Susumu Tonegawa: From antibody enigma to memory engrams

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At the height of his fame, Susumu Tonegawa did something science rarely rewards: he walked away. The discovery that earned him the 1987 Nobel Prize had solved one of immunology's deepest riddles and secured his place in history. Yet he entered neuroscience as a relative newcomer, carrying forward the molecular-genetic expertise that had defined his earlier work.

When he died on July 11, 2026, at the age of 86, he was remembered for two scientific lives—one that revealed the genetic logic of antibody diversity, and another that helped turn the elusive idea of a memory engram into an experimental reality. His career was shaped by departures: from Japan to the United States, from chemistry to molecular biology, from viruses to immunity, and finally from lymphocytes to neurons. For Tonegawa, every summit was also a threshold (Figure 1).

How did a chemist with almost no training in immunology uncover the genetic machinery of antibody diversity? Why, after winning the Nobel Prize and transforming a field, did he choose to leave it? And how did that second beginning lead him to trace the physical imprint of memory in the brain?

AN OUTSIDER IN MOTION

Born in Nagoya in 1939, Tonegawa studied chemistry at Kyoto University as molecular biology was beginning to reorder the life sciences. His Kyoto adviser urged him to pursue graduate training in the United States. At the University of California, San Diego, he studied gene transcription in bacteriophages and received his PhD in 1968. He then joined Renato Dulbecco's laboratory at the Salk Institute, where tumor viruses offered a bridge from bacterial genetics to mammalian cells. He was developing a habit that would govern his career: approach a vast biological mystery with the sharpest molecular tools available.

Then circumstance intervened. His US visa was expiring, and Dulbecco suggested the newly founded Basel Institute for Immunology in Switzerland. Tonegawa knew little immunology. The institute, led by Niels Kaj Jerne, nevertheless offered him a position. In 1971, he arrived in Basel as an outsider surrounded by immunologists. The first year was difficult, but he began learning the field and soon encountered one of its central puzzles.

Figure 1. Susumu Tonegawa Photo by Webb Chappell/MIT

THE GENETIC RIDDLE OF IMMUNITY

The immune system can recognize an extraordinary number of foreign structures, including many it has never encountered. Each B-cell clone produces an antibody with a particular specificity. Yet the genome contains far too few genes to encode a separate antibody for every possibility. In the 1970s, the contradiction divided immunology. Were vast numbers of antibody genes inherited, or did antibody-producing cells alter their genes during development? The arguments were sophisticated; decisive evidence was missing.

Tonegawa saw an opening because he was not bound by the field's traditions. Restriction enzymes, DNA hybridization, and recombinant DNA methods were beginning to let scientists compare genes directly. Instead of asking only what antibodies looked like, he asked whether the DNA in an antibody-producing cell remained identical to inherited DNA.

The answer was startling.

By comparing immunoglobulin DNA from mouse embryos with DNA from antibody-producing plasmacytoma cells, Tonegawa and Nobumichi Hozumi showed in 1976 that variable- and constant-region sequences of an immunoglobulin light-chain gene occupied different configurations in germline and tumor-cell DNA. This provided decisive evidence that immunoglobulin genes undergo somatic rearrangement during B-cell development. Subsequent work by Tonegawa's group and others established the broader architecture now called V(D)J recombination: light chains assemble V and J segments, whereas heavy chains assemble V, D, and J segments. Variation at the joins adds further diversity, while somatic hypermutation is a separate process that diversifies and refines antibodies during an immune response.

The mechanism was radical and elegant. The immune system did not store a complete library of finished antibody genes. It carried modular genetic pieces and generated diversity by rearranging them. A limited inherited vocabulary could produce an enormous repertoire of molecular sentences.

The discovery resolved a long-running debate and demonstrated that programmed DNA rearrangement is a normal part of lymphocyte development. V(D)J recombination became central to understanding adaptive immunity and the generation of B-cell and T-cell receptor repertoires. That knowledge has provided a foundation for antibody engineering, immune-repertoire analysis, diagnostic interpretation, studies of vaccine responses, and the development of antibody-based therapies.

THE NOBEL PRIZE—AND ANOTHER BEGINNING

In 1987, Tonegawa became the sole recipient of the Nobel Prize in Physiology or Medicine "for his discovery of the genetic principle for generation of antibody diversity." The prize confirmed what immunologists already knew: he had solved one of the field's foundational problems.

Tonegawa moved to MIT in 1981, where he extended his work to immunoglobulin gene regulation and T-cell receptors. Meanwhile, molecular genetics and transgenic methods were making the nervous system increasingly accessible to mechanistic study, allowing him to redeploy his expertise. Yet the broad outlines of the antibody-diversity problem no longer felt mysterious to him. He began looking for a question that would again force him into unfamiliar territory. As he later explained, he chose research problems according to whether they genuinely interested him, not whether a move seemed safe for his career. Learning and memory offered such a problem: where, physically, is a memory stored, and how is it recalled?

MAKING MEMORY VISIBLE

The question had haunted neuroscience for more than a century. Richard Semon had proposed that experience leaves a lasting physical trace, an "engram," in the nervous system. Brain lesions and recordings could identify regions important for memory, particularly the hippocampus, but they could not isolate the cells representing one specific experience and prove that those cells were sufficient to recall it.

Tonegawa entered neuroscience as a relative newcomer, but with deep expertise in molecular genetics. His laboratory combined activity-dependent genetic labeling with optogenetics, which uses light-sensitive proteins to control selected neurons. In a landmark 2012 experiment, Tonegawa's team, including Xu Liu, labeled a sparse population of hippocampal neurons active while mice formed a contextual fear memory. Later, in a different setting, light was used to reactivate those same cells. The stimulation induced freezing, the conditioned fear response, showing that activation of the tagged ensemble was sufficient to elicit behavioral recall in this mouse model.

The experiment did more than correlate neurons with memory. It showed that activating a defined neuronal ensemble could trigger recall. An idea that had hovered between psychology and philosophy became an experimentally testable biological entity. The result was specific to an optogenetic mouse fear-conditioning paradigm: activating the tagged ensemble was sufficient to evoke a conditioned response, not to map the full neural-circuit architecture of memory.

Tonegawa's group then pushed into territory that once sounded like science fiction. By reactivating the representation of one context while mice experienced a foot shock in another, Tonegawa's group produced a false contextual fear association. Subsequent studies from the group distinguished memory storage from natural retrieval. In a protein-synthesis-inhibitor model of retrograde amnesia and in transgenic mouse models of early Alzheimer's disease, memory information appeared to persist despite impaired natural recall and could be accessed by direct optogenetic activation of tagged engram cells. These findings did not mean that human memory loss could be reversed with light. They suggested, within specific mouse models, that apparent forgetting can sometimes reflect failed access rather than complete destruction of a stored trace.

THE COURAGE TO BEGIN AGAIN

His two scientific lives were less disconnected than they appeared. Antibodies and memories belong to different biological worlds, yet both confront the same mystery: how can finite components generate immense diversity, preserve information, and respond selectively to experience? Tonegawa searched beneath complexity for mechanisms simple enough to test and powerful enough to reorganize a field.

He was demanding, intensely focused, and impatient with explanations that stopped at description. Colleagues later described his passion, energy, and relentless pursuit of the fundamental mechanisms of memory as an inspiration to generations of neuroscientists. Tonegawa himself credited people who encouraged his major turns: the adviser who sent him abroad, Dulbecco who pointed him toward Basel, Jerne who recognized the power of molecular biology in immunology, and institutions that gave him room to change direction.

Modern science rewards specialization, established expertise, and predictable productivity. Tonegawa's life offers the opposite model. He did not confuse a field with an identity. He allowed curiosity to make him inexperienced again.

For Tonegawa, the answer was a refusal to let success decide the boundaries of curiosity. He solved the genetic riddle of antibody diversity, then turned to the physical basis of memory. Either achievement could have defined a lifetime. Together they reveal something rarer than brilliance: the courage to abandon one's strongest position in order to ask a better question.

His greatest legacy may lie not only in how the immune system remembers a pathogen, or how the brain remembers an experience. It lies in the example of a scientist who treated every destination as a departure—and who proved, twice, that becoming a beginner can be the beginning of a revolution.

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