



Ralph M. Steinman

Since the start of clinical trials involving dendritic cells, Ralph Steinman has felt the need to stay close. He now spends most weeknights in a faculty apartment near his lab at the Rockefeller University in Manhattan. But Steinman likes to knock off early on Fridays and go home to Westport, CT, where he was sitting on his deck last August when the phone rang. It was Joe Goldstein, Nobel laureate and head of the Lasker Foundation, with the news that Steinman had just won the 2007 Albert Lasker Award for Basic Medical Research. Steinman says he was shocked. Steinman's collaborators, colleagues, and former students say they were shocked that it took this long. Wider public recognition is long overdue, Steinman's friends contend, for his discovery of dendritic cells, which the Lasker citation describes as the "preeminent component of the immune system that initiates and regulates the body's response to foreign antigens."

Steinman discovered dendritic cells in 1972. It took him six years to build a case for their role in initiating the immune response and nearly two decades to overcome the last of the scientific challenges that undercut their acceptance. Through much of that time, Steinman's dendritic cell theory was met in the field by "downright nasty hostility," according to Ira Mellman, who is now at Genentech in South San Francisco.

"It's quite an extraordinary story," says Mellman, who was a postdoc in the Rockefeller lab of Steinman's mentor, Zanvil Cohn, in the early days of the dendritic cell work. Mellman would later collaborate with Steinman on antigen processing in dendritic cells while Mellman was at Yale in the early 1990s. "It was not all smooth sailing. A lesser individual would have given it up and gone on to something else." Mellman believes that Cohn's unwavering support guided Steinman in the early years. "Plus, there was Ralph's quintessential scientific courage. He didn't care how many people thought it was wrong, but until he'd either proved it or found that he was wrong, he would not stop."

A Cell Biology Perspective

"There's no doubt about it. Ralph was alone in the desert for many years," says Michel Nussenzweig, one of Steinman's first

graduate students, who later returned to the Rockefeller to found his own dendritic cell lab there. "People couldn't reproduce Ralph's results because they didn't have his expertise [in culturing dendritic cells]," Nussenzweig explains. Working with dendritic cells was an "onerous task" until the development of tissue culture methods that yielded cells in larger numbers, says Nussenzweig. "Once that happened, everybody could see what Ralph had been talking about for so many years."

Today Steinman brushes off his years in the wilderness as the result of normal scientific skepticism. ("If Ralph says it was skepticism, he's being much too kind," comments Mellman.) According to Steinman, the immunological cell community was paying proper attention to other important things like antigen presentation when he first proposed his dendritic cell theory. Moreover, Steinman says that his original evidence came from a perspective that was novel to many immunologists of the time—cell biology.

Steinman gained that perspective from Cohn and Jim Hirsch, whose joint Rockefeller lab in the early 1970s was studying the cell biology of phagocytes. When Steinman put a heterogeneous mixture of what were then called "accessory cells" from mouse spleen under the microscope, he was already primed to notice the unusual. "We were looking through the eyes of cell biologists. We were trained that way. Everybody in Zan's and Jim's lab knew how to look at cells and how structure was related to function." A tiny fraction of the cells under his microscope had a most unusual appearance, Steinman reports. "We were used to looking at living phagocytes. So when I looked at these dendritic cells, they had this unusual capacity to constantly send out these little feeler processes and pull them back in. The nucleus would just throb back and forth within the cytoplasm. It was something we'd never seen."

Steinman called them "dendritic cells" after their long waving processes, which reminded him of tree roots and branches. Over the next 20 years, Steinman proved that dendritic cells were, in fact, the primers of the immune system. He discovered that their apparent inability to ingest antigen particles was explained by their derivation in skin from Langerhans cells as immature dendritic cell precursors that could capture and display antigen proteins on their

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surface. The restlessly probing dendritic cells observed in lymph tissue were more mature forms, unable to ingest new antigens but able to stop and activate passing T cells. Along the way, Steinman discovered that injecting mature dendritic cells primed with an antigen could trigger a stable immune response and thus could sensitize animals against a chosen antigen. There were therapeutic possibilities here, he noted.

An AIDS Vaccine Candidate

Researchers are now pursuing those therapeutic possibilities on a variety of fronts, including clinical trials in cancer therapy and early-stage trials of an AIDS vaccine. Recent discoveries have tied dendritic cells to the process of silencing, or tolerance, whereby the immune system learns to ignore its own cells. Such powers for dendritic cells, says Steinman, suggest new insights into autoimmune disorders, allergies, and transplant rejection.

Moving from such basic research discoveries to human application is the classic “translational research” so beloved by medical school deans. Steinman is in favor of the process but loathes the expression “translational.” Declares Steinman, “It demeans the type of research. It implies that it’s not basic. It implies that the concepts are already known and all you have to do is ask, ‘Gee, does it work in patients?’” A simpler experimental system can give researchers incredibly important concepts and tools, but turning to humans poses distinct basic research questions, he contends.

Whatever he calls it, Steinman does it exceedingly well, says Sarah Schlesinger, a pathologist who began in the Steinman lab as a 17-year-old high school student and later established her own dendritic cell lab at Walter Reed. Five years ago, she returned to manage Steinman’s AIDS vaccine candidate trials at the Rockefeller. According to Schlesinger, “Ralph really does think and work on the most basic problems in antigen presentation. One moment he is thinking about, ‘How does an antigen get into a dendritic cell?’ And the next minute he is discussing with me how to get this vaccine into people—the regulatory problems, the clinical issues, and sometimes the ethical issues. He goes back and forth with an ease and grace that I’ve never seen in anyone else.”

Lighting His Scientific Imagination

Steinman was born and raised in Sherbrooke, Quebec, a small city about 100 miles from Montreal, where his father founded a family department store called Mozart’s. The whole family helped at the store, including Steinman

himself. He worked weekends and summers until medical school. Education, however, was always the family priority. Taking freshman biology at McGill University in Montreal lit up his scientific imagination. He also credits the McGill honors program and his senior research project with pushing him toward a life at the bench. A medical degree seemed the best career path to train in science in those days, Steinman recalls. He took his from Harvard Medical School (HMS), but he also took a year off to work in the HMS lab of Betty Hay. Hay made him a cell biologist by, among other things, sending him to ASCB meetings, Steinman says. He has been a regular member since 1974. In 1970, he joined the Cohn–Hirsch lab as a postdoc and has been at the Rockefeller ever since.

When not keeping watch on clinical trials, Steinman lives in Westport with his wife, Claudia. “She was trained as a medical social worker, so we met over a patient,” Steinman recalls. “Claudia switched over about 20 years ago to real estate, which is really social work when you come right down to it.” They dance, he says. It started out as a gift from their daughters of a few ballroom lessons but the Steinmans now regularly enjoy an evening stepping out.

Their daughters are twins. Lesley is in public health at the University of Washington and Alexis is in film in Los Angeles. Their son, Adam, is a law professor at the University of Cincinnati. Adam and his wife, Jenny, are the parents of Isla, who is three, and Syla, who arrived just weeks after her grandfather picked up his Lasker.

Breaking the “No Thanks” Rule

Schlesinger was at the Hotel Pierre for the Lasker ceremony last fall. The whole Steinman family was there, including his mother who is 91, Schlesinger recalls. “Ralph had been told that he had only three minutes to talk and not to thank people. I guess they didn’t want an Academy Awards speech. Ralph gave this incredibly eloquent speech about the importance of clinical investigation. And then he said, ‘Against my directions, I’m going to thank the one person who supported my work through my entire life, and that’s my mother, who is here today.’”

There wasn’t a dry eye in the house, Schlesinger reports. When Schlesinger got home that evening, she called her oldest son, a freshman at Harvard. “I told him all about it. Then I said, ‘Note to file.’” ■

—John Fleischman

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