RETROSPECTIVE

Paul Greengard (1925–2019)

Pioneer in nerve cell signaling and brain diseases

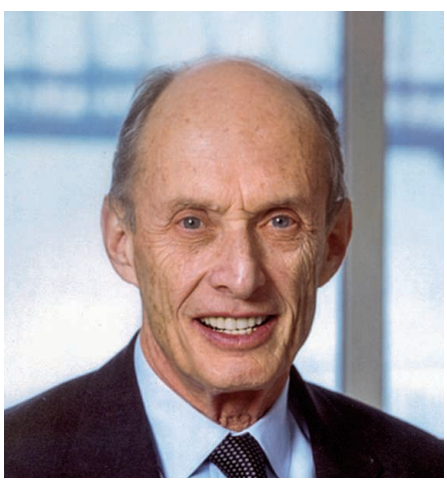
By **Pietro De Camilli**

Paul Greengard, esteemed neuroscientist and beloved mentor, died on 13 April. He was 93. Greengard pioneered the elucidation of intracellular signaling in nervous system function and provided key insights into neurological and psychiatric diseases. His work helped shape modern neuroscience and had a broad impact in a variety of other fields.

Greengard was born in New York City. During World War II, he spent 3 years in the Navy as an electronic technician. In 1948, he graduated from Hamilton College in Clinton, New York, where he majored in mathematics and physics. Because the theoretical physics field was dominated by research on nonpeaceful uses of atomic energy, he planned instead to enter the nascent field of biophysics. However, a seminar by Allen Hodgkin about his still-unpublished (and future Nobel Prize–winning) work with Andrew Huxley convinced Greengard that the major questions about neuronal excitability that could be addressed with then-current methodology had already been solved. This prompted him to turn to biochemistry to explore new approaches to study nervous system function.

After receiving his Ph.D. from Johns Hopkins University in 1953, he spent 5 years as a postdoctoral student in England and then, after a short period at the U.S. National Institutes of Health, he became director of the Department of Biochemistry at Geigy Research Laboratories. Not long afterward, his passion for frontier basic science led him back to academia, and in 1968 he took a position as a professor in the Department of Pharmacology at Yale University, where he spent the next 15 years. In 1983, he was recruited to The Rockefeller University, where he remained until his death.

A defining moment in Greengard's career was a semester as a visiting scientist at Vanderbilt University with Earl Sutherland, who had discovered the role of cyclic adenosine monophosphate (cAMP) as a key intracellular mediator of the actions of hormones on glucose metabolism. This finding was followed by biochemist Edward Krebs' discovery that cAMP acts by controlling an enzyme that regulates proteins by adding a phosphate group to them, a reversible reaction called phosphorylation. Greengard saw the broad implications of these findings and formulated two hypotheses that became a cornerstone of his subsequent work. First, he proposed that reversible protein phosphorylation is a general mechanism through which intracellular functions are regulated by intracellular second messengers. Second, he hypothesized that these reactions are also used in nerve cells to transduce, process, and integrate neurotransmitter and electrical signals. His second hypothesis met with great resistance at first, as intracellular biochemical reactions seemed too slow compared with the fast speed of neural signals. It seemed inconceivable that reactions used to control metabolism would also be used as a basis for the noble functions of the brain.



Greengard persisted, undeterred by this skepticism. He showed that phosphorylation cascades triggered by second messengers play a fundamental role in mediating effects of neurotransmitters and neuronal activity on neuronal function. He then identified brain proteins whose phosphorylation was controlled by these second messengers and characterized their function. Not surprisingly, some of these proteins turned out to act as central nodes in neuronal physiology, and their study advanced not only neuroscience but also cell biology and medicine. Eventually, Greengard's hypothesis proved correct. Electrical mechanisms of fast signal propagation in the brain and slower biochemical mechanisms function together and synergistically. Biochemical machinery mediates learning and helps encode memories. For his discoveries concerning signal transduction in the nervous system, Greengard was awarded the 2000 Nobel Prize in Physiology or Medicine, which he shared with Eric Kandel and Arvid Carlsson.

This recognition did not slow Greengard down. He continued to run a large and productive lab until his very last day. In his later years, he made key contributions to the elucidation of molecular mechanisms of brain diseases, including Alzheimer's, Parkinson's, drug addiction, and depression, with the goal of developing new therapeutic strategies. Through his exploration of the biochemical heterogeneity of neurons, a field that he greatly helped to advance, he contributed to the foundation of a pharmacology that selectively targets intracellular signaling pathways of specific neuronal subpopulations.

Greengard's ideas and concepts permeate modern neuroscience. His lab has been an important crossroad for generations of collaborators and trainees, many of whom have gone on to become scientific leaders. As a mentor, he had a special ability to inspire self-confidence in his lab members, as I experienced firsthand as a postdoc with him in the late 1970s. His trust made us work at our best. He took genuine interest in our lives, an interest that lasted well after we left the lab and that for many of us turned into a lifelong friendship. Despite managing a very large lab, he always made each of us feel that we were his priority; he was always ready to listen and to provide advice. Most important, he inspired us with his passion for knowledge and his excitement for every new discovery, small or big. His eagerness for learning and understanding extended beyond science. He followed with interest and sharp insight current events. With his marriage to artist Ursula von Rydingsvard, his beloved spouse of the past 33 years, he became close to the world of the arts, and he embraced this world with fresh curiosity and passion.

Greengard had a special ability to connect to people from all walks of life. His generous spirit, his willingness to listen and to empathize, and his sense of humor and quick wit made him dear to many. A strong advocate of gender equality in science, he used the proceeds of his Nobel Prize to establish the Pearl Meister Greengard Prize, which recognizes outstanding achievements of women scientists and honors the memory of his mother, Pearl Meister, who died giving birth to him.

Greengard's indomitable energy and his determination to live life at its fullest will continue to be an inspiration for the many of us who crossed his path. We will miss him tremendously. ■

10.1126/science.aax9357

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Science

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Science **364** (6442), 740.
DOI: 10.1126/science.aax9357