



ACNP Bulletin

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SPECIAL EDITION – PAUL GREENGARD, PH.D. MEMORIES

REFLECTIONS ON PAUL GREENGARD (1925-2019)

I met Paul Greengard in September 1974 during my junior year at Yale College. I completed a senior thesis in his laboratory and was fortunate to have the opportunity to remain at Yale for my MD-PhD training so that I could pursue my graduate dissertation research in Paul's lab. Paul and I remained close—both scientifically and personally—ever since and he became a second father to me. I miss Paul terribly, but his legacy lives on not only based on his scientific contributions, but also with the literally hundreds of scientists around the world who think of Paul the same way I do.

Paul made transformational contributions to our understanding of cell signaling, particularly in the nervous system. Before Paul, the field of neuroscience focused primarily on the electrical activity of nerve cells and on the generation of electrical synaptic potentials, with little attention paid to the biochemical processes that mediate or modulate such functions. Over the course of several decades, the Greengard laboratory provided the scientific evidence to support a radically more expansive view of neural signaling, establishing the central role of protein phosphorylation as the major mode of cell regulation—Greengard cascades—that control virtually all aspects of neuronal function, including the generation of neural and synaptic potentials, the structure of nerve cells, their metabolic state, and ongoing transcriptional and translational adaptations that maintain neuronal function over a lifetime. Paul was thus one of the very few scientists across generations whose work truly stimulates a paradigm shift in our thinking about brain function.

Paul's impact on our field, however, goes far beyond the papers he published and the scientific insight his work provided. He trained hundreds of students and postdocs many of whom are now leaders in academic medicine, including deans, department chairs, institute and center directors, and innumerable leading research groups in neuroscience and other fields. Paul was unusually generative, promoting the careers of members of his own laboratory, as well as countless other faculty colleagues to whom he gave regular scientific and career advice. One of Paul's essential ingredients was his very special sense of humor. He had one of the quickest wits—I still laugh out loud when I think of things that Paul has said over the years. He was hysterical but also irreverent and mischievous and loved to challenge the status quo, just as he did with his science.

Despite the fact that I left the Greengard laboratory in 1983, I relied on Paul for personal and professional advice for several decades thereafter. I would schedule trips to NYC just to have dinner with him to get that advice, and I left each and every visit reinfused with that distinctive sense of wellbeing and confidence that only Paul was able to offer me over the course of my own career. And I know dozens of other leading scientists nationally and internationally who feel exactly the same way about their time with Paul. Meeting Paul at the age of 20, and working with him closely for almost 45 years thereafter, changed my life for the better in so many ways. I am a better scientist, a better person, and a better mentor and leader because of what I learned from him. Paul's unparalleled legacy continues through the many generations of scientists who will always be part of the extended Greengard family.



Dr. Greengard at the Nobel Laureate Celebration



Dr. Eric Nestler and Dr. Paul Greengard
from 1999

Eric J. Nestler, M.D., Ph.D.

PAUL GREENGARD: A FRIEND TO MENTAL HEALTH

The National Institute of Mental Health (NIMH) fondly remembers the life and career of Dr. Paul Greengard, who passed away on April 13, 2019, at the age of 93. Dr. Greengard dedicated his 50-year research career to the study of signal transduction in the nervous system, for which he shared the Nobel Prize for Physiology or Medicine with Drs. Arvid Carlsson and Eric Kandel in 2000.

Dr. Greengard's early work in the 1960s and 1970s laid the groundwork for the field of neuronal signaling and began to decipher the mechanisms of action of drugs used in the treatment of psychiatric disorders. He discovered that increases in cAMP and cGMP led to the phosphorylation of substrate proteins in neurons, that these second messengers could be activated by monoamines such as dopamine and serotonin, and that antipsychotic drugs blocked the monoamine-induced increases in second messengers and protein phosphorylation. In the 1980s, this work led to discoveries of the downstream effects of neurotransmitter-activated protein phosphorylation, such as gene transcription, cell surface trafficking of receptors and ion channels, and changes in neuronal excitability. An important implication of this work was deciphering how chemical signaling between neurons translates into electrical activation of the cells. Much of Dr. Greengard's work in the 1980s and 1990s focused on delineating the specific kinases that catalyze neuronal protein phosphorylation, the range of phosphorylation substrates in neurons, and the downstream effects of neuronal signaling on brain function.

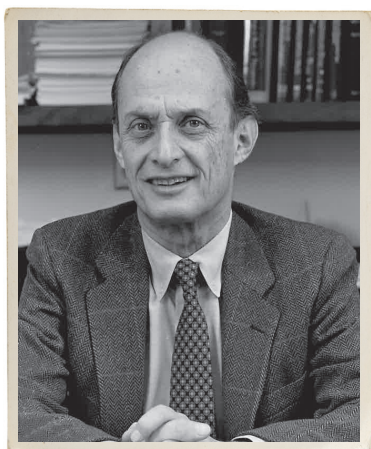
The effects of antipsychotic drugs on neurons was a theme that ran throughout Dr. Greengard's research career. He believed that determining the signaling mechanisms and downstream effects of existing drugs would facilitate the discovery of downstream targets that could lead to the development of new medications with better specificity for therapeutic effects and fewer unwanted side effects. Such new drug discovery would result in improved treatments for people suffering from mental illness. From 2005-2015, Dr. Greengard directed an NIMH-supported Silvio O. Conte Center for Neuroscience Research focused on signaling mechanisms underlying antipsychotic drug action. This research center used modern, cell type-specific approaches to analyze the molecular and cellular events following drug treatment in individual types of neurons in the striatum and frontal cortex.

In summary, Paul Greengard's work on neuronal signal transduction formed the basis of the field and has provided insights into the discovery of new potential targets for improved medications for psychiatric disorders. Dr. Greengard's legacy is providing hope and paving the way for new treatments and cures for people with mental illnesses.

Laurie Nadler, Ph.D., Jamie Driscoll, B.A. and Chisato (Chikko) Asanuma, Ph.D.

Many years ago, I was returning from a meeting in Europe. Upon boarding the plane, the seat next to mine was open. As boarding proceeded the seat remained unfilled, and I thought I might be in luck. I was luckier: Paul Greengard, returning to NY from a different meeting, was assigned to the seat.

After the plane took off, Paul called his wife, Ursula, who was in China attending to an installation. Talking loudly into the phone "Sweetie..." (for those who know Lee Limbird, it was a "Sweetie" to rival Lee's in volume), Paul proceeded to talk to her for 10 minutes, yet nary a glance from the flight attendants. It was clear I was in the presence of someone of stature. Even catching only snatches of the conversation, the phone call revealed Paul's warmth and kindness.



After chitchat about Serra and Di Suvero (one of whom he praised, the other he considered overrated), we discussed science. For the next six hours Paul was entirely and fully focused on what studies I was doing. Suffice it to say that I felt like a graduate student undergoing three qualifying exams in one sitting. The only reason there wasn't a fourth exam was that the plane was getting ready to land. Suffice it to say that I was not surprised to learn subsequently that Paul's lab meetings could last longer than a trans-Atlantic flight.

Paul's focus and ability to get to the most critical (and often missing) aspects of a body of work were remarkable, as was his capacity for keeping in mind new and very different material. Coupled with his creativity, from early studies of CaMKII to a more dopaminergic focus on GPCR signaling, Paul reshaped our approach to neuroscience. And with his generosity and kindness left the world a better place.

Ariel Deutch, Ph.D.

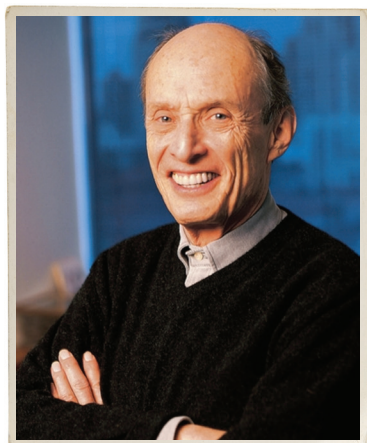
MEMORIES OF NOBEL LAUREATE PAUL GREENGARD

In 2000, Paul Greengard received the Nobel Prize together with Arvid Carlsson and Eric R. Kandel for their discoveries on signal transduction in the nervous system. Of all the many outstanding achievements made by Greengard and his group at Rockefeller University I will only mention their pioneering work on understanding the molecular basis of the intracellular signaling pathways that mediated the activation of G protein coupled receptors. The key role of protein kinases and phosphatases was demonstrated and the discovery of a novel phosphoprotein in DA receptor signaling pathways was made. It was called DA and cAMP regulated phosphoprotein 32 (DARPP-32, 32 stands for 32 kDa). It represented a unique example of how a single molecule in the intracellular signaling pathways can integrate signals originating from different types of plasma membrane receptors. Through a DA D1 receptor activation that led to phosphorylation of threonine 34 of DARPP-32, this molecule was turned into a highly potent inhibitor of protein phosphatase 1. This produced enhancement of phosphorylation of multiple receptors, ion channels and transmitter transporters in the plasma membrane. The molecular area of signal transduction had begun.

I got to know Paul Greengard via my friend Menek Goldstein at New York University Medical Center already in the 1980s. We were all interested in dopamine, its receptors and its role in Parkinson's disease and mental disease. Through our fascinating discussions in his laboratory at Rockefeller University and Paul's ideas on the molecular neurobiology of DA transduction, he became my role model in neuroscience. I remember his great eyes when he was happy and enjoyed our interactions. It was also inspiring to meet several members of his famous group.

Several years we went to the US open together since we both loved tennis. Even if we were seated far away from the tennis court it was fun and we discussed the tennis stars and ranked them. In fact, we had similar ranking and he was also fond of Björn Borg. After a good day of tennis, we sometimes ended up in a fine Italian restaurant.

My thoughts also go back to the day of the 70 years birthday celebration of Paul Greengard at Rockefeller University. I congratulated him on behalf of the Swedish group invited to this celebration and remember me saying that we had Paul Greengard fan clubs all over Sweden. Paul liked the joke and could not resist to show a genuine smile. I remember that also Solomon Snyder was there and acted as chairman in the celebration of Paul Greengard.



Thus, there are lots of happy memories of Paul when looking back. However, there are also sad memories. We remember that his mother, Pearl Meister, died giving birth to him. This fact must have been a heavy burden for him to carry all his life. Hopefully the burden was reduced when Paul used his Nobel Prize honorarium to help fund the Pearl Meister Greengard Prize, an award for women scientists. I genuinely hope so.

Kjell Fuxe, M.D.

Paul lived down the block from me on 69th Street.

He was nothing but gracious, thoughtful and helpful to me as a young member as he tried to help me understand the neuroscience – clinical psychopharmacology interface.

His loss is a tremendous loss for the field.

Ira Glick, M.D.



Catecholamine Symposium in Gothenburg in 1983 with Dr. Annica Dahlström and Dr. Guy Everitt. Photo provided by Tomas Hökfelt.

As a scientist who has been at the Rockefeller University since 1964, I had the pleasure of getting to know Professor Paul Greengard soon after he arrived here from Yale in 1983.

Because Paul was such an enthusiastic and communicative scientist, in 1995 I asked him if he would be willing to take my 17-year-old daughter, Esperance Anne Kreek Schaefer, as a summer student in his Laboratory. She had always been interested in medicine but during high school became equally interested in basic science. He and his Laboratory were wonderful mentors to a young student. Dr. E.A.K. Schaefer, MD, MPH is now on the faculty of Harvard Medical School, at the Massachusetts General Hospital where she has a 60 percent effort in basic laboratory research and 40 percent effort in clinical medicine (gastroenterology and liver disease.) Both she and I realize that Paul was instrumental in directing her toward a career in research as a physician scientist.

I personally had the privilege of collaborating directly with Paul Greengard to conduct special studies using in his DARPP-32 mice. Paul asked if my Laboratory of the Biology of Addictive Diseases and I would collaborate with him since, at that time, he was not working with any rodent models of addictions. Yong Zhang and other members of my Laboratory performed extensive cocaine self-administration studies using his DARPP-32 mice, work which resulted in a 2006 publication in the *Journal of Neuroscience* (Zhang, Y.....Greengard, P & Kreek, MJ: Cocaine self-administration in mice is inversely related to phosphorylation at Thr34 (Protein Kinase A site) and Ser130 (Kinase CK1 site) of DARPP-32. *J. Neurosci.* 26:2645-2561, 2006).

I saw and spoke briefly with Paul who was walking on campus with another colleague, Friday, the day before he passed. We all will continue to miss him.

Mary Jeanne Kreek, M.D.



Reception preceding Dr. Greengard's 90th birthday party at Rockefeller University. In the photo, from left to right: Dr. Robert Schaefer (late husband of Dr. Mary Jeanne Kreek), Dr. Mary Jeanne Kreek, Ursula von Rydingsvard (Dr. Greengard's wife) and Dr. Paul Greengard

I first met Paul at Wesleyan, where his sons received their undergraduate degrees. He came up from New Haven and gave a marvelous lecture and, as a graduate student interested in cAMP, we got to spend some time together. When I was a postdoc at Yale, I was across the street from the building in which his group was housed (they did eventually build a "satellite" in our building), but spent several hours in his lab when people needed help dissecting invertebrate nervous systems. They were developing a phylogenetic catalog of synapsin. He would often peer in and chat and I remember fondly his kindness and engagement. This went beyond the lab, as after my wife, Helene Shambelan, suffered a miscarriage and was hospitalized for a D&C, Paul and his then wife Corolla (a Wesleyan faculty member) were in the hospital to visit a friend of hers with a much more serious medical problem. They saw us and stopped by the room for a while. A few days later, Paul called to inquire about Helene.



We also had tickets to the same series at Long Wharf (a New Haven Theatre) and spent many intermissions chatting with Paul and Ursula. His knowledge of and appreciation for art and drama was as compelling as his scientific prowess. The last time I spoke with Paul was September or October. He told me that he still worked every day, but that the commute was largely by elevator, so not very difficult. I was struck by not only his complete engagement but by his current awareness of published data, but by his total recall of events from 40 years ago. What an amazing man. May his memory serve as both a blessing and an inspiration.

Mark M. Rasenick, Ph.D.

PAUL GREENGARD: THE PHOSPHOPROTEIN KID

Paul Greengard was a singular force of nature; smart, driven, analytic, ascerbic, wryly funny. I first met him in the mid 1990's, before he won the Nobel prize, at a (then called) NARSAD event. He was distant, intimidating, caustic. His visage even looked menacing. We were seated at the same table but didn't exchange more than a few words.

The next time I saw him was in the early 2000 aughts. We were at a scientific meeting in Switzerland and during a free afternoon we found ourselves in the same hiking group that elected to trek up a mountain as our recreational activity. As a young lad of 40 something, I was struck by the energy of a man who was pushing 70, had flown from NYC the day before and I was struggling to keep up with on the slopes of the Alps.

At the time I was at UNC and had been told by one of my colleagues in the neuroscience dept who had done her post-doc with Paul that he had changed after winning the Nobel prize in 2000. Where over the course of his career he had been obsessively focused, very serious and notorious for not suffering fools gladly or tolerating mistakes, after Stockholm, he had mellowed and slowed down. That's not to say he ceased being a productive scientist at the cutting edge of molecular neuroscience, but he took more time to enjoy life and was more pleasant.

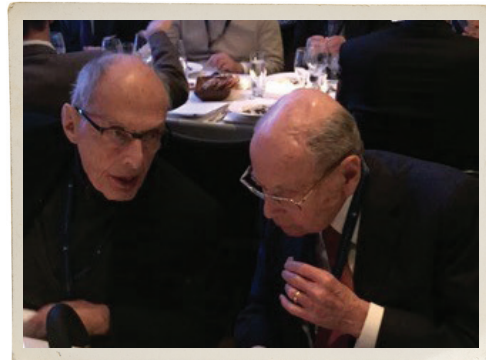
In the course of that afternoon, tramping across the Swiss Alps I got to see a different Paul and found him immensely engaging not to mention knowledgeable on a wide range of subjects. Whether it was his marriage to Ursula, an accomplished artist, or his innate erudition, he could speak authoritatively on any number of subjects in addition to science. He also loved to tell humorous, slightly scandalous stories with a mischievous glint in his eyes.

I got to know Paul even better when he started a biotech company aptly named *Intra-Cellular Therapies* and entered the psychotropic drug development business. This was an interesting and important development in two ways. First it was necessary for Paul to extend himself from the cloistered conditions of the laboratory to where the scientific rubber meets the road in the clinic and patient care.

The second was the unique nature of the company which bore the signs of an academic enterprise embedded in a commercial company. ITC was small, focused and comprised by smart people who even though they came from industry did not exhibit the vestiges of the corporate culture. Paul hired Sharon Mates, brilliant scientist with a pharma background in ID and vaccine development, and from San Diego Bob Davis from Acadia and Kim Vanover from UCSD and Lederle. The company valued real science and was not interested in developing "me-too" drugs. This was evidenced when they completed a successful phase II study. Armed with positive results from a novel "first in class" antipsychotic drug (lumateperone) ITC shopped it around to big pharma to partner in conducting the much larger and more expensive phase III studies as is the usual custom with smaller companies. However, when they didn't like the development strategies proposed by any of the deep pocketed other companies, they decided to go it alone and raised the necessary funds to take it to FDA review. I'm sure that Paul's reputation and prestige, as well as Sharon's negotiating skill and belief in the drug were major reasons why they were able to raise the necessary funds to sustain its development.

Shortly before Paul died, there were a couple of memorable interactions. One Saturday morning my cousin called me to say that she had attended a dinner party the night before and was seated next to Paul. Not being in science or academia, she didn't know who he was. When he told her that he did brain research and drug development, she asked if he might know me. She called me the very next day and asked if my ears were burning as apparently, he spoke very well of me. She only learned afterwards that he was not just any scientist but a Nobel laureate, which raised my stock in her mind which is why she rushed to call me.

The last time I saw Paul, it was during the Levy Foundation Conference at Rockefeller University April 2, 2019. I had to exit the conference room to take a phone call and passed Paul seated in a wheelchair on the aisle. He grabbed my arm and pulled me toward him whispering in my ear that he wanted to discuss the latest lumateperone data with me and would schedule a time to meet. We never did get to meet, but he surely would be gratified by the fact that the drug's NDA has been submitted to the FDA and it should be launched in 2020. His final contribution to science and society would benefit patients, a fitting end to the career of a great scientist, colleague and friend.



Dr. Greengard talking to Howard Solomon at Neuroscience Summit at the Alexandria Center in NYC Jan 2015

Jeffrey Lieberman, M.D.

PAUL GREENGARD AND HORMONES EFFECTS ON THE BRAIN

One aspect of Paul Greengard's scientific interests that is not well-known was his curiosity about hormone actions on the brain. This led to an ongoing collaboration with my laboratory over many years as well as an ongoing friendship.

I met Paul when he was at Yale and when Eric Nestler was in his laboratory as an MD/PhD student. My lab had discovered receptors for glucocorticoids in hippocampus of rodents and primates and Paul, Eric and I wanted to know how they affected this brain structure that is so important for memory and mood regulation. What we found was that corticosterone treatment of adrenalectomized rats markedly increased Protein 1 (now called Synapsin1) levels in hippocampus and did not do so in hypothalamus. Dexamethasone, a glucocorticoid which is actively prevented from entering the brain, had no effect (Nestler et al 1981). Synapsin 1 is now known to mediate glutamate release from synaptic vesicles and plays a role in both positive and negative effects on the hippocampus including remodeling of neuronal structure and memory formation.



Dr. Greengard and Ursula von Rydingsvard (Dr. Greengard's wife) at Dr. Greengard's 80th birthday party. Photo provided by Tomas Hökfelt.

What fascinated Paul, as well as me, was that hormones act not just in the hypothalamus to regulate their own secretion or basic vegetative functions and sexual behavior but also in brain regions involved in higher cognitive function and emotional regulation. This is also the case for sex hormones. My lab also discovered estrogen receptors in the hippocampus and uncovered the ability of ovarian hormones to mediate a cyclic turnover of spine synapses in hippocampus with effects on spatial working memory. Together with Paul we showed that other synaptic proteins, namely, spinophilin, syntaxin and synaptophysin, as well as PSD95, are all up-regulated by estrogen treatment in both rat and mouse hippocampus (Brake et al 2001, Li et al 2004). Since similar processes occur in primate brain, these findings provide a basis for understanding beneficial effects of postmenopausal estrogen therapy and the potential of estrogen to protect from stroke damage and dementia.

Since chronic stress can precipitate depression in humans, in part through the actions of glucocorticoids as well as excitatory amino acids, we as well as the Greengard lab study animal models of depression. We have collaborated on a number of mechanistic studies of antidepressants. One of them compared a serotonin reuptake inhibitor with a novel antidepressant, tianeptine, and showed a convergence of action on two different phosphorylation sites on the AMPA receptor, with a similar functional outcome (Svenningsson et al 2007). Tianeptine has turned out to be a minimally-addictive mu receptor agonist (Samuels et al 2017) and this opens a new direction in antidepressant action and whether there are convergent or divergent mechanisms. And because glutamate dysregulation is a major factor of how chronic stress generates depressive-like behavior, we most recently collaborated with Paul on a mechanism by which glutamate homeostasis is maintained via regulation of an astroglial glutamate exchanger, xCT (Nasca et al 2017).

Brake WG, Alves SE, Dunlop JC, Lee SJ, Bulloch K, et al. 2001. Novel target sites for estrogen action in the dorsal hippocampus: an examination of synaptic proteins. *Endocrinology* 142: 1284-9

Li C, Brake WG, Romeo RD, Dunlop JC, Gordon M, et al. 2004. Estrogen alters hippocampal dendritic spine shape and enhances synaptic protein immunoreactivity and spatial memory in female mice. *Proc Natl Acad Sci U S A* 101: 2185-90

Nasca C, Bigio B, Zelli D, de Angelis P, Lau T, et al. 2017. Role of the Astroglial Glutamate Exchanger xCT in Ventral Hippocampus in Resilience to Stress. *Neuron* 96: 402-13 e5

Nestler E, Rainbow T, McEwen BS, Greengard P. 1981. Corticosterone increases the level of protein I, a neuron-specific protein, in rat hippocampus. *Science* 212: 1162-64

Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, et al. 2017. The Behavioral Effects of the Antidepressant Tianeptine Require the Mu-Opioid Receptor. *Neuropsychopharmacology* 42: 2052-63

Svenningsson P, Bateup H, Qi H, Takamiya K, Huganir RL, et al. 2007. Involvement of AMPA receptor phosphorylation in antidepressant actions with special reference to tianeptine. *Eur J Neurosci* 26: 3509-17

Bruce McEwen, Ph.D.

Paul Greengard's great accomplishments in our field are widely acknowledged, no less by the Nobel Committee. My experience with Paul, however, goes back to my medical school days at Yale. Paul was the principal Professor who taught us pharmacology during our second year (1970-1971). We knew he was pretty famous - and smart - but we knew him most as an excellent teacher. Clear, concise without being laconic, and most importantly to us at the time - a very good guy. I have found Paul's research to be both fundamental and current to my world as a clinical scientist. I thank you, Paul, for being here. You will be missed.

David Pickar, M.D.

I had a pride privilege of visiting Dr. Paul Greengard and his research colleagues at Rockefeller more than once. I recall his pleasant reception and chats. What I recall most is what I heard from his co-workers at his lab. They were highly motivated to go deep in the hypotheses they were testing. My regret that I do not remember their names even though I recall their faces. The neuroscience will certainly miss Paul.

Harbans Lal, Ph.D., D.Phil.



Dr. Greengard with Christer Lingström, the Chef of Edsbacka Inn in Stockholm. Chef Lingström received the 2nd, first ever in Sweden, Michelin star in 2000, the same year as Dr. Greengard was awarded the Nobel Prize. Photo provided by Tomas Hökfelt.

I primarily got to know Paul through my many years of support from the McKnight Foundation and from Spencer Dinners.... I will never forget flying to my first McKnight interview. Somehow, I ended up seated next to The Paul Greengard. This was a bit terrifying for me as of course, I knew his work and was more than a little in awe (having trained with Robert Perlman - of Perlman & Pastan fame - I had been raised to be a signaling fan - despite having gone to the dark side and becoming a physiologist). Paul started by asking the usual - where was I headed? (McKnight Foundation). He replied "oh, me too - are you on the board?" (no, applying for an award, to be interviewed). He sat back, squinted a bit and then asked a firestorm of questions about my science. I answered as best and as quickly as I could. He then paused again and said, in an obvious imitation of some scary monster "WELL, (mwah hah ha) I THINK YOU MIGHT BE READY FOR THIS MCKNIGHT INTERVIEW (mwah hah, again) and then burst out laughing. The interview itself was a piece of cake after this.

I'll never forget his half joking half serious always perceptive wonderful manner.

Lorna W. Role, Ph.D.

Dr. Paul Greengard's pioneering research described a cascade of intracellular events that occurs following dopamine's stimulation of a receptor, and his work led to a cascade of discoveries leading to the development of novel treatments for neuropsychiatric diseases. In 2002, together with Dr. Sharon Mates, Dr. Allen Fienberg, and Moshe Alafi, Dr. Greengard co-founded Intra-Cellular Therapies whose mission is to develop innovative treatments to improve the lives of individuals suffering from neuropsychiatric and neurologic disorders, thereby reducing the burden on patients and their caregivers. To those of us at Intra-Cellular Therapies fortunate enough to know and work with him, Paul provided inspiration, collaboration, critical thought, humor and support. He is greatly missed.

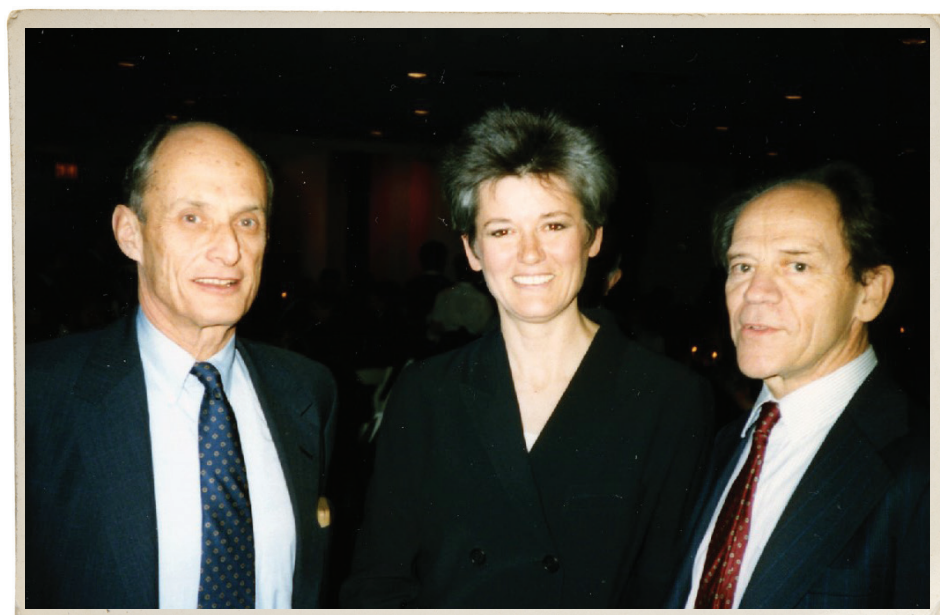
Kimberly Vanover, Ph.D.



In the photo taken in 2002 when Intra-Cellular Therapies was founded, Dr. Greengard is joined by co-founders Sharon Mates, PhD and Allen Fienberg, PhD.



In the photo taken in 2018 at a Medical Advisory Board Dinner for Intra-Cellular Therapies, Dr. Greengard is joined by Martin Paulus, MD (Laureate Institute for Brain Research; ACNP Fellow) and Kimberly Vanover, PhD (Intra-Cellular Therapies; ACNP Member).



Dr. Greengard and Ursula von Rydingsvard with Dr. Torsten Wiesel, also a Nobel Laureate, at Dr. Greengard's 80th birthday party. Photo provided by Tomas Hökfelt.

I am deeply saddened by the passing of my dear and admired friend and colleague, Dr. Paul Greengard. Paul and I had extensive contacts through several foundations which supported our mutual work in the New York area. Paul's work was, of course, celebrated throughout the world. When I visited Paul's lab at Rockefeller, it was always very vibrant with numerous investigators involved in many areas of research. It was evident that Paul's enthusiasm for his work had infected his entire team. I have very much missed Paul's presence since his passing,

Naturally, Paul will be remembered, not only by me, but by the entire world.

Barry Reisberg, M.D.

Alteration of dopamine signaling in the brain's reward circuits in response to drugs is now one of the cornerstones of addiction science. We have Paul Greengard to thank for the insights and discoveries that led to this paradigm. His findings in the early 1970s about dopamine signaling and the complex intracellular processes that mediate neurotransmission significantly shaped our current understanding of the brain's neuroadaptations to drugs.

As a graduate student at Johns Hopkins, Greengard had studied electrophysiology, but he presciently shifted to biochemistry, suspecting that the secrets to the brain's functioning might be chemical, not electrical as was then the dominant assumption. The research Greengard then pursued in his lab at Yale was based in his then-radical hunch that signaling in the brain might be similar to the way hormones produce effects elsewhere in the body, via receptors on cell membranes. It was radical because chemical signals were thought to be too slow a mechanism to account for activity in the nervous system.

Although dopamine's likely role as a neurotransmitter had already been argued by Arvid Carlsson, with whom he later shared the Nobel Prize, it was Greengard's patient and persistent work to isolate a molecular receptor responsible for dopamine's effects in areas of the brain associated with the movement problems in Parkinson's that unlocked the understanding of brain signaling. Ultimately, Greengard discovered that dopamine interacts with multiple receptors. But even more important were his discoveries about the signaling cascades that occur within the cell when a dopamine molecule binds to a receptor.

As Greengard and his coauthors John W. Kebabian and Gary L. Petzold wrote in their hugely influential 1972 PNAS paper, "Dopamine-sensitive Adenylate cyclase in caudate nucleus of rat brain, and its similarity to the 'dopamine receptor'" (1), this binding triggers an increase in cyclic AMP (cAMP), which in turn causes proteins within the cell to gain or lose phosphate groups, the process called phosphorylation. Phosphorylation was found to be a key mediator of neurotransmitters' effects. It can change the permeability of the synaptic membrane to ions, altering its electric potential, and make the cell more or less sensitive to further stimulation by moving more receptors to the surface or removing them from the surface, respectively. It also facilitates protein transcription.

Greengard also is responsible for the important discovery of dopamine- and cAMP-regulated phosphoprotein (DARPP)-32, a phosphorylated protein that affects many other proteins and acts as a central regulator of neuronal function. Among other functions, DARPP-32 has been found in rodent studies to play an important role in regulating reward and the cellular response to several drugs of abuse, including stimulants, morphine, alcohol, and nicotine (2).

The importance of Greengard's contributions cannot be overstated. His work to characterize dopamine neurotransmission opened new realms of discovery for neuroscience, and his discovery of phosphorylation forced the field to pay close attention to signaling cascades within neurons. These contributions have proven to be central to our evolving understanding of the brain and of drug addiction, and they continue to be central in the development of medications to treat various psychiatric and neurological disorders.

1. Kebabian JW, Petzold GL, Greengard P. Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the "dopamine receptor." *PNAS*. 1972;69(8):2145-2149. doi:10.1073/pnas.69.8.2145

2. Yger M, Girault JA. DARPP-32, Jack of All Trades... Master of Which?. *Front Behav Neurosci*. 2011;5:56. doi:10.3389/fnbeh.2011.00056



Dr. Greengard with Dr. Ralf Pettersson, Chairman of the Nobel Committee in 2000. Photo provided by Tomas Hökfelt.

BRILLIANT, QUANTITATIVE THINKER, STUBBORN EXPERIMENTER, LOYAL, GENEROUS FRIEND AND COLLEAGUE

Axelrod and Sutherland, while visiting Ulf von Euler in the early seventies, had advised me to go to work with Paul “who has generalized the idea of how cAMP worked through protein-phosphorylation of multiple substrates” and was now back in academia at Yale so I joined Paul’s lab.

In New Haven, after work on five consecutive hot summer evenings, we drove in Paul’s Checker to the Chinese restaurant, where on the fifth day, the cook came up from the kitchen brandishing a big knife: “Are you going to buy the place or not” - he asked: No one else but a restaurant-buyer (or Paul) would order dishes #1 and #2 on day one, then dishes #3 and #4 on the next day, etc. We did so for 5 days while arguing the possibility that famous scientists made up their published data, this being why Bob Study and I could not repeat their results - in 23 experiments, each taking a week and being checked meticulously by Paul. We developed a new assay, we consulted Al Gilman, but the published results could not be repeated. For 23 weeks Paul would not give us a pause. To have been the first “Swede” in the lab and to have brought along the home-made slab-gel apparatus that changed the quality of studies on protein phosphorylation - was of no help in getting Paul off my back, but he respected that we did not accept promotion of small experimental noise to publishable data. When their retraction came in *Nature*, Paul called me at once in Stockholm to tell.

After having worked in industry, Paul fought his way back into and to the top of academia; a tough act, as I found out myself. He published original, rigorous, high-quality papers in *JBC*, *BBRC* and *PNAS*, and did not insist that everything had to be published in *Science* and *Nature*. “Original, reproducible data, in respectable journals” was his motto; some 100 publications later *Science* started to ask for his papers.



Dr. Greengard with Dr. Floyd Bloom at Dr. Greengard’s 80th birthday party. Photo provided by Tomas Hökfelt.

He trained hundreds. We were all waiting for the famous “Columbo moments”; when in the middle of the lab seminar slide 15 was shown, and Paul would ask: “Could you explain again what was on slide 3?” - Yes, he was still working through the implications of slide 3, and the other 14 slides.

Decades later when going to New York Hospital for my open-heart surgery at 5:30 am, the only man on windy York Avenue happened to be - “accidentally” as he said - Paul with his Bernese Mountain Dog: Alpha, and, equally accidentally, he helped me in the coming six months on a daily basis to recover.

Loyal to a fault, generous, deeply funny, unforgiving of dishonesty - this is how I saw Paul for 48 years; I am glad to have sent him many of my best students and also many of my colleagues.

Tamas Bartfai

PAUL GREENGARD – A BRILLIANT SCIENTIST AND TRUE FRIEND

Asked about their favorite city in the world, many say New York. And I agree, not only because it is thrilling and vibrant, but also because of its science. Such a high density of outstanding scientists, such excellent universities, perhaps first among them Rockefeller. And Paul Greengard. It was a privilege and exciting to know and interact with Paul, to learn from him. He was never President or Dean, but fully committed to his research, including spending time discussing results in detail, even histochemistry, with external collaborators like me. As a fringe benefit, I was invited and attended several of his birthday parties and listened to his wonderfully humorous and profound after dinner speeches, and got to know his immensely talented wife, Ursula. And, finally, we saw him on the scene in the concert hall in Stockholm in 2000. Great, but eight years too late, I think. Paul understood and provided the evidence for the fundamental role of phosphorylation, it took years for us others, decades for some, to catch up. Finally, I am tremendously grateful for all the help by Paul and Ursula, and their warm embracement, when treated for a serious disease in New York. The photo, a gift from Paul, shows in addition some other important colleagues in my professional life: Kjell Fuxe (right) and the late Menek Goldstein (far left) of New York University Medical Center, thus also from New York. Future visits to New York will be less fun and less inspirational.



Dr. Paul Greengard is joined by Dr. Kjell Fuxe, Dr. Tomas Hökfelt, and Dr. Menek Goldstein.

Tomas Hökfelt, M.D., Ph.D.



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