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A conversation with Paul Greengard

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Conversations with Giants in Medicine

If you, or someone you know, has Parkinson's disease, mental health issues, or other neurological disorders, medication can often help. The bulk of these medications have been established based on the work of neuroscientist Paul Greengard (Figure 1) from the Rockefeller University, who worked out just how the brain responds to neurotransmitters — the chemicals that help the brain signal. The bulk of what most neuroscientists know today about neurotransmission, and specifically the dynamics of slow synaptic transmission, is predicated on the work of Paul Greengard. The full interview, with many more stories about his seminal research discoveries and his competitive streak in potato sack races, can be seen on the JCI website, http://www.jci.org/kiosk/cgm. JCI: Can you tell us a little bit about your path towards becoming a scientist? Greengard: I grew up in New York City. My mother died giving birth to me, and then my father remarried when I was one year old. He was a businessman; she was a housewife. They were both very anti-intellectual, and so I did not get the bug for doing scientific research at home. It was a very anti-intellectual atmosphere at home and to a certain extent, possibly a rebellion against that, was what made me very committed to science. They did not want me to go to college, but fortunately I […]

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JCI: What did you study?

Greengard: In college I studied mathematics and physics. After that, I was going to go to graduate school, and I had been planning to work in theoretical physics. But this was almost immediately after the dropping of the atomic bombs on Hiroshima and Nagasaki, and I felt that was not an area I wanted to be really involved in because I thought there were better ways of spending my life than trying to destroy mankind. I had heard about the nascent field of medical physics or biophysics. And at that time, there were two biophysics departments in the country. One was at the Lawrence Laboratory in Berkeley, which was involved in doing radioisotope studies in biology and the other one was the Department of Biophysics at Penn which was involved in studying the electrical properties of nerve cells.

I started at Penn but then the chairman of the department, Detlev Bronk, moved to Johns Hopkins to become the president and to start a new department of biophysics. He took a few of us with him, and I ended up doing a PhD degree there at Hopkins. Keffer Hartline was the first scientist I worked with. He was a vision person who went on to win a Nobel Prize. At the time, everybody in the department was studying the electrical properties of nerve cells. Alan Hodgkin came and gave a beautiful lecture about understanding the ionic basis of the nerve impulse, and I thought it might be a long time between that discovery and the next major advance in biophysics of the nervous system. So, I decided it would be interesting to understand more about the underlying molecular properties of nerve cells.

JCI: In the autobiography that accompanied your Nobel lecture, you remarked that the lecture by Alan Hodgkin was one of your first Aha moments that helped you to shape the direction of your career.

Greengard: Yes, that's true. He was a marvelous lecturer and a marvelous human being, and it was very inspiring, but it inspired me in sort of a negative way. I said, "I don't want to be in this research area anymore." Hodgkin had solved the biophysical problems that were solvable at that time. So, I turned to studying the biochemistry of nerve cells and their function.

JCI: After you finished your PhD at Hopkins, you then spent several years abroad in England and in Holland. How did that time shape your path and your discoveries?

Greengard: I spent a lot of time thinking about how the rapidly increasing knowledge of biochemistry could be applied to an understanding of nerve cell function. It was a difficult period in the sense that biochemists were only interested in the brain as a source of enzymes. There are thousands of enzymes that are much more active in the brain than any place else. The neurophysiologists were not really interested in the underlying molecular mechanisms.

I went to a pharmacology department for three of the five years that I was doing my postdoctoral studies because they had both biochemical and electrophysiological equipment that one could use. While I was there in the laboratory of a very distinguished scientist named Wilhelm Feldberg, I was able to gain a lot more experience in both biochemistry and electrophysiology.

While in the Feldberg laboratory, I was approached about a position in a pharmaceutical company. I was very young, and they offered me this very senior position. I thought it might be exciting to take my knowledge of basic science and apply it to new drug discovery. And so, I worked for nine years in a pharmaceutical company which was called Geigy at the time, then merged with Ciba and became Ciba-Geigy, and then merged with Sandoz to become what's today known as Novartis.

JCI: How did that time at Geigy shape the way that you did your research or how you thought about targets?

Greengard: I think it did a couple of things for me. It gave me an education of the sort one might have gotten in medical school. At the time, when I was ready to do advanced studies, I decided not to go to medical school because it was very much a hands-on profession where the physicians really couldn't do very much for their patients. There were brilliant clinicians, but there was a very limited repertoire of tools they had. Instead, I decided to do a PhD. But, I got a kind of education while I was in the pharmaceutical industry similar to that which I would have gotten in medical school, as I learned much more about the biology of the body, particularly of the brain, and what the major issues were, and began to think about ways of studying them.

At the end of that nine-year period, I did one semester as a Visiting Professor at Vanderbilt University with a brilliant scientist named Earl Sutherland who discovered cyclic AMP. That was an excellent experience. At the time I was a graduate student at Johns Hopkins, Sutherland was publishing some amazing papers on how hormones were producing their effects and showing that they acted through cyclic AMP. In another line of study, Edwin Krebs and his colleagues had been studying protein phosphorylation and discovered cyclic AMP regulation of protein phosphorylation. After nine years of developing CNS drugs, I returned to my interest in the biochemical basis of nerve cell function and leaned very heavily on the discoveries of the Sutherland lab and the Krebs lab to try to determine what was going on in the brain. One key to progress was my considering the possibility that what Sutherland had been studying, namely how hormones work in the endocrine system, might be applicable to nerve cells — that a neurotransmitter released from a presynaptic terminal and activating post-synaptic receptors might

Figure 1
Paul Greengard on January 10, 2013, in New York City. Image credit: Semyon Maltsev.

work through an analogous pathway. We found neurotransmitter-sensitive adenylyl cyclases in the nervous system and showed that they are present in the plasma membrane. It became clear that the nervous system responded to neurotransmitters the way the endocrine system responded to hormones even though there's a million-fold difference in the distances traversed.

JCI: That must have been a rather heretical proposal to have at the time.

Greengard: It was. People said a lot of unkind things. The interesting thing about it was that because it was considered so unlikely to be true, I had basically 15 years, from about 1968 to 1983, to develop the story. And by the time people accepted it, my research group had laid a lot of the foundation of the molecular basis for neurotransmission. So, we didn't have this ultra heavy competition. I've talked to other people who have had the fortune of being recognized as Nobel Prize winners and, in many instances, it has been the same thing. They've done something very unconventional, and nobody believed them for a while, and then it was shown to be true.

JCI: After short stints at both Vanderbilt and Einstein, where you had the germinal seeds of some of these ideas, you spent 15 years at Yale working on some of the early bases for what you would later be lauded with the Nobel Prize. What was that time like — when you were first building an independent lab?

Greengard: Even though my thinking was considered extremely unconventional by my friends and radical by my non-friends, it was a very friendly atmosphere. I mean the colleagues at Yale were all wonderful and had an open mind to a large extent, and funding was much more ample then than it is now. There was more support for people with unconventional ideas at that time.

The first part of my career at Yale had to do with elucidating the signaling pathways by which nerve cells responded to neurotransmitters and how nerve cells receiving signals from several different places could integrate that information, and explain a lot of the electrophysiological responses. In the last 15 years or so, and since I've been at Rockefeller, I became increasingly interested in studying the molecular basis for various diseases because we now know more about the pathways involved. And so today, much of the work of our research group is dedicated to studies of depression, Alzheimer's disease, Parkinson's disease, and schizophrenia. These diseases seem very different but the signaling pathways have a lot in common and the techniques to study them have even more in common.

JCI: In the year 2000 you were awarded the Nobel Prize in Physiology or Medicine.

Greengard: Each year, I had been told that I was going to win the Nobel Prize that year. On a Monday morning in 2000, the announcement came. Our daughter was staying with us in our apartment and somebody called at 5:15 in the morning. We had gotten to bed very late the night before. By the time I picked up the telephone, I heard my daughter saying, "But he's sound asleep. You really want me to wake him up?" And then the reply, "Well, my name is Hans Jörnvall and I am the Secretary of the Nobel Prize Committee." I said, "It's okay. I'm awake." So, that was how I first learned about it.

JCI: You used your share of the winnings to endow a prize in the name of your mother, The Pearl Meister Greengard Award for women in science. Why did you decide to use your honorarium in that way?

Greengard: When I grew up it was pretty much universally accepted, by both men and women, that women were inferior. It's hard to believe now but almost everybody I knew thought men were smarter than women. It took a long time, and a lot of fighting by a lot of courageous women and some supportive men, to put that idea to rest. Having seen all this discrimination, I thought it'd be nice to do something to help champion these women who were struggling and still are today. The situation today is incomparably better than what it was but there's still a lot of discrimination.

JCI: How do you approach mentoring of young trainees?

Greengard: I don't have a formula. A number of former students have said they learned a lot, but I've also been told by a number of students that the most unpleasant experience of their life was writing a manuscript with me. They thought it was sheer hell, and then they would tell me 15 years later, "I had no idea how much I learned."

This mentoring thing, I think one can get more credit than one deserves. For example, I've had the pleasure of observing many of my former students and post-docs become leaders in neuroscience. I don't think that I was brilliant in teaching them how to be such good scientists. I think that the younger generation tends to have an instinct about what the important new directions are. Since they were brilliant to begin with, they went on to very successful careers.

JCI: If you were to have considered an alternate career, what would you have done?

Greengard: Recently, my granddaughter, who is an attorney, was trying to search out what exactly she would like to do in the long run. She asked me what I would do. I told her that I thought I would like to be a constitutional lawyer. And, in my wilder dreams, either a professor in constitutional law; or in my even wilder dreams, a Supreme Court Justice; and in my wildest dreams, I would be the Chief Justice of the Supreme Court.

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