Paul Greengard

(1925–2019)

Nobel laureate who traced signals through the brain.

Paul Greengard shared the Nobel Prize in Physiology or Medicine in 2000 for discovering pathways that modulate signalling between neurons in the brain. This fundamental advance transformed the search for new ways to treat neurodegenerative diseases, such as Parkinson's and Alzheimer's, a search in which he and his group at the Rockefeller University in New York City were involved right up to his death on 13 April, at the age of 93.

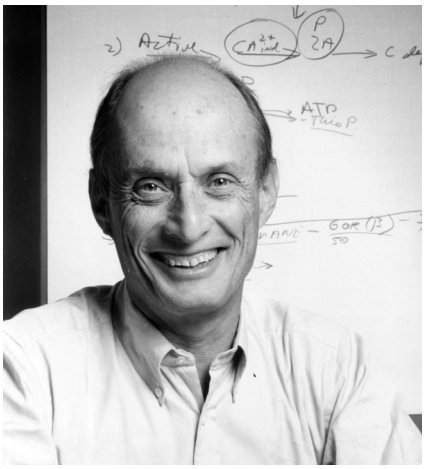
Greengard used his US$400,000 Nobel-prize money to found (with his wife, sculptor Ursula von Rydingsvard) an annual prize for outstanding female biomedical scientists. Named after Greengard's mother, who died giving birth to him, the Pearl Meister Greengard Prize has been awarded since 2004. Recipients include genetics pioneers Mary Lyon, Elizabeth Blackburn and Jennifer Doudna.

When Greengard was a young researcher in the 1950s, neuroscience was in its infancy. Most biophysicists thought nerve impulses simply triggered the release of neurotransmitters such as glutamate and GABA into the tiny gap between cells, and that the interaction of these with receptors passed on the signal by causing rapid electrical changes across the cell membrane. Such a mechanism, however, could not account for longer-term changes that might underlie learning and memory.

During his biochemical studies, Greengard learnt that glucose metabolism involved a reaction in which enzymes catalysed the phosphorylation of proteins, tuning their function. His hunch that a similar mechanism might be at work in neurons led to his discovery in the late 1960s that 'fast' signal transmission is underpinned by a cascade of slower, intracellular changes in response to neurotransmitters such as dopamine.

Greengard was born in New York in 1925 into a Jewish family, but was brought up a Christian by his Episcopalian stepmother. He joined the US Navy aged 17, in 1942, and worked at the Massachusetts Institute of Technology in Cambridge on an airborne early-warning system against Japanese kamikaze aircraft. After the end of the Second World War, he received a degree in mathematics and physics from Hamilton College in Clinton, New York. He decided against graduate work in physics because the only funding available at the time was for atomic-energy projects.

Turning to neuroscience, he decided to deploy both biophysics and biochemistry in the study of neurons, after



THE ROCKEFELLER UNIVERSITY

hearing an inspiring lecture by British Nobel prizewinner and biophysicist Alan Hodgkin. With a PhD from Johns Hopkins University in Baltimore, Maryland (he studied metabolic changes accompanying degeneration in frog peripheral nerves), in 1953 he went to Europe. He spent several years in the United Kingdom and the Netherlands. His postdoctoral work included looking at the effects of drugs on neurotransmitter release in excised nerves at the National Institute for Medical Research in Mill Hill, London.

Soon after returning to the United States in 1959 — he liked England, but not its cold houses or bewildering choice of schools for his two young sons — he joined the research arm of the drug company Geigy Research Laboratories in Ardsley, New York, as director of biochemistry. He later said it was easier to set up drug-development research programmes in a university laboratory than in a drug company. In 1968, he joined Yale University in New Haven, Connecticut.

It was here he made the first breakthroughs that would lead to the Nobel he shared with Eric Kandel and Arvid Carlsson for their independent work on signal transduction in the nervous system. Studying extracts of rat brain tissue, Greengard's group first found an enzyme that was sensitive to dopamine (the depletion of which Carlsson had discovered to be related to Parkinson's disease). The enzyme converted ATP (adenosine triphosphate) to the second messenger cyclic AMP (adenosine monophosphate).

Soon afterwards, the group found the rest of the links in this and other chains that lead to the phosphorylation of target proteins. Many of these targets turned out to be neurotransmitter receptors; others were associated with the release of neurotransmitters, with controlling the electrical potential across the cell membrane, or with regulating protein production through altered DNA transcription.

These slow, long-term changes suggested a neural basis for learning and memory, later demonstrated by Kandel in his work on the sea slug *Aplysia*. Greengard's proposal, as he wrote in his Nobel lecture, was "greeted initially with enormous scepticism, and at times downright hostility".

One issue was that neurophysiologists could not see how such slow mechanisms (hundreds of milliseconds to seconds) could mediate much faster physiological responses, such as identifying an image. Greengard explained that slow synaptic transmission is "the software that controls fast transmission", which he dubbed "the hardware of the brain". He went on to show that molecules that participate in these second-messenger cascades (such as the dopamine-modulated protein DARPP-32) are depleted or altered in conditions such as schizophrenia and substance-use disorder. They are also implicated in the side effects of L-dopa treatment for Parkinson's disease.

Greengard made his final move, to the Rockefeller University, in 1983, and from 1995, he also headed its Fisher Center for Alzheimer's Research. His group continues to work on potential drug targets for degenerative brain diseases, depression and schizophrenia. Greengard set up a company, Intra-Cellular Therapies, that aims to develop improved treatments based on the findings of his group. Some have reached phase III clinical trials, notably, lumateperone for schizophrenia.

Throughout more than six decades as group leader, Greengard surrounded himself with young researchers, chosen for their commitment to his vision. He was meticulous in crediting them with discoveries made under his general direction. His own drive was relentless, and although he appreciated the world of the arts that he encountered through his wife, there was really nowhere he would rather be than in the lab.

Greengard did not learn of his mother's death until he was aged 20. The absence of any photo or other physical record of her existence affected him deeply. Hence the prize in which her name — like his — lives on. ■

Georgina Ferry *is a science writer from Oxford, UK.*
e-mail: mgf@georginaferry.com