

# Profile of Lawrence Steinman

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Amyloid is often considered to be a trigger for neurodegenerative disease. Lawrence Steinman, the Zimmermann Professor of Pediatrics, Neurology, and Neurological Sciences at Stanford University, has shown that amyloid proteins, which clump together in sticky tendrils, instead protect against neurodegenerative disease (1). Different kinds of proteins can form amyloids, and  $\beta$ -amyloid is a specific type associated with Alzheimer's disease. In his Inaugural Article, Steinman, elected to the National Academy of Sciences in 2015, investigates why injecting different types of amyloid proteins, including  $\beta$ -amyloid, dampens the immune response and reverses paralysis in a mouse model of multiple sclerosis (MS) (2).

## **Immunology by Way of Physics**

The son of a pharmacist and teacher, Steinman was born in Culver City, California in 1947. "I grew up in a very protected time, after World War II and after the Depression," Steinman says. With the advent of Sputnik and the Space Race, "The time was wonderful to

be a kid interested in science," he explains. Steinman enjoyed math and physics and published his first paper, on a mathematical theory, while still in high school (3).

In 1964, Steinman began his freshman year at Dartmouth College. "Having grown up in Southern California, I wanted to try something really different," he says. Initially, Steinman wanted to be a physicist or mathematician and majored in physics. During the summer after his junior year, Steinman arranged to work at the Salk Institute in the laboratory of physicist Edwin Lennox. Surprisingly, this experience provided Steinman's initial exposure to immunology. "My first job in science was doing an experiment on

genetic control of the immune response to influenza," he says.

With a growing interest in clinical science, Steinman began to think about medical school, seeking out schools with a strong research component. Upon entering Harvard Medical School in 1968, Steinman aspired to a career devoted to treating patients, doing research, and teaching. Steinman adds that he didn't anticipate what has become a fourth pillar, namely, that he would go on to found businesses and start biotech companies. Steinman's opportunity to pursue research came early. Interested in neurobiology, Steinman took the opportunity to work with neuroscientist Torsten Wiesel and attempted the task of injecting dye into delicate neuronal cells in the visual cortex. The work proved difficult. "I thought, maybe I should do something easier technically, maybe immunology."

#### **Experience with the Pipeline**

Steinman received his medical degree in 1973, and, after a brief fellowship in neurosurgery at Stanford, traveled to the Weizmann Institute of Science in Rehovot, Israel for a postdoctoral fellowship in chemical immunology with Michael Sela. The laboratory was developing glatiramer, an MS drug still in use today. MS is an autoimmune disease in which the body mistakenly treats one of its own proteins as a foreign invader. In this case, inflammation targeted at nerve cell sheaths results in demyelination and progressive disability as scar tissue accumulates. Steinman investigated how the immune system gets sensitized to myelin basic protein, part of the protective myelin sheath, using a mouse model of MS. The work showed that mice develop experimental autoimmune encephalomyelitis (EAE) only when macrophages, the immune system's sentinel cells, take up myelin basic protein and present it to the immune system, triggering an inflammatory cascade; the protein did not trigger the cascade on its own (4).

When he finished his residency in 1980, Steinman decided to continue working on MS in the neurobiology department at Stanford. "Since I was going to focus on the brain and disease, it was natural," Steinman says. MS, he adds, was the "most prevalent



Lawrence Steinman. Image courtesy of Norbert von der Groeben (Stanford School of Medicine, Stanford, CA).

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 15016 in issue 49 of volume 112.

immunological disease of brain." During his first years on the faculty at Stanford, Steinman recalls that his fellow colleagues helped him come up to speed quickly. "They provided an environment where you could sit and talk for hours," enabling him to hone ideas. Among his new neighbors was immunologist Hugh McDevitt, who pioneered studies on the genetic control of the immune response. Together, they investigated how genetic components of the immune system's MHC affect susceptibility to EAE in mice and found that blocking specific portions of the MHC with antibodies prevented paralytic disease (5).

Steinman also received a warm welcome from geneticists Lenore and Leonard Herzenberg. Even after Leonard's death in 2013, Steinman continues to collaborate with Lenore, a coauthor on the Inaugural Article (2). In the 1980s, as monoclonal antibody production was becoming state-of-the-art, they studied how antibodies to various immune system proteins can block the development of EAE (6). One of the first therapeutic antibodies that Steinman developed was the anti-CD4 antibody. He explains that emerging knowledge of the CD4 receptor and overwhelming immune suppression attributed to HIV's destruction of CD4<sup>+</sup> T cells resulted in underwhelming clinical results (7, 8).

# Homing in on MS

Steinman's experience with applied research in Israel influenced his pursuits. "I really wanted to develop new therapeutics," he says. The MS model, EAE, induced paralysis in mice, and thus offered an objective way to test treatments. In the late 1980s, Steinman began collaborating with Ted Yednock at Athena Pharmaceuticals. Because MS is caused by inflammation in the brain, the team looked for homing signal molecules involved in trafficking across the blood-brain barrier. Steinman surmised that stopping the homing mechanism would prevent the immune cells responsible for inflammation from entering the brain. Using an adhesion assay, they found that antialpha 4 integrin antibodies prevented immune system cell trafficking (9). Further work showed reduction in paralysis in mice, effects that persisted through all levels of clinical trials and resulted in a new drug called natalizumab (10).

Clinical problems emerged after the drug's debut in 2004 when a subset of patients developed a viral disease known as progressive multifocal leukoencephalopathy. "Natalizumab has a real Achilles' heel," Steinman explains. "If you can't get immune cells into the brain, you can't have immune surveillance." Without immune surveillance, latent virus reactivated in a subset of patients. Now, clinicians test for the presence of the virus before treatment. "When we detect a footprint of an antibody to the virus, we don't treat with the drug," says Steinman, who continues to treat patients.

In addition to developing clinical therapies, Steinman has devoted much of his work to discerning the basis of MS. In the early 2000s, when most researchers were taking a genetic approach to the problem, "We did something different," he says. "We did all the

'omics' we could think of, including transcriptomics, proteomics, and lipidomics." They used a rapid autopsy approach to gather tissue samples from the brain lesions of patients with MS to discern what molecules were present and what they might be doing, a proteomic and lipidomic analytic process that he later patented, one of 45 patents he holds (11, 12).

## Fresh Perspective on Amyloid

In the MS lesions, Steinman found several types of amyloid proteins, all of them misfolded in the generic, canonical β-pleated sheet format. Amyloid, explains Steinman, "is both a generic term and a specific term," and that duality can be confusing. The amyloid proteins he found in the tissue samples included tau; aB crystallin, the major lens protein in the eye; and the precursor of  $\beta$ -amyloid, the specific type of amyloid protein that accumulates in Alzheimer's lesions (11). Given the association of amyloid proteins with neurodegenerative diseases, Steinman expected that administering amyloid proteins in the EAE model would exacerbate the inflammation. Instead, mice receiving an intravenous infusion of amyloid "started walking around" (13). Steinman was as surprised as anyone else, but he now sees a different role for amyloid proteins in MS. "If you look under the microscope at diseases like Alzheimer's or Parkinson's, you don't see much evidence of an inflammatory response. Yet, there's a lot of amyloid in those diseases," he notes, "but inflammation is prominent in MS, where there is far less amyloid than in Alzheimer's."

Steinman and a collaborator of 30 years, biochemist Jonathan Rothbard, investigated the startling results closely. They synthesized a collection of six amino acid amyloid peptides described by biochemist David Eisenberg (14) and injected them into mice. These hexapeptides represented "some of the most evil proteins," says Steinman, including prions and β-amyloid, but they found that, "If you can form amyloid, we can turn off paralysis" (1). Steinman knows that his work goes against the current thinking in the field. "The correct answer on the medical school exam right now is that amyloid is the root of neurodegenerative disease," he explains. The controversy doesn't faze Steinman. "It's fun to try things that challenge the popular notions of others," he says. In his Inaugural Article, Steinman deepens the investigation by looking for the mechanism of action of the immunedampening response. The work shows that in the presence of intraperitoneal, or even intranasal, administration of amyloids, regulatory B cells secrete IL-10 and suppress neuroinflammation (2).

Amyloids suppress inflammation globally. Much of the clinical research and therapeutic development is centered on nonspecific approaches, Steinman notes, but he has also worked on agents that help acclimate the immune system to specific antigens (15, 16). "In a few of the autoimmune diseases, we know the antigens that are being attacked." In MS, similar acclimating treatments have not been clinically successful, a fact that Steinman attributes to not knowing the culprit antigen. "If you asked the field which antigen is

Steinman finds himself devoting much of his time trying to garner industry interest in his research. "Except for a few fortunate people, we all have to be salesmen for the science if we want to see these

therapies developed," he says. Once a clinical trial begins, however, Steinman is out of the picture. "I am an interested observer, but don't participate," he notes. "The ethical environment, with which I agree, is that if you discover something at the bench, you best keep your hands out of the testing."

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