patient, compassionate-use protocol was submitted to and approved by the FDA. The line-up included three vaccines to prime his immune system, all of which were based on dendritic cell science. One of those, GVAX, ~~made by~~ [[made by whom?]], used material from his own tumor cells to recruit dendritic cells [[I thought dendritic cells did the recruiting of other immune cells?]] to the cancer. Another, developed by Argos Therapeutics of Durham, North Carolina, used his tumor’s RNA to program [[not really sure what 'program' means in this context?]] Steinman’s own dendritic cells—the The RNA-loaded cells were then injected back into him in an attempt to program induce his immune system to recognize and attack the disease. The third, in clinical trials at Baylor College of Medicine in Houston, loaded his dendritic cells with peptides from the surface of the tumor. [[is this another way to achieve the same thing—to get his dendritic cells to kick off a stronger response to the tumor?]]

“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 personalized [[are we using 'personalized' in a different way here – rather than 'tailored for Steinman', we seem to use it to mean 'exactly what Steinman desires' – it jarred for me because it made me think the next sentence described a 'personalised therapy', and then was confused when it didn't turn out that way ...]] as Steinman would have liked, however. He believed that the vaccines he was receiving should be combined with something to strengthen a cancer-suppressed immune response, something like the monoclonal antibody ipilimumab; [[id like to switch this sentence round so we define what a monoclonal antibody is]], which was only just approved ~~this past~~ in May ~~for~~ to treat melanoma. Together with dendritic cell vaccines, Steinman believed, the two therapies could act as a one-two punch. But although he received them each separately he never got to try them in combination. Neither the vaccines nor ipilimumab were FDA-approved at the time, making simultaneous use verboten- [[why is it ok to use them individually, but not together?]].

“Ralph’s decision to undergo this vaccine strategy and others was a reflection of his desire to learn more about how these cells could be used in pancreatic cancer,” says Glenn Dranoff, an immunologist at the Dana Farber Cancer Institute in Boston and the investigator who coordinated Steinman’s GVAX therapy. ~~Which~~

Yet it is impossible to know which, if any, of the therapies extended Steinman's life ~~is nearly impossible to know~~. He lived years longer than his initial prognosis ~~predicted~~—typical survival time for patients with stage IV pancreatic cancer is most often 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 regime note that he was particularly responsive to a conventional chemotherapy, gemcitabine, one that most pancreatic cancer patients develop resistance to after just one or two treatment cycles. They also know that he had a measurable immune response [[how do you measure an immune response?]] against his pancreatic tumor, although whether that response was induced by the dendritic cell vaccine he received or was due to some natural immunity, ~~they aren't completely sure~~. is unclear. They also don't know whether that immune response played a role in extending the cancer's susceptibility 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 Ralph Steinman's one-man trial moved the field ~~forward~~ forwards in subtle ways. It showed that traditional chemotherapy could be given in conjunction with dendritic cell vaccines, something that was a big question mark hanging over the field. It emphasized Steinman's belief in the importance of testing new, experimental therapies in human patients as quickly as possible, ~~as given the limitations of~~ animal models ~~can only inform so much~~. And it united the best minds in the field, all of them fighting for a common cause. -

Anna Karolina Palucka, the investigator who oversaw the development of Steinman's dendritic cell vaccine at Baylor, notes that she and her colleagues are developing a full program of immunotherapy against pancreatic cancer based on the data gathered from Steinman's solo trial. And, in honor of him, the university will be opening a

Ralph Steinman Center for Cancer Vaccines. “He started a completely new field,” Palucka says.

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