

# Hamilton

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THE ALUMNI  
ALL-STARS AND  
THE BUFFERS:  
SALUTING TWO  
HILL TRADITIONS

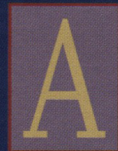
PAUL GREENGARD '48:  
PIONEERING IN  
NEUROSCIENCE

THE GALAPAGOS:  
EXPLORING NATURE'S  
WONDERLAND



# Opening New Paths in Neuroscience

Nobel Laureate  
**Paul Greengard '48**



AT 5:30 A.M. LAST OCTOBER 9TH, THE telephone echoed through the three floors of the Greengard home, located on Manhattan's Upper East Side. Bleary-eyed, Dr. Paul Greengard began reaching about in the dark, trying to find the cordless phone which he had left off its base. His grandson, Philip, was sleeping at the foot of his bed, and his daughter and son-in-law were staying in the room beside his. Dr. Greengard picked up the phone in time to hear his daughter, Ursie, saying, "I'm sorry, he's asleep. It's the middle of the night." He recalls, "I heard this man saying, 'My name is Hans Jornvall, I'm the Secretary of the Nobel Assembly.' I said, 'It's okay, I'm awake!'"

by Heather Won Tesoriero '96

Paul Greengard '48 was informed that he had won the world's most distinguished prize. "That's nice," he responded. "Thank you." He offers a scientific explanation for his stoic reply: "It's very funny, the reaction I had was very much like that of someone getting very bad news, or any sort of astounding news that affects the equilibrium." Once he realized he had won, and given his wife Ursula a thumbs up, he asked who was sharing the Prize with him and what the citation was for his award. "A few seconds of shock, and then you go into denial. I think our brains can only take in so many things at once."

He would know. Paul Greengard's brain has taken in — and put out — some of the past century's most valuable information regarding how the mind's gray matter works. He has devoted the past 50 years of his life to revealing how brain cells communicate with each other. When he embarked on his studies, the field of neuroscience was virtually unheard of, and because of that, he was a renegade in his pursuits. "At the time that I started in this area, neuroscience wasn't even a field, literally." He recalls that people in physiology departments "were studying the electrical properties of nerve cells, and they didn't know anything about, nor were they interested in, the biochemical basis of how these electrical properties were generated."

According to Hamilton's Stone Professor of Psychology, Douglas Weldon, "Paul Greengard created the framework that scientists use to understand neurotransmission." This framework has led to some of the key discoveries and advances in schizophrenia, Parkinson's disease and Alzheimer's disease, all afflictions that result from neuronal cell malfunction.

Throughout the course of his career, Dr. Greengard's work has been incorporated into course work on the Hill, and is featured in the two-year-old neuroscience concentration at Hamilton. Assistant Professor of Biology Herman Lehman says, "Anyone who has taken a course in neuroscience has heard of Paul Greengard. Some of the things that impress me about him are his productivity, his creativity, and his longevity. He was doing this in the '60s and has been pounding it out since then. He has a tremendous publication list. I really admire him."

Born in Manhattan in 1925, Paul Greengard grew up in Brooklyn and Queens. His work in physics began in his teens, when he was serving in the U.S. Navy during World War II. His affinity for scientific matter did not go unnoticed in the military. "At the time, the Japanese were using these suicide planes and they would fly very low over the water, and because of the curvature of the earth, you couldn't detect them until they were 20 miles away. And by that time, you couldn't get your planes up in the air to fight them. So they conceived of an idea of having a radar system in the plane, and then you could get your planes off the deck of the carrier and try to intercept the suicide planes." At the age of 17, he and

and so I was told from the age of six years old, ever since I can remember, that I was going to Hamilton College," says Dr. Greengard. "I never questioned it."

He remembers his days on the Hill and the men he knew there with pleasure, and he thought one student in particular was quite amusing. "Peter Falk was one of our classmates. He was on our floor and he had the room next to me. I lost touch with him and I turned on the television one day and saw him there."

Peter Falk roomed with Harold "Bud" Coleman '50, now a retired anesthesiologist. Dr. Coleman recalls that Paul Greengard's astounding intellectual acumen was clear to those who knew him even then. "He was unquestionably brilliant, unbelievably bright." And it was Greengard who passed on a skill to Coleman that the latter has made use of throughout his life. "These three guys needed a fourth hand for their bridge game, and I was the only one around who was willing to take the time to learn. Paul Greengard taught me how to play bridge," he recalls.

Though he concentrated his academic efforts in the sciences, and majored in physics, Dr. Greengard fondly remembers an impassioned English professor, Robert Barnes "Bobo" Rudd. "This one man taught us 18th and 19th century literature and he read us a poem of Robert Burns, *A Red, Red Rose*. He read it to us and then said, 'I'd rather have written that poem than be the President of the United States.' And his eyes welled with tears. It left such an unbelievable impression on me."

Paul Greengard devoted much of his time to his studies and was on an accelerated program born out of the war, allowing him to graduate in two and a half years. Because many men were returning from military service, there was an age gap between students, some being only 17 and 18 and others 23 to 25. According to Dr. Greengard, there was a certain informality that set in on the Hill after the war. "A lot of people had been in dangerous situations and a lot of these veterans didn't want to put up with formalities, or dress codes, etc. They didn't even think of it as rebellion."

Paul Greengard roomed with Edward "Pete" Bakwin '50. Now chairman of a bank holding company in Chicago, Pete Bakwin remembers Dr. Greengard as someone with intense interest



**Paul Greengard, being presented with the Nobel Prize by Sweden's King Carl XVI Gustaf**

another young man were selected to go to MIT to help develop an early-warning airborne detection system.

Paul Greengard arrived at Hamilton after three years of active duty with the Navy in 1946. "My father and uncle went to Hamilton



*because very, very few people believed I was right and so that was the bad news. It's very frustrating to hear people say, "Oh, that's nonsense." The good news was that I had basically no competition in my field for 15 years and I virtually worked alone. And gradually people began to believe in the validity in it and now it's one of the most active areas of all brain research. We defined what we did as understanding how neurotransmitters produced their effects on their target cells, and that's what 3/4 of brain science is about today.*

DR. GREENGARD SPENT EIGHT YEARS AT THE GEIGY Research Laboratories, and also taught at the Albert Einstein College of Medicine and later at Yale University. It was during his tenure as a professor at the Yale School of Medicine that he met his wife, Ursula von Rydingsvard, who was a faculty member at Yale's art and architecture school.

In 1983, Paul Greengard became the director of the neuroscience laboratory at Rockefeller University, where he is now the Vincent Astor Professor. His lab, which has been home to some of the most innovative neurological discoveries of the past century, is known to people at the University as simply the Greengard Lab. It looks like the stuff of science fiction. Walking through the brightly lit room, with its generous view of the East River, there are aisles of microscopes, tubes, and reams

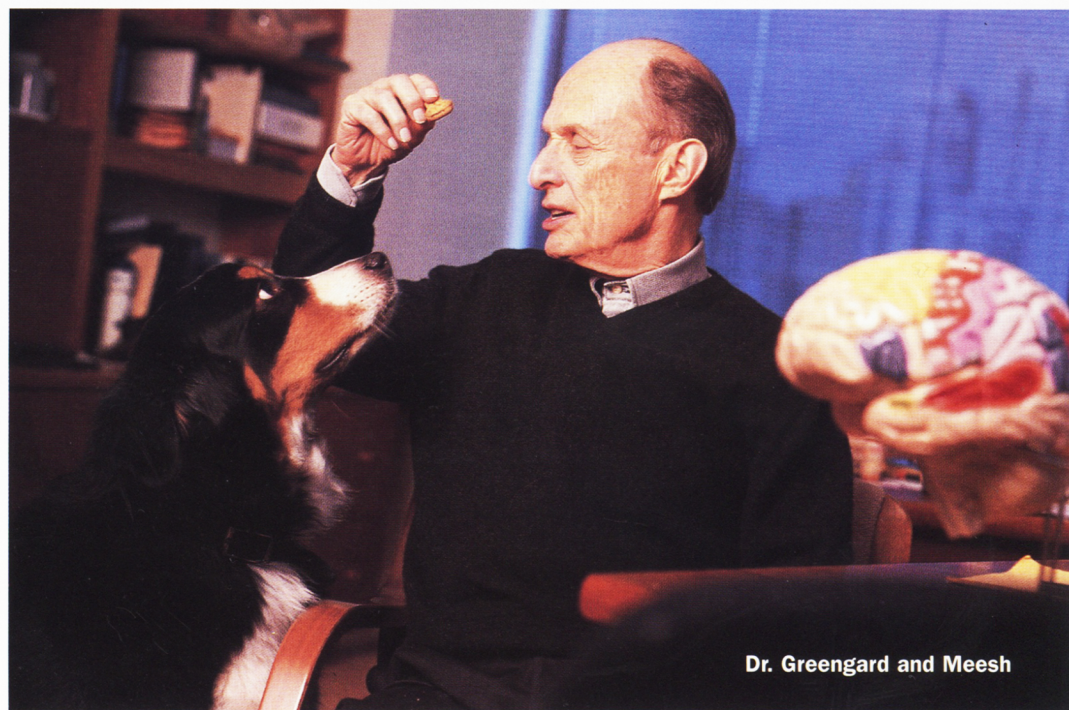
After graduating Phi Beta Kappa from Hamilton in 1948, Paul Greengard went on to graduate study in biochemistry at the Johns Hopkins University. He then spent five years in London doing postdoctoral work at various universities. As he remembers:

*There was virtually no one studying the biochemical basis of how nerve cells function. It was a very interesting period of my life*

in whatever he was involved with, a trait that would later nurture his distinguished career. "It used to scare people to ride in a car with him because he would be driving and talking and then he'd start using his hands," laughs Pete Bakwin. "I remember we went to Canada for a long weekend and Paul was behind the wheel and cars were swerving all around us. He was so very much involved in anything he did that it took precedence over things like driving."

Pete Bakwin came from a prominent Manhattan family, and both of his parents were successful pediatricians. They were also great patrons of the arts and music, and Dr. Greengard recalls them having string quartets playing in their brownstone on East 71st Street. "Their house was like this incredible art museum, lots of French Impressionists. There was this very famous painter named Ben Shahn who used to go there a lot and he helped them assemble their collection. I got to know him and many other interesting people there."

The couple influenced Paul Greengard's vision of his future. He came to the realization that he didn't want to pursue a career in physics. "During that time, the main way to get scholarships was from the Atomic Energy Commission. That was right after the atomic bomb and I didn't want to be involved in that field," he says. "I thought I'd like to use my talents for something more gratifying." It was the Bakwins who suggested that he steer his interests toward the newly emerging field of biophysics, or the application of physics to medicine.



**Dr. Greengard and Meesh**

of wire piled on counters. A machine tilts some mysterious blue substance back and forth and human-size nitrogen vats lurk in the corner.

But at the back of the lab, an adoring and eager face awaits behind a door, ready to greet all visitors. Meesh, a hearty seven-year-old Bernese mountain dog, accompanies his owner to the lab every day, and at the press conference the morning the Nobel Prizes were announced, Meesh's presence was not left unmentioned.

On a gray Saturday afternoon in the lab, Paul Greengard is clad in an ivory fisherman's sweater and hiking boots. Meesh follows his owner into the elegant corner office and quietly lays down. A caramel-colored conference table is dotted with small piles of papers and

pads, and a flat-screen computer monitor. There is a white drawing board built into a wall that has a molecular structure limned on its surface. Most noticeable is a 12-foot von Rydingsvard wood sculpture. He later notes, "That's rather small. She works on quite a large scale." One of von Rydingsvard's pieces currently sits at the southeast corner of Central Park.

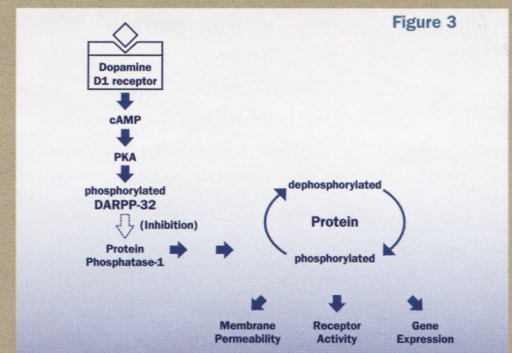
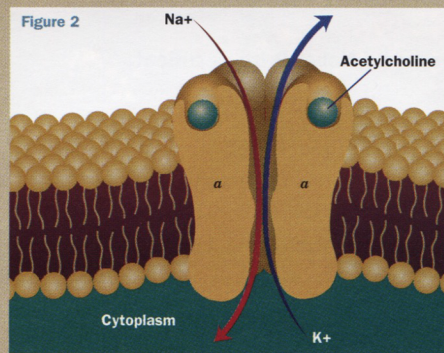
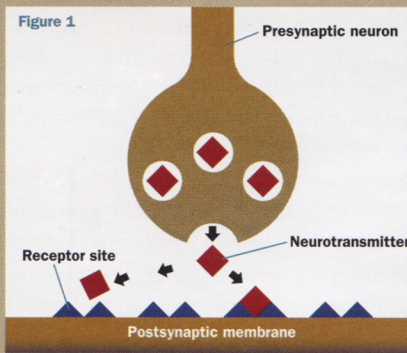
Dr. Greengard is a handsome man with quick, intelligent eyes, and at 75 shows no signs of slowing down. He speaks softly and bears an unassuming, relaxed air. During a conversation, he will pause politely to jot something on a pad to remember for later. Before the Nobel Prize, and certainly since, his time has been well occupied. He works six days a week and plans his time away (often spent giving

lectures around the globe) carefully so as not to disrupt the pace and consistency of the lab. "I love my work, but workaholics are people who are miserable unless they're working," he muses. Unlike them, "there are lots of things I love doing. I love travel. When I'm traveling, I don't say, 'Gee, I wish I was back at the lab.'"

He and Meesh walk to the University each day, and the morning the prizes were announced they were accompanied by a throng of reporters. "We came in and the security guards were applauding. I was so moved."

If his equilibrium was thrown by a 5:30 a.m. phone call, he has had little chance to regain it, as his life has since been jolted with media, dinners, the awards presentation in Stockholm, and what seems like infinite public interest in

## Paul Greengard and Signal Transduction in Neurons



**NEURONS COMMUNICATE WITH OTHER CELLS** by releasing chemical messengers called neurotransmitters. These signals are received by the subsequent cell when the neurotransmitter molecules bind to receptors situated in the cell membrane (see [Figure 1](#)). Some of the most exciting work in neuroscience is the attempt to elucidate the process of signal transduction (i.e., the events by which neurotransmitter stimulation can lead to changes in the electrochemical state of a cell).

There are two general ways in which receptors mediate neurotransmitter effects. In the simplest case, neurotransmitter molecules bind to a receptor that also serves as a pore in the membrane. Upon stimulation, the structure of the receptor changes such that the pore opens, allowing ions to flow into or out of the cell (see [Figure 2](#)). In contrast with this mechanism, other neurotransmitters act more slowly and with a wide variety of cellular consequences.

Paul Greengard proposed that these neurotransmitters have their effects by way of second messenger molecules that are linked to receptor activation. These molecules lead to protein kinase reactions that induce protein phosphorylation (adding of a phosphorous molecule). Phosphorylation changes the functional state of proteins, leading to a variety of intracellular effects.

Dr. Greengard's prediction was right in every respect, and his research has described in exquisite detail the cascade of reactions involved in the effects of stimulation of receptors for the neurotransmitter dopamine.

An example of this cascade is shown in [Figure 3](#) for one of the subtypes of dopamine receptors. When dopamine stimulates the D1 receptor subtype, a second messenger called cyclic adenosine monophosphate (cAMP) is produced, which in turn activates protein kinase A (PKA). This enzyme leads to the phosphorylation of a protein called DARPP-32, which inhibits protein phosphatase-1 (PP-1). This inhibition permits a phosphorylated state of other proteins that produce a constellation of cellular events, including membrane changes, receptor activations, and gene expressions.

Although this work provides a model for other neurotransmitter systems, the understanding of neurons that have dopamine receptors is particularly important. In Parkinson's disease, dopamine-producing neurons in the brain degenerate, and in Huntington's chorea, it is the neurons stimulated by dopamine that are lost. In the treatment of schizophrenia, one consistent characteristic about antipsychotic drugs is that they block dopamine receptors, suggesting that this neurotransmitter might also be involved in the cause of the disease. Likewise, drugs of abuse have some of their addictive effects mediated by dopaminergic systems.

Thus, understanding the signal transduction cascade for dopaminergic neurons provides scientists with new ways to directly affect these systems in a variety of therapeutic contexts.

by Douglas A. Weldon, Stone Professor of Psychology, and Herman K. Lehman, Assistant Professor of Biology

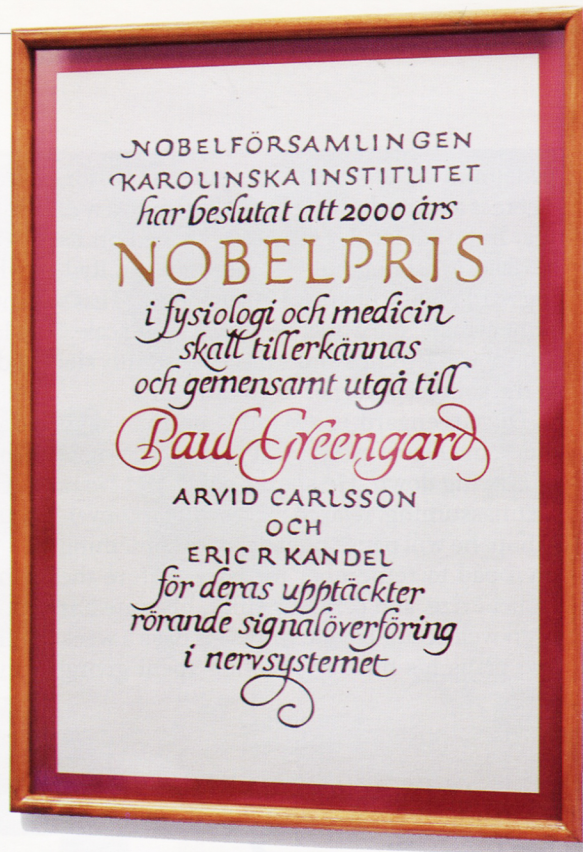
Dr. Paul Greengard. His sister, Chris Chase, even published a piece in *The New York Times* titled, "My Brother, the Genius: Now I Know What He Does," in which she confesses that in her entire life, she has never been able to comprehend the mysterious and abstract work of her brilliant brother.

The experience of the Prize ceremonies, a five-day-affair filled with all the glitz of Hollywood and the grace of a symphony, leaves Dr. Greengard in amazement. (On being escorted by a police motorcade to do a television spot, he says, "I felt like Tom Hanks.") He describes the event which is nationally televised in Sweden as "a cross between the Superbowl here and a coronation in England," with the entire nation watching its monarch bestow the prizes.

Paul Greengard and his entire family, Ursula, sons Claude and Leslie, daughter Ursie, their spouses, his four grandchildren, and his sisters and brothers-in-law were flown to Stockholm for the ceremonies. On the night of the awards, he was the escort of Princess Madeleine, who is third in line to the throne of Sweden. The Nobel Prizes marked the 18-year-old princess's debut. The European paparazzi took every opportunity to document her introduction to society on the arm of a Nobel Laureate. Thus Paul Greengard's photo appeared in dozens of European publications for weeks on end. A generous, colorful spread hangs on a bulletin board in the lab. Dr. Greengard chuckles as he remembers the buzz: "The Swedes are all so excited. You can't believe the reverence for which that Nobel day is held."

Another member of his family, grandson Daniel, 15, says, "It was the best week of my life." He and his brother and cousin were astounded by their grandfather's recognition, and Daniel even had a hard time convincing friends that he wasn't joking when he shared the news. "The ceremony was at the concert hall, and when he went up there I felt so proud." Daniel was also floored upon boarding the flight for home when a Swedish Airlines flight attendant remarked that she recognized him after seeing him on television the day before.

Paul Greengard's sons both earned Ph.D.s in mathematics. Claude, 45, works in finance at IBM, and Leslie, 43, teaches at New York University. Ursie is a television producer. Although none of his children went to Hamilton, grandson Daniel spent some time on the Hill last



Dr. Greengard's Nobel Prize certificate

summer as part of the Johns Hopkins Center for Talented Youth enrichment program. "I took classes at Root Hall and my grandpa said he had taken classes there." Inspired by his grandfather's achievement, Daniel will be taking a summer class in neuroscience this year.

One very special family member has perhaps received the greatest mention as a result of the Nobel Prize. Paul Greengard's mother, Pearl Meister, died while giving birth to her only son. He and his wife have decided to donate his prize money to establish an award for women scientists in his mother's name. "About two years ago I won a prize of \$50,000 from the Metropolitan Life Insurance Foundation for my work on Alzheimer's disease. My wife and I took that and another \$50,000 of our own savings and set up an award for the most outstanding woman scientist." Ursula von Rydingsvard says, "Inasmuch as the Nobel Prize was an homage to his intellectual achievements, his decision to donate the money to the Pearl Meister Fund is an homage to who he is emotionally, and in some ways I'm even more proud of that." Bud Coleman remarks, "I cannot say enough about that bequest and what it says about his feelings for science and his mother. It distinguishes him as a person, as well as a great scientist."

The decision has brought praise and appreciation from women all over the world, and Dr. Greengard continues to receive scores of

E-mail messages and letters from women in science telling him how much it means to them. "Some of these, if you read them, you'd cry. They're so moving, unbelievably moving, the things they wrote."

"I wanted to do it for two reasons," he continues. "I thought it was an important way to connect with my mother because she had always been a kind of figment of my imagination. The other reason is that I've observed in my own career, terrible discrimination against women, in top schools. It's slowly disappearing, but it's clear that women still feel discriminated against." With Rockefeller University's support, Dr. Greengard says the award is starting to take on a life of its own, and he hopes that it will acquire prestige as a sort of Nobel Prize for women.

After reaching such a pinnacle of recognition for achievement, one might be motivated to relax and reflect. But for Paul Greengard this is far too exciting a time in medicine to contemplate a life of leisure.

He believes there will be great advances in drug technology for both Parkinson's and Alzheimer's:

*This foundation we've built now opens a whole lot of other areas for research. So now if you put them all together, the more interesting questions arise and some of those I'm fascinated by. You might say, "Well, why don't you just take the rest of your life and enjoy it, go off and sightsee?" I guess the reason is that I've loved my work and I continue to love it. The process of making scientific discoveries is an extremely exciting thing.*

Despite planning a trip this year to Japan, and one next year to China, Paul Greengard continues to keep his attention focused on the lab. "For scientists, people think it's more like work than for, say, musicians. You wouldn't say to Beethoven, so now you've written eight symphonies, why don't you go to Italy and travel around?"

Are we awaiting the ninth symphony of Paul Greengard? "I am," he says. "We have this tremendous foundation of knowledge now and there's a lot of exciting things to do which I think can be done."

*Heather Won Tesoriero '96 writes for Time magazine, and she has recently completed a screenplay.*