

Paul Greengard (1925–2019)

We share with great sadness and personal loss the recent death of Paul Greengard, PhD on Saturday, April 13 at the age of 93. Paul made transformational contributions to neuroscience and cell signaling and shaped and nurtured the careers of hundreds of women and men in science. We are forever grateful for his mentorship and friendship. He will remain the highest standard of what curiosity-driven science should always be—rigorous, adventurous, and fun.

We both had the life-changing opportunity to work in Paul's laboratory almost 40 years ago. At that time, the field of neuroscience was focused primarily on the electrical activity of nerve cells and on the generation of synaptic and axonal electrical signaling, with little attention paid to the biochemical processes that mediate or modulate such functions. Based on work by Ed Krebs, Ed Fisher, and others in peripheral tissues, which demonstrated a role for protein kinase A and phosphorylase kinase (a calcium-activated protein kinase) in controlling glucose metabolism, Paul hypothesized—beginning in the late 1960s—that similar signaling mechanisms might also contribute to neuronal regulation. He further speculated a far broader range of such mechanisms through the discovery of protein kinase G and two additional forms of calcium/calmodulin-dependent protein kinases, including CaMKII—the most broadly expressed member of the family. Later discoveries identified several protein phosphatases and their regulatory proteins in the brain. This work led him to propose in 1978 that neurotransmitters and nerve impulses produce many of their more slowly developing actions (e.g., slower ion currents, changes in neuronal structure and gene expression) through the regulation of diverse types of protein kinases and protein phosphatases and the consequent changes in phosphorylation state of diverse types of neural proteins.

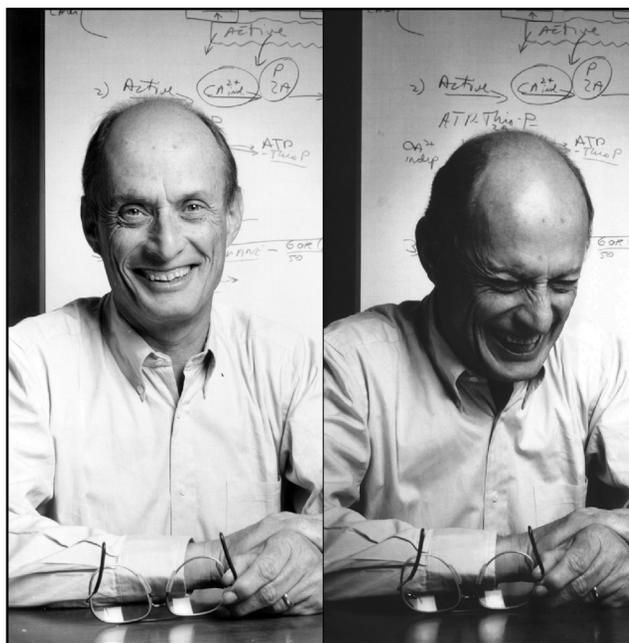
This hypothesis—of the central role of protein phosphorylation as the most important and widely used mode of neurobio-

logical regulation—was greeted with considerable skepticism when initially presented. One of us (E.N.) was in the Greengard laboratory in the late 1970s when Paul returned from giving a research seminar at one of the country's foremost departments of neuroscience at the time. He returned frustrated by the lack of embrace of his novel hypothesis and the continued belief by most leaders in the field that biochemical processes are surely important in the metabolism of nerve cells, but not in their neurobiological signaling. Paul responded by doubling down and by having his laboratory build an ever-expanding amount of compelling experimental evidence to prove the veracity of his hypothesis. The rest is history: today's graduate students and postdoctoral fellows enter the field of neuroscience with the matter-of-fact certainty of the primary role played by protein kinases and protein phosphatases in regulating virtually every aspect of neuronal function through the phosphorylation of virtually every class of protein. These kinases and phosphatases regulate the strength of synaptic and axonal electrical signaling and underlie most forms of synaptic plasticity in the brain. Moreover, these "Greengard cas-

cases" of kinases and phosphatases mediate the downstream signaling of many of the brain's major neuromodulators, including dopamine, serotonin, and norepinephrine, which regulate reward, motivation, mood, attention, and arousal and are critical in many neuropsychiatric diseases, including Parkinson's disease, depression, and addiction. For his paradigm-shifting contributions, Paul received the Nobel Prize in Physiology or Medicine in 2000. He was a member of the US National Academy of Sciences and National Academy of Medicine and received many honors, including the NAS Award in the Neurosciences, the Ralph Gerard Prize from the Society for Neuroscience, and the Karl Spencer Lashley Award, among many others.

Paul's trajectory in his scientific career was a winding road. A graduate of Forest Hills High School in New York City, Paul joined the Navy where he worked on early-warning radar systems. He later graduated from Hamilton College, a liberal arts college, in upstate New York as a physics and mathematics major. He wanted to apply his expertise in computational sciences to biological systems and obtained his PhD from Johns

Hopkins University in 1953 after having worked in the laboratory of Haldan Hartline, a leader in biophysics at the time. Paul went on to receive postdoctoral training in Wilhelm Feldberg's laboratory at the National Institute for Medical Research in London; Feldberg was one of the few leaders in neuroscience interested in combining biochemical and electrophysiological approaches. Upon completion of his training, Paul joined the pharmaceutical company Geigy in 1959, where he became head of Biochemistry and remained there until 1967. He then decided to join academia—we think that Paul was drawn to academia by his interest in basic mechanisms—and, after brief sabbaticals at Albert Einstein College of Medicine and in Earl Sutherland's laboratory at Vanderbilt University, Paul was appointed a full professor of pharmacology at Yale University in 1968. In



Paul Greengard

These are some of our favorite pictures of Paul. One of us (R.L.H.) was present at this photo shoot in 1987 and remembers it well. Paul always had a hard time keeping a straight face while posing for photographers.

1983, he relocated to The Rockefeller University as the head of the Laboratory of Molecular and Cellular Neuroscience, where he remained until his death. At Rockefeller, Paul maintained a large productive lab for 36 years through his 70s, 80s and 90s, expanding his research into translational work studying Alzheimer's and Parkinson's diseases, depression, and schizophrenia. During this career, Paul continually adopted the newest, innovative techniques in his lab and developed his own even into his ninth decade. His path, from physics to neuroscience and from industry to academia—both highly unusual then and now—greatly informed Paul's approach to his science and the drive for fundamental discoveries that ultimately inform human health and disease.

Those of us who have had the privilege of working in the Greengard laboratory all marveled at Paul's own unique brain! He had an unmatched intense and indefatigable capacity to focus and to ask penetrating, incisive questions when reviewing experimental findings and interpretations. He was meticulous in his writings. We all spent hours working with Paul in preparing manuscripts for publication, often debating whether the use of “a” or “the” or “and” or “and to” offers more precise clarity to the text. These hours and hours of time were sometimes excruciating at the moment, but we treasure them in retrospect for what they taught us about how to write about our own scientific discoveries and how to interact with our own trainees. They were also hysterically amusing because of Paul's one-of-a-kind sense of humor that was as quick as it was irreverent. When you saw that beautiful sparkle in his eyes appear, you knew he was about to say something that would sum up a situation—poignant, funny, and perfectly delivered. Many hours were spent

wandering off track; talking about politics, art, and science; and gossiping and laughing until our sides ached. It was not the most efficient process but, in the end, produced eloquent, concise, and clear manuscripts, and it was a lot of fun. The enormous amount of time spent with Paul at these marathon writing sessions defined what being in his laboratory was all about and remains among the most valuable experiences of our careers.

Both of us often describe our relationship with Paul by saying that he was a second father. But the remarkable truth is that there are more than a hundred people who feel the very same way. Time and space seemed to not exist for Paul. He was everywhere, always available, always present. He had an extraordinary magnanimity of spirit and gave of himself selflessly to his students and postdocs, as well as to enumerable collaborators and other colleagues. All of us have particular stories to tell. Paul helped us all navigate through our own careers in academia and industry, not only when we first left his lab but through several decades thereafter. He enjoyed debating the pros and cons of various job possibilities many of us entertained and very often offered unique perspectives and insights. Both of us have been chairs of departments and presidents of the Society for Neuroscience, taking on many administrative roles against Paul's recommendation. For Paul, administration would only take away time from his laser focus on his passion: science and discovery. Paul's advice and support went far beyond careers and employment. Paul served as a marriage counselor, real estate advisor, and an all-around personal trainer and therapist for countless of his trainees! After talking with Paul, or making special trips to NYC just to have dinner with him, many of us felt better

about ourselves, infused with greater confidence and well-being, and recharged to face our own challenges at work and at home.

Paul's generosity of spirit and his support for women in science is exemplified by his decision to donate the proceeds of his Nobel Prize to Rockefeller University to endow the Pearl Meister Greengard Prize, named after his mother who died giving birth to him, for women scientists in biology. Paul was a staunch women's advocate by promoting the enormous need for more women in the field and by creating invaluable opportunities and training.

Paul's legacy lives on not only through his scientific contributions, but also through this impact on others. His former students and postdocs are department chairs, institute and center directors, deans, National Academy members, and HHMI investigators. His trainees and others who circled his orbit feel both tremendous gratitude and a great sense of loss. We all are better people for knowing him. Very few individuals match Paul's generativity in number, scope, and influence. Paul's life ended the way he always wanted: with his boots on. He remained the head of a large laboratory, at last count 61 lab members, the largest lab at Rockefeller University, with robust funding, continuing to publish research findings utilizing state-of-the-art experimental approaches in the nation's top journals until his last day. Over his career, he published over 1,000 papers, which were cited over 100,000 times, giving him an H factor that even Google Scholar has trouble calculating. Our lives, and so many others', are forever enriched personally and professionally by the life-changing opportunity to be part of the Greengard family. He will be missed, and he will live on in each of us.

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